June 1998 Chem. Pharm. Bull. 46(6) 893—899 (1998)

Practical Synthesis of 1β-Methylcarbapenem Antibiotics: Side-Chain Substitution Reaction of 2-Arylsulfinyl and 2-Arylsulfonyl Carbapenems

Kozo ODA* and Akira YOSHIDA

Medicinal Chemistry Research Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan.

Received November 10, 1997; accepted February 6, 1998

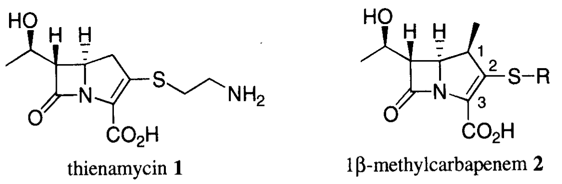
The C-2 side-chain substitution reaction of a sulfoxide and a sulfone derived from a *p*-nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-[2-(diethylcarbamoyl)phenylthio]-1-methylcarbapen-2-em-3-carboxylate with various mercaptans progressed smoothly in the presence of magnesium bromide. Bromomagnesium thiolate prepared from mercaptans proved to be especially effective for the substitution reaction and gave precursors of 1β-methylcarbapenem antibiotics in high yield.

Key words 1β-methylcarbapenem; sulfoxide; sulfone; side-chain substitution reaction; magnesium thiolate

Since the discovery of thienamycin **1** in 1976 by a Merck research group,1) hundreds of analogues have been synthesized in order to find superior candidates. Although carbapenems have potent and broad-spectrum antimicrobial activity, they suffer from chemical instability and lability to renal dehydropeptidase-I (DHP-I). Therefore, the clinically used carbapenems imipenem and panipenem have to be administrated with an adjuvant such as an inhibitor of DHP-I and a renal protectant which inhibits active transport of the carbapenem in the renal cortex. In 1984, Merck scientists reported a new class of carbapenem analogues (**2**), possessing a methyl group with a β-configuration at the C-1 position of carbapenem.2) Because these 1β-methylcarbapenems show enhanced chemical stability and resistance to DHP-I, they have attracted a great deal of attention.

Many methodologies for the synthesis of this class of compounds have been developed to date.3) In particular, one of the most important synthetic methods, *via* the intermediate **3**, was developed by Merck's scientists.2) Several reaction sequences, including the intramolecular carbenoid insertion reaction, gave a vinyl phosphate (**4**), a diverging intermediate from which protected 1β-methylcarbapenems (**5**) were obtained by means of a side-chain substitution reaction with various mercaptans (Chart 2). Another successful approach *via* an intramolecular Wittig-type cyclization of the ylide (**8**) derived from azetidinylthiopropionate (**6**) was also reported.4) However, it was unsuitable for structure–activity relationship studies because a troublesome thermal cyclization step was necessary in the preparation of each derivative.

We have designed a new route leading to a 1β-methylcarbapenem precursor (**9**), in which the required C-2 substituent is incorporated by means of a side-chain substitution reaction of 2-sulfinyl (**10**) and 2-sulfonyl (**11**) derivatives with mercaptans (Chart 3). This convergent procedure is as efficient as that of the Merck group, as the side-chain mercaptan is introduced at a late stage of synthesis. The required intermediates **10** and **11** were prepared from an azetidinylthiopropionate derivative (**12**) *via* the cyclization sequence employed for the transformation from **6** to **9**,4,5a) followed by an oxidation process. The stereoselective preparation of **12** was performed by a zinc chloride-catalyzed reaction of the *E*-silylenolate of *S*-[2-(diethylaminocarbonyl)phenyl] propanethioate and commercially available (3*S*,4*R*)-3-[(1*R*)-1-(*tert*-butyldi-



thienamycin **1** 1β-methylcarbapenem **2**

Chart 1

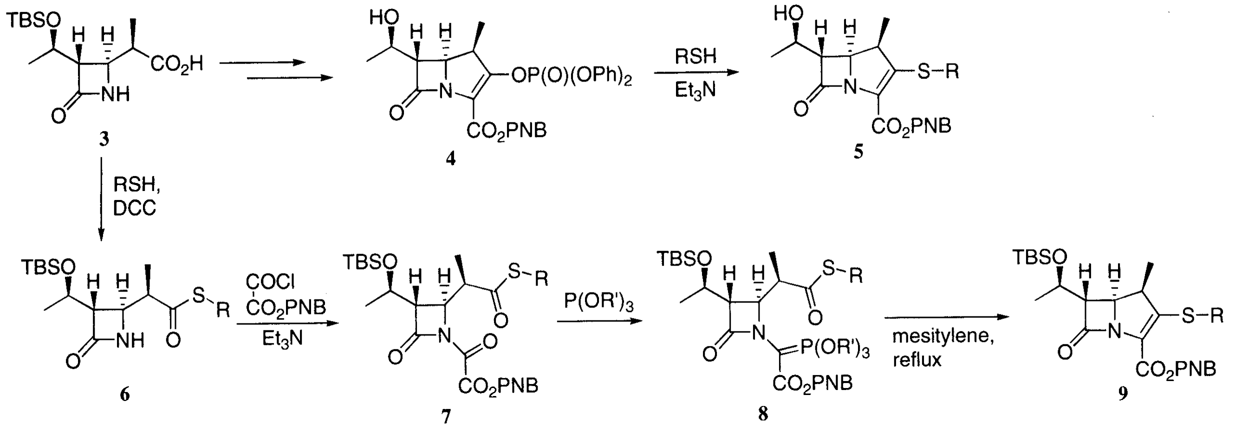


Chart 2

---

* To whom correspondence should be addressed.

