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# A Novel Synthetic Route to 7α-Methoxycephalosporins[1]

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Treatment of 7β-sulfenamidocephalosporins **7** with an oxidizing agent such as active manganese dioxide gave the sulfenimines **8**, which were easily methoxylated to the 7α-methoxy-sulfenamides **9** with lithium methoxide. The 7α-methoxy-sulfenamidocephalosporins **9** were converted to the free amine **10** by reaction with sodium iodide. Acylation of **10** afforded the cephamycin derivative **11**. This method was also successfully applied to the penicillin series, leading to the sulfenimine **13**, which was methoxylated to furnish the desired 6α-methoxy-penicillin **14** together with the ring-opened product **15**.

**Keywords**——cephamycin; cephalosporin; sulfenamide; sulfenimine; sulfenimide; methoxylation; oxidation

Almost eight years have passed since the isolation of cephamycins (7-methoxycephalosporins) was reported by Lilly[3] and Merck.[4] During this time, many attempts have been made to introduce a methoxy group at the seven position of the cephalosporin nucleus[5] as well as to exchange the side chain of cephamycins at the 7β-position[6] to improve their resistance to β-lactamase.[7]

As a part of our attempts to introduce a methoxy group at the 7-position of cephalosporins, we considered the utilization of a sulfenamide moiety, because this functionality is often used in peptide chemistry for protecting an amino group[8] and thus may also be useful in cephalosporin chemistry. Some work has been done on the sulfenamide group attached to a β-lactam ring.[9]

The reaction of *tert*-butyl 7β-amino-3-methyl-3-cephem-4-carboxylate (**1**) (1 eq.) with benzenesulfenyl chloride (1 eq.) in the presence of triethylamine (1.2 eq.) in tetrahydrofuran afforded *tert*-butyl 7β-benzenesulfenamido-3-methyl-3-cephem-4-carboxylate (**2**) as a major product (76.4%), together with *tert*-butyl 7β-bis-benzenesulfenimido-3-methyl-3-cephem-4-carboxylate (**3**) (7.5%) and *tert*-butyl 7-benzenesulfenimino-3-methyl-3-cephem-4-carboxylate (**4**) (6.9%), which were separated by preparative thin-layer chromatography. The structure of the sulfenimine **4** was easily elucidated on the basis of its nuclear magnetic resonance

1) A part of this work has been published in T. Kobayashi, K. Iino, and T. Hiraoka, *J. Am. Chem. Soc.*, **99**, 5505 (1977) in the form of a communication.
2) Location: *1-2-58, Hiromachi, Shinagawa-ku, Tokyo, 140, Japan.*
3) R. Nagarajan, L.D. Boeck, M. Gorman, R.L. Hamill, C.E. Higgens, M.M. Hoehn, W.M. Stark, and J.G. Whitney, *J. Am. Chem. Soc.*, **93**, 2308 (1971).
4) *a*) E.O. Stapley, M. Jackson, S. Hernandez, S.B. Zimmerman, S.A. Currie, S. Mochales, J.M. Mata, H.B. Woodruff, and D. Hendlin, *Antimicrob. Agents Chemother.*, **2**, 122 (1972); *b*) T.W. Miller, R.T. Goegelman, R.G. Weston, I. Putter, and F.J. Wolf, *ibid.*, **2**, 132 (1972).
5) see T. Hiraoka, Y. Sugimura, T. Saito, and T. Kobayashi, *Heterocycles*, **8**, 719 (1977) and references cited therein.
6) *a*) W.H.W. Lunn, R.W. Burchfield, T.K. Elzey, and E.V. Mason, *Tetrahedron Lett.*, **1974**, 1307; *b*) M. Shiozaki, N. Ishida, K. Iino, and T. Hiraoka, *ibid.*, **1977**, 4059; *c*) S. Karady, J.S. Amato, L.M. Weinstock, and M. Sletzinger, *ibid.*, **1978**, 407; *d*) M. Shiozaki, N. Ishida, K. Iino, and T. Hiraoka, *Chem. Commun.*, **1978**, 517.
7) *a*) H. Wallick and D. Hendlin, *Antimicrob. Agents Chemother.*, **5**, 25 (1974); *b*) P.P.K. Ho, R.D. Towner, J.M. Indelicato, W.J. Wilham, W.A. Spitzer, and G.A. Koppel, *J. Antibiot.* (Tokyo), **26**, 313 (1973); *c*) H. Nakao, H. Yanagisawa, B. Shimizu, M. Kaneko, M. Nagano, and S. Sugawara, *ibid.*, **29**, 554 (1976).
8) E. Wünsch, "Methoden der Organischen Chemie," Bd. XV/1, Houben-weyl, Stuttgart, 1974, p. 203.
9) W.M. Welch, *J. Org. Chem.*, **41**, 2220 (1976).

