# A Synthesis of 7α-Methoxycephalosporins through Selenenamides

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The *o*-nitrobenzeneselenenamides were oxidized with active manganese dioxide to give the imines, which were converted to the 7α-methoxycephalosporins **3** by the reaction with lithium methoxide. The selenenamides **3** were acylated with phenoxyacetyl chloride to afford the desired cephamycin derivatives **4** *via* tertiary amide **5**, which was not isolable. This methoxylation reaction was also carried out in penicillin series to give the desired 6α-methoxypenicillin **8** although the ring opening compound **9** was a major product. The difference between sulfenamides and selenenamides in their acylation reactions was discussed.

Much attention has been focused on 7α-methoxycephalosporins after isolation of cephamycins from cultures of *streptomyces* species[1] and subsequent modification of the original compound to those with enhanced activity.[2] Several methods have been developed for introduction of a methoxyl group at the seven position of cephalosporins starting from 7-aminocephalosporins or 7-acylaminocephalosporins.[3] However, some difficulties still remain in the synthesis of 7α-methoxycephalosporins having a complex 7β-acylamino side chain.[4] Recently, we have shown that 7β-sulfenamidocephalosporins and 7β-sulfinamidocephalosporins were converted to 7α-methoxycephalosporins *via* the intermediacy of novel 7-sulfenylimine β-lactams.[5]

As a part of program to device a new method for introduction of a methoxyl group at the seven position of cephalosporins, we were interested in a synthesis of an analog of the sulfenamide in which the sulfur atom is suitably substituted by selenium atom. We now describe a method for a synthesis of 7α-methoxycephalosporins utilizing selenenamidocephalosporins *via* selenenylimine intermediates.

The chemistry of selenenamides (amide of selenenic acid) has been little studied and only a very limited number of examples of this class are known[6-8] owing to the lack of the stabilities of those compounds. In view of the scope and limitations of selenenamides, a study of selenenamidocephalosporins is of considerable interest. A recent study of selenenamides has suggested that the Se–N bond is hydrolyzed slowly at room temperature and rapidly with acids or at an elevated temperature.[6] The method generally used for the preparation of selenenamides is the reaction of corresponding amines with selenenyl halides. Of several possible starting materials, first, we chose benzeneselenenamidocephalosporins. Treatment of *t*-butyl 7β-amino-3-methyl-3-cephem-4-carboxylate with benzeneselenenyl chloride in the presence of triethylamine gave a spot ascribable to the benzeneselenenamide **1c** on silica gel thin layer chromatography, by short time development, but this spot vanished on further development. The isolation of the benzeneselenenamide **1c** also failed by chromatography on silicic acid. Difficulty in isolation of benzeneselenenamide **1c** probably results from the known instability of Se–N bond.

It is frequently observed that benzeneselenenyl compounds without *o*-substituent exhibit properties differing from those of the corresponding *o*-substituted derivatives with higher stabilities.[9] Thus we examined *o*-nitrophenylselenenamidocephalosporin which has an electron-withdrawing group on the ortho position of the aromatic ring, expecting more stable Se–N bond. Treatment of *t*-butyl 7β-amino-3-methyl-3-cephem-4-carboxylate with *o*-nitrophenylselenenyl chloride in the presence of triethylamine afforded *o*-nitrophenylseleneamide **1a** in 79.0% yield after silica-gel chromatography. This procedure using ortho-nitrophenylselenenyl compound, also worked well in the case of benzhydryl 3-acetoxymethyl-7β-amino-3-cephem-4-carboxylate and *p*-bromophenacyl 6β-aminopenicillanate to give **1b** and **6** in 60.0% and 53.3% yields, respectively. When *p*-nitrophenylselenenyl bromide was used in place of *o*-nitrophenylselenenyl chloride in the reaction with *t*-butyl 7β-amino-3-methyl-3-cephem-4-carboxylate, a clear spot ascribable to the desired selenenamide was observed in thin layer chromatography; however, attempted isolation of selenenamide **1d** by chromatography on silica gel resulted in decomposition of the product. Thus the synthesis of selenenamides of cephalosporins and penicillin derivatives was successful only in *o*-nitrophenylselenenamide series.

