Syntheses of 1β-Methylcarbapenems Bearing 5-Methyl-4-hydroxypyrrolidinone

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A new series of 1β-methylcarbapenems 1a—d bearing 5-methyl-4-mercaptopyrrolidinone rings has been prepared and evaluated for *in vitro* antibacterial activity and pharmacokinetic parameters. Most compounds showed excellent antibacterial activity and high stability to dehydropeptidase-1. We have synthesized optically active 5-methyl-4-hydroxypyrrolidinones from enantiomerically pure aziridine esters.

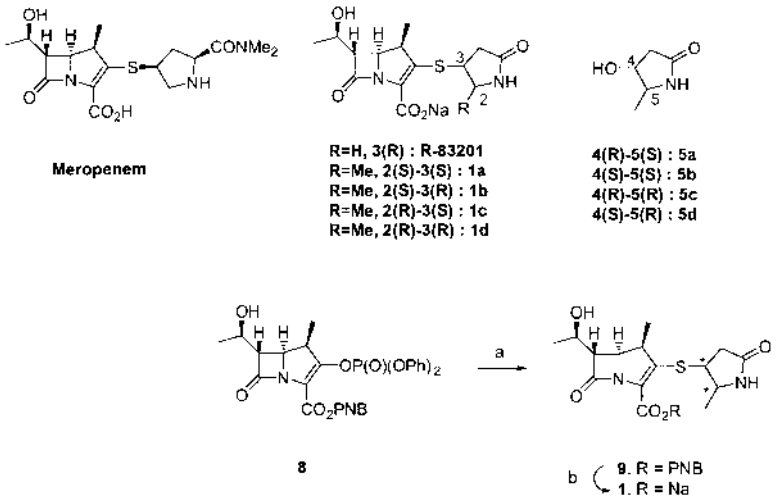
Key words carbapenem; β-ketoester; hydrogenation; Mitsunobu reaction; α-hydroxy-β-amino acid

Carbapenems are the most potent β-lactam antibiotics, which have a broad spectrum of antibacterial activity against both gram-positive and gram-negative organisms.[1,2] The introduction of the 1β-methyl moiety to the carbapenem skeleton resulted in increased stability of carbapenems against dehydropeptidase-1 (DHP-1). For parenteral use, imipenem,[3] panipenem,[4] and meropenem[5] have been launched on the market, and several compounds are currently under clinical evaluation.

Our attention was focused on the synthesis of 5-methyl-4-hydroxypyrrolidinone which could be used as the synthon of α-hydroxy-β-amino acid. Furthermore, we synthesized four enantio pure isomers of a 1β-methylcarbapenem derivative at the C-2 side chain, which were modified from R-83201,[6] and evaluated them for antibacterial activities and other biological properties. We prepared the 5-methyl-4-mercaptopyrrolidinones from enantiomerically pure aziridine ester.[7] In this paper, we describe the synthesis of the 1β-methylcarbapenems (**1a**—**d**) and optically active 5-methyl-4-hydroxypyrrolidinones (**5a**—**d**).

The C-2 substituted derivatives of 1β-methylcarbapenem were synthesized through the general procedure shown in Chart 1. Treatment of the PNB-protected carbapenem enolphosphate **8**[8] with freshly prepared thiols **7a**—**d** in the presence of DIPEA in CH_3CN at 0—5 °C afforded the PNB-protected 1β-methylcarbapenems **9a**—**d**, respectively (Chart 1). Deprotection of the 4-nitrobenzyl group was accomplished by catalytic hydrogenation using 10% palladium on charcoal in tetrahydrofuran (THF), EtOH, and morphorinopropanesulfonate (MOPS). The resulting carbapenem derivatives **1a**—**d** were purified by reverse-phase column chromatography and subsequent lyophilization. Optically active 5-methyl-4-mercaptopyrrolidinones **7a**—**d** were prepared from enantiomerically pure aziridine ester **2**, respectively, as shown in Chart 2.

β-Keto esters **3**[9] of aziridine were obtained from aziridine ester **2** with the lithium enolate from ethyl acetate and LiHMDS in THF. Reduction of the β-keto ester **3** with $NaBH_4$ in the presence of NH_4Cl resulted in a diastereomeric mixture of hydroxy aziridines **4** (approximately *R*/*S*=1/1 to 2/1), which were readily separable by flash chromatography. We did not optimize reduction conditions to obtain high stereoselectivity. 5-Methyl-4-hydroxypyrrolidinones **5a**—**d** were prepared from the aziridine propionates **4a**—**d** through regioselective reductive cleavage by catalytic hydrogenation in



Reagents and conditions: (a) **7a**—**d**, DIPEA, CH_3CN, 2 h, (b) Pd/C, H_2, THF/EtOH/0.1 M MOPS buffer, 12 h.