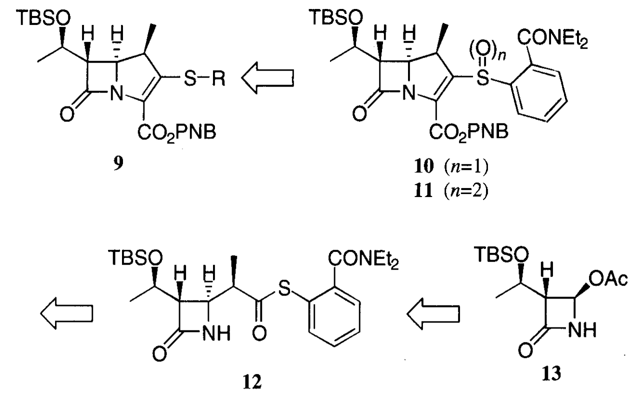


Chart 3

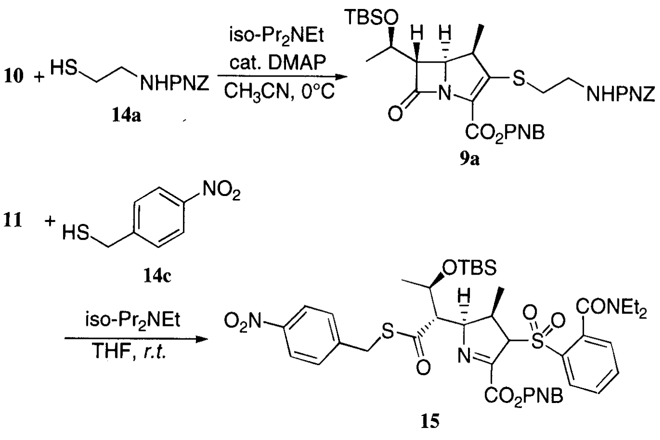


Chart 4

methylsilyloxy)ethyl]-4-acetoxy-2-azetidinone (**13**).[5a] In our previous communication, we reported an efficient substitution reaction of **10** and **11** with mercaptans in the presence of $MgBr_2 \cdot Et_2O$ and iso-Pr_2NEt.[5b] However, we could not obtain an acceptable yield from the reaction with some secondary and aromatic mercaptans. In this paper, the details of the early work on the substitution reaction and the results of further improvements are described.

Results and Discussion

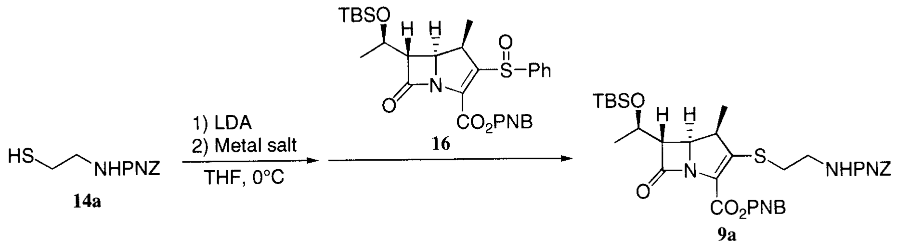
The organic-base-promoted reaction between a 2-sulfinyl carbapenem lacking the methyl group at the C-1 position and mercaptans was reported to give a moderate yield of products.[6] However, the corresponding reaction of 1β-methylcarbapenem gave a poor result, with a yield of around 31%.[7] Moreover, attempts to perform a substitution reaction of 1β-methyl-2-sulfonylcarbapenem with mercaptans have not been reported to our knowledge. In our first attempt (Chart 4), the reaction of the sulfoxide (**10**) with the mercaptan (**14a**) (2.0 eq) in the presence of iso-Pr_2NEt resulted in only 4% yield of the 1β-methylcarbapenem (**9a**) accompanied by several unidentified by-products. The substitution reaction of the sulfone (**11**) with the mercaptan (**14c**) under the same condition was unsuccessful. The β-lactam-ring-cleaved compound (**15**) was formed as a sole product. This kind of ring cleavage was also observed in the conventional base-promoted reaction between a sulfoxide and a mercaptan.[7]

The side-chain substitution reaction of carbapenems involves the initial addition of mercaptan to the C-2 position of carbapenem, which corresponds to the β-position of the α,β-unsaturated ester system, and subsequent elimination of a leaving group, *i.e.*, diphenylphosphonate, sulfenic acid, and sulfinic acid in the reactions of **4**, **10**, and **11**, respectively. A crucial difference between **4** and the sulfur-containing compounds (**10**, **11**) is the presence of an electron-withdrawing substituent at the C-2 position. The electron-withdrawing substituent in **10** and **11** weakens the polarization of the C-2, 3 double bond and impedes the initial addition of mercaptan at the C-2 position. In addition, such a C-2 substituent reduces the electron density of the β-lactam nitrogen and, consequently, causes the β-lactam ring to be susceptible to cleavage by nucleophilic attack at the C-5 carbonyl. This was especially true for compound **11**, which has the most strongly electron-withdrawing sulfonyl group and which exclusively afforded **15**. Therefore, for a successful substitution reaction it is necessary to increase the reactivity at the C-2 position over that of the C-5 position by enhancing the electrophilicity of the carboxylate group at the C-3 position. At the outset, we searched for a Lewis acid counter-cation of the mercaptan salt which could effect the activation of the carboxylate. The mercaptan (**14a**) was converted to several types of metal thiolates by deprotonation with lithium diisopropylamide (LDA) followed by the addition of metal salts. These thiolates were allowed to react with the 1β-methyl-2-phenylsulfinylcarbapenem (**16**) as the basal substrate. The results are summarized in Table 1.

As shown in Table 1, addition of alkaline-earth metal salts such as calcium bromide or magnesium bromide improved the result of the original iso-Pr_2NEt promoted reaction (Chart 4). The magnesium salt exhibited the best efficiency for the substitution reaction (entry 6). The success of the magnesium thiolate was due to the rather weak Lewis acidity of the magnesium salt. Strong Lewis acids such as aluminum chloride could not fulfill their function in a basic solvent such as tetrahydrofuran (THF), because they more strongly coordinate to the solvent than to the substrate. Although a good result was obtained in the model experiment, the use of LDA in the preparation of the magnesium thiolate seemed to be too severe a condition to apply to unstable mercaptans. Thus, we attempted the combination of $MgBr_2 \cdot Et_2O$ with iso-Pr_2NEt instead of LDA. Substitution reactions of the sulfoxide (**10**) and sulfone (**11**) using various mercaptans are summarized in Table 2.

The efficiency of the reaction was dramatically improved by the combination of $MgBr_2 \cdot Et_2O$ and iso-Pr_2NEt. For example, the desired product (**9a**) was obtained in 74% yield from the reaction between the sulfoxide (**10**) and mercaptan (**14a**) (entry 2), but was obtained in only 4% yield under conventional base-promoted conditions (Chart 4). The reaction yield from the sulfone (**11**) also notably increased under these conditions. The regio-selectivity of the reaction was completely changed from the β-lactam carbonyl (C-5) to the C-2 position by the addition of

