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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 2-FUNCTIONALIZED-VINYL 1β-METHYLCARBAPENEMS AND RELATED COMPOUNDS

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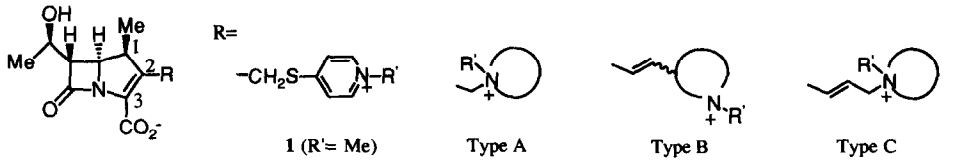
Abstract: The synthesis and antibacterial activity of the title compounds are described. Both 2-hydroxymethyl and 2-hydroxypropenyl carbapenems (**3** and **14**) served as the common key intermediates for the preparation of these compounds. The characteristic antibacterial activity was observed in the three types (A, B, and C) of derivatives prepared.

Although many modification studies on carbapenem antibiotics have been reported, chemical manipulation has been limited to the alkylthio or naturally occurring cysteamino group at the C-2 position. Our interest in this area was to maximize the activity displayed from hybridization of the carbapenem nucleus and cephalosporin C-3 side chains.[1,2]

Recently we reported that 1β-methylcarbapenems having quaternary heteroaromatic-thiomethyl groups at the C-2 position exemplified by compound **1** exhibited broad and well-balanced antibacterial activity, except against *Pseudomonas aeruginosa*.[3] This finding led us to inquire whether the interposition of different spacers between the carbapenem nucleus and the quaternary nitrogen would influence their antibacterial properties. Here we report the synthesis and antibacterial activity of a new class of carbapenems represented by types A, B, and C.

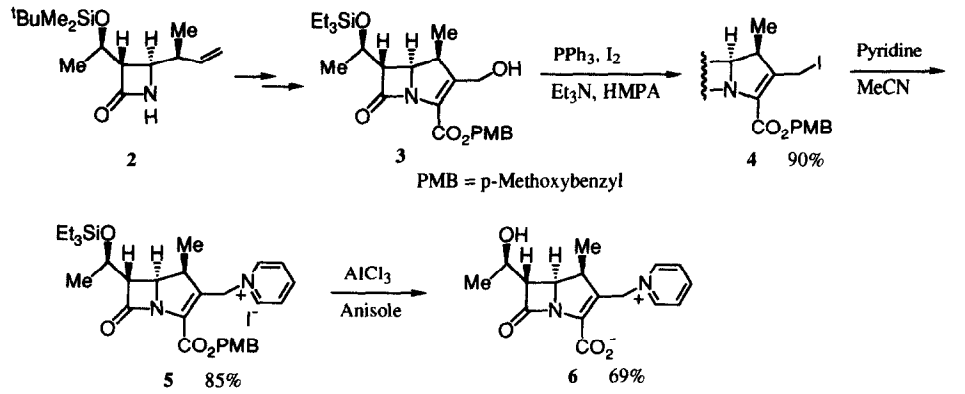


1 (R'= Me) Type A Type B Type C

Chemistry

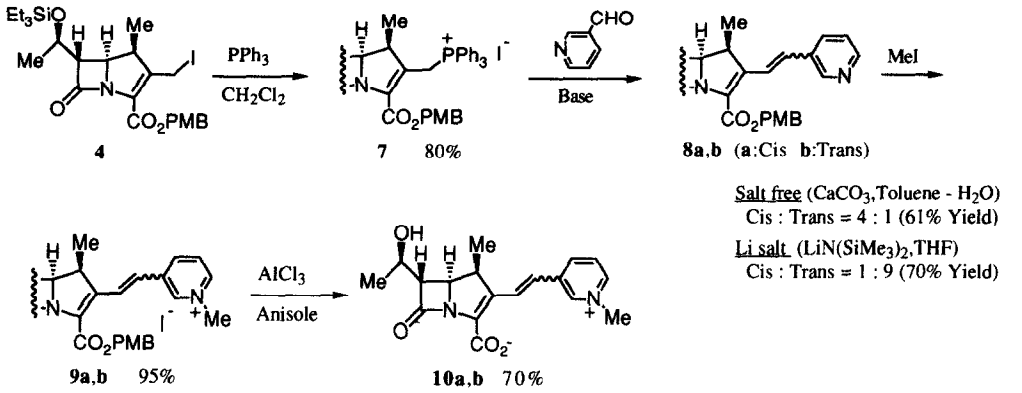
From the viewpoint of synthetic efficiency, introduction of variously functionalized C-2' groups should occur as late as possible in the synthetic sequence. Our synthesis started with the 2-hydroxymethyl carbapenem **3** synthesized by our original procedure using the pivotal building block **2**.[4]