Chart 1

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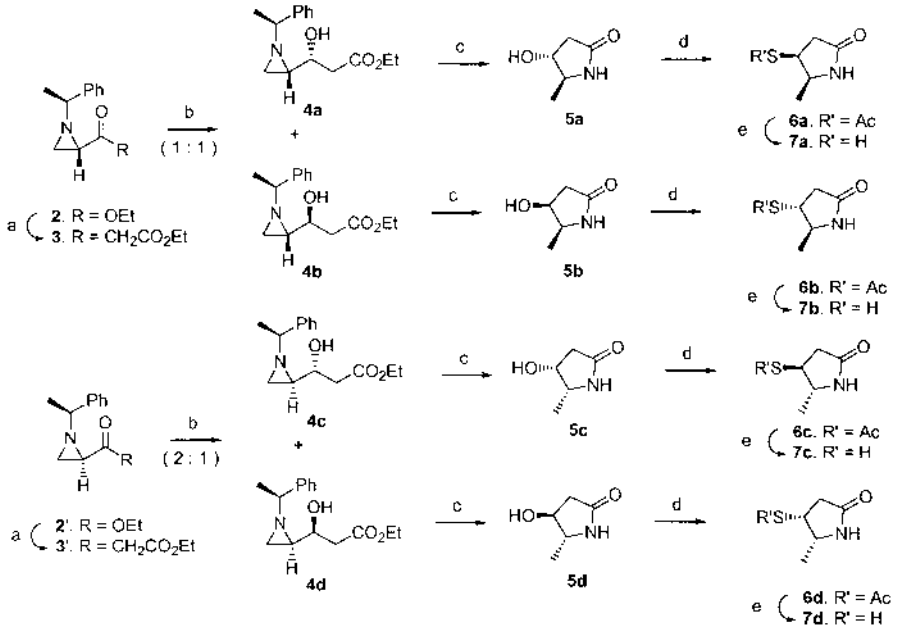

Reagents and conditions: (a) EtOAc, LiHMDS, THF, −78 °C, 1.5 h, (b) NH_4Cl, $NaBH_4$, H_2O/EtOH, 1 h, (c) $Pd(OH)_2$, H_2 (60 psi), EtOH, 12 h, (d) PPh_3, DEAD, AcSH, DMF/THF, 3 h, (e) 2 N-NaOH, MeOH, 0.5 h.

Chart 2

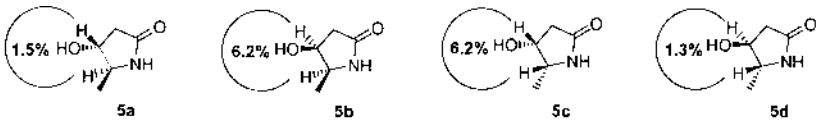

Fig. 1. NOE Enhancement of **5a**—**d**

Table 1. *In Vitro* Antibacterial Activity of Carbapenem-Substituted 5-Methyl-4-mercaptopyrrolidinone (MIC, μg/ml)

Strains	**1a**	**1b**	**1c**	**1d**	Meropenem	R-83201
Streptococcus pyogenes 308A	0.025	0.025	0.013	0.049	0.013	0.013
Streptococcus pyogenes 77A	0.025	0.049	0.025	0.025	0.007	0.013
Streptococcus faecium MD8b	6.250	6.250	6.250	6.250	6.250	6.250
Staphylococcus aureus 285	0.195	0.781	0.391	0.391	0.195	0.098
Staphylococcus aureus 503	0.195	0.192	0.195	0.195	0.049	0.049
Escherichia coli 078	0.025	0.049	0.098	0.025	0.025	0.025
Escherichia coli DC0	0.025	0.098	0.781	0.049	0.025	0.025
Escherichia coli TEM	0.013	0.098	0.098	0.025	0.025	0.013
Pseudomonas aeruginosa 9027	25.0	25.0	50.0	25.0	0.195	6.250
Pseudomonas aeruginosa 1771M	1.563	1.563	1.563	6.250	0.098	0.781
Salmonella typhimurium	0.049	0.195	0.195	0.049	0.049	0.049
Klebsiella oxytoca 1082E	0.195	3.125	1.563	0.391	0.049	0.195
Klebsiella aerogenes 1522E	0.025	0.195	0.195	0.049	0.049	0.025
Enterobacter cloacae P99	0.391	3.125	1.563	1.563	0.098	0.195
Enterobacter cloacae 1321E	0.025	0.098	0.098	0.025	0.025	0.013
DHP-1 stability	141	63	102	60	100	—

the presence of $Pd(OH)_2$.

