Practical Synthesis of a 1β-Methylcarbapenem, J-111,225, Using 4-Mercapto-2-[4-(*N*-methylaminomethyl)phenyl]pyrrolidine as a Precursor

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An effective and practical procedure for the synthesis of J-111,225 (1), a new 1β-methylcarbapenem, was developed using 4-mercapto-2-[4-(*N*-methylaminomethyl)phenyl]pyrrolidine (2a) as a precursor. The coupling reaction of 2a with *p*-nitrobenzyl (PNB)-protected 1β-methylcarbapenem enolphosphate 3a and successive removal of PNB group afforded J-111,225 (1) in significantly increased yield compared to the ordinary procedure using a C-2 side-chain thiol with amino-protective groups.

Key words 1β-methylcarbapenem; J-111,225; non-protected side-chain thiol; practical synthesis

We reported J-111,225 (**1**) as a new class of 1β-methylcarbapenem antibiotic which shows broad-spectrum antibacterial activity against gram-positive organisms including methicillin-resistant *Staphlococcus aureus* (MRSA) and gram-negative organisms including *Pseudomonas aeruginosa*.[1] As described in our preceding paper,[2] J-111,225 (**1**) was synthesized by the coupling reaction of a side-chain thiol **2c**, the amino groups of which were protected with an allyloxycarbonyl (Alloc) group, with allyl-protected carbapenem enolphosphate **3b**,[3] followed by deprotection of the resulting fully-protected J-111,225 (**4c**). Due to moderate yield (28%)[4] of the final process yielding J-111,225 in addition to poor stability of enolphosphate **3b** and potential toxicity of tributyltin hydride used for deprotection,[5] this allyl-protection procedure seemed unsuitable for preparation of a safety assessment sample.

Here, we describe the preparation of 4-mercapto-2-[4-(*N*-methylaminomethyl)phenyl]pyrrolidine **2a**, and its conversion to J-111,225 (**1**) in significantly improved yield by a coupling reaction with 1β-methylcarbapenem *p*-nitrobenzyl (PNB) ester **3a** and subsequent deprotection.

Results and Discussion

In carbapenem chemistry, the amino function of the side-chain thiol precursor is ordinarily protected by carbamate-type protective groups, such as *p*-nitrobenzyloxycarbonyl (PNZ) or Alloc, to avoid cleavage of the unstable β-lactam moiety for the feasible synthesis of new carbapenems. In the case of J-111,225 (**1**), deprotection of **4b**, a coupling product of the PNB-protected carbapenem enolphosphate **3a**[3] and the PNZ-protected side-chain thiol **2b**, resulted in low yield (22%).[6] Simultaneous and complete removal of two PNZ groups and one PNB group from **4b** was practically impossible under usual conditions. When deprotection of **4b** was carried out under accelerated conditions, significant decomposition of the product and of the partially deprotected intermediate were observed. The PNB- or PNZ-derived benzyl residue formed by reductive deprotection of **4b** obstructs purification of the resulting crude carbapenem to produce J-111,225 (**1**) with unacceptable yield and purity.

The use of non-protected thiol side-chain without PNZ protective groups would probably eliminate disadvantages such as those described above. In fact, large amounts of BO-2727, a carbapenem developed previously in our laboratory, was prepared in high yield using a non-protected thiol and **3a**.[7] Based on this finding, we developed an effective and practical procedure for the synthesis of J-111,225 (**1**) using the non-protected C-2 side-chain thiol, 4-mercapto-2-[4-(*N*-methylaminomethyl)phenyl]pyrrolidine **2a**.

The non-protected thiol **2a** was prepared starting from an aldehyde **5** as shown in Chart 2.[8] Since reductive amination of aldehyde **5** to introduce the *N*-methylamino function did not proceed in a reasonable yield, aldehyde **5** was first reduced with sodium borohydride ($NaBH_4$) in MeOH at 0 °C to afford an alcohol **6** (91%), which was in turn treated with methanesulfonyl chloride (MsCl) and substituted with methylamine. Successive *tert*-butoxycarbonyl (Boc) protection by di-*tert*-butyldicarbonate (Boc_2O) formed **7** (77%), and desilylation of **7** provided an alcohol **8** (90%) as crystals. Thioacetate **9** was obtained in high yield (91%) by substitution of a mesylate of **8** with potassium thioacetate (AcSK). All protective groups of **9**, one Ac group and two Boc groups, were removed simultaneously in HCl/MeOH at reflux temperature to afford a naked side-chain thiol **2a** as crystals with two molar of HCl in 88% yield. Thus, multigrams of the crystalline non-protected thiol **2a** were obtained in excellent overall yield from aldehyde **5** (50%).

