SYNTHESIS AND *IN VITRO* ACTIVITY OF A NEW CARBAPENEM, RS-533

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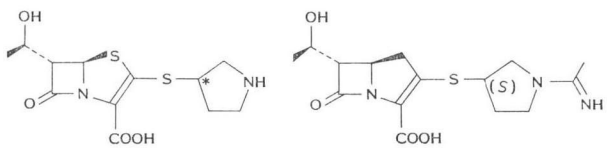
The synthesis and *in vitro* antimicrobial activity of a new synthetic carbapenem, (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-[(*S*)-1-acetimidoylpyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylic acid (RS-533), are described. The MIC values of related penems and carbapenems are also given for comparison with those of the new carbapenem.

The discovery of the potent broad-spectrum antibiotic thienamycin (THM)[1~4] has arisen chemical and microbiological interest in carbapenems and structurally related penems. Extensive molecular modifications of THM and penems have been made in pursuit of greater stability and potency and, as a result, clinically useful β-lactams, *N*-formimidoylthienamycin (MK0787)[5~7] and an oral penem (Sch 29482)[8] have been obtained. Prior to the present work on carbapenems, we were concerned with the synthesis[9,10] and bioassay of new penems, during which we discovered 6-(1-hydroxyethyl)-2-(pyrrolidin-3-ylthio)penem-3-carboxylic acids (**R-1** and **S-1**)[11,12] which were found to have potent *in vitro* activity comparable to THM. This finding led us to synthesize carbapenem congeners in the expectation that the carbapenems would display greater activity than either the penems or THM. As a result of extensive syntheses ranging from penems to carbapenems, we ultimately obtained a new carbapenem, RS-533; one of the most promising antibiotics in view of the potent *in vitro* and *in vivo* activity[13] against a wide range of bacteria.

Chart 1.



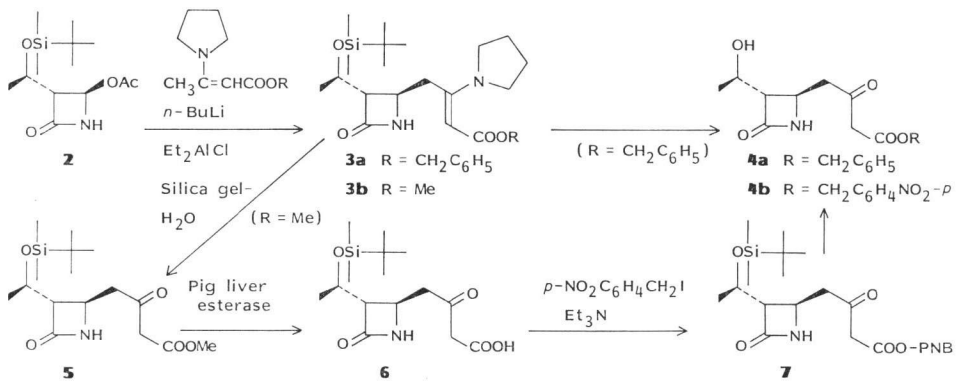
R-1 * (*R*)
S-1 * (*S*)

RS-533

Synthesis

In preparing the desired carbapenem compound, we utilized the 2-oxocarbapenam (**9b**), first synthesized by the Merck group,[14] as the most reliable intermediate for carbapenem synthesis. Although **9a** and **9b** have been synthesized by way of the β-keto esters (**4a** and **4b**) by several routes,[15~18] we prepared **4a** and **4b** starting from the acetoxyazetidinone (**2**) and the 3-pyrrolidinocrotonic acid esters as shown in Chart 2.

Chart 2.