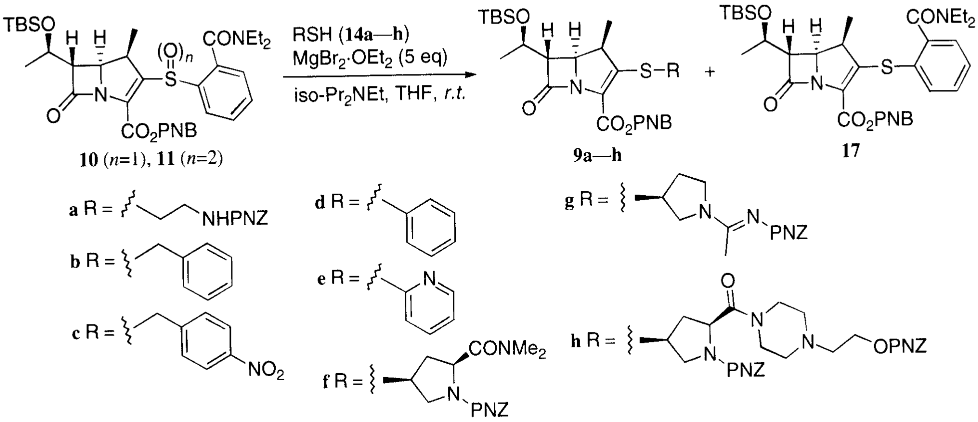
Table 1. Substitution Reaction of Various Metal Thiolates Derived from Mercaptan



Entry	Metal salt	Reaction temperature	Reaction time	Yield (%)
1	$CaBr_2$	0 °C	35 min	47
2	$AlCl_3$	0 °C	5 h	No reaction
3	$BiCl_3$	0 °C—r.t.	18 h	—[a]
4	CuBr	0 °C—r.t.	18 h	No reaction
5	$FeCl_3$	0 °C	30 min	—[b]
6	$MgBr_2 \cdot Et_2O$	0 °C	15 min	84

a) The sulfoxide decomposed. b) The mercaptan immediately decomposed.

Table 2. $MgBr_2 \cdot Et_2O$ Mediated Substitution of Sulfoxide and Sulfone



Entry	Substrate	Mercaptan (eq)	^{i}Pr$_2$NEt (eq)	Reaction time	Product	Yield (%)	**17** (%)
1	**10**	**14a** (1.1)	1.0	120 min	**9a**	55	Trace
2	**10**	**14a** (2.2)	1.1	60 min	**9a**	74	19
3	**10**	**14a** (2.2)	—	22 h	**9a**	68	14
4	**11**	**14a** (1.2)	2.0	19 h	**9a**	87	—
5	**10**	**14b** (2.0)	1.1[a]	60 min	**9b**	79	Trace
6	**10**	**14c** (2.0)	—	45 min	**9c**	88	Trace
7	**11**	**14c** (1.2)	2.2	6 h (50 °C)	**9c**	56	—
8	**10**	**14d** (2.2)	—	40 min	**9d**	65	28
9	**10**	**14e** (2.2)	2.0[a]	90 min	**9e**	70	Trace
10	**10**	**14f** (2.0)	—	45 min	**9f**	45	46
11	**11**	**14f** (1.2)	3.0	19 h	**9f**	73	—
12	**10**	**14g** (2.2)	—	6 h	**9g**	64	10
13	**11**	**14g** (1.3)	2.0	26 h	**9g**	39	—
14	**11**	**14h** (1.2)	2.0	22 h	**9h**	60	—

a) The reactions were quite slow without the addition of iso-Pr_2NEt.

$MgBr_2 \cdot Et_2O$, and the desired product was obtained in 56% yield in the reaction between **11** and **14c** (entry 7). In the reaction of the sulfoxide (**10**), the mercaptans **14a**, **14c**, **14d**, **14f**, and **14g** gave reasonable yields of products even in the absence of iso-Pr_2NEt, although a longer reaction time was necessary in some cases (entries 3, 12). The base was unnecessary for some reactions due to the high acidity of mercaptan, as this characteristic increases the concentration of the thiolate anion, which is the active species for nucleophilic substitution. For example, a simple benzylmercaptan (**14b**) required the addition of iso-Pr_2NEt (entry 5), whereas 4-nitrobenzylmercaptan (**14c**) gave an 88% yield of **9c** without the base (entry 6). The presence of an electron-withdrawing nitro group in **14c** increased the acidity of the mercaptan.

One disadvantage of this method is the need for at least 2 eq of mercaptans to complete the reaction of the sulfoxide (**10**). Use of 1.1 eq reduced the yield of the product, leaving

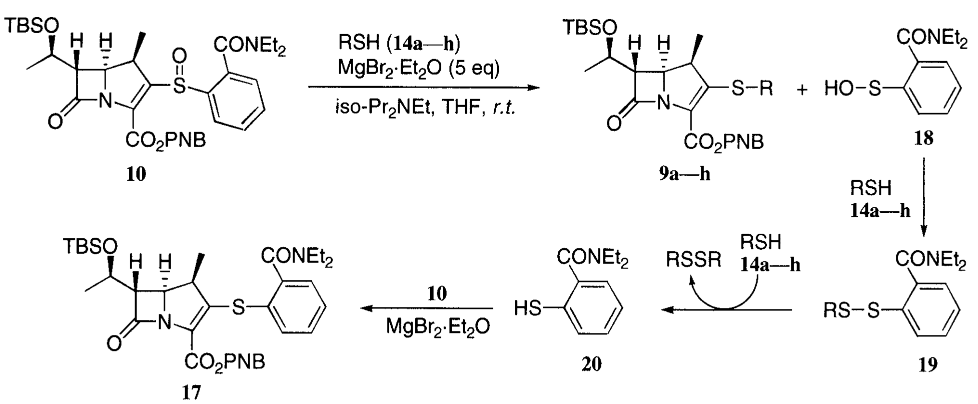
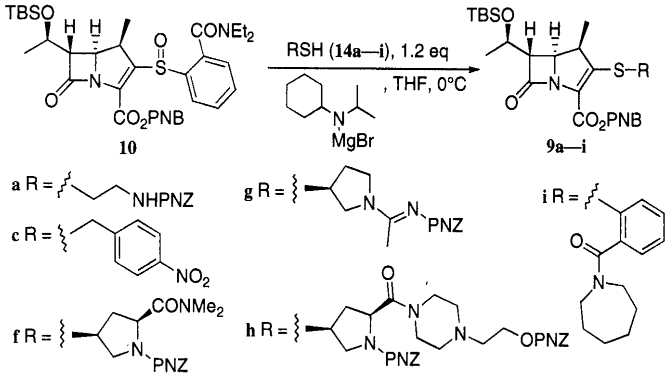