The coupling reaction of **2a** and PNB-protected enolphosphate **3a** proceeded smoothly in the presence of triethylamine (TEA) in *N*,*N*-dimethylformamide (DMF) at 4 °C. Undesired cleavage of the β-lactam ring by the amino function of **2a** was not observed in this coupling reaction. The reaction mixture containing the resulting unstable adduct was immediately poured into morpholinopropanesulfonate (MOPS) buffer–tetrahydrofuran (THF) (pH 6.4) and subjected to catalytic hydrogenation to remove PNB protection. Purification using reversed-phase column chromatography and subsequent lyophilization afforded **1** in 58% yield. The yield of the final stages including the coupling reaction and deprotection was greatly improved by employing naked thiol **2a** as a precursor. Especially, the deprotection process of **4a** proceeded smoothly compared to that of highly protected **4b** and **4c**.[9]

Thus, the resulting amorphous solid was crystallized to afford J-111,225 (**1**) in crystalline form in high yield (92%);

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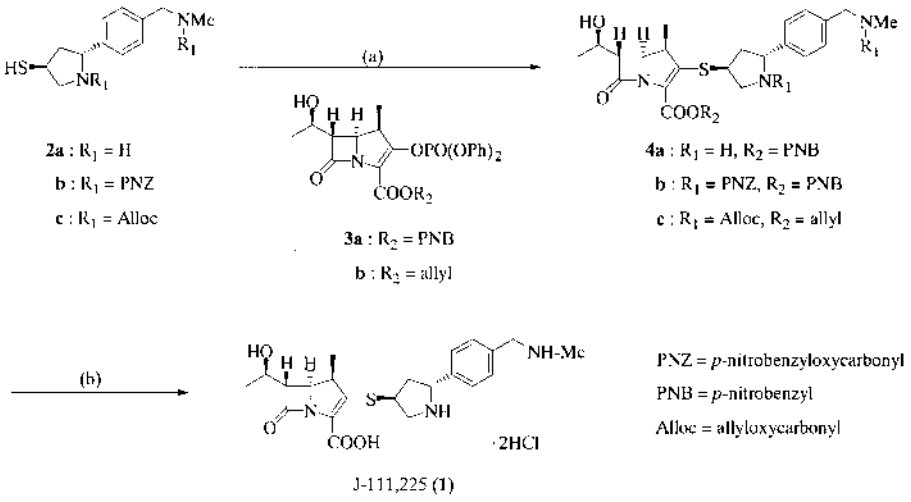
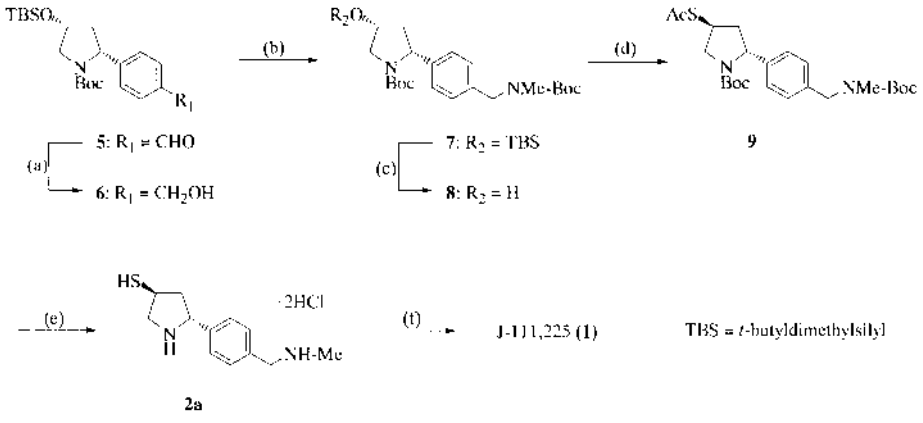


Reagents: (a) TEA or *i*-Pr_2NEt, (b) H_2, Pd/C [for **4a** and **4b**]; *n*-Bu_4SnH, $(PPh_3)_2PdCl_2$, H_2O [for **4c**]

Chart 1



Reagents: (a) $NaBH_4$, MeOH, 0°C, (b) i: MsCl, TEA, CH_2Cl_2, −30 °C; ii: $MeNH_2$, MeOH, −10 °C; iii: Boc_2O, Dioxane-H_2O, 10 ~ 15 °C, (c) *n*-Bu_4NF, THF, 0 °C, (d) i: MsCl, TEA, CH_2Cl_2, −30 °C; ii: AcSK, DMF, 55 °C, (e) HCl-MeOH, reflux (f) i: **3a**, *i*-Pr_2NEt, TEA, DMF, 4 °C; ii: H_2, Pd/C, DMF-THF.