We found that aziridine ring reduction proceeded much faster than debenzylation during the catalytic hydrogenation of the aziridine propionates. Subsequent ring opening, debenzylation, and intramolecular cyclization proceeded in a one-pot process. The best result of the reductive clevage of the C(3)–N bond was obtained when using 20 wt% of Pearlman's catalyst and the concentration of the substrate was 0.2 M in MeOH. The absolute stereochemistry of **5a**—**d** was confirmed by ^{1}H-NMR and nuclear Overhauser effect (NOE) experiments (Fig. 1). 5-Methyl-4-hydroxypyrrolidinones **5a**—**d** were converted to the thioacetates **6a**—**d** by the Mitsunobu reaction using PPh_3, diethylazodicarboxylate (DEAD), and thiolacetic acid in *N*,*N*-dimethylformamide (DMF) and THF. Thiols **7a**—**d**, applicable for coupling with carbapenem enolphosphate **8**, were prepared by deacetylation under basic conditions.

Conclusion

5-Methyl-4-hydroxypyrrolidinones (**5a**—**d**) were synthesized from the enantiomerically pure aziridine ester (**2**) in 3 steps, with subsequent 50% overall yield. The nonprotected side-chain thiols (**7a**—**d**) were prepared from **5a**—**d** by the Mitsunobu reaction and deacetylation. 1β-Methylcarbapenems bearing 5-methyl-4-mercaptopyrrolidinones were synthesized from PNB-protected carbapenem enolphosphate (**8**) and thiols (**7a**—**d**). Some effects of the chiral center in the C-2 side chain were observed on *in vitro* activities and pharmacokinetic parameters. Comparison of stereoisomers indicated that **1a** shows greater antibacterial activity than the others. In addition, the degradation rate of **1a** with DHP-1 was slower than the others.

Experimental

General NMR spectra were recorded on Varian Gemini 200 spectrometers operating at 200 MHz (^{1}H) and 50 MHz (^{13}C) in deuteriochloroform ($CDCl_3$), deuteriomethanol (CD_3OD), or deuterium oxide (D_2O). THF and ether were distilled from sodium-benzophenone ketyl at atmospheric pressure immediately prior to use. Methylene chloride and dimethyl sulfoxide (DMSO) were distilled from calcium hydride. All other reagents and solvents used were of reagent grade.

Ethyl 3-Oxo-3-[1-(1′(*S*)-α-methylbenzyl)-aziridin-2(*S*)-yl]-propionate (3) To a solution of LiHMDS (9.95 ml, 9.95 mmol) in 15 ml of THF under a nitrogen atmosphere at −78 °C was added EtOAc (1.0 ml, 9.94 mmol). The reaction mixture was stirred for 30 min at −78 °C and then treated with **2** (1.09 g, 4.97 mmol) in 10 ml of THF at −78 °C. The mixture was stirred for 1 h, quenched with 3 ml of water at −78 °C, and then warmed to room temperature. The combined organic layer was separated and washed with 5 ml of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/*n*-hexane=1 : 4) gave 0.97 g (75%) of **3** as a yellow oil. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.31—7.26 (m, 5H), 4.10 (q, J=7.2 Hz, 2H), 3.36 (d, J=5.4 Hz, 2H), 2.58 (q, J=6.5 Hz, 1H), 2.34 (d, J=3.0 Hz, 1H), 2.21 (dd, J=3.0, 7.0 Hz, 1H), 1.86 (d, J=7.0 Hz, 1H), 1.44 (d, J=6.5 Hz, 3H), 1.21 (t, J=7.2 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 200.8, 167.0, 143.4, 128.3, 127.2, 126.3, 69.4, 61.0, 44.3, 44.0, 34.9, 23.3, 13.8; high resolution (HR)-MS (electron impact (EI)) Calcd for $C_{15}H_{19}NO_3$, 261.1364; Found 261.1373.

Ethyl 3-Oxo-3-[1-(1′(*S*)-α-methylbenzyl)-aziridin-2(*R*)-yl]-propionate (3′) ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.37—7.26 (m, 5H), 4.19 (q, J=7.2 Hz, 2H), 3.42 (d, J=11.2 Hz, 2H), 2.59 (q, J=6.5 Hz, 1H), 2.34 (dd, J=3.0, 6.8 Hz, 1H), 2.11 (d, J=3.0 Hz, 1H), 1.72 (d, J=6.8 Hz, 1H), 1.42 (d, J=6.5 Hz, 3H), 1.28 (t, J=7.2 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 201.4, 167.0, 143.4, 128.2, 127.1, 126.4, 68.9, 61.0, 44.9, 43.6, 34.0, 23.0, 13.8; HR-MS (EI) Calcd for $C_{15}H_{19}NO_3$, 261.1364; Found 261.1366.