Next our effort was directed to the conversion of selenenamides **1** to selenenylimines **2**. Only a few selenenylimines have been reported in the literature and they were prepared by addition of benzeneselenenyl and *p*-nitrophenylselenenyl chlorides to 1,1-di-*p*-tolylmethanimine in the presence of triethylamine.[8] These crystalline selenenylimines were observed to decompose to an oil after several weeks under nitrogen in the dark. So, we had a great concern about the stability of the selenenyliminocephalosporins. Treatment of *o*-nitrophenylselenenamidocephalosporins **1a** and **1b** with active manganese dioxide in benzene solution according to the sulfenamide oxidation[5a] gave the corresponding selenenyliminocephalosporins **2a** and **2b** in 60.0% and 41.0% yields, respectively, which were crystalline solids and stable on exposure to air at room temperature for several weeks. The structure of the imines **2a** and **2b** was unambiguous on the basis of their NMR spectra which showed a sharp singlet at 5.32 and 5.42 ppm, respectively, due to the hydrogen at the six position. In the penicillin series the reaction leading to the selenenylimine took place similarly as in the cephalosporin series. Thus, the reaction of the selenenamidopenicillin **6** with active manganese dioxide gave the selenenyliminopenicillin **7** as an amorphous solid in 49.7% yield, which was also stable under the same conditions as the selenenylimines of cephalosporins.

Treatment of the selenenylimines **2a** and **2b** with

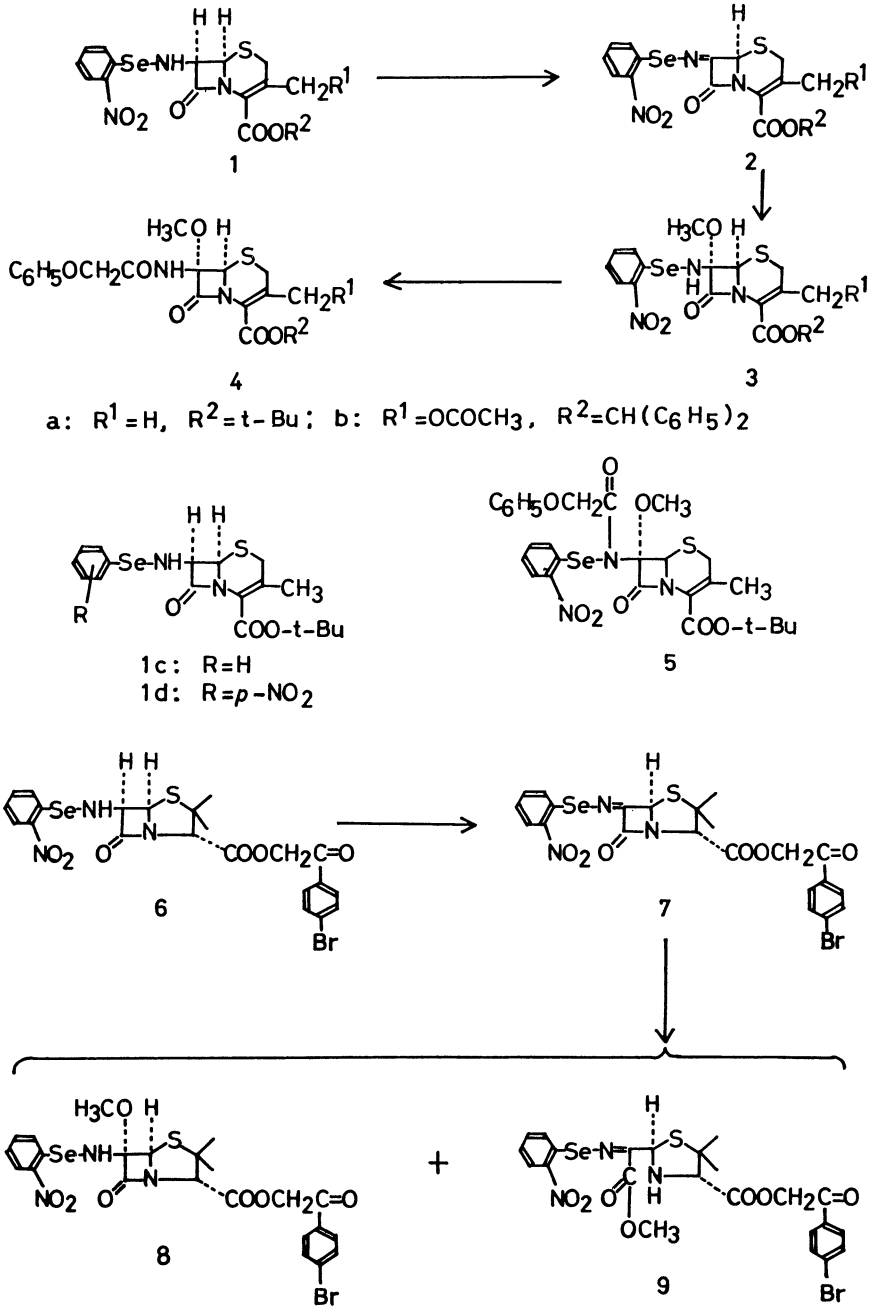
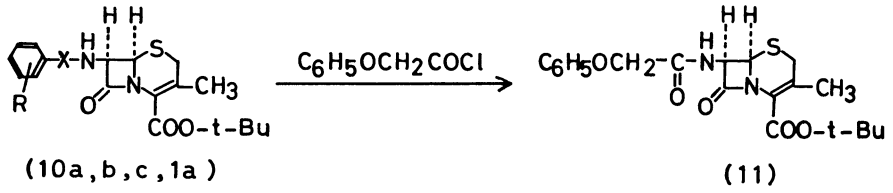