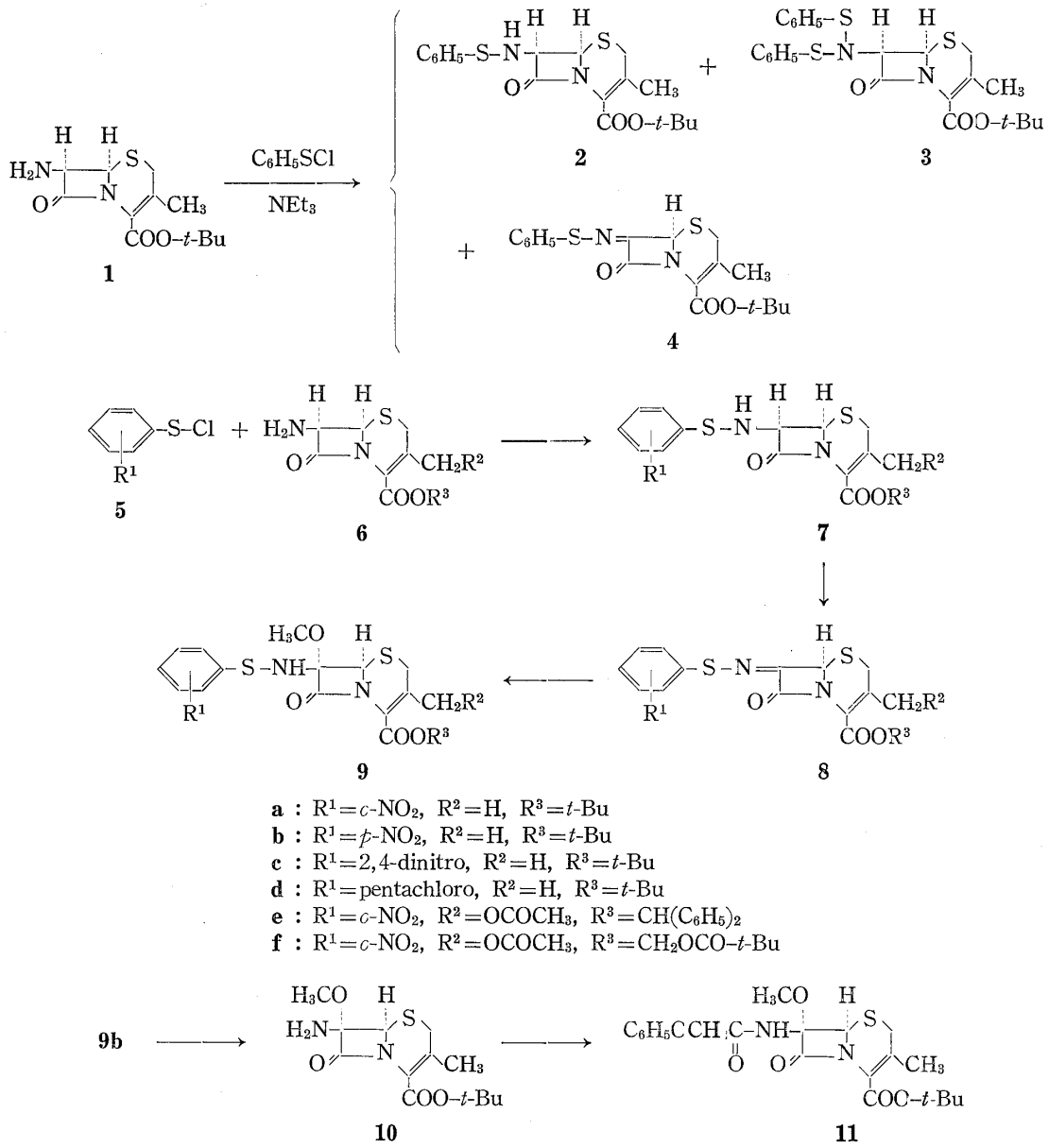

Chart 1

(NMR) spectrum, which showed a sharp singlet at 5.27 ppm ascribable to the hydrogen at the 6 position. The formation of *bis*-benzenesulfenimide **3** can be explained by the $\alpha$-effect,[10] but production of sulfenimine **4** is unexpected even as a minor product. When 2 eq. of benzenesulfenyl chloride was used in the above reaction with 2.4 eq. of triethylamine, the major product was the bis-benzenesulfenyl compound **3** (82.6%) although the yield of sulfenimine **4** increased slightly (12.1%). Since bis-benzenesulfenimide **3** was stable on treatment with triethylamine, formation of the sulfenimine **4** can not be due to simple 1,2-elimination of thiophenol from the bis-compound **3**. At this point we did not further investigate the reaction of bis-benzenesulfenimide **3**; our efforts were concentrated on the oxidation of the sulfenamide **2** with an oxidizing agent. When our work on this subject had been completed we found that Gordon *et al.*[11] in the Squibb Institute had reported a

10) For example, see reference 9).
11) *a*) Private communication from Dr. Cimarusti; *b*) E.M. Gordon, H.W. Chang, and C.M. Cimarusti, *J. Am. Chem. Soc.*, **99**, 5504 (1977).

similar reaction and obtained the sulfenimine **4** in high yield using 3 eq. of *p*-tolylsulfenyl chloride in the presence of a mixture of propylene oxide and a molecular sieve (type 4A). Squibb's result showed that a $-\overset{+}{S}-N-$species is probably involved in the formation of the sulfenimine, since at least 3 eq. of the sulfenyl chloride was required to obtain a high yield.

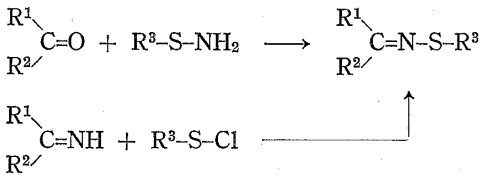

Chart 2

A survey of the literature showed that no method is available for the oxidation of a sulfenamide leading to a sulfenimine; the latter compounds are generally prepared by the reaction of a ketone with $-SNH_2$ or reaction of an imine with sulfenyl halide, as shown in Chart 2.[12] First, metallic oxidizing agents were examined for dehydrogenation of the sulfenamide **2**, and active manganese dioxide was found to be extremely effective for the oxidation of sulfenamides to sulfenimines under mild conditions. Thus, treatment of the sulfenamide **2** with active manganese dioxide in benzene solution at room temperature for 1 hour afforded the desired sulfenimine **4** cleanly in 90% yield. Other oxidizing agents such as lead oxide or dichlorodicyano-*p*-benzoquinone were not effective. Other methods with combinations of halogenating reagents and a base also failed to give satisfactory results. Thus, NCS–triethylamine, trichloroisocyanuric acid–triethylamine and *t*-butyl hypochlorite–lithium methoxide were examined, but lower yields were obtained as compared with manganese dioxide (see "Experimental").

Methoxylation of the sulfenimine **4** was attempted using lithium methoxide in methanol under various conditions to afford only traces of the methoxylated compound. It might be possible to circumvent this difficulty by introducing electron withdrawing group(s) into the benzene ring. Thus, compound **1** was treated with *o*-nitrobenzenesulfenyl chloride, giving the desired sulfenamide **7a** in good yield without formation of bis-*o*-nitrobenzenesulfenimide. Even if excess *o*-nitrobenzenesulfenyl chloride was used, no bis-*o*-nitrobenzenesulfenimide corresponding to **3** was produced, indicating that the $\alpha$-effect is reduced by the electron-attracting nitro substituent, as well as by steric effects. *p*-Nitrobenzenesulfenamide **7b**, 2,4-dinitrobenzenesulfenamide **7c**, and pentachlorobenzenesulfenamide **7d** were prepared analogously. Furthermore, the sulfenamide benzhydryl-ester **7e** and pivaloyloxymethyl-ester **7f** were prepared starting from 3-acetoxymethyl-7$\beta$-amino-3-cephem-4-carboxylic acid. Oxidation of these sulfenamides which have electron attracting group(s) in the benzene ring might be expected to be difficult as compared to the compound without such substituent(s). However, oxidation of the sulfenamides (**7a**—**f**) using manganese dioxide occurred smoothly in good yields at room temperature, as in the case of **2**. One exception was pentachlorobenzenesulfenamide **7d**, in which both electron withdrawing and steric effects were operative. Thus oxidation of **7d** was rather slow and the yield of sulfenimine **8d** was low (19.6%).