In the first attempt methyl 3-pyrrolidinocrotonate was, after lithiation with *n*-butyllithium,[19] allowed to react with **2** to furnish **5** in very poor yield. The β-keto ester (**5**) was, however, produced in reasonable yield when diethylaluminum chloride was added to the lithiated enamino ester prior to reaction with **2**. In this process, the initially formed enamino ester (**3b**) was treated with silica gel containing a small amount of water to give the β-keto ester (**5**). The enamino ester (**3a**) similarly prepared was treated with aqueous HCl - MeOH followed by hydrolysis using silica gel - H_2O to give **4a** in 33% yield from **2**, while *p*-nitrobenzyl 3-pyrrolidinocrotonate failed to yield the corresponding β-keto ester (**4b**). The β-keto ester (**7**) could be obtained by the hydrolysis of the β-keto methyl ester (**5**) with pig liver esterase to the β-keto acid (**6**) followed by esterification with *p*-nitrobenzyl iodide. The enzymatic hydrolysis has advantage over the acid or alkaline hydrolysis of β-keto esters to β-keto carboxylic acids which accompanies decarboxylation. Removal of the *tert*-butyldimethylsilyl group of **7** was performed by treatment with aqueous HCl in methanol. The β-keto esters (**4a** and **4b**) were converted into **9a** and **9b**, respectively, *via* diazo compounds (**8a** and **8b**) according to the established method.[14] The 2-oxocarbapenams (**9a** and **9b**) were treated with diphenylphosphoryl chloride in the presence of diisopropylethylamine[14] and then with (*S*)-1-*p*-nitrobenzyloxycarbonyl-3-mercaptopyrrolidine* to furnish the carbapenem derivatives (**10a** and **10b**). Deprotection of the *p*-nitrobenzyl and *p*-nitrobenzyloxycarbonyl groups of **10b** was performed by hydrogenolysis over 10% Pd-C yielding **11** in good yield, while similar treatment of **10a** gave **11** in poor yield. The pyrrolidinylthiocarbapenem (**11**) was crystallized from water to give the semihydrate of **11** as colorless fine prisms. Treatment of **11** with ethyl acetimidate afforded RS-533. The two carbapenems, **11** and RS-533, may be represented as zwitter ions. The NMR spectrum of RS-533 indicates that it exists in water as two interconvertible rotamers (approximately 1: 1) possibly responsible for a double bond character of the acetimidoylpyrrolidinyl linkage. Details will be given in the near future. The *R*-epimer of RS-533 was similarly prepared starting from **9b** and (*R*)-1-*p*-nitrobenzyloxycarbonyl-3-mercaptopyrrolidine. The isomeric carbapenem will be described elsewhere, along with the *N*-formimidoyl derivative of **11** and other alicyclic amine derivatives. Alternative synthesis of carbapenems is now in progress.

* (*S*)-1-*p*-Nitrobenzyloxycarbonyl-3-mercaptopyrrolidine was prepared in the following four steps starting from (*R*)-3-hydroxypyrrolidine: 1) *p*-$NO_2C_6H_4CH_2OCOCl$, Et_3N/cyclohexanol, 0°C; 2) $MeSO_2Cl$, Et_3N/CH_2Cl_2, 0°C; 3) AcSNa/DMF, 60°C; 4) MeONa/MeOH, 0°C. (*R*)-3-Hydroxypyrrolidine was prepared from *trans*-4-hydroxy-L-proline according to the known method.[20]

Chart 3.

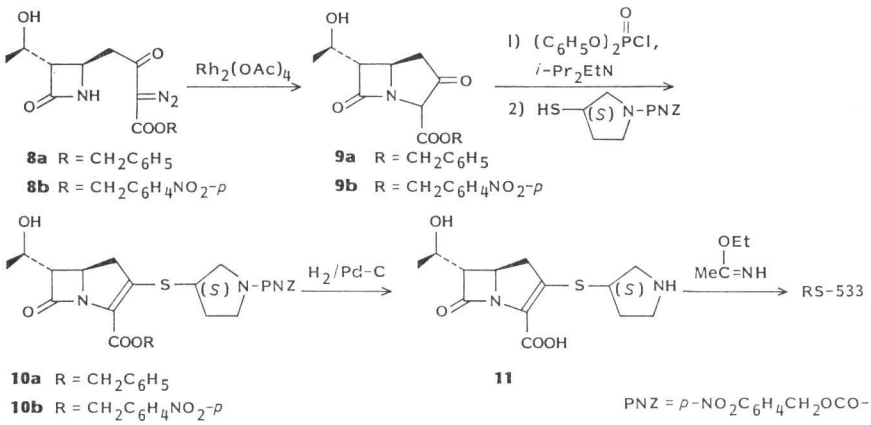


Table 1. Antimicrobial activities of RS-533, **11**, **S-1**, **R-1**, and THM.