Chart 1.

excess of lithium methoxide in methanol and tetrahydrofuran at −78 °C for 3 h afforded 7α-methoxyselenenamidocephalosporins **3a** and **3b** in 87.1% and 21.6% yields, respectively. The low yield of **3b** was due to the production of 2-cephem isomer (benzhydryl 3-acetoxymethyl-7α-methoxy-7β-*o*-nitrophenylselenenylamino-2-cephem-4-carboxylate) (26.8%), whose formation was frequently observed in the compound having 3-acetoxymethyl group in a basic medium. As in the case of the sulfenyliminocephalosporins[5a] only α-methoxy isomers were obtained by attack of methoxide anion from less hindered α-face of the molecules. Methoxylation of the selenenyliminopenicillin **7** under the same reaction conditions gave the desired 6α-methoxy-6β-(selenenylamino)-penicillin **8** only in 8.8% yield together with the ring opened diester **9** (79.9%) as a major product. It should be noted that the ratio of **8**/**9** (8.8/79.9) was significantly small as compared with the case of the corresponding sulfenyliminopenicillin in which the ratio of the methoxylated product to the ring cleaved compound was 30.9/58.4. This difference might arise from the less effective overlapping of the d-orbital of the selenium of the compound **7** with the imine part and *o*-nitrobenzene ring. Thus, electrophilicity at the six position of **7** would decrease as compared with the corresponding sulfenyliminopenicillin. We should also note that the ring opened selenenylimine **9** was not attacked by methoxide any more.