Methoxylation of the sulfenimines **8a**—**f** was accomplished with lithium methoxide in methanol at low temperature in good yield without difficulty. The stereochemistry of the resulting methoxysulfenamides **9a**—**f** was established as $\alpha$ after conversion to the known 7$\alpha$-methoxy-7$\beta$-amide derivatives **11**[13] (*vide infra*). Inspection of the NMR spectrum of the crude methoxylated product **9** revealed that only the 7$\alpha$-isomer was produced on treatment of **8a**—**f** with lithium methoxide. On the other hand, methoxylation of the sulfenimines **8e** with methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid or methanesulfonic acid at room temperature gave a mixture of the 7$\alpha$- and 7$\beta$-methoxy derivatives in a ratio of 1:2. This ratio was easily determined by examining the methoxy signals in

12) *a*) C. Brown and B.T. Grayson, *Mec. Reactions Sulfur Comp.*, **5**, 93 (1970); *b*) C. Brown, B.T. Grayson, and R.F. Hudson, *Chem. Commun.*, **1974**, 1007.
13) T. Saito, Y. Sugimura, Y. Iwano, K. Iino, and T. Hiraoka, *Chem. Commun.*, **1976**, 516.

the NMR spectrum; a singlet peak due to the 7$\alpha$-isomer appeared at lower field compared to that of the 7$\beta$-isomer. In the methoxylation of **8** with methoxide anion, the reagent attacked from the less hindered side to afford only the 7$\alpha$-isomer, as in the case of 7-acyliminocephalosporin.[14] However, with an acidic catalyst the first site of reaction is the nitrogen of the sulfenimine **8** (protonation) and kinetic control would be a major factor in the subsequent methoxylation reaction.

The conversion of the methoxysulfenamides **9** to the desired free amine **10** was expected to be very easy, since this kind of transformation is well known in amino acid chemistry.[8] However, in our case many reactions had to be carried out to obtain a successful result because the 7$\alpha$-methoxy-7$\beta$-amino compounds were not stable, and the conditions usually used to remove the substituted benzenesulfenyl group destroyed the free amino compound **10**. The best conditions for the formation of **10** were as follows: treatment of **9b** with potassium iodide–acetic acid in methanol–methylene chloride at 0°. The resulting amino compound **10** was converted into the acylamino derivative **11** in the usual way. Cleavage of the S–N bond in the methoxysulfenamide **9b** was also achieved by treatment with benzenethiol in the presence of triethylamine or with hexamethylphosphorus triamide and triethylamine at room temperature. The resulting free amine **10** was acylated with phenoxyacetyl chloride without isolation to afford the desired amide **11** as a mixture of $\Delta^2$- and $\Delta^3$-isomers.

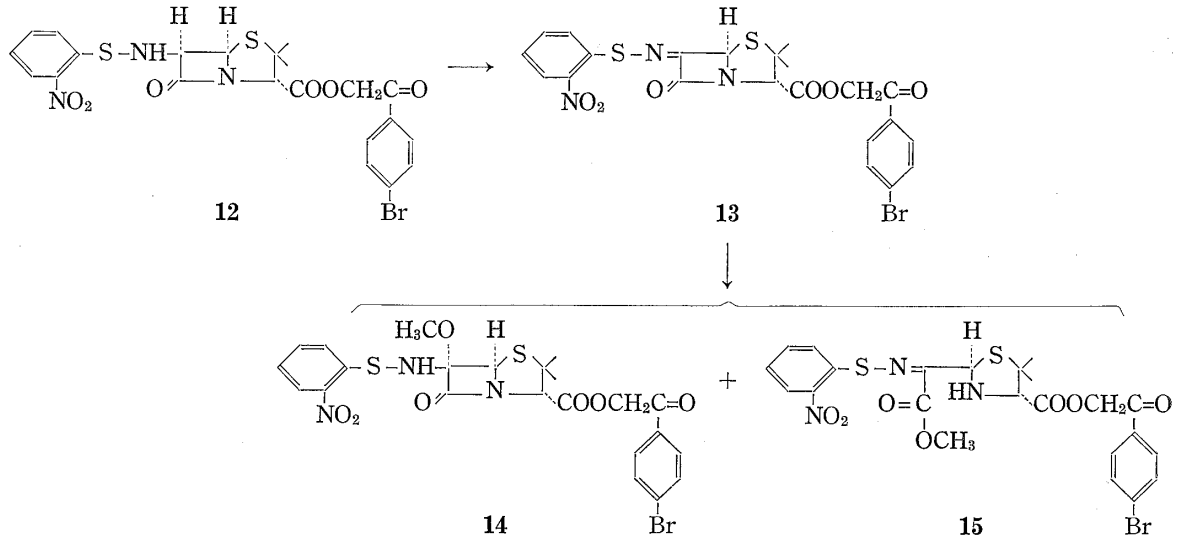


Chart 3

These reactions starting from 7-H-cephalosporins to give 7$\alpha$-methoxy-7$\beta$-acylaminocephalosporins were also successfully applied to penicillin. Thus, *p*-bromophenacyl 6$\beta$-*o*-nitrobenzenesulfenylaminopenicillanate **12** prepared from 6$\beta$-amino-penicillanic acid was oxidized to the sulfenimine **13** with manganese dioxide in 69% yield. Methoxylation of the imine **13** with lithium methoxide in methanol at −78° gave the desired methoxylated penicillin **14** together with the ring-opened product **15** in 31% and 58% yields, respectively. It is noteworthy that the ring-cleaved product **15** was not methoxylated, and the double bond between nitrogen and carbon remained. The double bond directly attached to the $\beta$-lactam ring was easily converted into an $sp^3$ carbon with less strain, but the imine **15** was not easily converted into the methoxylated compound because the release of strain is not as large during the transformation of $sp^2$ to $sp^3$ carbon as that in the case of the exocyclic double bond of the $\beta$-lactam ring.

14) *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).

Thus, we have developed a new method for the synthesis of 7$\alpha$-methoxycephalosporins using sulfenamides which are easily prepared. This method is comparable to that devised by Yanagisawa *et al.* in our research laboratories.[15]

## Experimental[16]

**Reaction of Benzenesulfenyl Chloride with *tert*-Butyl 7$\beta$-Amino-3-methyl-3-cephem-4-carboxylate (1)**——(a) With One Equivalent of Benzenesulfenyl Chloride: A solution of *tert*-butyl 7$\beta$-amino-3-methyl-3-cephem-4-carboxylate **1** (650 mg, 2.40 mmol) and triethylamine (0.4 ml, 2.88 mmol) in dry THF (10 ml) was treated with benzenesulfenyl chloride (350 mg, 2.40 mmol) in dry THF (3 ml) at −78° and stirred for 2 hr at −78°, then 3 hr at room temperature. The mixture was diluted with ethyl acetate, then the resulting solution was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give an oily residue. Subsequent preparative thin-layer chromatography (TLC) on silica gel, developing with benzene, provided benzenesulfenamide **2** (694 mg, 76.4%), bis-benzenesulfenimide **3** (87 mg, 7.5%), and benzenesulfenimine **4** (63 mg, 6.9%).