Chart 5

Table 3. Substitution Reaction of Bromomagnesium Thiolate from Mercaptan



Entry	Mercaptan	Reaction time	Product	Yield (%)
1	**14a**	30 min	**9a**	92
2	**14c**	40 min	**9c**	81
3	**14f**	30 min	**9f**	89
4	**14g**	30 min	**9g**	79
5	**14h**	60 min	**9h**	86
6	**14i**	25 min	**9i**	95

unreacted sulfoxide (entries 1, 2). Furthermore, different amounts of the sulfide (**17**) were formed. In particular, a substantial amount of **17** was formed in the reaction of a secondary mercaptan (entry 10). These drawbacks resulted from incomplete formation of thiolate from mercaptans. A sulfenic acid (**18**), which was formed by the reaction between **10** and **14**, consumed the remaining free mercaptan (**14**) to form a mixed disulfide (**19**) as shown in Chart 5. 2-(Diethylaminocarbonyl)phenylmercaptan (**20**) arose from the reaction between the disulfide and another molecule of free mercaptan. Compound **20** and the mercaptan (**14**) competed for the sulfoxide, and considerable amounts of **17** were formed, especially in the case of a secondary mercaptan for which steric hindrance interfered with the substitution. In contrast, when the sulfone (**11**) was used as a substrate, the substrate was totally consumed at a slight excess of mercaptan (1.2 eq) and formation of **17** was not observed at all (entries 4, 7, 11, 13, 14). In this case, a sulfinic acid which was inert toward free mercaptan was liberated instead of **18** and formation of **20** did not occur. The only drawback in the case of sulfone was the need for a prolonged reaction time or elevated temperature. Thermally unstable mercaptan gave comparatively unsatisfactory results under such conditions (entry 13). Thus, the sulfoxide seemed to be preferable to the sulfone as a substrate from a practical point of view, because of its superior reactivity. Therefore, we continued with further investigation of the substitution reaction of the sulfoxide to resolve the remaining problems.

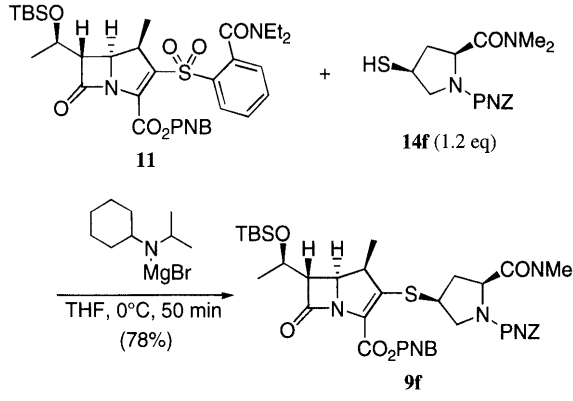


Chart 6

We next returned to the reaction of preliminarily generated magnesium thiolate, because a good result had been noted (entry 6 of Table 1). In order to avoid employing strongly basic LDA, a magnesium thiolate of mercaptan (**14a**) was prepared by deprotonation using bromomagnesium cyclohexylisopropylamide at 0 °C and reacted with the sulfoxide (**10**) at the same temperature. The reaction proceeded quite smoothly and afforded the substituted product (**9a**) in 92% yield even when only a slight excess (1.2 eq) of mercaptan was used. Encouraged by this observation, we attempted to apply these conditions to some mercaptans that had previously shown unsatisfactory results (Table 2). The results are summarized in Table 3.

The reactions proceeded effectively regardless of the nature of the mercaptans. For example, compound **9f** was obtained in 89% yield even for the reaction of a secondary mercaptan (**14f**), whereas the yield of the $MgBr_2 \cdot Et_2O$-mediated reaction remained at 45% (entry 10 in Table 2). As mercaptans exist totally in the form of thiolate anions under the conditions described in Table 3, the substitution reaction proceeded immediately and was completed before the formation of the disulfide (**19**) from the liberated sulfenic acid (**18**). On the other hand, because of the insufficient acidity of mercaptans, the concentration of a thiolate anion under the conditions employing $MgBr_2 \cdot Et_2O$ and iso-Pr_2NEt (Table 2) is low. Therefore, the substitution reaction proceeded gradually and the liberated sulfenic acid instantaneously reacted with the remaining free mercaptan to give considerable amounts of reduced product (**17**).

When the condition which had been employed in Table 3 was applied to the reaction of the sulfone (**11**) with mercaptan (**14f**), compound **9f** was obtained in a comparatively short time by the corresponding reaction to that shown in Table 2 (Chart 6).

Conclusion

The C-2 side-chain substitution reactions of the sulfoxide (**10**) and sulfone (**11**) with various mercaptans were performed in the presence of magnesium salt. Preliminarily prepared bromomagnesium thiolates of mercaptans were especially effective for the substitution reaction of the sulfoxide (**10**). This improved magnesium-mediated substitution reaction allows easy and quick access to various 1β-methylcarbapenems. Thus, a new synthetic procedure for 1β-methylcarbapenems from commercially available acetoxyazetidinone (**13**) was developed. This method is suitable for industrial preparation of 1β-methylcarbapenem antibiotics.

Experimental

Reagents were used as purchased. Anhydrous THF, $MgBr_2 \cdot Et_2O$, bromomagnesium cyclohexylisopropylamide (1.0 M THF solution) and LDA (1.5 M cyclohexane solution of mono THF complex) were purchased from Aldrich Chemical Co., Ltd. Other solvents for anhydrous reactions were dried over 4A molecular sieves before use. Chromatography columns were prepared with Aluminum oxide 90 (70—230 mesh) or Silica gel 60 (230—400 mesh) from E. Merck Co., Ltd. Reactions were carried out under a nitrogen atmosphere. IR spectra were recorded on a JASCO A-102, FT/IR-5300 or FT/IR-8300 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-EX-270 (270 MHz) spectrometer. Chemical shifts are shown in ppm downfield from internal tetramethylsilane in $CDCl_3$. The abbreviations used in ^{1}H-NMR data are as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. Mass spectra (MS) were obtained on a JEOL JMS-01SG, JMS-D300, JMS-AX505H (EI) or JMS-SX/SX102A (FAB and high-resolution (HR)-MS) spectrometer. Compound **17**,[5a)] *p*-nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-butyldimethylsilyl)oxyethyl]-1-methyl-2-(phenylthio)carbapen-2-em-3-carboxylate,[2)] and mercaptans, **14a**,[8a)] **14f**,[8b)] **14g**,[8c)] **14h**,[8b)] **14i**[8d)] were prepared according to the literature.