Chart 2

crystalline J-111,225 (**1**) possessed excellent purity and exhibited good solubility in water (>5%).

Conclusion

The non-protected side-chain thiol **2a** was synthesized from the aldehyde **5** in 8 steps, with 50% overall yield. The coupling reaction of **2a** and the PNB ester **3a**, as well as subsequent deprotection, proceeded smoothly to afford J-111,225 (**1**) in 58% yield, while the PNZ-protected thiol **2b** and the Alloc-protected thiol **2c** produced yields of 22% and 28%, respectively. The crystalline form of **1** was obtained in high yield (92%) from the resulting amorphous powder. Further optimization for the preparation of large amounts of J-111,225 (**1**) is now under way, and the results will be reported in the future.

Experimental

Melting points were measured on a Yanaco mp micromelting point apparatus and were not corrected. The ^{1}H-NMR spectra were recorded on a Varian VXR-300 spectrometer, a Varian Gemini-300 and a JEOL JNM-A500 spectrometer with tetramethylsilane (TMS) as an internal standard. ^{13}C-NMR spectra were recorded on a JEOL JNM-A500 and a JEOL JNM-EX270. IR absorption spectra were recorded with a Horiba FT-200 spectrometer. Specific rotations were measured with a Jasco DIP-370 polarimeter. Mass spectra (MS) were measured on a JEOL JMS-SX102A spectrometer. TLC was performed with Merck Kieselgel F_{254} precoated plates. The silica gel used for column chromatography was WAKO gel C-300. Reversed-phase column chromatography was carried out using YMC-gel ODS-AQ 120-S50. All reactions involving air-sensitive reagents were performed under nitrogen using syringe-septum cap techniques.

(2*R*,4*R*)-1-*tert*-Butoxycarbonyl-4-*tert*-butyldimethylsiloxy-2-[4-(hydroxymethyl)phenyl]pyrrolidine (6) To a solution of **5** (214.5 g, 530 mmol) in MeOH (4500 ml) was added $NaBH_4$ (22.2 g, 587 mmol) dropwise under a nitrogen atmosphere at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was quenched by adding 10% aqueous NH_4Cl (500 ml) and poured into H_2O (4500 ml). The whole was extracted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=5 : 1—4 : 1) to give **6** (196.5 g, 91.1%) as a colorless oil. $[\alpha]_D^{20}$ +34.6° (*c*=1.0, $CHCl_3$); IR (KBr) ν_{max} 1700 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.08 (6H, s), 0.80 (9H, s), 1.16 (6H, s), 1.44 (3H, s), 1.87 (1H, m), 2.50 (1H, m), 3.40 (1H, m), 3.86 (1H, m), 4.37 (1H, m), 4.66 (2H, s), [4.72 (0.7H, m), 4.87 (0.3H, m), each rotamer], 7.26 (4H,

s); ^{13}C-NMR (67.5 MHz, $CDCl_3$, major signals) δ: −5.0, −4.9, 17.8, 25.6, 28.0, 44.6, 54.6, 60.0, 64.6, 69.8, 79.4, 125.9, 126.5, 139.3, 143.8, 154.4; FAB-HR-MS Calcd for $C_{22}H_{38}NO_4Si$ $(M+H)^+$: 408.2570, Found 408.2572.