*tert*-Butyl 7$\beta$-Benzenesulfenamido-3-methyl-3-cephem-4-carboxylate (**2**): mp 112—113° (diisopropyl ether); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1780; NMR ($CDCl_3$) $\delta$: 1.43 (9H, s), 1.97 (3H, s), 3.09 and 3.42 (2H, ABq, $J$=18.5 Hz), 3.76 (1H, d, $J$=10 Hz), 4.60 (1H, dd, $J$=10 and 4 Hz), 4.84 (1H, d, $J$=4 Hz), 6.88—7.12 (5H, m).

*tert*-Butyl 7$\beta$-Bisbenzenesulfenimido-3-methyl-3-cephem-4-carboxylate (**3**): oil; IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1780; NMR ($CDCl_3$) $\delta$: 1.47 (9H, s), 2.07 (3H, s), 3.15 (2H, s), 4.78 (1H, d, $J$=4.5 Hz), 5.30 (1H, d, $J$=4.5 Hz), 7.07—7.68 (10H, m).

*tert*-Butyl 7-Benzenesulfenimino-3-methyl-3-cephem-4-carboxylate (**4**): mp 170—171° (diisopropyl ether); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1750; NMR ($CDCl_3$) $\delta$: 1.55 (9H, s), 2.08 (3H, s), 3.12 and 3.48 (2H, ABq, $J$=19 Hz), 3.27 (1H, s), 7.16—7.70 (5H, m).

(b) With Two Equivalent of Benzenesulfenyl Chloride: Benzenesulfenyl chloride (700 mg, 4.80 mmol) in dry THF (6 ml) was added to a stirred solution of *tert*-butyl 7$\beta$-amino-3-methyl-3-cephem-4-carboxylate **1** (0.65 g, 2.40 mmol) and triethylamine (0.80 ml, 5.76 mmol) in dry THF (10 ml) at −78°. After stirring at −78° for 2 hr then at room temperature for 3 hr, the solution was worked up as described in (a). Purification by preparative TLC on silica gel using benzene gave bisbenzenesulfenimide **3** (968 mg, 82.6%) and benzenesulfenimine **4** (141 mg, 12.1%).

**General Procedure for the Reaction of Arylsulfenyl Chlorides with *tert*-Butyl 7$\beta$-Amino-3-methyl-3-cephem-4-carboxylate (1)**——A solution of *tert*-butyl 7$\beta$-amino-3-methyl-3-cephem-4-carboxylate **1** (20 mmol) and triethylamine (20 mmol) in dry THF (100 ml) was slowly added to a solution of arylsulfenyl chloride (20 mmol) in dry THF (40 ml) while the temperature of the solution was maintained at 0°. The resulting suspension was stirred for 2 hr at 0° then 3 hr at room temperature. The mixture was then diluted with EtOAc, washed with water, and dried with $MgSO_4$. The solvents were removed *in vacuo* to give a residue, which was purified by chromatography using silica gel to afford an arylsulfenamide.

*tert*-Butyl 3-Methyl-7$\beta$-*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (**7a**): mp 171—172° (diisopropyl ether–$CHCl_3$); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1775; NMR ($CDCl_3$) $\delta$: 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); (85.1%).

*tert*-Butyl 3-Methyl-7$\beta$-*p*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (**7b**): mp 119—120° (diisopropyl ether–EtOAc); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1780; NMR ($CDCl_3$) $\delta$: 1.50 (9H, s), 2.07 (3H, s), 3.18 and 3.52 (2H, ABq, $J$=18 Hz), 3.74 (1H, d, $J$=9 Hz), 4.72 (1H, dd, $J$=9 and 5 Hz), 4.93 (1H, d, $J$=5 Hz), 7.28—8.23 (4H, m); (71.8%).

*tert*-Butyl 7$\beta$-(2,4-Dinitrobenzenesulfenamido)-3-methyl-3-cephem-4-carboxylate (**7c**): mp 151—152° (hexane–EtOAc); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1750; NMR ($CDCl_3$) $\delta$: 1.48 (9H, s), 2.08 (3H, s), 3.23 and 3.55 (2H, ABq, $J$=18 Hz), 3.88 (1H, d, $J$=9.5 Hz), 4.72 (1H, dd, $J$=9.5 and 4 Hz), 4.97 (1H, d, $J$=4 Hz), 8.37—9.13 (3H, m); (76.5%).

***tert*-Butyl 3-Methyl-7$\beta$-pentachlorobenzenesulfenamido-3-cephem-4-carboxylate (7d)**——A solution of *tert*-butyl 7$\beta$-amino-3-methyl-3-cephem-4-carboxylate **1** (1.35 g, 5.0 mmol) and propylene oxide (870 mg) in dry $CH_2Cl_2$ (20 ml) was treated with pentachlorobenzenesulfenyl chloride (1.58 g, 5.0 mmol) in dry $CH_2Cl_2$ (10 ml) at 0° and stirred for 1 hr at room temperature. After diluting the mixture with methylene chloride, the solution was washed with water. Concentration of the dried ($Na_2SO_4$) solution *in vacuo* provided a residue, which was chromatographed on silica gel (solvent: benzene) to give pentachlorobenzenesulfenamide

15) H. Yanagisawa, M. Fukushima, A. Ando, and H. Nakao, *Tetrahedron Lett.*, **1975**, 2705.

16) Melting points are not corrected. Infrared (IR) spectra were recorded with a JASCO A-2 spectrometer. NMR spectra were measured with a 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.

**7d** (1.33 g, 70.5%): mp 156—158° (diisopropyl ether); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1790; NMR ($CDCl_3$) $\delta$: 1.49 (9H,s), 2.03 (3H, s), 3.13 and 3.36 (2H, ABq. $J$=18 Hz), 4.03 (1H, d, $J$=8 Hz), 4.79 (1H, d, $J$=4.5 Hz), 4.89 (1H, dd, $J$=9 and 4.5 Hz).