***p*-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-[2-(diethylcarbamoyl)phenylsulfinyl]-1-methylcarbapen-2-em-3-carboxylate (10)** A solution of *p*-nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-[2-(diethylaminocarbonyl)phenylthio]-1-methylcarbapen-2-em-3-carboxylate (**17**)[5a)] (2.44 g, 3.66 mmol) in CH_2Cl_2 (40 ml) was added to a mixture of 1.0 N $NaHCO_3$ (5.5 ml) and a solution of *m*-chloroperoxybenzoic acid (80%, 797 mg, 3.69 mmol) in CH_2Cl_2 (10 ml) at 0 °C over a period of 5 min. The reaction mixture was stirred for 1 h, and then quenched by adding a saturated aqueous Na_2SO_3. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extract was dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 1/1) to give **10** (2.22 g, 89%) as a colorless foam. Compound **10** appeared to be about a 1-to-1 mixture of stereoisomers around sulfoxide from the ^{1}H-NMR spectrum. $[\alpha]_D^{27}$ −110.4° (c = 1.3, $CHCl_3$). IR (Nujol) 1787, 1735, 1631, 1524, 1460, 1376, 1200, 1058 cm^{-1}. ^{1}H-NMR δ: 0.03—0.06 (6H, m), 0.83 (4.5H, s), 0.84 (4.5H, s), 1.05—1.29 (12H, m), 2.98—3.53 (5.5H, m), 3.59 (0.5H, d of q, J = 10.3, 6.9 Hz), 4.20—4.28 (1H, m), 4.30 (0.5H, dd, J = 10.5, 3.4 Hz), 4.39 (0.5H, dd, J = 10.5, 3.4 Hz), 5.30—5.52 (2H, m), 7.29—7.36 (1H, m), 7.50—7.71 (4H, m), 7.84—7.90 (0.5H, m), 8.15—8.25 (2.5H, m). MS (EI) m/z: 683 (M$^+$), 553, 423, 208. FAB-HR-MS 684.2782 (Calcd for $C_{34}H_{46}N_3O_8SSi$ (M$^+$ + H): 684.2775).

***p*-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-[2-(diethylcarbamoyl)phenylsulfonyl]-1-methylcarbapen-2-em-3-carboxylate (11)** Using 2.2 eq of *m*-chloroperoxybenzoic acid, **17** was oxidized for 4 h at room temperature to give **11** (90%) as a colorless foam. $[\alpha]_D^{27}$ −4.4° (c = 1.3, $CHCl_3$). IR (film) 1794, 1748, 1636, 1320, 1266, 1161, 1104 cm^{-1}. ^{1}H-NMR δ: 0.03 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.06 (3H, t, J = 7.3 Hz), 1.16 (3H, d, J = 6.4 Hz), 1.22—1.40 (6H, m), 3.03—3.16 (2H, m), 3.26—3.80 (4H, m), 4.20—4.28 (1H, m), 4.43—4.50 (1H, m), 5.39 (2H, br s), 7.30—7.34 (1H, m), 7.48—7.58 (2H, m), 7.62 (2H, d, J = 8.8 Hz), 8.11 (1H, d, J = 7.6 Hz), 8.21 (2H, d, J = 8.8 Hz). MS (EI) m/z: 699 (M$^+$), 684, 642, 512, 359. FAB-HR-MS 700.2715 (Calcd for $C_{34}H_{46}N_3O_9SSi$ (M$^+$ + H): 700.2724).

***p*-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-methyl-2-(phenylsulfinyl)carbapen-2-em-3-carboxylate (16)** *p*-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-1-methyl-2-(phenylthio)carbapen-2-em-3-carboxylate[2)] was oxidized to give the sulfoxide as a separable mixture of diastereomers. The major product (the less polar isomer) (**16**) was employed for the experiments in Table 1. Less polar isomer (**16**): 62% yield. Colorless needles. mp 150—151 °C (EtOAc/hexane). $[\alpha]_D^{27}$ −177.6° (c = 1.4, $CHCl_3$). IR (KBr) 1796, 1715, 1528, 1335, 1206, 1044, 965 cm^{-1}. ^{1}H-NMR δ: 0.06 (3H, s), 0.07 (3H, s), 0.73 (3H, d, J = 7.3 Hz), 0.85 (9H, s), 1.18 (3H, d, J = 6.4 Hz), 3.27 (1H, dd, J = 3.4, 5.4 Hz), 3.90 (1H, d of q, J = 10.7, 7.3 Hz), 4.23 (1H, d of q, J = 5.4, 6.4 Hz), 4.41 (1H, dd, J = 3.4, 10.7 Hz), 5.36 (1H, d, J = 13.7 Hz), 5.55 (1H, d, J = 13.7 Hz), 7.46—7.53 (3H, m), 7.66 (2H, d, J = 8.8 Hz), 7.73—7.77 (2H, m), 8.24 (2H, d, J = 8.8 Hz). MS (EI) m/z: 584 (M$^+$), 527, 441. *Anal.* Calcd for $C_{29}H_{36}N_2O_7SSi$: C, 59.57; H, 6.21; N, 4.79; S, 5.48. Found: C, 59.58; H, 6.18; N, 4.84; S, 5.46. More polar isomer: 30% yield. Colorless foam. $[\alpha]_D^{27}$ 21.9° (c = 1.2, $CHCl_3$). IR (KBr) 1788, 1730, 1524, 1320, 1273, 1206, 1048 cm^{-1}. ^{1}H-NMR δ: 0.04 (3H, s), 0.05 (3H, s), 0.83 (9H, s), 1.15 (3H, d, J = 5.9 Hz), 1.39 (3H, d, J = 7.3 Hz), 3.16 (1H, d of q, J = 10.3, 7.3 Hz), 3.40 (1H, dd, J = 3.4, 4.4 Hz), 4.16 (1H, dd, J = 3.4, 10.3 Hz), 4.26 (1H, d of q, J = 4.4, 5.9 Hz), 5.40 (1H, d, J = 13.7 Hz), 5.49 (1H, d, J = 13.7 Hz), 7.51—7.56 (3H, m), 7.68—7.73 (4H, m), 8.23 (2H, d, J = 8.8 Hz). MS (EI) m/z: 585 (M$^+$ + 1) FAB-HR-MS 607.1933 (Calcd for $C_{29}H_{36}N_2O_7SSiNa$ (M$^+$ + Na): 607.1910).

Reaction of the Sulfone (11) with *p*-Nitrobenzylmercaptan iso-Pr_2NEt (0.030 ml, 0.17 mmol) was added to a solution of **11** (100 mg, 0.143 mmol) and *p*-nitrobenzylmercaptan (31 mg, 0.183 mol) in THF (2 ml). The reaction mixture was stirred for 16 h at room temperature and then concentrated. The oily residue was purified by silica gel flash column chromatography (EtOAc/hexane = 2/3) to give **15** (121 mg, 97%) as a colorless foam. IR (film) 1750, 1690, 1630, 1347, 1318, 1262, 1152, 1109 cm^{-1}. ^{1}H-NMR δ: 0.07—0.17 (6H, m), 0.84—0.91 (9H, m), 1.05—1.29 (12H, m), 2.75—3.81 (6H, m), 4.03—4.47 (3H, m), 4.75—4.83 (1.75H, m), 5.18—5.24 (1.75H, m), 5.37—5.52 (0.5H, m), 7.24—7.83 (8H, m), 8.08—8.16 (4H, m). MS (EI) m/z: 811(M$^+$-*tert*-Bu), 732, 632.