(2*R*,4*R*)-2-[4-(*N*-*tert*-Butoxycarbonyl-*N*-methylaminomethyl)phenyl]-1-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsiloxypyrrolidine (7) To a solution of **6** (239 g, 587 mmol) in CH_2Cl_2 (4700 ml) were added TEA (119 g, 1.17 mol) and MsCl (50 ml, 746 mmol) under a nitrogen atmosphere at −30 °C. After stirring for 15 min at −30 °C, the reaction mixture was poured into H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Forty percent methylamine/MeOH (1920 ml, 25 mol) was immediately added to the filtrate at −10 °C after removal of $MgSO_4$ by filtration, and the mixture was stirred for 30 min at the same temperature. The mixture was evaporated under reduced pressure, and the residue was dissolved in 1,4-dioxane (1000 ml) and H_2O (250 ml). To this solution were added TEA (119 g, 1.17 mol) and Boc_2O (128 g, 588 mmol) at 10—15 °C, and the mixture was stirred for 30 min at 10—15 °C. The reaction mixture was poured into H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=5 : 1) to give **7** (237 g, 77.4%) as a colorless oil. $[\alpha]_D^{20}$ +31.6° (*c*=1.0, $CHCl_3$); IR (Nujol) ν_{max} 1704 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.08 (6H, s), 0.78 (9H, s), 1.14 (6H, s), 1.44 (12H, s), 1.88 (1H, m), 2.48 (1H, m), 2.73 (3H, br s), 3.42 (1H, m), 3.83 (1H, m), 4.32 (1H, m), 4.43 (2H, s), 4.69 [(0.7H, m), 4.88 (0.3H, m), each rotamer], 7.12 (2H, d, *J*=7.3 Hz), 7.20 (2H, d, *J*=7.3 Hz); ^{13}C-NMR (67.5 MHz, $CDCl_3$, major signals) δ: −4.7, −4.6, 18.1, 25.9, 28.4, 28.7, 34.0, 44.9, 53.7, 55.1, 60.3, 70.3, 79.6, 126.5, 127.2, 136.3, 144.2, 154.7, 156.7; FAB-HR-MS Calcd for $C_{28}H_{49}N_2O_5Si$ $(M+H)^+$: 521.3411, Found 521.3426.

(2*R*,4*R*)-2-[4-(*N*-*tert*-Butoxycarbonyl-*N*-methylaminomethyl)phenyl]-1-*tert*-butoxycarbonyl-4-hydroxypyrrolidine (8) To a solution of **7** (182 g, 350 mmol) in THF (2000 ml) was added tetra-*n*-butylammonium fluoride (1 M in THF, 368 ml, 368 mmol) under a nitrogen atmosphere at 0 °C. After stirring for 1 h at 0 °C, the mixture was poured into H_2O (2000 ml), and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=1 : 2) to give **8** (128 g, 90.1%) as colorless crystals. mp 123—124 °C; $[\alpha]_D^{20}$ +53.6° (*c*=1.0, $CHCl_3$); IR (Nujol) ν_{max} 3401, 1702, 1666 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.18 (6H, s), 1.41 (12H, s), 1.96 (1H, m), 2.54 (1H, m), 2.77 (3H, br s), 3.53(1H, dd, *J*=11.7, 4.3 Hz), 3.83 (1H, m), 4.39 (2H, s), 4.43 (1H, m), [4.69 (0.6H, m), 4.94 (0.4H, m), each rotamer], 7.15 (2H, d, *J*=7.9 Hz), 7.24 (2H, d, *J*=7.9 Hz); ^{13}C-NMR (67.5 MHz, $CDCl_3$, major signals) δ: 28.3, 28.6, 34.0, 44.3, 52.4, 55.4, 60.3, 69.2, 79.7, 126.3, 127.6, 136.3, 144.1, 154.6, 156.1; FAB-HR-MS Calcd for $C_{22}H_{35}N_2O_5$ $(M+H)^+$: 407.2546, Found 407.2547. *Anal*. Calcd for $C_{22}H_{34}N_2O_5$: C, 65.00; H, 8.43; N, 6.89, Found: C, 64.92; H, 8.55; N, 6.84.