**Benzhydryl 3-Acetoxymethyl-7β-*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (7e)**——A solution of 3-acetoxymethyl-7β-amino-3-cephem-4-carboxylic acid (7.46 g, 27.4 mmol) and triethylamine (7.65 ml, 54.9 mmol) in dry $CH_2Cl_2$ (140 ml) was stirred and cooled to 0°. *o*-Nitrobenzenesulfenyl chloride (5.2 g, 27.4 mmol) in dry $CH_2Cl_2$ (60 ml) was added and the mixture was stirred for 2 hr at 0°, then 3 hr at room temperature. The mixture was then poured into ice-water. Ethyl acetate was added, and the aqueous layer was adjusted to pH 3.0 (1 N HCl) then quickly extracted with EtOAc twice. After washing with water and drying over $MgSO_4$, the organic solution was concentrated. The residue was dissolved in EtOAc (200 ml) and excess diphenyldiazomethane was added. The solution was left to stand 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 10: 1) to give *o*-nitrobenzenesulfenamide **7e** (13.2 g, 89.3%).: mp 123—124° (diisopropyl ether–EtOAc); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1770; NMR ($CDCl_3$) $\delta$: 2.01 (3H, s), 3.42 and 3.67 (2H, ABq, $J$=19 Hz), 3.63 (1H, d, $J$=9 Hz), 4.85 and 5.08 (2H, ABq, $J$=14 Hz), 4.85 (1H, dd, $J$=9 and 5.5 Hz), 5.02 (1H, d, $J$=5.5 Hz), 7.03 (1H, s), 7.20—8.43 (14H, m).

**Pivaloyloxymethyl 3-Acetoxymethyl-7β-*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (7f)**——A cold solution of 3-acetoxymethyl-7β-amino-3-cephem-4-carboxylic acid (4.23 g, 15.5 mmol) and triethylamine (4.55 ml, 32.6 mmol) in dry $CH_2Cl_2$ (125 ml) was treated with *o*-nitrobenzenesulfenyl chloride (2.94 g, 15.5 mmol) in dry $CH_2Cl_2$ (30 ml). The mixture was stirred at 0° for 2 hr then at room temperature for 3 hr. The mixture was poured into ice-water, acidified with 1 N HCl to pH 3.0, and extracted with EtOAc. The combined extracts were dried ($MgSO_4$) and evaporated down to give a yellow solid (7.0 g). The solid was dissolved in dry THF (70 ml), and 2 M potassium 2-ethylhexanoate in butanol (34 mmol, 17 ml) was slowly added. The resulting slurry was stirred for 2 hr, filtered rapidly, and washed with EtOAc to give *o*-nitrobenzenesulfenamide potassium salt (7.3 g). A stirred suspension of the potassium salt in acetone (70 ml) was treated with pivaloyloxymethyl chloride (2.5 g, 16.6 mmol), followed immediately by the addition of sodium iodide (350 mg) in $H_2O$ (1.8 ml) with vigorous stirring. After refluxing for 6.5 hr, the mixture was diluted with EtOAc and washed successively with water, aqueous $NaHCO_3$, and water. Removal of the organic phase (after drying over $MgSO_4$) and chromatography of the residue on silica gel (solvent: benzene–EtOAc 10: 1) gave *o*-nitrobenzenesulfenamide **7f** (3.05 g, 34.3%).: yellow amorphous solid; IR $\nu_{max}^{CHCl_3}$ ($cm^{-1}$): 1790; NMR ($CDCl_3$) $\delta$: 1.18 (9H, s), 2.03 (3H, s), 3.33 and 3.70 (2H, ABq, $J$=19 Hz), 3.58 (1H, d, $J$=9 Hz), 4.77 and 5.15 (2H, ABq, $J$=13 Hz), 4.82 (1H, dd, $J$=4.5 and 9 Hz), 5.00 (1H, d, $J$=4.5 Hz), 5.82 and 5.97 (2H, ABq, $J$=6 Hz), 7.15—8.43 (4H, m).

***p*-Bromophenacyl 6β-*o*-Nitrobenzenesulfenamido-penicillanate (12)**——A mixture of *p*-bromophenacyl 6β-amino-penicillanate hydrochloride (11.3 g, 25 mmol) and triethylamine (7.0 ml, 50 mmol) in dry THF (225 ml) was stirred for a short time and cooled to 0°. *o*-Nitrobenzenesulfenyl chloride (4.74 g, 25 mmol) in dry THF (10 ml) was added, and the mixture was stirred at 0° for 2 hr, then at room temperature for 3 hr. The solution was diluted with EtOAc, then washed successively with water, saturated $NaHCO_3$ solution, and water. Removal of the dried ($MgSO_4$) organic solvent *in vacuo* provided a residue, which was chromatographed on silica gel using benzene–EtOAc (10: 1) to give *o*-nitrobenzenesulfenamide **12** (17.8 g, 62.5%).: yellow amorphous solid; IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1780; NMR ($CDCl_3$) $\delta$: 1.73 (3H, s), 1.78 (3H, s), 3.67 (1H, d, $J$= 10 Hz), 4.62 (1H, s), 4.67 (1H, dd, $J$=10 and 4 Hz), 5.30 and 5.55 (2H, ABq, $J$=16 Hz), 5.65 (1H, d, $J$= 4 Hz), 7.18—8.42 (8H, m).

**General Procedure for the Oxidation of Arylsulfenamide with Active Manganese Dioxide**——Active manganese dioxide (60—70 g) (purchased from Merck) was slowly added to a vigorously stirred solution of an arylsulfenamide (2.0 g) in benzene (100 ml). The mixture was stirred for 1 hr at room temperature. The solid was removed by filtration and washed with a small amount of benzene. The filtrate and washings were combined and concentrated under reduced pressure. The residue was generally essentially pure, judging from the NMR data, and was used in the next reaction without further purification. If necessary, the sulfenimine could be purified by chromatography using silica gel.

*tert*-Butyl 7-Benzenesulfenimino-3-methyl-3-cephem-4-carboxylate (**4**): (a) Oxidation with *tert*-Butyl Hypochlorite and Lithium Methoxide: A stirred solution of benzenesulfenamide **2** (175 mg, 0.5 mmol) in dry THF (7 ml) was treated with lithium methoxide (prepared from 31.5 mg of lithium, 4.5 mmol) in dry MeOH (2 ml) at −78°, followed immediately by dropwise addition of *tert*-butyl hypochlorite (0.06 ml, 0.55 mmol) with vigorous stirring. The mixture was stirred for 30 min at −78°, and then glacial AcOH was added. The mixture was washed successively with water, aqueous $NaHCO_3$, and water. The organic layer was dried ($MgSO_4$) and concentrated, then the residue was chromatographed on silica gel. Benzenesulfenimine **4** (86.3 mg, 49.5%) was eluted with benzene. The NMR and IR spectra of **4** were identical with those of **4** obtained by the reaction of **1** with benzenesulfenyl chloride.