Organism	MIC (μg/ml)				
	RS-533	**11**	**S-1**	**R-1**	THM
Bacillus subtilis PCI-219	≦0.01	≦0.01	≦0.01	≦0.01	≦0.01
Staphylococcus aureus 209P	≦0.01	≦0.01	≦0.01	≦0.01	≦0.01
Staphylococcus aureus 56*	≦0.01	≦0.01	≦0.01	≦0.01	≦0.01
Escherichia coli NIHJ	0.05	0.02	0.1	0.05	0.1
Escherichia coli 609**	0.05	0.02	0.1	0.05	0.1
Salmonella enteritidis Gaertner	0.05	0.05	0.2	0.1	0.2
Shigella flexneri 2a Komagome	0.02	≦0.01	0.1	0.05	0.1
Klebsiella pneumoniae 806	0.05	0.02	0.2	0.1	0.1
Enterobacter cloacae 963	0.4	0.4	3.1	3.1	
Serratia marcescens 1850	0.1	0.05	0.4	0.2	
Proteus vulgaris 1420	1.5	3.1	6.2	3.1	3.1
Pseudomonas aeruginosa 1001	6.2	1.5	6.2	6.2	6.2

* Penicillinase producer.
** Cephalosporinase producer.
Nutrient agar: Inocula were diluted 100-fold after overnight culture. Final inoculum size was one-loopful of 10^7 cfu/ml.

Antimicrobial Activity

The *in vitro* antimicrobial activities of RS-533 and **11** were tested by the serial agar dilution method. The minimal inhibitory concentrations (MIC) against a variety of Gram-positive and Gram-negative bacteria are listed in Table 1 and compared with those of THM, **R-1** and **S-1**. The carbapenem **11** is 4~5 times more active than THM against *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, etc.* Although RS-533 is slightly less active than **11** as far as the *in vitro* activity concerned, the former proved to be better in mice infected with a variety of bacteria.

Experimental

IR spectra were recorded on a Jasco A-2 spectrometer and UV spectra were obtained on a Cary 14 CM-50 (Serial 1258) spectrometer. Nuclear magnetic resonance spectra were recorded on a Jeol

JNM GX-400 or a Varian EM 360L spectrometer. Chemical shifts are reported in parts per million (δ) using, unless otherwise specified, tetramethylsilane (TMS) as an internal standard. Rotations were determined on a Perkin-Elmer 241 polarimeter.

Benzyl 4-[(3*S*,4*R*)-3-[(*R*)-1-Hydroxyethyl]-2-oxoazetidin-4-yl]-3-oxobutyrate (**4a**)

A solution of benzyl 3-pyrrolidinocrotonate (5.81 g, 20 mmol) in THF (70 ml) was treated with a solution of *n*-BuLi (20 mmol) of hexane (12.3 ml, 1.63 mmol/ml) according to the procedure given in ref 19. To the resulting solution was added a solution of Et_2AlCl (20 mmol) in hexane (23.0 ml, 0.871 mmol/ml) at $-60°C$ with stirring. The mixture was stirred for 45 minutes at the same temperature and a solution of **2** (1.15 g, 4 mmol) in THF (10 ml) was added dropwise. After being stirred at $-60°C$ for 0.5 hour and at 0°C for 45 minutes, the mixture was poured into ice-water and extracted with EtOAc. After removal of the insoluble material by filtration, the extract was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to leave an oily residue. The oil was dissolved in a mixture of conc. HCl (10 ml) and MeOH (50 ml) and the solution was stirred at 0°C for 1 hour. The mixture was neutralized with 5% aq. $NaHCO_3$ and extracted with EtOAc. The extract was washed with aq. NaCl and dried over $MgSO_4$, and the residue obtained by removal of the solvent was treated with silica gel (30 g) in benzene (50 ml) - H_2O (4.5 ml) at room temperature for 1 hour. The mixture was loaded on silica gel and chromatographed eluting with EtOAc - MeOH (30: 1) to give **4a** (402 mg, 33% yield) as an oil. NMR ($CDCl_3$) δ 1.22 (3H, d, J=6.0 Hz), 2.6~3.0 (3H, m), 3.50 (2H, s), 3.3~4.3 (3H, m), 5.11 (2H, s), 6.77 (1H, br.s), 7.31 (5H, s). IR ($CHCl_3$) 3430, 1755, 1710 cm^{-1}.