Ethyl 3(*R*)-Hydroxy-3-[1-(1′(*S*)-α-methylbenzyl)-aziridin-2(*S*)-yl]-propionate (4a) and Ethyl 3(*S*)-hydroxy-3-[1-(1′(*S*)-α-methylbenzyl)-aziridin-2(*S*)-yl]-propionate (4b) To a solution of **3** (1.56 g, 5.96 mmol) and NH_4Cl (6.38 g, 0.11 mol) in 95 ml of 80% aqueous EtOH was added $NaBH_4$ (1.13 g, 29.84 mol) in three portions. The mixture was stirred for 1 h at room temperature and then quenched with water. The mixture was concentrated under reduced pressure and then extracted with EtOAc (30 ml). The combined organic layer separated was washed with 10 ml of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/*n*-hexane=1 : 4) gave 0.65 g (41%) of **4a** and 0.68 g (44%) of **4b** as yellow oil. **4a**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.38—7.21 (m, 5H), 4.27 (q, J=7.1 Hz, 2H), 4.05 (q, J=6.5 Hz, 1H), 3.17 (s, 1H), 2.65 (dd, J=2.7, 4.3 Hz, 2H), 2.57 (q, J=6.5 Hz, 1H), 1.75 (dd, J=1.7, 3.0 Hz, 2H), 1.45 (d, J=6.5 Hz, 3H), 1.28 (t, J=7.1 Hz, 3H); HR-MS (EI) Calcd for $C_{15}H_{21}NO_3$, 263.1521; Found 263.1520. **4b**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.38—7.25 (m, 5H), 4.19 (q, J=7.1 Hz, 2H), 3.91—3.80 (m, 1H), 2.82 (d, J=6.3 Hz, 1H), 2.62 (dd, J=2.8, 4.3 Hz, 2H), 2.55 (q, J=6.5 Hz, 1H), 1.75 (dd, J=1.7, 3.1 Hz, 2H), 1.43 (d, J=6.5 Hz, 3H), 1.28 (t, J=7.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 171.0, 143.8, 127.9, 126.7, 126.4, 68.7, 67.8, 60.2, 43.4, 40.2, 30.5, 23.1, 13.8; HR-MS (EI) Calcd for $C_{15}H_{21}NO_3$, 263.1521; Found 263.1518.

Ethyl 3(*R*)-Hydroxy-3-[1-(1′(*S*)-α-methylbenzyl)-aziridin-2(*R*)-yl]-propionate (4c) and Ethyl 3(*S*)-Hydroxy-3-[1-(1′(*S*)-α-methylbenzyl)-aziridin-2(*R*)-yl]-propionate (4d) **4c**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 7.34—7.26 (m, 5H), 4.06 (q, J=7.1 Hz, 2H), 3.77 (m, 1H), 2.49 (q, J=6.5 Hz, 1H), 2.25 (s, 1H), 2.15 (d, J=7.7 Hz, 1H), 2.06 (d, J=5.7 Hz, 1H), 1.96 (d, J=3.5 Hz, 1H), 1.65 (m, 1H), 1.49 (d, J=6.5 Hz, 3H), 1.44 (d, J=6.5 Hz, 3H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 171.1, 144.0, 128.3, 127.2, 126.7, 69.3, 66.7, 60.0, 41.3, 40.0, 30.9, 22.2, 13.9; HR-MS (EI) Calcd for $C_{15}H_{21}NO_3$, 263.1521; Found 263.1509. **4d**: ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.34—7.25 (m, 5H), 4.06 (q, J=7.1 Hz, 2H), 3.75 (dd, J=5.1, 12.0 Hz, 1H), 2.97 (s, 1H), 2.53 (q, J=6.5 Hz, 1H), 2.21 (dd, J=2.0, 5.0 Hz, 2H), 1.96 (d, J=3.5 Hz, 1H), 1.69—1.62 (m, 1H), 1.48 (d, J=6.5 Hz, 1H), 1.43 (d, J=6.5 Hz, 3H), 1.20 (t, J=7.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 171.7, 143.9, 128.3, 127.1, 126.6, 69.3, 66.9, 60.3, 41.1, 39.1, 30.8, 22.5, 13.9; HR-MS (EI) Calcd for $C_{15}H_{21}NO_3$, 263.1521; Found 263.1502.