(b) Oxidation with N-Chlorosuccinimide and Triethylamine: A suspension of benzenesulfenamide **2** (190 mg, 0.5 mmol) and triethylamine (0.1 ml, 0.7 mmol) in $CCl_4$ (5 ml) was treated with N-chlorosuccinimide (84.0 mg, 0.62 mmol). The mixture was heated at 40° for 1 hr. The precipitate was removed by filtration and the filtrate was concentrated *in vacuo* to afford a residue. Purification by chromatography on silica gel

using benzene afforded benzenesulfenimine **4** (89.7 mg, 47.3%).

(c) Oxidation with Manganese Dioxide: Using the general procedure, benzenesulfenamide **2** (2.0 g, 5.28 mmol) and active manganese dioxide (60 g) gave benzenesulfenimine **4** (1.80 g, 90.0%).

*tert*-Butyl 3-Methyl-7-*o*-nitrobenzenesulfenimino-3-cephem-4-carboxylate (**8a**): (a) Oxidation with Trichloroisocyanuric Acid and Triethylamine: A stirred suspension of *o*-nitrobenzenesulfenamide **7a** (656 mg, 1.55 mmol) and triethylamine (0.35 ml, 2.5 mmol) in $CCl_4$ (15 ml) was treated with trichloroisocyanuric acid (545 mg, 2.3 mmol). After stirring for 1 hr at 0°, the solid was filtered off, and the filtrate was concentrated under reduced pressure. The crude product was purified by TLC on silica gel using benzene–EtOAc (10: 1) to give *o*-nitrobenzenesulfenimine **8a** (145 mg, 22.8%).: mp 183—184° (diisopropyl ether–$CHCl_3$); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1780; NMR ($CDCl_3$) $\delta$: 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).

(b) Oxidation with Manganese Dioxide: *o*-Nitrobenzenesulfenimine **8a** (86.4%).

*tert*-Butyl 3-Methyl-7-*p*-nitrobenzenesulfenimino-3-cephem-4-carboxylate (**8b**): (a) Oxidation with N-Chlorosuccinimide and Triethylamine: A stirred suspension of *p*-nitrobenzenesulfenamide **7b** (205 mg, 0.48 mmol) and triethylamine (0.16 ml, 1.10 mmol) in $CCl_4$ (6 ml) was treated with N-chlorosuccinimide (148 mg, 1.10 mmol). The mixture was then heated at 40° for 1 hr. The precipitate was filtered off and the organic solution was concentrated *in vacuo* to give a residue. Purification of the residue by TLC on silica gel (solvent: benzene–EtOAc 10: 1) gave *p*-nitrobenzenesulfenimine **8b** (134 mg, 65.8%): mp 169—170° (diisopropyl ether–EtOAc); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1790; NMR ($CDCl_3$) $\delta$: 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).

(b) Oxidation with Manganese Dioxide: *p*-Nitrobenzenesulfenimine **8b** (82.9%).

*tert*-Butyl 7-(2,4-Dinitrobenzenesulfenimino)-3-methyl-3-cephem-4-carboxylate (**8c**): mp 187—188° (*n*-hexane–EtOAc); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1780; NMR ($CDCl_3$) $\delta$: 1.58 (9H, s), 2.18 (3H, s), 3.25 and 3.60 (2H, ABq, $J$=18.5 Hz), 5.45 (1H, s), 8.38—9.23 (3H, m); (67.8%).

*tert*-Butyl 3-Methyl-7-pentachlorobenzenesulfenimino-3-cephem-4-carboxylate (**8d**): mp 195—197°; IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1760; NMR ($CDCl_3$) $\delta$: 1.56 (9H, s), 2.10 (3H, s), 3.22 and 3.45 (2H, ABq, $J$=18 Hz), 5.28 (1H, s); (19.6%).

Benzhydryl 3-Acetoxymethyl-7-*o*-nitrobenzenesulfenimino-3-cephem-4-carboxylate (**8e**): mp 134—135° (*n*-hexane–EtOAc); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1780; NMR ($CDCl_3$) $\delta$: 2.01 (3H, s), 3.99 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); (70.2%).

Pivaloyloxymethyl 3-Acetoxymethyl-7-*o*-nitrobenzenesulfenimino-3-cephem-4-carboxylate (**8f**): yellow amorphous solid; IR $\nu_{max}^{CHCl_3}$ ($cm^{-1}$): 1785; NMR ($CDCl_3$) $\delta$: 1.25 (9H, s), 2.10 (3H, s), 3.40 and 3.77 (2H, ABq, $J$=18 Hz), 4.85 and 5.20 (2H, ABq, $J$=14 Hz), 5.50 (1H, s), 6.00 (2H, s), 7.33—8.63 (4H, m); (55.9%).

*p*-Bromophenacyl 6-*o*-Nitrobenzenesulfenimino-penicillanate (**13**): yellow amorphous solid; IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1780; NMR ($CDCl_3$) $\delta$: 1.65 (3H, s), 1.72 (3H, s), 4.80 (1H, s), 5.43 (2H, s), 5.97 (1H, s), 7.22—8.53 (8H, m); (69.3%).

**General Procedure for the Methoxylation of Arylsulfenimine with Lithium Methoxide**——A stirred solution of an arylsulfenimine (4 mmol) in dry MeOH (60 ml) was cooled to −78°, and lithium methoxide (prepared from 20—40 mmol of lithium) in dry MeOH (24 ml) was added with vigorous stirring. After stirring for 30 min, dry THF (70 ml) was added and the reaction was continued for a further 3.5 hr at −78°, then glacial AcOH was added. After dilution with EtOAc, the organic layer was washed successively with water, saturated aq. $NaHCO_3$, and water. The solution was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by chromatography on silica gel using a suitable solvent gave 7 (or 6)-methoxy-arylsulfenamide.

*tert*-Butyl 7α-Methoxy-3-methyl-7β-*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (**9a**): mp 149—150° (MeOH); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1765; NMR ($CDCl_3$) $\delta$: 1.50 (9H, s), 2.12 (3H, s), 3.18 and 3.39 (2H, ABq, $J$=18 Hz), 3.57 (3H, s), 4.30 (1H, s), 4.90 (1H, s), 7.12—8.35 (4H, m); (63.2%).