Methyl 4-[3*S*,4*R*)-3-[(*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-2-oxoazetidin-4-yl]-3-oxobutyrate (**5**)

Methyl 3-pyrrolidinocrotonate[19] (10.2 g, 60.3 mmol) was treated successively with *n*-BuLi (37.0 ml, 60.3 mmol), Et_2AlCl (69.3 ml, 0.870 mmol/ml) and **2** (3.47 g, 12.1 mmol) as described for **4a**. Without HCl treatment the crude product was subjected to hydrolysis with silica gel - H_2O and then chromatographed on silica gel with cyclohexane - EtOAc (1: 4) to give **5** (1.25 g, 30% yield) as an oil. NMR ($CDCl_3$) δ 0.08 (6H, s), 0.88 (9H, s), 1.22 (3H, d, J=6.5 Hz), 2.4~3.1 (3H, m), 3.48 (2H, s), 3.75 (3H, s), 3.8~4.4 (2H, m), 6.15 (1H, br.s). IR ($CHCl_3$) 3420, 1755, 1720 cm^{-1}.

p-Nitrobenzyl 4-[(3*S*,4*R*)-3-[(*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-2-oxoazetidin-4-yl]-3-oxobutyrate (**7**)

A mixture of **5** (2.0 g, 5.8 mmol) and pig liver esterase (Sigma, 100 mg) in 0.2 M phosphate buffer (pH 8.0, 150 ml) was vigorously stirred for 75 minutes at 36°C until it turned to be a homogeneous solution The reaction mixture was diluted with EtOAc and the insoluble material was removed by filtration. The aqueous layer was washed with EtOAc, adjusted to pH 2.5 with aq. 10% $KHSO_4$ and extracted with EtOAc. The extract was washed with aq. NaCl, dried over $MgSO_4$ and evaporated *in vacuo* to give **6** (1.33 g) as a powder. The crude **6** (1.33 g) was esterified by treating with a solution of *p*-nitrobenzyl iodide (2.0 g, 5.51 mmol) and Et_3N (771 μl, 5.51 mmol) in DMF (30 ml) at 0°C for 2 hours. The mixture was quenched with AcOH, poured into ice-water and extracted with EtOAc. The extract was washed successively with aq. 5% HCl, aq. $NaHCO_3$ and aq. NaCl, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel eluting with cyclohexane - EtOAc (1: 2) to give **7** (0.9 g) as an oil. Spectral data of **7** were in accord with the literature[14] in all respects.

p-Nitrobenzyl (5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-[(*S*)-1-*p*-nitrobenzyloxycarbonylpyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylate (**10b**)

Diphenylphosphoryl chloride (1.76 ml, 8.62 mmol) and *iso*-Pr_2EtN (1.50 ml, 8.62 mmol) were added to an ice-cooled solution of **9b** (2.50 g, 7.18 mmol) in anhydrous CH_3CN (100 ml) and the mixture was stirred for 0.5 hour. Then *iso*-Pr_2EtN (1.50 ml, 8.62 mmol) and a solution of 3-(*S*)-mercapto-1-*p*-nitrobenzyloxycarbonylpyrrolidine (2.43 g, 8.62 mmol) in CH_3CN (7 ml) were added and the mixture was stirred at 0°C for 1 hour. The reaction mixture was diluted with EtOAc, washed successively with H_2O, aq. 5% $NaHCO_3$ and aq. NaCl, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to leave a residue which was treated with a small amount of EtOAc to give **10b** (2.79 g) as a powder. The filtrate was chromatographed on silica gel with EtOAc to give additional amount of **10b** (1.00 g)

as a powder. Yield 86%. NMR ($CDCl_3$) δ 1.34 (3H, d, J=6.0 Hz), 1.9~3.0 (3H, m), 3.1~4.5 (10H, m), 5.24 (2H, s), 5.22, 5.53 (2H, AB-q, J=14.0 Hz), 7.52, 8.21 (4H, A_2B_2, J=9.0 Hz), 7.66, 8.21 (4H, A_2B_2, J=9.0 Hz). IR (KBr) 3560, 1780, 1705, 1350 cm^{-1}.

Benzyl (5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-[(*S*)-1-*p*-nitrobenzyloxycarbonylpyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylate (**10a**)

The benzyl ester **10a** (303 mg) was obtained from **9a** (280 mg, 0.92 mmol) as described for **10b**. NMR (DMF-d_7) δ 1.23 (3H, d, J=6.0 Hz), 1.7~2.7 (2H, m), 3.1~4.5 (10 H, m), 5.06, 5.33 (2H, AB-q, J=16.5 Hz), 5.31 (2H, s), 7.2~7.7 (5H, m), 7.73, 8.26 (4H, A_2B_2, J=8.5 Hz). IR (Nujol) 3400, 1770, 1708, 1695, 1350 cm^{-1}.