5(*S*)-Methyl-4(*R*)-hydroxypyrrolidinone (5a) To a solution of **4a** (1.13 g, 4.32 mmol) in 21 ml of EtOH was added $Pd(OH)_2$ (350 mg). The mixture was stirred under 60 psi of hydrogen for 12 h at room temperature. The reaction mixture was filtered and washed with 10 ml of MeOH and then concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/*n*-hexane=1 : 4) gave 390 mg (80%) of **5a** as a white solid. ^{1}H-NMR (CD_3OD, 200 MHz) δ: 4.01 (ddd, J=3.0, 4.0, 6.8 Hz, 1H), 3.51 (dq, J=3.0, 6.5 Hz, 1H), 2.68 (dd, J=6.8, 17.1 Hz, 1H), 2.18 (dd, J=4.0, 17.1 Hz, 1H), 1.20 (d, J=6.5 Hz, 3H); ^{13}C-NMR (CD_3OD, 50 MHz) δ: 177.9, 74.5, 60.4, 40.3, 19.7; HR-MS (EI) Calcd for $C_5H_9NO_2$, 115.0633; Found 115.0632.

5(*S*)-Methyl-4(*S*)-hydroxypyrrolidinone (5b) ^{1}H-NMR (CD_3OD, 200 MHz) δ: 4.31 (dd, J=2.6, 4.4 Hz, 1H), 3.77 (dd, J=5.0, 6.5 Hz, 1H), 2.62 (dd, J=6.2, 17.1 Hz, 1H), 2.21 (dd, J=2.6, 17.1 Hz, 1H), 1.19 (d, J=6.5 Hz, 3H); ^{13}C-NMR (CD_3OD, 50 MHz) δ: 178.8, 70.0, 56.6, 41.6, 14.6; HR-MS (EI) Calcd for $C_5H_9NO_2$, 115.0633; Found 115.0634.

5(*R*)-Methyl-4(*R*)-hydroxypyrrolidinone (5c) ^{1}H-NMR (CD_3OD, 200 MHz) δ: 4.31 (ddd, J=2.5, 5.0, 6.0 Hz, 1H), 3.77 (dq, J=5.0, 6.5 Hz, 1H), 2.64 (dd, J=6.1, 17.0 Hz, 1H), 2.21 (dd, J=2.6, 17.0 Hz, 1H), 1.20 (d, J=6.5 Hz, 3H); ^{13}C-NMR (CD_3OD, 50 MHz) δ: 178.7, 70.0, 56.5, 41.6, 14.6; HR-MS (EI) Calcd for $C_5H_9NO_2$, 115.0633; Found 115.0632.

5(*R*)-Methyl-4(*S*)-hydroxypyrrolidinone (5d) ^{1}H-NMR (CD_3OD, 200 MHz) δ: 4.01 (dt, J=3.1, 4.1 Hz, 1H), 3.52 (dq, J=3.1, 6.5 Hz, 1H), 2.68 (dd, J=6.7, 17.2 Hz, 1H), 2.18 (dd, J=4.1, 17.2 Hz, 1H), 1.20 (d, J=6.5 Hz, 3H); ^{13}C-NMR (CD_3OD, 50 MHz) δ: 178.1, 75.3, 61.2, 41.2, 20.5; HR-MS (EI) Calcd for $C_5H_9NO_2$, 115.0633; Found 115.0633.

5(*S*)-Methyl-4(*S*)-acetylthiopyrrolidinone (6a) To a solution of **5a** (310 mg, 2.76 mmol) in 13.5 ml of THF/DMF (11.5/2 ml) under nitrogen at 0 °C was added PPh_3 (870 mg, 3.31 mmol) and DEAD (0.52 ml, 3.31 mmol). The mixture was stirred for 30 min at 0 °C and then AcSH (0.39 ml, 3.59 mmol) added. The mixture was stirred for 2 h at room temperature and then concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/*n*-hexane=1 : 4) gave 285 mg (60%) of **6a** as a white foam. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 6.86 (s, 1H), 4.28 (dd, J=2.6, 4.4 Hz, 1H), 4.06 (dd, J=5.0, 6.5 Hz, 1H), 2.88 (dd, J=8.3, 18.0 Hz, 1H), 2.36 (s, 3H), 2.33 (dd, J=7.1, 16.7 Hz, 1H), 1.18 (d, J=6.6 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 194.4, 175.1, 53.4, 43.1, 36.6, 29.8, 18.5; HR-MS (EI) Calcd for $C_7H_{11}NO_2S$, 173.0510; Found 173.0507.

5(*S*)-Methyl-4(*R*)-acetylthiopyrrolidinone (6b) ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 6.21 (s, 1H), 3.79—3.60 (m, 2H), 2.88 (dd, J=6.8, 17.1 Hz, 1H), 2.35 (s, 3H), 2.33 (dd, J=4.0, 17.1 Hz, 1H), 1.30 (d, J=6.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 194.2, 174.8, 56.0, 43.0, 36.8, 30.0, 19.9; HR-MS (EI) Calcd for $C_7H_{11}NO_2S$, 173.0510; Found 173.0513.