We first investigated the direct introduction of the pyridinium moiety (partial structure of the compound **1**) at the C-2' position which may participate as an electron sink and as a potential leaving group (Type A). Quaternization of the pyridine ring nitrogen by a Menschutkin-type reaction necessitates transformation of **3** into advanced intermediate **4**. Iodination of **3** by the direct method (PPh_3 / I_2 / Et_3N / HMPA)[5] led to the desired compound **4** as the sole product in good yield.[6] Nucleophilic displacement of the iodine by a variety of substituted pyridines in acetonitrile at ambient temperature successfully gave the expected quaternized carbapenems. Removal of the triethylsilyl group, together with the p-methoxybenzyl (PMB) moiety, was readily accomplished by the conventional $AlCl_3$-anisole method.[7]



Scheme 1

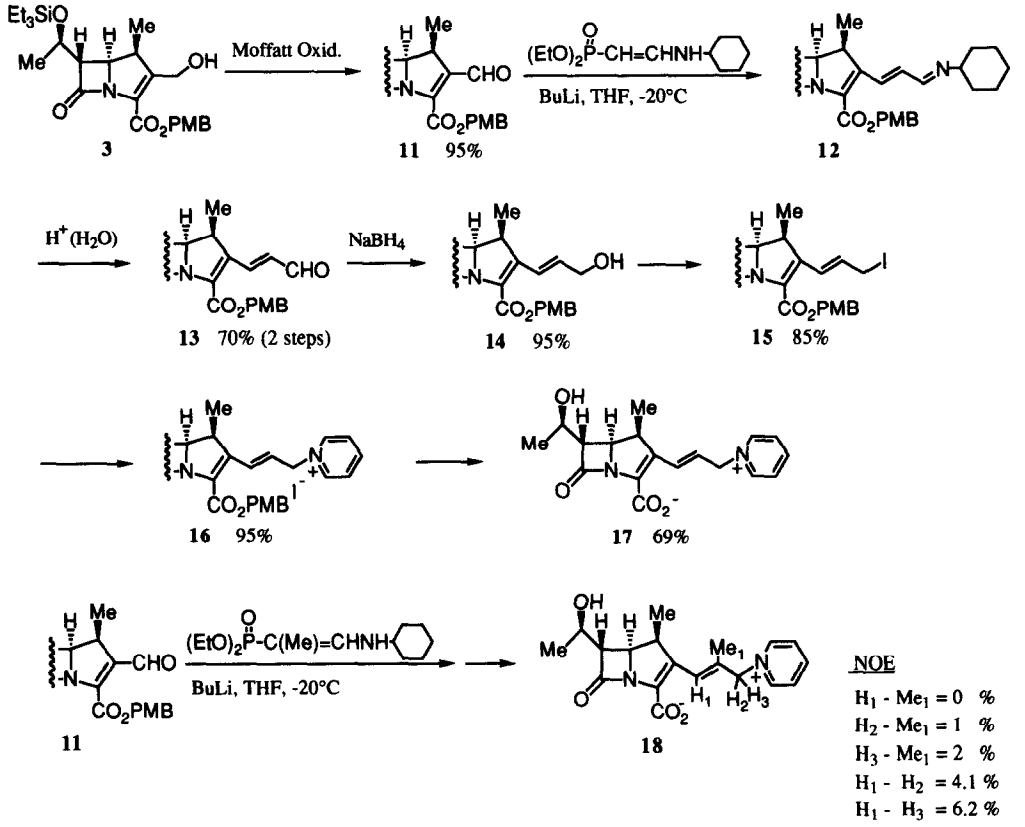
Utilization of the above intermediate **4** provided facile access toward 2-functionalized-vinyl carbapenems not easily prepared via total synthesis. Thus, treatment of **4** with triphenylphosphine in CH_2Cl_2 resulted in the formation of a stable phosphonium derivative **7**. The product stereospecificity in the Wittig reaction of **7** with nicotinaldehyde could be controlled by altering the reaction conditions shown in Scheme 2. Cis and trans isomers (**8a** and **8b**) were separated by silica gel chromatography. The olefin geometries were unambiguously assigned by ^1H NMR on the basis of the coupling constants for the vinylic protons; $J_{CH=CH}$ for the cis product was 12 Hz but 17 Hz for the trans isomer.