*tert*-Butyl 7α-Methoxy-3-methyl-7β-*p*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (**9b**): mp 120—121° (MeOH); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1765; NMR ($CDCl_3$) $\delta$: 1.52 (9H, s), 2.12 (3H, s), 3.15 and 3.38 (2H, ABq, $J$=18 Hz), 3.53 (3H, s), 4.48 (1H, s), 4.88 (1H, s), 7.27—8.28 (4H, m); (50.0%).

*tert*-Butyl 7β-(2,4-Dinitrobenzenesulfenamido)-7α-methoxy-3-methyl-3-cephem-4-carboxylate (**9c**): yellow amorphous solid; IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1780; NMR ($CDCl_3$) $\delta$: 1.49 (9H, s), 2.12 (3H, s), 3.20 and 3.40 (2H, ABq, $J$=18 Hz), 3.58 (3H, s), 4.58 (1H, s), 4.93 (1H, s), 8.35—9.08 (3H, m); (83.2%).

***tert*-Butyl 7α-Methoxy-3-methyl-7β-pentachlorobenzenesulfenamido-3-cephem-4-carboxylate** (**9d**)——A stirred solution of pentachlorobenzenesulfenimine **8d** (55 mg, 0.146 mmol) in dry $CHCl_3$ (3 ml) and dry MeOH (2 ml) was treated with lithium methoxide (prepared from 7.6 mg of lithium, 1.09 mmol) in dry MeOH (1 ml) at −78°, and the mixture was vigorously stirred at −40° for 45 min, then at −20° for 1.5 hr. Next, glacial AcOH was added and the reaction mixture was diluted with EtOAc and washed successively with water, aqueous $NaHCO_3$, and water. Concentration of the organic fraction (after drying on $MgSO_4$) and chromatography of the residue, eluting with benzene, gave 7α-methoxy-pentachlorobenzenesulfenamide **9d** (29.8 mg, 50.0%): IR $\nu_{max}^{CHCl_3}$ ($cm^{-1}$): 1775; NMR ($CDCl_3$) $\delta$: 1.49 (9H, s), 2.08 (3H, s), 3.21 and 3.31 (2H, ABq, $J$=18 Hz), 3.23 (3H, s), 4.79 (1H, s), 4.89 (1H, s).

Benzhydryl 3-Acetoxymethyl-7α-methoxy-7β-*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (**9e**): yellow amorphous solid; IR $\nu_{max}^{CHCl_3}$ ($cm^{-1}$): 1788; NMR ($CDCl_3$) δ: 1.99 (3H, s), 3.32 and 3.47 (2H, ABq, $J$=18.5 Hz), 3.56 (3H, s), 4.32 (1H, s), 4.93 (1H, s), 6.98 (1H, s), 7.25—8.45 (14H, m); (42.0%). Benzhydryl 3-acetoxymethyl-7α-methoxy-7β-*o*-nitrobenzenesulfenamido-2-cephem-4-carboxylate: yellow amorphous solid; IR $\nu_{max}^{CHCl_3}$ ($cm^{-1}$): 1785; NMR ($CDCl_3$) δ: 1.98 (3H, s), 3.48 (3H, s), 4.33 (1H, s), 4.73 (2H, bs), 5.27 (2H, s), 6.56 (1H, bs), 7.03 (1H, s), 7.18—8.52 (14H, m); (30.8%).

**Pivaloyloxymethyl 3-Acetoxymethyl-7α-methoxy-7β-*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (9f)**——A stirred solution of *o*-nitrobenzenesulfenimine **8f** (542 mg, 1.0 mmol) in dry MeOH (15 ml) and dry THF (20 ml) was cooled to −78°, and lithium methoxide (prepared from 51.4 mg of lithium, 7.40 mmol) in dry MeOH (5 ml) was added with vigorous stirring. The mixture was stirred for 5 hr at −78°, then glacial AcOH was added. After dilution with EtOAc, the organic phase was washed successively with water, aqueous $NaHCO_3$, and water. The solution was dried over $MgSO_4$ and concentrated *in vacuo* to afford a residue. Purification by chromatography on silica gel using benzene–EtOAc (5: 1) gave 7α-methoxy-*o*-nitrobenzenesulfenamide **9f** (159.0 mg, 27.7%; $Rf$=0.44: benzene–EtOAc 5: 1) and methyl 3-acetoxymethyl-7α-methoxy-7β-*o*-nitrobenzenesulfenamido-2-cephem-4-carboxylate (109.7 mg, 21.8%; $Rf$=0.28: benzene–EtOAc 5: 1). **9f**: yellow amorphous solid; IR $\nu_{max}^{CHCl_3}$ ($cm^{-1}$): 1780; NMR ($CDCl_3$) δ: 1.20 (9H, s), 2.08 (3H, s), 3.27 and 3.63 (2H, ABq, $J$=18 Hz), 3.60 (3H, s), 4.30 (1H, s), 4.82 and 5.15 (2H, ABq, $J$=13 Hz), 4,97 (1H, s), 4.23 and 4.37 (2H, ABq, $J$=6 Hz), 7.17—8.55 (4H, m). Methyl 3-acetoxymethyl-7α-methoxy-2β-*o*-nitrobenzenesulfenamido-2-cephem-4-carboxylate: yellow amorphous solid; IR $\nu_{max}^{CHCl_3}$ ($cm^{-1}$): 1780; NMR ($CDCl_3$) δ: 2.07 (3H, s), 3.55 (3H, s), 3.80 (3H, s), 4.24 (1H, s), 4.69 (2H, s), 5.09 (1H, bs), 5.28 (1H, s), 6.48 (1H, bs), 7.13—8.48 (4H, m).

*p*-Bromophenacyl 6α-Methoxy-6β-*o*-nitrobenzenesulfenamidopenicillanate (**14**): mp 148—150° (diisopropyl ether–$CHCl_3$); IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1790; NMR ($CDCl_3$) δ: 1.68 (6H, s), 3.53 (3H, s), 4.30 (1H, s), 4.80 (1H, s), 5.38 (2H, s), 5.45 (1H, s), 7.23—8.38 (8H, m); (30.9%). **15**:[17] yellow oil; IR $\nu_{max}^{Nujol}$ ($cm^{-1}$): 1750; NMR ($CDCl_3$) δ: 1.48 (3H, s), 1.65 (3H, s), 3.93 (3H, s), 4.13 (1H, s), 5.41 (2H, s), 5.90 (1H, s), 7.18—8.73 (7H, m); (58.4%).