Acylation of 7α-methoxyselenenamide **3a** with phenoxyacetyl chloride in dichloromethane in the absence of any base gave **5** judging from silica gel thin

TABLE 1.




| run | cephalosporin | condition | product(11) |
|---|---|---|---|
| 1 | o-nitrobenzenesulfenamide(10a) R=o-$NO_2$ ,X=S | rt,24h | trace[a] |
| 2 | p-nitrobenzenesulfenamide(10b) R=p-$NO_2$ ,X=S | 0°C,90min | 96.3%[b] |
| 3 | 2,4-dinitrobenzenesulfenamide(10c) R=2,4-$NO_2$,X=S | rt,24h | trace[a] |
| 4 | o-nitrobenzeneselenenamide(1a) R=o-$NO_2$ ,X=Se | 0°C,30min | 92.9%[b] |

a) the reaction was checked by silica gel TLC plate
b) isolated yield

layer chromatography, which showed a less polar spot ascribable to the tertiary amide **5**. Attempted purification of **5** by chromatography on silica gel resulted in decomposition. Therefore the obtained compound was used in the subsequent reaction without further purification. The crude compound **5** was treated with lithium methoxide or sodium benzenethiolate to furnish 7α-methoxy-7β-phenoxyacetamidocephalosporin **4** in 18% and 15% yields, respectively. The physical properties of **4** were identical in all respects with an authentic sample.[5]

A comparison of selenenamidocephalosporins with sulfenamidocephalosporins in the reaction with an acyl chloride is interesting in connection with the bonding character between nitrogen and sulfur or selenium. Thus we examined the reaction of sulfenamides and selenenamide with phenoxyacetyl chloride in dichloromethane. Results are summarized in Table 1. *o*-Nitrophenylselenenamide **1a** was found to be more reactive than *p*-nitrophenylsulfenamide **10b**, which was the most reactive in the sulfenamide series. Namely, ortho-substituted benzenesulfenamides **10a** and **10c** did not react with phenoxyacetyl chloride, while the *p*-nitro derivative **10b**, was easily converted into phenoxyacetamide **11**, and in the case of the selenenamide ortho-substitution gave no effect on the reaction with phenoxyacetyl chloride to afford the desired amide **11** with great ease without detection of the tertiary amide corresponding to **5**.

Although the Se–N bond in selenenamide is generally unstable and sensitive to nucleophiles, the method *via* the intermediacy of selenenyliminocephalosporins provides a versatile and useful alternative to functionalization at the 7(6) position of cephalosporins (penicillins).

## Experimental

All melting points are not corrected. 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.

t-*Butyl 3-Methyl-7β-o-nitrophenylselenenylamino-3-cephem-4-carboxylate (**1a**).* A solution of *t*-butyl 7β-amino-3-methyl-3-cephem-4-carboxylate (6.50 g, 24 mmol) and triethylamine (3.36 ml, 24 mmol) in chloroform (150 ml) was stirred and cooled to 0—5 °C. To this solution was added *o*-nitrophenylselenenyl chloride (4.73 g, 20 mmol) dissolved in chloroform (50 ml) over a period of 10 min. The mixture was then stirred for an additional 2 h at 0—5 °C. The mixture was diluted with ethyl acetate, washed successively with saturated $NaHCO_3$ solution and water. Evaporation of the dried ($MgSO_4$) organic phase *in vacuo* provided a residue, which was chromatographed on silica gel using benzene–EtOAc (10:1) to give *o*-nitrophenylselenenamide **1a** (7.25 g, 79.0%) as yellow crystals. **1a**: mp 133—134 °C (EtOAc–diisopropyl ether); IR ($CHCl_3$) 1780 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=1.55 (9H, s), 2.10 (3H, s), 3.35 and 3.60 (2H, ABq, $J$=18 Hz), 3.53 (1H, d, $J$=13.5 Hz), 4.95 (1H, dd, $J$=13.5 and 4.5 Hz), 5.08 (1H, d, $J$=4.5 Hz), 7.3—8.7 (4H, m).