5(*R*)-Methyl-4(*S*)-acetylthiopyrrolidinone (6c) ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 6.05 (s, 1H), 3.79—3.63 (m, 2H), 2.87 (dd, J=6.7, 17.2 Hz, 1H), 2.34 (s, 3H), 2.31 (dd, J=4.1, 17.2 Hz, 1H), 1.30 (d, J=6.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 194.1, 174.2, 55.9, 43.0, 36.8, 29.9, 19.9; HR-MS (EI) Calcd for $C_7H_{11}NO_2S$, 173.0510; Found 173.0503.

5(*R*)-Methyl-4(*R*)-acetylthiopyrrolidinone (6d) ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 6.33 (s, 1H), 4.31 (ddd, J=2.5, 5.0, 6.0 Hz, 1H), 4.10 (dq, J=5.0, 6.0 Hz, 1H), 2.77 (dd, J=8.4, 17.2 Hz, 1H), 2.36 (s, 3H), 2.33 (dd, J=8.4, 16.6 Hz, 1H), 1.18 (d, J=6.5 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 194.6, 175.5, 52.3, 42.1, 36.7, 30.4, 17.6; HR-MS (EI) Calcd for $C_7H_{11}NO_2S$, 173.0510; Found 173.0503.

5(*S*)-Methyl-4(*S*)-thiopyrrolidinone (7a) To a solution of **6a** (135 mg, 0.77 mmol) in 8 ml of MeOH at 0 °C was added 2 N-NaOH (0.38 ml). The mixture was stirred for 30 min and then treated AcOH (0.04 ml, 0.85 mmol). The mixture was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/*n*-hexane=1 : 4) gave 92 mg (91%) of **6a** as a white foam. ^{1}H-NMR (CD_3OD, 200 MHz) δ: 3.89 (quin, J=6.4 Hz, 1H), 3.73 (dd, J=5.7, 13.5 Hz, 1H), 2.79 (dd, J=7.6, 17.0 Hz, 1H), 2.27 (dd, J=5.8, 17.0 Hz, 1H), 1.24 (d, J=6.4 Hz,

3H).

5(*S*)-Methyl-4(*R*)-thiopyrrolidinone (7b) ^{1}H-NMR (CD_3OD, 200 MHz) δ: 3.52 (quin, J=6.5 Hz, 1H), 3.05 (dd, J=8.4, 15.2 Hz, 1H), 2.77 (dd, J=7.1, 16.8 Hz, 1H), 2.31 (dd, J=8.6, 16.8 Hz, 1H), 1.27 (d, J=6.5 Hz, 3H).

5(*R*)-Methyl-4(*S*)-thiopyrrolidinone (7c) ^{1}H-NMR (CD_3OD, 200 MHz) δ: 3.54 (quin, J=6.2 Hz, 1H), 3.07 (dd, J=8.4, 15.1 Hz, 1H), 2.79 (dd, J=8.2, 16.8 Hz, 1H), 2.32 (dd, J=8.6, 16.8 Hz, 1H), 1.28 (d, J=6.2 Hz, 3H).

5(*R*)-Methyl-4(*R*)-thiopyrrolidinone (7d) ^{1}H-NMR (CD_3OD, 200 MHz) δ: 3.89 (quin, J=6.5 Hz, 1H), 3.71 (dd, J=7.1, 13.5 Hz, 1H), 2.77 (dd, J=7.7, 16.8 Hz, 1H), 2.26 (dd, J=5.9, 16.8 Hz, 1H), 1.24 (d, J=6.4 Hz, 3H).

4-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-1-methyl-2-[(*S*)-2(*S*)-methyl-5-oxopyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylate (9a) To a solution of **7a** (140 mg, 0.91 mmol) in 7 ml of CH_3CN under nitrogen at 0 °C was added *p*-nitrobenzyl (1*R*,5*S*,6*S*)-2-diphenylphosporyloxy-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate **8** (430 mg, 0.72 mmol) and DIPEA (0.12 ml, 1.00 mmol). The mixture was stirred for 2 h at 0—5 °C and then quenched with phosphate buffer solution (pH 7.0). The mixture was extracted with Et_2O and washed with brine. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/*n*-hexane=1 : 4) gave 175 mg (40%) of **9a** as a yellow foam. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.23 (d, J=8.7 Hz, 2H), 7.68 (d, J=8.6 Hz, 2H), 5.40 (dd, J=13.8, 49.2 Hz, 2H), 4.24 (dd, J=2.5, 9.0 Hz, 1H), 4.2—3.97 (m, 3H), 3.46—3.35 (m, 1H), 3.28 (dd, J=2.5, 7.1 Hz, 1H), 2.76 (dd, J=7.9, 17.1 Hz, 1H), 2.38 (dd, J=8.3, 17.1 Hz, 1H), 1.34 (d, J=6.3 Hz, 3H), 1.28 (d, J=7.3 Hz, 3H), 1.24 (d, J=6.3 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 174.7, 173.0, 159.9, 150.0, 147.2, 142.6, 127.9, 124.3, 123.3, 65.1, 59.5, 56.1, 53.6, 43.8, 42.0, 35.5, 21.1, 17.1, 16.4; HR-MS (FAB) Calcd for $C_{22}H_{26}N_3O_7S$, 476.1491; Found 476.1494.