**Methoxylation of Benzhydryl 3-Acetoxymethyl-7-*o*-nitrobenzenesulfenimino-3-cephem-4-carboxylate (8e) with *p*-Toluenesulfonic Acid**——A stirred solution of *o*-nitrobenzenesulfenimine **8e** (515 mg, 0.87 mmol) in MeOH (60 ml) and benzene (40 ml) was treated with *p*-toluenesulfonic acid monohydrate (155 mg, 2.6 mmol) at 0°. The mixture was stirred for 30 min at room temperature. Saturated $NaHCO_3$ solution was added, and the mixture was stirred for 30 min at room temperature. The mixture was diluted with EtOAc, and the organic layer was washed with water. After drying over $MgSO_4$ the solvent were evaporated off *in vacuo* to afford a residue. Purification by chromatography on silica gel using benzene–EtOAc (10: 1) gave a mixture of benzhydryl 3-acetoxymethyl-7β-methoxy-7α-*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate and benzhydryl 3-acetoxymethyl-7α-methoxy-7β-*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate **9e** (388 mg, 71.8%) in a ratio of 2: 1, as determined by NMR spectroscopy. NMR ($CDCl_3$) δ: 3.40 (2/3H, s; 7β-methoxy) and 3.53 (1/3H, s; 7α-methoxy).

***tert*-Butyl 7β-Amino-7α-methoxy-3-methyl-3-cephem-4-carboxylate (10)**——7α-Methoxy-*p*-nitrobenzenesulfenamide **9b** (102 mg, 0.23 mmol) in $CH_2Cl_2$ (2 ml) was added to a stirred solution of sodium iodide (399 mg, 2.66 mmol) in MeOH (2 ml) and AcOH (0.4 ml) at 0°. The mixture was stirred for 30 min at 0°. After rapid cooling to −78°, EtOAc was added and the organic solution was washed successively with aqueous $NaHCO_3$, aqueous $Na_2S_2O_3$, and water. Concentration of the dried ($MgSO_4$) solution *in vacuo* provided a residue, which was subjected to preparative TLC (silica gel) using benzene–EtOAc (3: 1) to give 7α-methoxycephalosporin **10** (36.0 mg, 53.1%).: amorphous solid; IR $\nu_{max}^{CHCl_3}$ ($cm^{-1}$): 1780; NMR ($CDCl_3$) δ: 1.25 (9H, s), 2.13 (3H, s), 1.96—2.40 (2H, bs), 3.19 (2H, s), 3.48 (3H, s), 4.79 (1H, s).

***tert*-Butyl 7α-Methoxy-3-methyl-7β-phenoxyacetamido-3-cephem-4-carboxylate (11)**——(a) Cleavage with Benzenethiol and Triethylamine: A cold solution of 7α-methoxy-*p*-nitrobenzenesulfenamide **9b** (33.1 mg, 0.072 mmol) in dry $CH_2Cl_2$ (1 ml) and dry MeOH (1 ml) was treated with benzenethiol (0.1 ml, 0.97 mmol) and triethylamine (0.04 ml, 0.29 mmol). The mixture was stirred at room temperature for 15 hr, and then concentrated *in vacuo*. The residue was dissolved in $CH_2Cl_2$ (2 ml) and phenoxyacetyl chloride (0.2 ml, 1.45 mmol) and diethylaniline (0.2 ml, 1.26 mmol) were added at −40°. After stirring for 2 hr at −20°, ethyl acetate was added and the mixture was washed successively with aqueous $KHSO_4$, water, saturated aq. $NaHCO_3$, and water. Concentration of the dried solution ($MgSO_4$) *in vacuo* gave a residue, which was subjected to preparative TLC (silica gel) using benzene–EtOAc (5: 1) to afford a 3: 2 mixture of *tert*-butyl 7α-methoxy-3-methyl-7β-phenoxyacetamido-3-cephem-4-carboxylate **11** and *tert*-butyl 7α-methoxy-3-methyl-7β-phenoxyacetamido-2-cephem-4-carboxylate (27.3 mg, 88.3%).

(b) Cleavage with Hexamethylphosphorous Triamide and Triethylamine: A cold solution of 7α-methoxy-*p*-nitrobenzenesulfenamide **9b** (30.0 mg, 0.066 mmol) in dry $CH_2Cl_2$ (1 ml) and dry MeOH (1 ml)

17) Compound **15** is a mixture of two isomers (*ca.* 2: 1) due to *syn-anti* thiooxime isomerism or isomerization at the 2 or 4 position during methoxylation. Only the NMR spectrum of the major isomer is described here.

was treated with hexamethylphosphorous triamide (0.1 ml, 0.55 mmol) and triethylamine (0.04 ml, 0.29 mmol). The solution was stirred for 15 hr at room temperature and concentrated *in vacuo*. The resulting product was dissolved in $CH_2Cl_2$ (2 ml), and phenoxyacetyl chloride (0.2 ml, 1.45 mmol) and diethylaniline (0.2 ml, 1.26 mmol) were added at $-40°$. The mixture was stirred at $-20°$ for 1 hr. After dilution with EtOAc, the organic phase was washed successively with aqueous $KHSO_4$, water, aqueous $NaHCO_3$, and water. The solution was dried over $MgSO_4$ and concentrated *in vacuo* to give a residue. Purification by preparative TLC using benzene–EtOAc (5: 1) afforded a 3: 2 mixture of *tert*-butyl 7$\alpha$-methoxy-3-methyl-7$\beta$-phenoxyacetamido-3-cephem-4-carboxylate **11** and *tert*-butyl 7$\alpha$-methoxy-3-methyl-7$\beta$-phenoxyacetamido-2-cephem-4-carboxylate (26.0 mg, 92.8%).

(c) Acylation of the Free Amine **10** with Phenoxyacetyl Chloride: Diethylaniline (0.1 ml, 0.60 mmol) and phenoxyacetyl chloride (0.08 ml, 0.60 mmol) were added to a solution of 7$\beta$-amino-7$\alpha$-methoxycephalosporin **10** (36.0 mg, 0.12 mmol) in dry $CH_2Cl_2$ (10 ml) at 0°. The reaction mixture was stirred at 0° for 2 hr. Ethyl acetate was then added, and the solution was washed successively with aqueous $KHSO_4$, water, aqueous $NaHCO_3$, and water. The organic fraction was dried over $MgSO_4$ and concentrated *in vacuo* to give a residue, which was chromatographed on silica gel using benzene–EtOAc (5: 1) to afford 7$\alpha$-methoxy-7$\beta$-phenoxyacetamide **11** (37.6 mg, 72.2%). **11**: oil; IR $\nu_{max}^{CHCl_3}$ ($cm^{-1}$): 1780; NMR ($CDCl_3$) $\delta$: 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).

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