*Benzhydryl 3-Acetoxymethyl-7β-o-nitrophenylselenenylamino-3-cephem-4-carboxylate (**1b**).* To a mixture of benzhydryl 7β-amino-3-acetoxymethyl-3-cephem-4-carboxylate hydrochloride (10.4 g, 22 mmol) and triethylamine (5.85 ml, 42 mmol) in dry chloroform (150 ml) under nitrogen was added *o*-nitrophenylselenenyl chloride (4.73 g, 20 mmol) in chloroform (25 ml) at 0—5 °C over a period of 10 min. The mixture was stirred for 3 h at 0—5 °C, and then EtOAc was added. The organic phase was washed with saturated $NaHCO_3$ solution and water, dried over $MgSO_4$, and evaporated *in vacuo* to give a residue. Subsequent chromatography on silica gel using benzene–EtOAc (10 : 1) provided *o*-nitrophenylselenenamide **1b** (7.61 g, 60.0%) as yellow crystals: **1b**: mp 124—125 °C ($CHCl_3$–diisopropyl ether); IR ($CHCl_3$) 1780 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=1.90 (3H, s), 3.35 and 3.50 (2H, ABq, $J$=18 Hz), 3.50 (1H, d, $J$=13.5 Hz), 4.75 and 4.98 (2H, ABq, $J$=13.5 Hz), 4.90 (1H, dd, $J$=13.5 and 4.5 Hz), 4.93 (1H, d, $J$=4.5 Hz), 6.97 (1H, s), 7.1—8.5 (14H, m).

p-*Bromophenacyl 6β-o-Nitrophenylselenenylaminopenicillanate (6).* To a stirred solution of *p*-bromophenacyl 6β-aminopenicillanate hydrochloride (4.95 g, 11 mmol) and triethylamine (2.79 ml, 20 mmol) in $CHCl_3$ (75 ml) was added a solution of *o*-nitrophenylselenenyl chloride (2.36 g, 20 mmol) in $CHCl_3$ (25 ml) at 0 °C. After 3 h at 0 °C, EtOAc was added and organic solution was washed successively with saturated $NaHCO_3$ solution and water, and then dried ($MgSO_4$). Evaporation of the organic part and chromatography of the residue using benzene–EtOAc (5 : 1) afforded *o*-nitrophenylselenenamide **6** (3.27 g, 53.3%) as amorphous solid. **6**: IR ($CHCl_3$) 1780 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=1.73 (3H, s), 1.77 (3H, s), 3.58 (1H, d, $J$=12 Hz), 4.63 (1H, s), 4.75 (1H, dd, $J$=12 and 4.5 Hz), 5.38 and 5.53 (2H, ABq, $J$=16.5 Hz), 5.65 (1H, d, $J$=4.5 Hz), 7.3—8.6 (8H, m).

t-*Butyl 3-Methyl-7-o-nitrophenylselenenylimino-3-cephem-4-carboxylate (2a).* To a solution of selenenamide **1a** (2.0 g, 4.25 mmol) in benzene (100 ml) was added active manganese dioxide (100 g) at room temperature and reaction mixture was stirred at room temperature for 60 min. The solid substance was filtered off, washed with benzene, and evaporation of the combined filtrates *in vacuo* afforded selenenylimine **2a** (1.20 g, 60.0%) which was practically pure judging by NMR and used for the next step without any purification. **2a**: mp 185—186 °C ($CHCl_3$–diisopropyl ether); IR ($CHCl_3$) 1780 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=1.58 (9H, s), 2.17 (3H, s), 3.25 and 3.52 (2H, ABq, $J$=18 Hz), 5.32 (1H, s), 7.2—8.8 (4H, m).

*Benzhydryl 3-Acetoxymethyl-7-o-nitrophenylselenenylimino-3-cephem-4-carboxylate (2b).* A solution of selenenamide **1b** (2.3 g, 3.6 mmol) in benzene (100 ml) was stirred at room temperature with active manganese dioxide (115 g). After 1 h the reaction mixture was filtered and active manganese dioxide was washed with benzene. The combined filtrates were evaporated *in vacuo* to give selenenylimine **2b** (944 mg, 41.0%), which was pure judging by NMR and used in the next reaction without further purification. **2b**: mp 126—127 °C (EtOAc–diisopropyl ether); IR ($CHCl_3$) 1790 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=2.03 (3H, s), 3.45 and 3.61 (2H, ABq, $J$=18 Hz), 4.90 and 5.08 (2H, ABq, $J$=13.5 Hz), 5.42 (1H, s), 6.26 (1H, s), 7.3—8.9 (14H, m).