Substitution Reaction of Various Metal Thiolates from Mercaptan (Table 1) A typical experimental procedure using $MgBr_2 \cdot Et_2O$ is described below. A 1.5 M cyclohexane solution of LDA (0.14 ml, 0.21 mmol) was added to an ice-cooled suspension of $MgBr_2 \cdot Et_2O$ (91 mg, 0.35 mmol). The mixture was stirred for 10 min, then a solution of **14a** (55 mg, 0.21 mmol) in THF (2 ml) was added. After another 10 min, **16** (102 mg, 0.174 mmol) was added and the reaction mixture was stirred for 15 min at 0 °C. Saturated aqueous NH_4Cl was added, and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine in turn, dried over anhydrous $MgSO_4$, and concentrated. The oily residue was purified by silica gel flash column chromatography (EtOAc/CH_2Cl_2 = 1/19) to give **9a** (104 mg, 84%) as a colorless foam.

p-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-1-methyl-2-[2-(*p*-nitrobenzyloxycarbonylamino)ethylthio]carbapen-2-em-3-carboxylate (**9a**): $[\alpha]_D^{26}$ 77.5° (c = 1.1, $CHCl_3$). IR (KBr) 1771, 1723, 1607, 1522, 1347, 1140, 839 cm^{-1}. ^{1}H-NMR δ: 0.07 (3H, s), 0.08 (3H, s), 0.86 (9H, s), 1.22—1.30 (6H, m), 2.93 (1H, quintet, J = 6.8 Hz), 3.11 (1H, quintet, J = 6.8 Hz), 3.26 (1H, dd, J = 2.4, 4.9 Hz), 3.32—3.60 (3H, m), 4.23—4.32 (2H, m), 5.20 (2H, s), 5.25 (1H, d, J = 14.2 Hz), 5.35 (1H, dull t, J = 5.7 Hz), 5.47 (1H, d, J = 14.2 Hz), 7.50 (2H, d, J = 8.8 Hz), 7.66 (2H, d, J = 8.8 Hz), 8.20 (2H, d, J = 8.8 Hz), 8.21 (2H, d, J = 8.8 Hz). MS (EI) m/z: 714 (M$^+$), 657, 504, 403, 159. *Anal.* Calcd for $C_{33}H_{42}N_4O_{10}SSi$: C, 55.45; H, 5.92; N, 7.84; S, 4.49. Found C, 55.46; H, 6.03; N, 7.83; S, 4.36.

$MgBr_2 \cdot Et_2O$-Mediated Substitution of the Sulfoxide (10) and Sulfone (11) (Table 2) A typical experimental procedure for the substitution reaction of the sulfoxide (**10**) with mercaptan (**14a**) (entry 2) is described below. $MgBr_2 \cdot Et_2O$ (657 mg, 2.54 mmol) was added to a solution of **10** (341 mg, 0.499 mmol) and mercaptan (**14a**) (294 mg, 1.11 mol) in THF (10 ml) at room temperature. Then iso-Pr_2NEt (0.097 ml, 0.56 mmol) was added, and the reaction mixture was stirred for 60 min. It was diluted with EtOAc, then the solution was washed with water and brine in turn, dried over anhydrous $MgSO_4$, and concentrated. The oily residue was purified by silica gel flash column chromatography to give **17** (63 mg, 19%) as a colorless crystalline solid from the less polar fraction (EtOAc/hexane = 1/1) and **9a** (264 mg, 74%) as a pale yellow foam from the more polar fraction (EtOAc/hexane = 3/2).

p-Nitrobenzyl (1*R*,5*S*,6*S*)-2-Benzylthio-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-1-methylcarbapen-2-em-3-carboxylate (**9b**): Colorless needles. mp 112.5—113.5 °C (isopropylether). IR (KBr) 1770, 1687, 1518, 1337, 1215, 1142, 838. ^{1}H-NMR δ: 0.06 (3H, s), 0.08 (3H, s), 0.86 (9H, s), 1.25 (3H, d, $J=5.9$ Hz), 1.26 (3H, d, $J=7.3$ Hz), 3.22 (1H, dd, $J=2.6$, 5.9 Hz), 3.35 (1H, d of q, $J=9.3$, 7.3 Hz), 4.09 (2H, s), 4.13 (1H, dd, $J=2.6$, 9.3 Hz), 4.25 (1H, quintet, $J=5.9$ Hz), 5.25 (1H, d, $J=13.9$ Hz), 5.46 (1H, d, $J=13.9$ Hz), 7.26—7.34 (5H, m), 7.65 (2H, d, $J=8.7$ Hz), 8.20 (2H, d, $J=8.7$ Hz). MS (FAB+) *m/z*: 583 ($M^+ + H$). *Anal.* Calcd for $C_{30}H_{38}N_2O_6SSi$: C, 61.83; H, 6.57; N, 4.81; S, 5.50. Found C, 61.64; H, 6.76; N, 4.85; S, 5.60.

p-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-methyl-2-(*p*-nitrobenzylthio)carbapen-2-em-3-carboxylate (**9c**): Pale yellow needles. mp 150.5—151 °C (EtOAc/isopropylether). $[\alpha]_D^{26}$ $-0.1°$ ($c=1.0$, $CHCl_3$). IR (KBr) 1773, 1711, 1605, 1522, 1345, 1140, 839 cm^{-1}. ^{1}H-NMR δ: 0.06 (3H, s), 0.08 (3H, s), 0.85 (9H, s), 1.24 (3H, d, $J=5.9$ Hz), 1.26 (3H, d, $J=6.3$ Hz), 3.24—3.37 (2H, m), 4.11—4.23 (3H, m), 4.25 (1H, quintet, $J=5.9$ Hz), 5.25 (1H, d, $J=13.7$ Hz), 5.46 (1H, d, $J=13.7$ Hz), 7.52 (2H, d, $J=8.3$ Hz), 7.65 (2H, d, $J=8.3$ Hz), 8.20 (2H, d, $J=8.3$ Hz), 8.21 (2H, d, $J=8.3$ Hz). MS (EI) *m/z*: 627(M^+), 570, 484, 159. *Anal.* Calcd for $C_{30}H_{37}N_3O_8SSi$: C, 57.40; H, 5.94; N, 6.69; S, 5.11. Found C, 57.44; H, 5.99; N, 6.76; S, 5.11.

