COMMUNICATIONS TO THE EDITOR

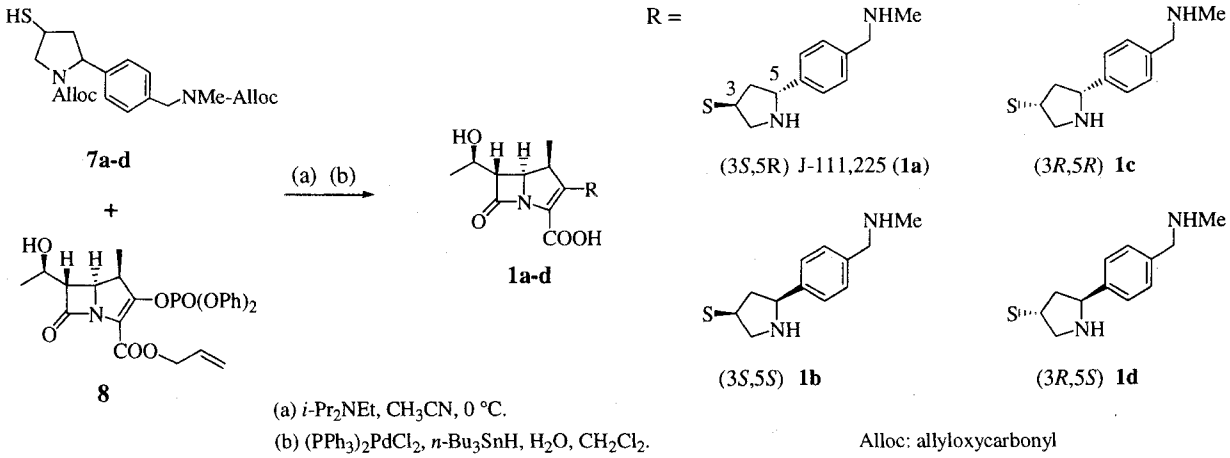
A Novel 1β-Methylcarbapenem, J-111,225: Effects of the C-3 and C-5 Stereochemistry of the Pyrrolidinylthio Side Chain on Antibacterial Activities

Sir:

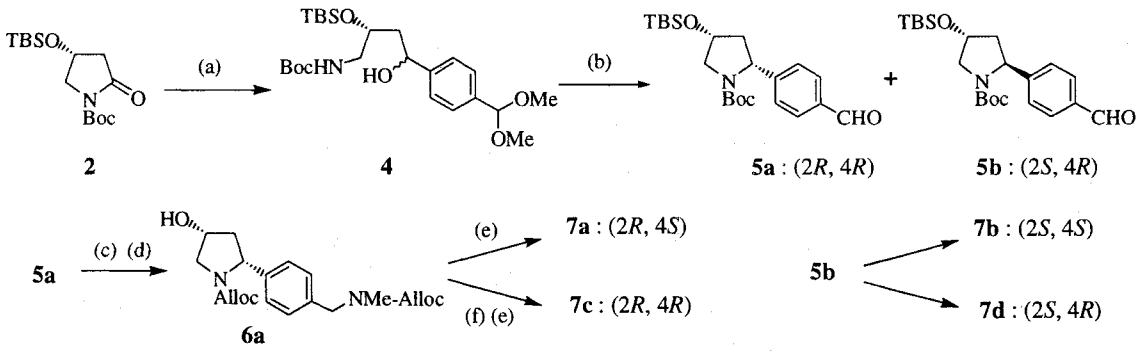
Recently, we demonstrated that J-111,225 (**1a**), J-114,870, and J-114,871, novel 1β-methylcarbapenems possessing *trans*-5-substituted-3-pyrrolidinylthio moieties as side chains at the C-2 position of the carbapenem nucleus, had good safety profiles and ultra-broad-spectrum antibacterial activity covering methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*.[1] These carbapenems showing unique biological activities could be distinguished by their unusual C-5 stereochemistry of the side chain, compared with those of known carbapenems possessing a *cis*-5-substituted-3-pyrrolidinylthio side chain, such as meropenem,[2] S-4661[3] and BO-2727.[4,5] Studies of structure-activity relationships showed that the carbapenems containing *trans*-(3*S*,5*R*)-5-arylpyrrolidine as a side chain provided better antibacterial activity than *cis*-(3*S*,5*S*) isomers. In order to investigate the influence of the C-3 and C-5 stereochemistry of the side chain on biological activity, J-111,225 (**1a**) and its diastereomers **1b**, **1c** and **1d** were synthesized and evaluated for antimicrobial activity as well as epileptogenicity (Figure 1).