Scheme 2

As for the synthesis of Type C derivatives, the allyl alcohol **14** seemed to be a desirable common intermediate. Since Nagata *et al.* in our laboratories had previously reported a facile method for converting aldehydes directly into the corresponding α,β-unsaturated aldehydes,[8] we applied this methodology to carbapenem chemistry. We transformed the alcohol **3** into aldehyde **11** by Moffatt oxidation, then applied the Nagata reaction to aldehyde **11**

with the carbanion generated from diethyl cyclohexyliminovinyl phosphonate, which went smoothly at -20°C in THF. This was followed by acid hydrolysis to stereoselectively form the trans α,β-unsaturated aldehyde **13** in 70% overall yield. Reduction of **13** with $NaBH_4$ gave allyl alcohol **14** in almost quantitative yield. Consequently, a variety of vinylogous carbapenems (Type C) including the Me-substituted derivative **18** were prepared by essentially the same procedure used for the Type A derivatives. The stereochemistry of compound **18** was assigned by the NOE experiments shown in Scheme 3. The characteristic carbamoyl and thiadiazolylthio derivatives were also readily prepared.[9]

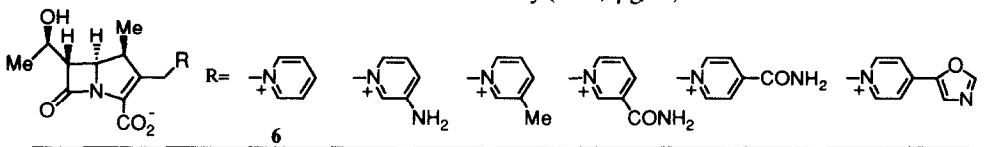


Scheme 3

Antibacterial Activity

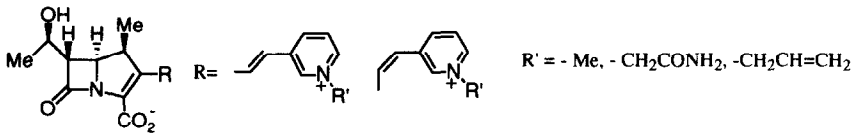
Type A derivatives: Compared with the lead compound **1**, the type A derivatives turned out to possess significantly better activity, particularly against *P. aeruginosa*. Among our synthesized derivatives tested, the following six pyridio derivatives showed MIC values of 1.6 μg/ml against *P. aeruginosa*. Of these, compound **6** exhibited the best overall activity (Table 1), indicating that additional substituents at various positions on the pyridine ring had a negative effect on the activity.

Table 1. Antibacterial Activity (MIC, μg/ml)[10]



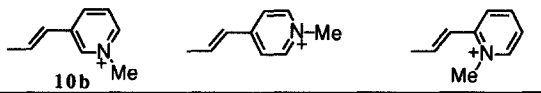
	6					
S. aureus FDA JC-1	<0.006	0.006	0.01	0.02	0.02	0.01
S. faecalis SR1004	6.3	6.3	12.5	25	25	6.3
E. coli NIHJ JC-2	0.1	0.2	0.2	0.4	0.4	0.2
P. aeruginosa SR24	1.6	1.6	1.6	1.6	1.6	1.6

Type B derivatives: The correlation between the olefin geometry and activity became clear. In the following three pairs of compounds, the trans isomers were found to be 2- to 3-fold more active than the corresponding cis isomers against both Gram-positive and Gram-negative bacteria.



Among the trans isomers of the N-Me pyridinio series, the 3-pyridinio (meta pyridinium ring) derivative proved to be the most active, while the 4-pyridinio (para) and 2-pyridinio (ortho) derivatives led to significantly reduced activity in that order (Table 2).

Table 2. Antibacterial Activity (MIC, μg/ml)[10]



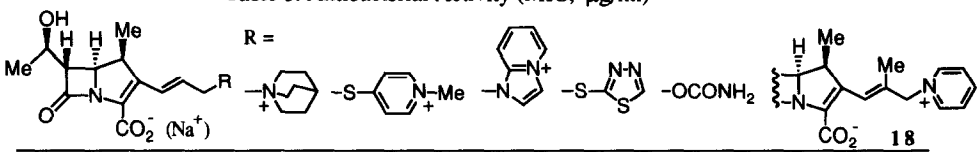
	10b		
S. aureus FDA JC-1	0.01	0.05	0.1
S. faecalis SR1004	0.2	1.6	6.3
E. coli NIHJ JC-2	0.1	0.4	1.6
P. aeruginosa SR24	25	25	50

Unlike other types, the anti-pseudomonal activity of the B type derivatives was disappointingly diminished. A striking difference was however observed in their biological stabilities. The urinary recovery of the trans isomer **10b** was 97% (monkey, 24 h) while that of the cis isomer **10a** was 89%.