p-*Bromophenacyl 6-o-Nitrophenylselenenyliminopenicillanate (7).* A solution of selenenamide **6** (1.0 g, 1.63 mmol) in benzene (50 ml) was stirred at room temperature with active manganese dioxide (50 g) for 60 min. Active manganese dioxide was filtered off and the filtrate was evaporated *in vacuo* to give selenenylimine **7** (497 mg, 49.7%), which was found to be pure by NMR and used in the subsequent reaction without further purification. **7**: amorphous solid; IR ($CHCl_3$) 1780 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=1.60 (3H, s), 1.67 (3H, s), 4.85 (1H, s), 5.50 (2H, s), 5.98 (1H, s), 7.3—8.8 (8H, m).

t-*Butyl 7α-Methoxy-3-methyl-7β-o-nitrophenylselenenylamino-3-cephem-4-carboxylate (3a).* A stirred solution of selenenylimine **2a** (939 mg, 2.0 mmol) in dry MeOH (30 ml) and dry THF (60 ml) was cooled to −78 °C, and lithium methoxide (prepared from 77 mg of lithium, 11 mmol) in dry MeOH (10 ml) was added with vigorous stirring. The mixture was stirred for 3 h at −78 °C, and then glacial AcOH was added. After dilution with EtOAc, the organic solution was washed successively with water, saturated $NaHCO_3$ solution, and water, dried ($MgSO_4$) and evaporated *in vacuo* to afford a residue. Purification by chromatography on silica gel using benzene–EtOAc (10:1) gave 7α-methoxyselenenamide **3a** (870 mg, 87.1%) as a yellow oil. **3a**: IR ($CHCl_3$) 1770 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=1.50 (9H, s), 2.12 (3H, s), 3.18 and 3.35 (2H, ABq, $J$=18 Hz), 3.58 (3H, s), 4.18 (1H, s), 4.93 (1H, s), 7.2—8.6 (4H, m).

*Benzhydryl 3-Acetoxymethyl-7α-methoxy-7β-o-nitrophenylselenenylamino-3-cephem-4-carboxylate (3b).* To a solution of selenenylimine **2b** (204 mg, 0.32 mmol) in dry MeOH (5 ml) and dry THF (10 ml) was added lithium methoxide in methanol (5 ml) (from 14.7 mg of lithium, 2.1 mmol) at −78 °C and the solution was vigorously stirred for 3 h. The reaction mixture was quenched with glacial AcOH and diluted with EtOAc. The organic solution was washed with water, aqueous $NaHCO_3$, and again water. Evaporation of the solvents (dried over $MgSO_4$) and chromatography of the residue gave 7α-methoxy-*o*-nitrophenylselenenamide **3b** (46.0 mg, 21.6%; $R_f$=0.39: benzene–EtOAc 10:1) and benzhydryl 3-acetoxymethyl-7α-methoxy-7β-*o*-nitrophenylselenenylamino-2-cephem-4-carboxylate (57.3 mg, 26.8%; $R_f$=0.33: benzene–EtOAc 10:1), which were eluted from the column with benzene–EtOAc (10:1). **3b**: yellow oil; IR ($CHCl_3$) 1770 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=2.05 (3H, s), 3.38 and 3.53 (2H, ABq, $J$=18 Hz), 3.63 (3H, s), 4.33 (1H, s), 4.90 and 5.03 (2H, ABq, $J$=13.5 Hz), 4.98 (1H, s), 7.03 (1H, s), 7.3—8.7 (14H, m). Benzhydryl 3-acetoxymethyl-7α-methoxy-7β-*o*-nitrophenylselenenylamino-2-cephem-4-carboxylate: yellow oil: IR ($CHCl_3$) 1775 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=1.97 (3H, s), 3.50 (3H, s), 4.22 (1H, s), 4.67 (2H, bs), 5.22 (2H, s), 6.48 (1H, bs), 6.98 (1H, s), 7.2—8.6 (14H, m).