Four diastereomers of the side chains **7a~d** were prepared by using commercially available (4*R*)-hydroxy-2-pyrrolidone as a starting material (Scheme 1).[6] Condensation of protected pyrrolidone **2** and Grignard reagent **3** furnished a diastereomeric mixture of carbinol **4**, which was in turn subjected to pyrrolidine formation to afford (2*R*)-aldehyde **5a** and (2*S*)-aldehyde **5b** after cleavage of dimethylacetal protection and crystallographic separation. (2*R*,4*R*)-Pyrrolidine **5a** was converted to (2*R*,4*R*)-4-hydroxypyrrolidine **6a** by the following process: 1) formation of a protected aminomethyl group (step c); 2) simultaneous removal of TBS and Boc protecting groups by means of HCl/MeOH treatment; and 3) protection of pyrrolidine nitrogen with an Alloc-group (step d). After mesylation of the secondary hydroxyl group of the pyrrolidine **6a**, the resulting mesylate was substituted with potassium thioacetate and subsequent alkaline hydrolysis (step e) yielded *trans*-(2*R*,4*S*)-thiol **7a**. Inversion at C-4 in the pyrrolidine **6a** by the Mitsunobu reaction prior to introduction of thiol function produced *cis*-(2*R*,4*R*)-thiol **7c**. In a similar manner, (2*S*,4*R*)-pyrrolidine **5b** was converted to *cis*-(2*S*,4*S*)-thiol **7b** and also to *trans*-(2*S*,4*R*)-thiol **7d** *via* C-4 inversion. The resulting thiols **7a~d** were individually coupled with carbapenem enolphosphate **8** and following deprotection of the adduct by the method of GUIBE *et al.*[7], yielded carbapenems **1a~d** as shown in

Fig. 1. Synthesis of J-111,225 (**1a**) and isomers **1b~d**.



Scheme 1. Syntheses of four diastereomers of side chains, **7a**, **7b**, **7c** and **7d**.



Reagents: (a) 4-$(MeO)_2CHC_6H_4MgBr$ **3**, THF, 0 °C, then $NaBH_4$, MeOH, −10 °C, (b) i: MsCl, TEA, CH_2Cl_2, −60 °C; ii: *p*-TsOH, THF-H_2O, r.t., (c) i: $NaBH_4$, MeOH, 0 °C, ii: MsCl, Et_3N, CH_2Cl_2, −30 °C; iii: $MeNH_2$-MeOH,−30 °C; iv: Alloc-Cl, Et_3N, 0 °C, (d) i: HCl-MeOH, 50 °C; ii: Alloc-Cl, Et_3N, 0 °C, (e) i: MsCl, Et_3N, CH_2Cl_2, 0 °C; ii: AcSK, DMF, 70 °C, iii: NaOH, MeOH, 0 °C; (f) i: DIAD, PPh_3, AcOH, THF, 0 °C, ii: NaOH, MeOH, 0 °C.

Table 1. Effects of stereochemistry on *in vitro* antibacterial activity (MIC; μg/ml) and epileptogenicity.

Compound / Organism	**1a** (3*S*,5*R*)	**1b** (3*S*,5*S*)	**1c** (3*R*,5*R*)	**1d** (3*R*,5*S*)	Vancomycin	Imipenem
S. aureus 209P NIHJ JC1	≤0.006	≤0.006	≤0.006	≤0.006	0.39	≤0.006
S. aureus pMS520/Smith[a]	0.78	3.13	12.5	6.25	0.78	50
S. epidermidis MB5181[a]	1.56	6.25	6.25	6.25	1.56	50
E. coli NIHJ JC2	0.025	0.05	0.025	0.012	>100	0.10
P. aeruginosa AK109	0.39	1.56	6.25	12.5	>100	1.56
P. aeruginosa AKR17[b]	1.56	12.5	>25	>25	>100	3.13
Epileptogenicity (200μg/rat head, n=5)	0/5	5/5	NT[c]	NT	——	ED_{50}: 17μg /rat head

[a] Methicillin-resistant. [b] Ceftazidime-resistant. [c] Not tested.

Figure 1.

The four stereoisomers, **1a**~**d**, obtained above were studied with respect to their *in vitro* antibacterial activities against *S. aureus*, including a MRSA strain (pMS520/Smith), a methicillin-resistant *Staphylococcus epidermidis* (MRSE) strain (MB5181), *E. coli* and *P. aeruginosa*, as well as their epileptogenicity, with imipenem and vancomycin used as reference drugs (Table 1).

As for the C-3 configuration, the (3*S*)-isomers, **1a** and **1b**, were significantly more active than the corresponding (3*R*)-isomers, **1c** and **1d**, not only against *P. aeruginosa* including a ceftazidime-resistant strain, but also against the MRSA strain (pMS520/Smith). Of the two (3*S*)-isomers, the *trans*-(5*R*)-isomer **1a** was 4-fold more active than the corresponding *cis*-(5*S*)-isomer **1b** against MRSA and *P. aeruginosa*. In addition, undesired epileptogenicity was not observed after intracerebroventricular injection of the *trans*-(3*S*,5*R*)-isomer **1a** at a dose of 200 μg/rat, whereas the *cis*-(3*S*,5*S*)-isomer **1b** produced severe adverse effects at the same dose.