Type C derivatives: As exemplified by comparison of the activity between **6** and **17** (Table 4), introduction of the double bond into the type A derivatives tended to increase the activity on the whole. Extension of the pyridine moiety to other heterocyclic rings including saturated systems turned out to diminish activity (Table 3). Confirming our earlier report,[3] we found that the positive charge in the quaternized heterocyclic ring possessed

significantly enhanced overall activity relative to their unquaternized counterparts. Among the type C derivatives tested (Table 3 and 4), compound **17** provided the best balanced activity including against *P. aeruginosa* as shown in Table 4.

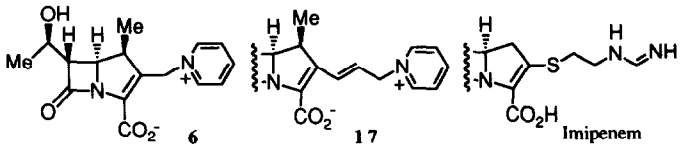
Table 3. Antibacterial Activity (MIC, μg/ml)[10]



18

S. aureus FDA JC-1	0.02	0.01	0.02	0.02	0.02	0.02
S. faecalis SR1004	0.8	0.4	0.8	1.6	1.6	0.8
E. coli NIHJ JC-2	0.2	0.2	0.1	3.1	0.2	0.1
P. aeruginosa SR24	50	12.5	25	100	50	6.3

Table 4. Antibacterial Activity (MIC, μg/ml)[10]



S. aureus FDA JC-1	<0.006	0.006	0.006
S. aureus SR3131(LR)[a)]	0.1	0.05	0.05
S. aureus SR3626(HR)[b)]	50	50	50
S. faecalis SR1004	6.3	0.4	1.6
E. coli NIHJ JC-2	0.1	0.05	0.1
P. vulgaris CN-329	0.4	0.2	0.4
E. cloacae A13047	0.2	0.2	0.4
S. marcescens A13880	1.6	0.8	0.8
P. aeruginosa SR24	1.6	1.6	1.6

a) Low-resistance groups of methicillin-resistant *S. aureus*.
b)High-resistance groups of methicillin-resistant *S. aureus*.[11]

In summary, we have synthesized a new series of quaternized carbapenems by a method involving C-C double bond forming steps at the C-2' position, and have shown that their antibacterial activity can be greatly influenced by the position of the positive charge in the side chain. While type B derivatives had considerably weak activity against *P. aeruginosa*, both type A and C derivatives revealed quite high and well-balanced activity comparable to

imipenem. In addition, it should be noted that quaternized type C derivatives exhibited a beneficial activity against *S. faecalis* better than that of imipenem.

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References and Notes

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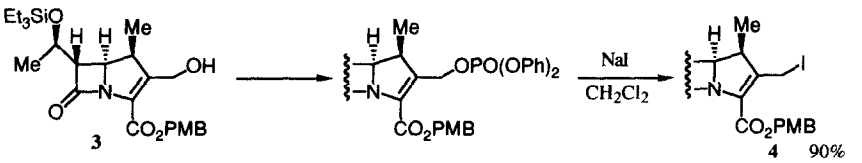
6) Alternatively, the 2-iodomethyl derivative **4** could be prepared from the compound **3** by the two step process (one pot procedure) via the phosphate intermediate in good yield as shown below.



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8) Nagata, W. ; Hayase, Y. *J. Chem. Soc. (c).* **1969**, 460.

9) The synthesis and antibacterial activity of 2-carbamoyloxymethyl and 2-thiadiazolylthiomethyl 1β-methylcarbapenems are reported in reference 2 (Imuta *et al. Chem. Pharm. Bull.* **1991**, 39, 663).

10) MICs were determined by the agar dilution method using sensitivity test agar (Eiken, Japan).

11) For classification of L-MRSA and H-MRSA, see Murakami, K. ; Nomura, K. ; Doi, M. ; Yoshida, T. *Antimicrob. Agents Chemother.* **1987**, 31, 1307.