(5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-[(*S*)-pyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylic Acid (**11**)

a) A mixture of **10b** (5.00 g, 8.17 mmol) in a solution of THF (100 ml) and 0.1 M phosphate buffer (pH 7.0, 100 ml) was shaken with 10% Pd-C (4.0 g) for 1.5 hours under a H_2 atmosphere. After removal of the catalyst by filtration through celite, the filtrate was concentrated *in vacuo* and filtered. The filtrate was washed with EtOAc, concentrated *in vacuo* to a half volume and chromatographed on a column of Diaion HP-20AG (Mitsubishi Chemical Industries, Ltd.). Fractions eluted with 5% aq. acetone were lyophilized to give **11** (1.8 g, 74% yield) as a powder which was crystallized from H_2O to give fine prisms, mp>270°C (dec.). $[\alpha]_D^{25}$ +73° (c 0.31, H_2O). NMR (400 MHz, D_2O/TMS_{ext}) δ 1.09 (3H, d, J=6.4 Hz, CH_3CH), 1.86 (1H, dddd, J=14, ~7, ~7, ~7 Hz, pyrrolidine H-4), 2.31 (1H, dddd, J=14, ~7, ~7, ~7 Hz, pyrrolidine H-4), 3.01, 3.03 (2H, qd, J_{gem}=17.5 Hz, J_{vic}=9.8, 8.8 Hz, respectively, 2×H-1), 3.16 (1H, dd, J=12.4, 4.4 Hz, pyrrolidine H-2), 3.20~3.25 (2H, m, H-6, pyrrolidine H-5), 3.31~3.37 (1H, m, pyrrolidine H-5), 3.51 (1H, dd, J=12.4, 6.6 Hz, pyrrolidine H-2), 3.80~3.85 (1H, m, SCH), 4.00~4.07 (2H, m, H-5, H-8). IR (KBr) 3400, 2800~2000, 1765, 1590 cm^{-1}. UV $\lambda_{max}^{H_2O}$ nm (ε) 297 (8,330).

Anal. Calcd. for $C_{13}H_{18}N_2O_4S \cdot \frac{1}{2}H_2O$: C 50.79, H 6.23, N 9.11, S 10.43.
Found: C 51.12, H 6.23, N 9.20, S 10.46.

b) The benzyl ester (**10a**) was treated with H_2/10% Pd-C and worked up as described above to give **11** in yield of 9%.

(5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-[(*S*)-1-acetimidoylpyrrolidin-3-ylthio]-1-carbapen-2-em-3-carboxylic Acid (RS-533)

A solution of **11** (3.3 g, 11.1 mmol) in 0.1 M phosphate buffer (pH 7.0, 350 ml) was adjusted to pH 8.5 with 1 N NaOH at 0°C and ethyl acetimidate hydrochloride (6.88 g, 55.5 mmol) was added in portions while adjusting to pH 8.5. After stirring for 10 minutes at pH 8.5 the reaction mixture was neutralized with aq. 5% HCl and passed through Diaion HP-20AG. Fractions eluted with aq. 5% acetone were lyophilized to give RS-533 (3.17 g, 84% yield) as a powder. NMR (400 MHz, D_2O/TMS_{ext}) δ 1.09 (3H, d, J=6.3 Hz, CH_3CH). 1.87~1.99 (1H, m, pyrrolidine H-4), 2.06, 2.08 (1.5 H each, s, CH_3C=N), 2.10~2.35 (1H, m, pyrrolidine H-4), 3.01, 3.05 (0.5 H each, qd, J_{gem}=17.6 Hz, J_{vic}=8.8, 9.8 Hz, respectively, H-1), 3.00, 3.06 (0.5 H each, qd, J_{gem}=17.6 Hz, J_{vic}=8.8, 9.8 Hz, respectively, H-1), 3.23 (1H, dd, J=5.9, 2.5 Hz, H-6), 3.24~3.89 (4H, m, pyrrolidine 2- & 5-methylene protons), 3.78~3.89 (1H, m, SCH), 4.00~4.06 (2H, m, H-5 & H-8). IR (KBr) 3400, 1760, 1675, 1590 cm^{-1}. An analytical sample was obtained as follows. The amorphous powder was dissolved in MeOH, seeded with crystals of previously obtained authentic sample and allowed to stand in a freezer to give colorless fine prisms, mp 198~200°C (dec.), which were dried at 40°C *in vacuo* for 46 hours. UV $\lambda_{max}^{H_2O}$ nm (ε) 298 (10,400).

Anal. Calcd. for $C_{15}H_{21}N_3O_4S \cdot \frac{1}{2}H_2O$: C 51.70, H 6.36, N 12.06, S 9.20.
Found: C 51.83, H 6.67, N 11.77, S 9.40.

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