p-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-methyl-2-(phenylthio)carbapen-2-em-3-carboxylate[9)] (**9d**): Colorless prism. mp 147—148 °C (EtOAc/hexane). $[\alpha]_D^{25}$ 229.0° ($c=1.2$, $CHCl_3$). IR (KBr) 1768, 1694, 1607, 1335, 1207, 1136, 839 cm^{-1}. ^{1}H-NMR δ: 0.06 (6H, s), 0.84 (9H, s), 0.95 (3H, d, $J=7.3$ Hz), 1.17 (3H, d, $J=6.4$ Hz), 3.06 (1H, d of q, $J=9.8$, 7.3 Hz), 3.19 (1H, dd, $J=2.4$, 5.9 Hz), 4.19 (1H, dd, $J=2.4$, 9.8 Hz), 4.25 (1H, d of q, $J=5.9$, 6.4 Hz), 5.33 (1H, d, $J=14.3$ Hz), 5.50 (1H, d, $J=14.3$ Hz), 7.37—7.43 (3H, m), 7.52—7.56 (2H, m), 7.69 (2H, d, $J=8.3$ Hz), 8.22 (2H, d, $J=8.3$ Hz). MS (EI) *m/z*: 568 (M^+), 511, 410, 368. *Anal.* Calcd for $C_{29}H_{36}N_2O_6SSi$: C, 61.24; H, 6.38; N, 4.93; S, 5.64. Found: C, 61.16; H, 6.51; N, 4.87; S, 5.64.

p-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-methyl-2-(2-pyridylthio)carbapen-2-em-3-carboxylate (**9e**): Colorless needles. mp 131—133 °C. $[\alpha]_D^{28}$ 149.2° ($c=1.1$ $CDCl_3$). IR (KBr) 1775, 1518, 1341, 1210, 1148, 1117, 841 cm^{-1}. ^{1}H-NMR δ: 0.07 (6H, s), 0.86 (9H, s), 1.00 (3H, d, $J=7.4$ Hz), 1.21 (3H, d, $J=6.2$ Hz), 3.25 (1H, dd, $J=3.0$, 5.1 Hz), 3.76 (1H, d of q, $J=10.0$, 7.4 Hz), 4.27 (1H, d of q, $J=5.1$, 6.2 Hz), 4.35 (1H, dd, $J=3.0$, 10.0 Hz), 5.29 (1H, d, $J=13.9$ Hz), 5.47 (1H, d, $J=13.9$ Hz), 7.21 (1H, ddd, $J=1.0$, 4.9, 7.4Hz), 7.47 (1H, d, $J=7.9$ Hz), 7.62—7.69 (3H, m), 8.21 (2H, d of t, $J=6.9$, 2.2 Hz), 8.55—8.58 (1H, m). *Anal.* Calcd for $C_{28}H_{35}N_3O_6SSi \cdot (1/2)H_2O$: C, 58.11; H, 6.27; N, 7.26; S, 5.54. Found C, 57.90; H, 6.12; N, 7.12; S, 5.43.

p-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-[(3*S*,5*S*)-5-dimethylcarbamoyl-1-(*p*-nitrobenzyloxycarbonyl)-3-pyrrolidinylthio]-1-methylcarbapen-2-em-3-carboxylate (**9f**): Colorless foam. $[\alpha]_D^{27}$ 52.6° ($c=1.1$, $CHCl_3$). IR (KBr) 1775, 1713, 1657, 1522, 1345, 1142, 837 cm^{-1}. ^{1}H-NMR δ: 0.07—0.09 (6H, m), 0.85 (4.5H, s), 0.87 (4.5H, s), 1.23—1.29 (6H, m), 1.88—2.00 (1H, m), 2.68—2.81 (1H, m), 2.94 (1.5H, s), 2.98 (1.5H, s), 3.00 (1.5H, s), 3.11 (1.5H, s), 3.24—3.38 (2H, m), 3.51 (1H, d of t, $J=7.8$, 10.3 Hz), 3.61—3.78 (1H, m), 4.03—4.30 (3H, m), 4.75 (1H, d of t, $J=10.3$, 8.8 Hz), 5.07 (0.5H, d, $J=13.7$ Hz), 5.22—5.33 (2.5H, m), 5.45 (1H, d, $J=13.7$ Hz), 7.45 (1H, d, $J=8.8$ Hz), 7.52 (1H, d, $J=8.8$ Hz), 7.65 (2H, d, $J=8.8$ Hz), 8.20 (1H, d, $J=8.8$ Hz), 8.21 (3H, d, $J=8.8$ Hz). MS (FAB+) *m/z*: 834 ($M^+ + Na$), 812 ($M^+ + H$). *Anal.* Calcd for $C_{38}H_{49}N_5O_{11}SSi$: C, 56.21; H, 6.08; N, 8.63; S, 3.95. Found C, 56.16; H, 6.29; N, 8.43; S, 3.85.

p-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-methyl-2-{(3*S*)-1-[1-(*p*-nitrobenzyloxycarbonylimino)ethyl]-3-pyrrolidinylthio}carbapen-2-em-3-carboxylate (**9g**): Colorless foam. $[\alpha]_D^{27}$ 72.3° ($c=1.2$, $CHCl_3$). IR (KBr) 1769, 1694, 1675, 1567, 1520, 1345, 1242, 839 cm^{-1}. ^{1}H-NMR δ: 0.08 (3H, s), 0.09 (3H, s), 0.87 (9H, s), 1.22—1.31 (6H, m), 1.96—2.16 (1H, m), 2.29 (0.75H, s), 2.32 (2.25H, s), 2.35—2.51 (1H, m), 3.23—3.35 (2H, m), 3.44—4.05 (5H, m), 4.24—4.32 (2H, m), 5.22 (2H, s), 5.24 (1H, d, $J=13.7$ Hz), 5.45 (1H, d, $J=13.7$ Hz), 7.56 (2H, d, $J=8.8$ Hz), 7.65 (2H, d, $J=8.8$ Hz), 8.19 (2H, d, $J=8.8$ Hz), 8.21 (2H, d, $J=8.8$ Hz). *Anal.* Calcd for $C_{37}H_{47}N_5O_{10}SSi$: C, 56.83; H, 6.06; N, 8.96; S, 4.10, Found C, 56.62; H, 6.09; N, 8.87; S, 3.97.