(2*R*,4*S*)-4-Acetylthio-2-[4-(*N*-*tert*-butoxycarbonyl-*N*-methylaminomethyl)phenyl]-1-*tert*-butoxycarbonylpyrrolidine (9) To a solution of **8** (128 g, 315 mmol) in CH_2Cl_2 (2600 ml) were added TEA (64 g, 631 mmol) and MsCl (25.6 ml, 331 mmol) under a nitrogen atmosphere at −30 °C. After stirring for 30 min at −30 °C, the reaction mixture was poured into H_2O (1300 ml), and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. To a solution of the residue in DMF (3000 ml) was added AcSK (108 g, 945 mmol) under a nitrogen atmosphere at room temperature, and the mixture was stirred for 10 h at 55 °C. The resulting mixture was poured into H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=3 : 1) to give **9** (133 g, 90.9%) as a brown oil. $[\alpha]_D^{20}$ +40.4° (*c*=1.0, $CHCl_3$); IR (Nujol) ν_{max} 1700 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.16 (6H, s), 1.43 (12H, s), 2.22 (2H, m), 2.78 (3H, br s), 3.46 (0.5H, br s), 3.61 (0.5H, br s), 4.02 (2H, m), 4.39 (2H, s), [4.81 (0.5H, m), 4.97 (0.5H, m), each rotamer], 7.14 (4H, br s); ^{13}C-NMR (67.5 MHz, $CDCl_3$, major signals) δ: 28.1, 28.5, 30.6, 34.0, 39.6, 41.9, 52.8, 60.4, 79.6, 125.8, 127.5, 136.8, 142.9, 154.1, 155.8, 194.9; FAB-HR-MS Calcd for $C_{24}H_{37}N_2O_5S$ $(M+H)^+$: 465.2423, Found 465.2402.

(2*R*,4*S*)-2-[4-(*N*-Methylaminomethyl)phenyl]-4-mercaptopyrrolidine Dihydrochloride (2a) A solution of **9** (100 g, 215 mmol) in 10% HCl/MeOH (1000 ml) was stirred for 1 h at reflux temperature under a nitrogen atmosphere. After the removal of the solvent under reduced pressure, the residue was dissolved in EtOH (1000 ml), and the solution was stirred for 1 h at reflux temperature under a nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature to form the precipitate and was subsequently stirred further for another hour at 0 °C. The resulting precipitates were collected by filtration and dried to give **2a** (55.7 g, 87.6%) as colorless crystals. $[\alpha]_D^{20}$ −30.6° (*c*=1.0, H_2O); IR (KBr) ν_{max} 2945, 1598 cm^{-1}; ^{1}H-NMR (500 MHz, D_2O) δ: 2.54 (1H, m), 2.79 (3H, s), 2.83 (1H, m), 3.48 (1H, dd, *J*=12.4, 4.1 Hz), 2.98 (1H, dd, *J*=12.4, 6.5 Hz), 4.10 (1H, m), 4.31 (2H, s), 5.22 (1H, dd, *J*=10.5, 7.0 Hz), 7.62 (4H, s); ^{13}C-NMR (125 MHz, D_2O) δ: 31.8, 34.7, 39.7, 51.4, 53.7, 60.8, 128.1, 130.2, 131.8, 134.9; FAB-HR-MS Calcd for $C_{12}H_{19}N_2S$ $(M+H)^+$: 223.1269, Found 223.1255. *Anal*. Calcd for $C_{12}H_{18}N_2S$ (2HCl: C, 48.81; H, 6.83; N, 9.49, Found: C, 48.88; H, 6.99; N, 9.35.

(1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-[(3*S*,5*R*)-5-(4-(*N*-methylaminomethyl)phenyl)pyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylic Acid Dihydrochloride (1) To a mixture of **2a** (1.46 g, 3.7 mmol) and *p*-nitrobenzyl (1*R*,5*S*,6*S*)-2-diphenylphosphoryloxy-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (2.2 g, 3.7 mmol) in DMF (27 ml) was added TEA (1.24 g, 12.2 mmol) dropwise at −40 °C, and the mixture was stirred for 10 h at 4 °C. The reaction mixture was poured into THF (66 ml) and 0.25 M sodium MOPS buffer (66 ml, pH 6.4), and to this mixture was added 10% Pd/C (420 mg). The mixture was stirred for 3 h under a hydrogen atmosphere (3.0 kg/cm^2) at room temperature. The catalyst was filtered off and washed with H_2O (*ca*. 200 ml). The combined filtrate and washings were washed with CH_2Cl_2 and concentrated under reduced pressure to *ca*. 30 ml. The aqueous layer was adjusted to pH 6.4 with 1 M aqueous HCl and subjected to reversed-phase column chromatography. The eluent was monitored by HPLC, and the fractions eluted with 10—15% CH_3CN/H_2O containing the desired compound were combined, and adjusted to pH 5.8 with 1 M aqueous HCl. The resulting solution was concentrated under reduced pressure to *ca*. 10 ml and lyophilized to give (1*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-[(3*S*,5*R*)-5-[4-(*N*-methylaminomethyl)phenyl]pyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylic acid monohydrochloride as a white amorphous powder (963 mg, 58.1%).