4-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-1-methyl-2-[(*R*)-2(*S*)-methyl-5-oxopyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylate (9b) ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.23 (d, J=8.7 Hz, 2H), 7.66 (d, J=9.0 Hz, 2H), 5.37 (dd, J=13.8, 46.6 Hz, 2H), 4.25 (dd, J=2.6, 9.3 Hz, 1H), 4.19 (q, J=6.5 Hz, 1H), 3.63 (q, J=6.1 Hz, 1H), 3.52—3.30 (m, 2H), 3.26 (dd, J=2.6, 7.3 Hz, 1H), 2.87 (dd, J=8.0, 17.1 Hz, 1H), 2.46 (dd, J=6.7, 17.1 Hz, 1H), 1.38 (d, J=6.1 Hz, 3H), 1.31 (d, J=7.4 Hz, 3H), 1.28 (d, J=7.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 174.1, 172.5, 159.2, 147.5, 142.2, 135.6, 127.4, 126.5, 122.0, 121.5, 118.9, 71.8, 63.4, 58.3, 55.7, 50.5, 43.8, 41.7, 36.8, 24.7, 19.9, 14.1; HR-MS (FAB) Calcd for $C_{22}H_{26}N_3O_7S$, 476.1491; Found 476.1504.

4-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-1-methyl-2-[(*S*)-2(*R*)-methyl-5-oxopyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylate (9c) ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.22 (d, J=8.7 Hz, 2H), 7.65 (d, J=8.9 Hz, 2H), 6.23 (s, 1H), 5.36 (dd, J=13.8, 56.0 Hz, 2H), 4.28 (dd, J=2.4, 9.3 Hz, 2H), 3.68 (q, J=6.0 Hz, 1H), 3.50—3.39 (m, 1H), 3.34 (m, 1H), 3.30 (dd, J=2.5, 6.7 Hz, 1H), 2.87 (dd, J=8.5, 17.4 Hz, 1H), 2.37 (dd, J=7.0, 17.4 Hz, 1H), 1.36 (d, J=6.3 Hz, 3H), 1.31 (d, J=6.3 Hz, 3H), 1.27 (d, J=7.2 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 174.5, 172.9, 159.9, 148.7, 147.2, 142.7, 127.9, 125.4, 123.4, 65.2, 59.8, 58.0, 55.7, 45.3, 43.8, 36.8, 21.5, 20.5, 16.6, 13.9; HR-MS (FAB) Calcd for $C_{22}H_{26}N_3O_7S$, 476.1491; Fund 476.1484.

4-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-1-methyl-2-[(*R*)-2(*R*)-methyl-5-oxopyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylate (9d) ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 8.06 (d, J=8.7 Hz, 2H), 7.50 (d, J=9.0 Hz, 2H), 5.21 (dd, J=13.8, 47.6 Hz, 2H), 4.06 (dd, J=2.4, 9.2 Hz, 1H), 4.03—3.79 (m, 3H), 3.25—3.16 (m, 1H), 3.09 (dd, J=2.5, 7.6 Hz, 1H), 2.65 (dd, J=7.4, 16.9 Hz, 1H), 2.27 (dd, J=5.7, 16.9 Hz, 1H), 1.17 (d, J=6.1 Hz, 3H), 1.15 (d, J=6.2 Hz, 3H), 1.09 (d, J=6.5 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 173.4, 172.4, 158.6, 147.7, 142.2, 137.7, 127.5, 126.6, 121.9, 121.4, 118.6, 72.9, 63.4, 58.5, 54.3, 50.5, 42.3, 41.7, 36.2, 24.7, 19.7, 14.9; HR-MS (FAB) Calcd for $C_{22}H_{26}N_3O_7S$, 476.1491; Found 476.1486.