p-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-1-methyl-2-[(3*S*,5*S*)-1-(*p*-nitrobenzyloxycarbonyl)-5-{4-[2-(*p*-nitrobenzyloxycarbonyloxy)ethyl]piperazinylcarbonyl}-3-pyrrolidinylthio]-carbapen-2-em-3-carboxylate (**9h**): Colorless foam. $[\alpha]_D^{27}$ 22.3° ($c=1.4$, $CHCl_3$). IR (KBr) 1773, 1750, 1709, 1653, 1522, 1345, 1260, 1146, 837 cm^{-1}. ^{1}H-NMR δ: 0.06—0.09 (6H, m), 0.85 (4.5H, s), 0.86 (4.5H, s), 1.22—1.29 (6H, m), 1.84—1.99 (1H, m), 2.38—2.78 (7H, m), 3.23—3.77 (8H, m), 4.07 (0.5H, dd, $J=7.0$, 10.3 Hz), 4.17 (0.5H, dd, $J=7.0$, 10.3 Hz), 4.24—4.32 (4H, m), 4.70 (0.5H, t, $J=7.8$ Hz), 4.75 (0.5H, t, $J=7.8$ Hz), 5.07 (0.5H, d, $J=13.7$ Hz), 5.22—5.32 (2.5H, m), 5.26 (2H, s), 5.45 (1H, d, $J=13.7$ Hz), 7.44 (1H, d, $J=8.8$ Hz), 7.52 (1H, d, $J=8.8$ Hz), 7.56 (2H, d, $J=8.8$ Hz), 7.65 (2H, d, $J=8.8$ Hz), 8.17—8.26 (6H, m). *Anal.* Calcd for $C_{50}H_{61}N_7O_{16}SSi$: C, 55.80; H, 5.71; N, 9.11; S, 2.98, Found C, 56.14; H, 5.86; N, 9.06; S, 2.81.

p-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-[2-(2*H*-1,3,4,5,6,7-hexahydroazepinylcarbonyl)phenylthio]-1-methylcarbapen-2-em-3-carboxylate (**9i**): Colorless needles. mp 210—211 °C (isopropylether). IR (KBr) 1757, 1700, 1632, 1341, 1212, 1138 cm^{-1}. ^{1}H-NMR δ: 0.06 (6H, s), 0.85 (9H, s), 0.95—1.03 (3H, m), 1.16 (3H, d, $J=6.3$ Hz), 1.40—1.85 (8H, m), 3.04—3.34 (5H, m), 3.45—3.65 (1H, br s), 4.20—4.36 (2H, m), 5.29 (1H, d, $J=14.2$ Hz), 5.46 (1H, d, $J=14.2$ Hz), 7.30—7.65 (4H, m), 7.68 (2H, d, $J=8.8$ Hz), 8.22 (2H, d, $J=8.8$ Hz). MS (EI) *m/z*: 693 (M^+), 678, 637, 506. *Anal.* Calcd for $C_{36}H_{47}N_3O_7SSi$: C, 62.31; H, 6.83; N, 6.06; S, 4.62. Found: C, 62.17; H, 6.87; N, 5.95; S, 4.60.

Substitution Reaction of Bromomagnesium Thiolate from Mercaptans (Table 3) A typical experimental procedure for the substitution reaction of the sulfoxide (**10**) with the mercaptan (**14f**) (entry 3) is described below. A 1.0 M THF solution of bromomagnesium cyclohexylisopropylamide (0.29 ml, 0.29 mmol) was added to an ice-cooled solution of the mercaptan (**14f**) (104 mg, 0.294 mmol) in THF (3 ml) over a period of 5 min. The mixture was stirred for 5 min, then a solution of the sulfoxide (**10**) (167 mg, 0.244 mmol) in THF (1 ml) was added, and stirred for 30 min at 0 °C. Saturated aqueous NH_4Cl was added, and the reaction mixture was extracted with EtOAc. The extract was washed with water and brine in turn, dried over anhydrous $MgSO_4$, and concentrated. The oily residue was purified by silica gel flash column chromatography (EtOAc) to give **9f** (176 mg, 89%) as a colorless foam.

References

1) *a*) Albers-Schönberg G., Arison B. H., Hensens O. D., Hirshfield J., Hoogsteen K., Kaczka E. A., Rhodes R. E., Kahan J. S., Kahan F. M., Ratcliffe R. W., Walton E., Ruswinkle L. J., Morin R. B., Christensen B. G., *J. Am. Chem. Soc.*, **100**, 6491—6499 (1978); *b*) Kahan J. S., Kahan F. M., Goegelman G., Currie S. A., Jackson M., Stapley E. O., Miller T. W., Miller A. K., Hendlin D., Mochales S., Hernandez S., Woodruff H. B., Birnbaum J., *J. Antibiotics*, **32**, 1—12 (1979).

2) *a*) Shih D. H., Baker F., Cama L., Christensen B. G., *Heterocycles*, **21**, 29—40 (1984); *b*) Shih D. H., Cama L., Christensen B. G., *Tetrahedron Lett.*, **26**, 587—590 (1985).

3) Recent review of synthetic work on 1β-methylcarbapenem antibiotics: Berks A. H., *Tetrahedron*, **52**, 331—375 (1996).

4) *a*) Yoshida A., Tajima Y., Takeda N., Oida S., *Tetrahedron Lett.*, **25**, 2793—2796 (1984); *b*) Shibata T., Iino K., Tanaka T., Hashimoto T., Kameyama Y., Sugimura Y., *ibid.*, **26**, 4739—4742 (1985); *c*) Shibata T., Sugimura Y., *J. Antibiotics*, **42**, 374—381 (1989).

5) *a*) Oda K., Yoshida A., *Chem. Pharm. Bull.*, **45**, 1439—1446 (1997); *b*) *Idem*, *Tetrahedron Lett.*, **38**, 5687—5690 (1997).

6) *a*) Yamamoto K., Yoshioka T., Kato Y., Isshiki K., Nishino M., Nakamura F., Shimauchi Y., Ishikura T., *Tetrahedron Lett.*, **23**, 897—900 (1982).; *b*) Takemura M., Higashi K., Fujiwara H., Sato M., Furukawa M., *Chem. Pharm. Bull.*, **34**, 1089—1093 (1986).

7) Rao V. S., Remillard R., Menard M., *Heteroatom Chemistry*, **3**,

25—31 (1992).

8) a) Shinkai I., Liu T., Reamer R., Sletzinger M., *Synthesis*, **1980**, 924—926; *b*) Sunagawa M., Matsumura H., Inoue T., Fukasawa M., Kato M., *J. Antibiotics*, **43**, 519—532 (1990); *c*) Shibata T., Iino, K., Sugimura Y., *Heterocycles*, **24**, 1331—1346 (1986); *d*) Gryff-Keller A., Szczecinski P., *Magnetic Resonance in Chemistry*, **23**, 655—658 (1985).

9) Sunagawa M., Sasaki A., Matsumura H., Goda K., Tamoto K., *Chem. Pharm. Bull.*, **42**, 1381—1387 (1994).