p-*Bromophenacyl 6α-Methoxy-6β-nitrophenylselenenylaminopenicillanate (8).* To a cold solution of selenenylimine **7** (201 mg, 0.33 mmol) in dry MeOH (5 ml) and dry THF (10 ml) was added lithium methoxide (prepared from 17.4 mg of lithium, 2.5 mmol) in dry MeOH (5 ml) at −78 °C. After vigorous stirring for 3 h, glacial AcOH was added. After dilution with EtOAc the organic solution was washed successively with water, saturated $NaHCO_3$ solution, and again water. The organic phase was dried ($MgSO_4$), evaporated, and the residue was chromatographed on silica gel. 7α-Methoxy-*o*-nitrophenylselenenamide **8** (18.7 mg, 8.84%; $R_f$=0.47: benzene–EtOAc 5:1) and diester **9** (169 mg, 79.9%, $R_f$=0.56: benzene–EtOAc 5:1) were eluted with benzene–EtOAc (5:1). **8**: yellow oil; IR ($CHCl_3$) 1780 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=1.58 (3H, s), 1.62 (3H, s), 3.53 (3H, s), 4.28 (1H, s), 4.67 (1H, s), 5.40 (2H, s), 5.48 (1H, s), 7.3—8.7 (8H, m). **9**: yellow oil; IR ($CHCl_3$) 1755 $cm^{-1}$; NMR ($CDCl_3$)[10] $\delta$=1.49 (3H, s), 1.63 (3H, s), 3.98 (3H, s), 4.26 (1H, s), 5.59 (2H, s), 5.93 (1H, s), 7.2—8.9 (8H, m).

t-*Butyl 7α-Methoxy-3-methyl-7β-phenoxyacetamido-3-cephem-4-carboxylate (4).* To a solution of 7α-methoxyselenenamide **3a** (50.0 mg, 0.10 mmol) in $CH_2Cl_2$ (5 ml) was added phenoxyacetyl chloride (0.08 ml, 0.58 mmol). The mixture was stirred for 3 h at room temperature and then the solvent was evaporated. The residue was dissolved again in dry THF (5 ml), and lithium methoxide (prepared from 8 mg of lithium, 1.2 mmol) in dry MeOH (3 ml) was added. The reaction mixture was stirred vigorously at −78 °C for 2.5 h, and quenched with glacial AcOH. After dilution with EtOAc the organic solution was washed with water, aqueous $NaHCO_3$, and water, and dried over $MgSO_4$. Evaporation of the solvents *in vacuo* and chromatography (solvent: benzene–EtOAc 10:1) afforded phenoxyacetamide **4** (8.0 mg, 18.0%). **4**: IR ($CHCl_3$) 1780 $cm^{-1}$; 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), 6.8—7.5 (6H, m).

t-*Butyl 3-Methyl-7β-phenoxyacetamido-3-cephem-4-carboxylate (11).* A stirred solution of *t*-butyl 3-methyl-7β-*o*-nitrophenylselenenylamino-3-cephem-4-carboxylate **1a** (47.8

mg, 0.10 mmol) in dry dichloromethane (5 ml) was cooled to 0 °C, and phenoxyacetyl chloride (0.06 ml, 0.35 mmol) was added under vigorous stirring. The mixture was stirred 30 min at 0 °C. Evaporation of the solvent *in vacuo* gave a residue, which was purified by preparative chromatography on silica gel to provide 7β-phenoxyacetamide **11** (38.2 mg, 92.9%) using benzene–EtOAc (5:1). **11**: oil: IR ($CHCl_3$) 1780 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=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), 6.8—7.8 (6H, m).

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10) The compound **9** is a mixture of two isomers (*ca.* 2:1) due to *syn-anti* isomerism of seleno-oxime or isomerization at 2 or 4 position during methoxylation. Only NMR spectrum of the major isomer was described here.