Sodium (1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-1-methyl-2-[(*S*)-2(*S*)-methyl-5-oxopyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylate (1a) To a solution of **9a** (134 mg, 0.28 mmol) in THF/EtOH/0.1 M-Mops buffer (4.5/7/11.5 ml) was added Pd/C (50 mg). The mixture was stirred under balloon pressure of hydrogen for 15 h at room temperature. The reaction mixture was filtered and washed with MeOH and then concentrated under reduced pressure. To a solution of residue was added SEH (47 mg, 0.28 mmol) and then stirred for 10 min. The aqueous layer washed with EtOAc. The combined aqueous layers were purified by reverse-phase column chromatography and then lyophilized to give **1a** (390 mg, 80%) as a white amorphous solid. ^{1}H-NMR (D_2O, 200 MHz) δ: 4.06—3.82 (m, 4H), 3.27—3.16 (m, 1H), 3.23 (dd, J=2.6, 6.2 Hz, 1H), 2.60 (dd, J=8.2, 17.1 Hz, 1H), 2.20 (dd, J=7.5, 17.1 Hz, 1H), 1.06 (d, J=6.1 Hz, 3H), 0.98 (d, J=6.5 Hz, 6H); ^{13}C-NMR (D_2O, 50 MHz) δ: 178.8, 178.1, 164.1, 131.5, 119.8, 65.4, 56.2, 54.8, 50.5, 41.9, 36.2, 20.7, 17.1, 16.2; HR-MS (FAB) Calcd for $C_{15}H_{20}N_2O_5NaS$, 363.0990; Found 363.0993.

Sodium (1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-1-methyl-2-[(*R*)-2(*S*)-methyl-5-oxopyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylate (1b) ^{1}H-NMR (D_2O, 200 MHz) δ: 3.77 (q, J=6.4 Hz, 1H), 3.94 (dd, J=2.5, 9.4 Hz, 1H), 3.42 (dq, J=6.0, 11.2 Hz, 1H), 3.39—3.33 (m, 1H), 3.17 (dd, J=2.5, 6.0 Hz, 1H), 3.06 (dt, J=7.5, 16.4 Hz, 1H), 2.75 (dd, J=7.9, 18.5 Hz, 1H), 2.18 (dd, J=5.3, 18.5 Hz, 1H), 1.06 (d, J=6.4 Hz, 3H), 1.02 (d, J=6.1 Hz, 3H), 0.94 (d, J=7.1 Hz, 3H); ^{13}C-NMR (D_2O, 50 MHz) δ: 168.4, 166.9, 164.4, 135.1, 114.8, 74.2, 68.1, 58.5, 48.6, 46.9, 35.8, 34.2, 26.5, 25.0, 10.0; HR-MS (FAB) Calcd for $C_{15}H_{20}N_2O_5NaS$, 363.0990; Found 363.0975.

Sodium (1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-1-methyl-2-[(*S*)-2(*R*)-methyl-5-oxopyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylate (1c) ^{1}H-NMR (D_2O, 200 MHz) δ: 4.27—4.20 (m, 2H), 3.74 (dd, J=3.9, 6.5 Hz, 1H), 3.62 (q, J=5.0 Hz, 1H), 3.46 (dd, J=2.8, 5.9 Hz, 1H), 3.41—3.31 (m, 1H), 2.98 (dd, J=8.6, 17.9 Hz, 1H), 2.34 (dd, J=7.9, 18.5 Hz, 1H), 1.28 (d, J=6.5 Hz, 6H), 1.20 (d, J=7.1 Hz, 3H); ^{13}C-NMR (D_2O, 50 MHz) δ: 178.1, 176.8, 175.5, 139.3, 98.1, 65.3, 61.5, 59.1, 56.1, 44.5, 42.9, 36.3, 20.3, 19.7, 16.1; HR-MS (FAB) Calcd for $C_{15}H_{20}N_2O_5NaS$, 363.0990; Found 363.0990.

Sodium (1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-1-methyl-2-[(*R*)-2(*R*)-methyl-5-oxopyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylate (1d) ^{1}H-NMR (D_2O, 200 MHz) δ: 4.28—4.10 (m, 4H), 3.45 (dd, J=2.5, 5.1 Hz, 1H), 3.38 (m, 1H), 2.94 (dd, J=6.8, 17.1 Hz, 1H), 2.46 (dd, J=4.3, 17.1 Hz, 1H), 1.33 (d, J=4.3 Hz, 3H), 1.31 (d, J=7.8 Hz, 3H), 1.20 (d, J=6.8 Hz, 3H); ^{13}C-NMR (D_2O, 50 MHz) δ: 177.2, 176.3, 170.2, 139.6, 109.8, 65.9, 59.2, 56.8, 53.8, 43.9, 43.1, 40.5, 27.2, 20.8, 16.5; HR-MS (FAB) Calcd for $C_{15}H_{20}N_2O_5NaS$, 363.0990; Found 363.0989.

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