Several previous reports mentioned the relationship between stereochemistry of the 5-substituted-3-pyrrolidinylthio side chain and antibacterial activities of carbapenems. SUNAGAWA *et al.* reported significant differences in anti-pseudomonal activity among the four

stereoisomers of 5-carbamoyl-pyrrolidin-3-ylthio carbapenem and concluded that the *cis*-isomers [(3*S*,5*S*) and (3*R*,5*R*)] were more active than the *trans*-isomers [(3*R*,5*S*) and (3*S*,5*R*)].[2] Moreover, ISO *et al.* investigated the anti-pseudomonal activity of 5-sulfamoylaminomethyl-pyrrolidin-3-ylthio-1β-methylcarbapenem and found that the (3*S*)-isomers [(3*S*,5*S*) and (3*S*,5*R*)] were more active than the (3*R*)-isomers [(3*R*,5*S*) and (3*R*,5*R*)], with the *cis*-(3*S*,5*S*)-isomer, namely, S-4661, providing the best activity.[8] In both cases, the *trans*-(3*S*,5*R*) isomer did not show better antibacterial activity than the *cis*-(3*S*,5*S*) isomer, unlike J-111,225 (**1a**), which possesses a *trans*-(3*S*,5*R*) configuration in its side chain.

In conclusion, J-111,225 (**1a**), which contains *trans*-(3*S*,5*R*)-5-aryl-3-pyrrolidine as a side chain exhibited the best activity against both MRSA and *P. aeruginosa*, compared with three other stereoisomers. In addition, the *trans*-(3*S*,5*R*)-isomer **1a** did not cause any appreciable epileptogenic effect after intracerebroventricular injection (200 μg/rat), whereas, the *cis*-(3*S*,5*S*)-isomer **1b** produced severe epileptogenicity.

Acknowledgments

We are grateful to Ms. DONNA LEBLANC and Ms. A. DOBBINS, Merck & Co., for their critical reading of this manuscript.

HIDEAKI IMAMURA*
AYA SHIMIZU
HIROKI SATO
YUICHI SUGIMOTO
SHUNJI SAKURABA
RIE NAGANO
KOJI YAMADA
TERUTAKA HASHIZUME
HAJIME MORISHIMA

Banyu Tsukuba Research Institute,
Okubo-3, Tsukuba, Ibaraki 300-2611, Japan

(Received December 1, 1999)

References

1) SHIMIZU, A.; H. IMAMURA, H. SATO, S. SAKURABA, Y. SUGIMOTO, H. KIYONAGA, M. OGAWA, M. NAKANO, N. OHTAKE, R. USHIJIMA, S. NAKAGAWA, C. SUZUKI, T. HASHIZUME & H. MORISHIMA: J-111,225, a novel *trans*-3,5-disubstituted pyrrolidinylthio-1β-methylcarbapenem; Synthesis and physicochemical properties. Program and Abstracts of 38th Intersci. Conf. on Antimicrob. Agents Chemother., No. F061, San Diego, 1998
2) SUNAGAWA, M.; H. MATSUMURA, T. INOUE, M. FUKASAWA & M. KATO: A novel carbapenem antibiotic, SM-7338: Structure-activity relationships. J. Antibiotics 43: 519~532, 1990
3) ISO, Y.; T. IRIE, Y. NISHINO, K. MOTOKAWA & Y. NISHITANI: A novel 1β-methylcarbapenem antibiotic, S-4661: Synthesis and structure-activity relationships of 2-(5-substituted pyrrolidin-3-ylthio)-1β-methylcarbapenems. J. Antibiotics 49: 199~209, 1996
4) OHTAKE, N.; O. OKAMOTO, R. MITOMO, Y. KATO, K. YAMAMOTO, Y. HAGA, H. FUKATSU & S. NAKAGAWA: 1β-Methyl-2-(5-substituted pyrrolidin-3-ylthio)carbapenems; 3. Synthesis and antibacterial activity of BO-2727 and its related compounds. J. Antibiotics 50: 598~613, 1997
5) NAKAGAWA, S.; T. HASHIZUME, K. MATSUDA, M. SANADA, O. OKAMOTO, H. FUKATSU & N. TANAKA: *In vitro* activity of a new carbapenem antibiotic, BO-2727, with potent antipseudomonal activity. Antimicrob. Agents Chemother. 37: 2756~2759, 1993
6) The details of the synthesis and structure determination of aldehydes **5a** and **5b** will be reported in a future paper.
7) DANGLES, O.; F. GUIBE, G. BALAVOINE, S. LAVIELLE & A. MARQUET: Selective cleavage of the allyl and allyloxycarbonyl groups through palladium-catalyzed hydrostannolysis with tributyltin hydride. Application to the selective protection-deprotection of amino acid derivatives and in peptide synthesis. J. Org. Chem. 52: 4984~4993, 1987
8) ISO, Y.; T. IRIE, T. IWAKI, M. KII, Y. SENDO, K. MOTOKAWA & Y. NISHITANI: Synthesis and modification of a novel 1β-methyl carbapenem antibiotic, S-4661. J. Antibiotics 49: 478~484, 1996