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Synthesis and Antibacterial Evaluation of Novel 2-[*N*-Imidoylpyrrolidinyl] Carbapenems

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Abstract—The synthesis, antibacterial activity and DHP-susceptibility of a series of novel carbapenems, directly linked with heterocyclic moiety are described. Especially, the compounds linked pyrrolidine-carbapenem exhibited to have a good antibacterial activity against *Staphylococcus aureus* (MRSA) as well as *Pseudomonas aeruginosa* to maintain a good stability towards DHP-I.
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Introduction

Since the discovery of (+)-thienamycin in the early 1980s,[1] the carbapenems have attracted considerable attention as the most promising β-lactam antibiotics due to their chemical and metabolic stability as well as their potent antimicrobial activities.[2] The earliest carbapenems to become available, namely Imipenem **1**[3] and Panipenem **2**,[4] possess a non-1-substituted carbapenem skeleton, as in the original, phenotype carbapenem, thienamycin. Whilst these compounds have a broad, potent spectra of antibacterial activity, they are unstable to the renal enzyme dehydropeptidase-I (DHP-I) and have a low urinary recovery. Effort to improve the intrinsic DHP-I stability of the carbapenem skeleton by introduction of a 1β-methyl substitution has been exhibited, such as Meropenem.[5] On the other hand, we have reported the discovery of 2-vinyl carbapenem derivatives that are remarkably stable toward renal DHP-I, particularly; the 1′-methyl compound **3** had the best balance of antibacterial activity.[6] As a continuation of these studies, we have carried out the chemical modification of side chain of **3** to increase antibacterial activity, especially against methicillin-resistant *Staphylococcus aureus* (MRSA). In this paper, we report the novel carbapenems **4**, directly linked with heterocyclic moiety, have significantly improved antibacterial activity while maintaining good stability toward DHP-I (Fig. 1).

Chemistry

The synthetic route to the target carbapenems was outlined in Scheme 1. Acetyl-azetizine, pyrrolidine, and piperidine derivatives were prepared from corresponding carboxylic acid derivatives **5** using Meldrum's acid by standard method.[7] The trimethylsilyl enol ether of ketones were formed with trimethylsilyl trifluoromethanesulfonate, followed trifrate mediated aldol condensation with the acetoxyazetidinone afforded in moderate good yield and regioselectivity.[8] Monobactams **7** were then performed cyclization via the oxalimides to give **8**. Desilylation, followed by a palladium-catalyzed deprotection of both the AOC and allyl ester produced **9** after purification by HP-20 column chromatography and lypophilization.

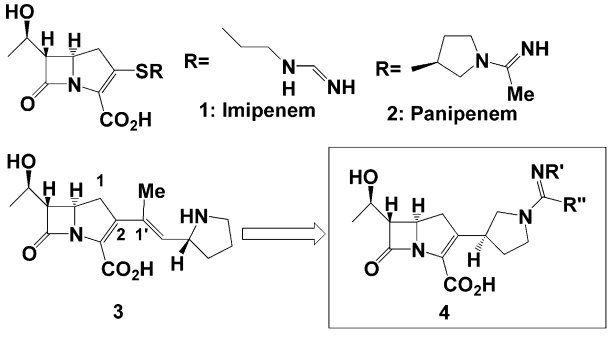

Figure 1.