Preparation of the Crystalline Form of J-111,225 (1) A solution of the amorphous powder (1.05 g, 2.23 mmol) in 85% EtOH/H_2O (21 ml) containing 5 M aqueous HCl (538 ml) was seeded at room temperature, and the mixture was stirred for 1 h at 0 °C. The resulting crystalline solid was collected by filtration, washed successively with 85% EtOH/H_2O and acetone, and dried to give **1** as dihydrochloride (1.04 g, 91.9%). $[\alpha]_D^{20}$ +9.0° (*c*=1.0, H_2O); IR (KBr) ν_{max} 3373, 1751, 1587, 1392, 1086 cm^{-1}; ^{1}H-NMR (500 MHz, D_2O, as monohydrochloride) δ: 1.02 (3H, d, *J*=7.3 Hz), 1.08 (3H, d, *J*=6.4 Hz), 2.33 (1H, dd, *J*=14.0, 6.7 Hz), 2.52 (3H, s), 2.57 (1H, m), 3.17 (1H, dq, *J*=9.1, 7.3 Hz), 3.27 (2H, m), 3.70 (1H, dd, *J*=12.8, 5.8 Hz), 4.04 (5H, m), 4.88 (1H, dd, *J*=11.0, 6.7 Hz), 7.35 (4H, m); ^{13}C-NMR (125 MHz, D_2O, as monohydrochloride) δ: 15.4, 19.7, 31.9, 35.9, 40.7, 42.1, 51.4, 51.9, 55.6, 58.5, 61.2, 64.7, 128.1, 130.2, 131.8, 134.2, 135.2, 136.7, 167.3, 176.3; FAB-HR-MS *m*/*z* Calcd for $C_{22}H_{30}N_3O_4S$ $(M+H)^+$: 432.1957, Found 432.1950; *Anal*. Calcd for $C_{22}H_{29}N_3O_4S$ (2HCl H_2O: C, 50.57; H, 6.37; N, 8.04; S, 6.14; Found: C, 50.87; H, 6.45; N, 7.83; S, 6.02.

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References and Notes

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6) The yields of the coupling reaction of **2b** with **3a** and subsequent deprotection were 63.6% and 34.6%, respectively.
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9) Spectral data were collected for **4b** and **4c**. *p*-Nitrobenzyl (1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(*N*-methyl-*N*-*p*-nitrobenzyloxycarbonylaminomethyl)-phenyl]pyrrolidin-1-*p*-nitrobenzyloxycarbonyl-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methy-1-carbapen-2-em-3-carboxylate (**4b**) IR (KBr) ν_{max} 3377, 1764, 1587 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, d, J=6.7 Hz), 1.25 (3H, m), 2.28 (1H, m), 2.32 (3H, s), 2.45 (1H, m), 3.32 (2H, m), 3.80 (2H, m), 4.05 (1H, m), 4.35 (5H, m), 5.15 (6H, m), 5.52 (2H, m), 7.37 (6H m), 7.66 (2H, d, J=8.8 Hz), 8.00 (2H, m), 8.22 (4H, d, J=8.8 Hz); FAB-HR-MS *m*/*z* Calcd for $C_{45}H_{45}N_6O_{14}S$ $(M+H)^+$: 925.2714, Found 925.2725. Allyl (1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-1-allyloxycarbonyl-5-[4-(*N*-methyl-*N*-allyloxycarbonylaminomethyl)-phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methy-1-carbapen-2-em-3-carboxylate (**4c**) IR (KBr) ν_{max} 3367, 1754 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, d, J=7.2 Hz), 1.36 (3H, d, J=6.3 Hz), 2.26 (1H, m), 2.40 (1H, m), 2.87 (3H, s), 3.23 (1H, dd, J=7.1, 2.6 Hz), 3.30 (1H, m), 3.73 (2H, m), 4.03 (1H, m), 4.24 (2H, m), 4.46 (2H s), 4.58 (1H, m), 4.64 (2H, m) 4.69 (1H m), 4.83 (1H, dd, J=13.5, 5.5 Hz), 4.93 (1H, m), 5.12 (1H, m), 5.34 (6H, m), 5.93 (3H, m), 7.17 (4H, m); FAB-HR-MS *m*/*z* Calcd for $C_{33}H_{42}N_3O_8S$ $(M+H)^+$: 640.2693, Found 640.2691.