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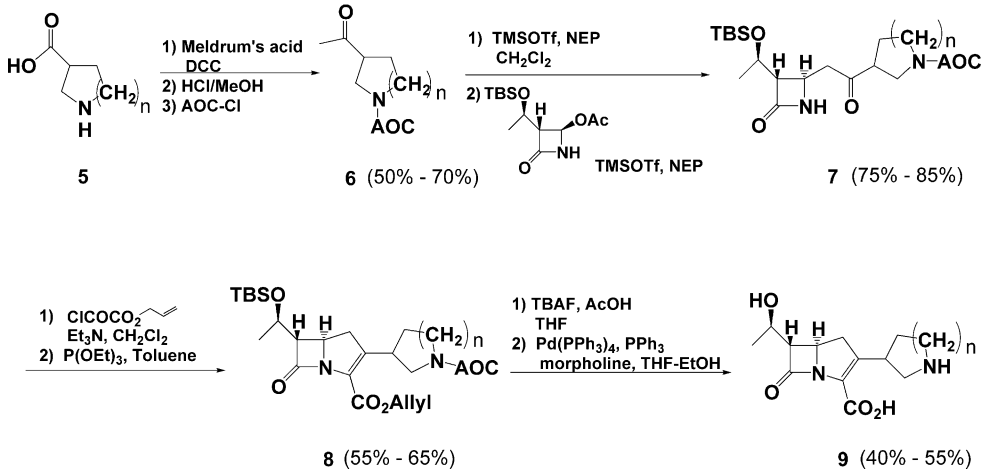
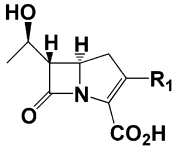
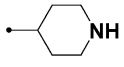
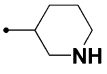
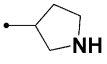
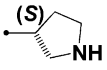
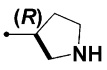
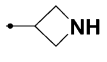


Scheme 1.

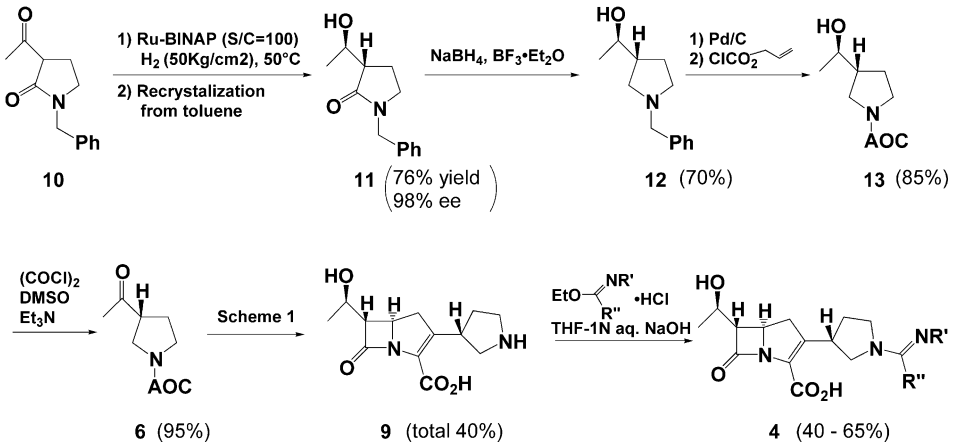
Scheme 2 was shown the synthetic route to the optically pure pyrrolidine substituted carbapenem. Dynamic kinetic resolution in Ru–BINAP catalysed hydrogenation developed by Noyori to give hydroxyethyl pyrrolidone **11**.[9] Purification by recyclization from toluene provided the optically pure adduct **11** in 76% yield and 98% ee. Reduction of 11 with $NaBH_4$-BF_3·Et_2O quantitatively afforded the reductive product **12**, which was converted protection group and subsequent Swern oxidation to give desired ketone **6**. The optically pure ketone **6** was corresponding carbapenem **9** in the same method. Furthermore, **9** was introduced several kind of imidoyl group to the pyrrolidine using corresponding iminoether by standard method.

Table 1. Biological evaluation of novel *N*-containing heterocycle carbapenems



Compd	R_1	*Staphylococcus aureus* 209P JC-1	*Staphylococcus aureus* 3004[a]	*Escherichia coli* NIHJ JC-2	*Proteus vulgaris* IAM 1025	*Ps. auruginosa* 26	DHP-I stability[b] human, swern	Urinary recovery[c] (%)
9a		0.050	>100	1.56	12.5	0.78	NT, 0.18	43
9b		<0.025	50	0.39	25	1.56	NT, 0.044	59
9c		<0.025	100	0.39	12.5	0.78	0.58, 0.13	42
9d		<0.025	50	0.20	6.25	0.39	0.48, 0.088	37
9e		<0.025	100	0.39	6.25	0.78	0.78, 0.16	46
9f		0.050	100	1.56	3.13	1.56	NT, 0.020	45
3		<0.025	50	0.39	1.56	3.13	0.45, 0.043	61
1: Imipenem		<0.025	100	0.78	3.1	0.78	1.0, 1.0	29
2: Panipenem		0.025	50	0.20	1.56	0.39	NT, NT	25

[a]Methicillin-resistant *S. aureus* (MRSA).
[b]DHP-I susceptibility is given relative to imipenem (IMP).
[c]Recovery (%) in mice after sc administration (20 mg/kg).

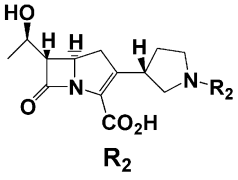


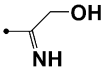
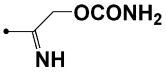
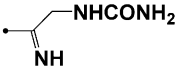
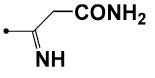
Scheme 2.

Biological Activity

Table 1 was shown the vitro antibacterial activity, the urinary recovery of mice, and stability to human and swine renal DHP-I of a variety of azetidinyl, pyrrolidinyl, and piperidinyl directly substituted carbapenems.[10] In spite of this type carbapenem **9a–f** not having a 1β-methyl substituent, it exhibits high stability to DHP-I and urinary recovery superior to imipenem. Generally, these compounds in this initial series were more active against *Pseudomonas aeruginosa*

Table 2. Biological evaluation of novel *N*-imidoylpyrrolidinyl carbapenems



Compd	R_2	*S. aureus* 209P JC-1	*S. aureus* 3004[a]	*E. coli* NIHJ JC-2	*P. vulgaris* IAM 1025	*Ps. aeruginosa* 26	DHP-I stability[b], human, swern	Urinary recovery[c] (%)
4a		<0.025	25	0.10	1.56	0.20	0.39, 0.15	41
4b		<0.025	6.25	0.20	1.56	0.78	0.34, 0.084	44
4c		<0.025	3.13	0.20	0.78	0.39	0.91, 0.078	48
4d		<0.025	12.5	0.20	1.56	0.39	0.28, 0.084	50
4e		<0.025	25	0.39	3.13	0.78	NT, 0.13	52
4f		<0.025	6.25	0.10	1.56	0.78	0.13, NT	42
4g		<0.025	25	0.20	3.13	0.39	0.20, NT	47
4h		<0.025	6.25	0.39	1.56	0.39	0.14, 0.13	43

[a]Methicillin-resistant *S. aureus* (MRSA).
[b]DHP-I susceptibility is given relative to imipenem (IMP).
[c]Recovery (%) in mice after sc administration (20 mg/kg).

than the our previous reported compound **3**, but were less active against *Proteus vulgaris* than **3** and imipenem (IMP) **1**. Amongst these compounds, pyrrolidinyl carbapenems had the best balance of antibacterial activity and (*S*)-isomer **9d** of the chiral center at C-3 of pyrrolidine was slightly improved activity compared to (*R*)-isomer **9e**.

Introduction of amidine unit was dramatically effect on antibacterial activity in shown Table 2. All of these compounds were increased activity against both MRSA and *P. vulgaris* and **4a**, **4c**, **4d**, **4g**, and **4h** were more active against *Ps. aeruginosa* than original compound **9d**. Especially, best compound **4c** was 30-fold more active than IMP against MRSA and 4-fold more active against *P. vulgaris*. And also these compounds were less susceptible to DHP-I than IMP and a good stable urinary recovery.

Conclusion

In this communication, we have reported directly linked pyrrolidine-carbapenem was synthesized and found to have a good antimicrobial spectrum showing activity against MRSA as well as *Ps. aeruginosa,* and to maintain a good stability toward DHP-I.

References and Notes

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8. The regio-isomer was produced with less than 5%, which was easily removed by column chromatograpy.
9. (a) Kitamura, M.; Tokunaga, M.; Noyori, R. *Tetrahedron: Asymmetry* **1990**, *1*, 1. (b) Yuwasa, Y.; Sotoguchi, T.; Seido, N. EP Patent 855390, 1998.
10. MICS were determined by the agar dilution method using heart infusion agar incubation at 37 °C for 20 h with an inoculum size of of 10^6 cfu/mL. DHP-I stability was determined as the relative rate of hydrolysis compared to the control compound, imipenem.