



## Synthesis and Biological Evaluation of Novel 2-Vinyl Carbapenems. Remarkable DHP-1 Stability of 1'-Substituted Analogs

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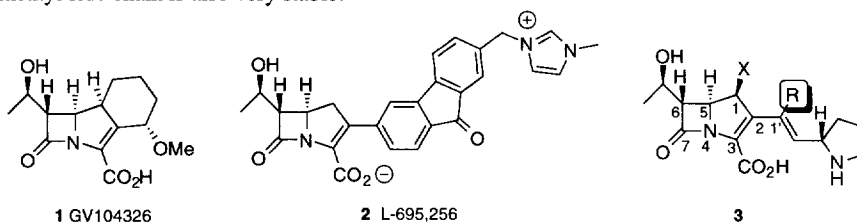
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**Abstract:** The synthesis, antibacterial activity and DHP-susceptibility of a series of novel 2-vinyl carbapenems is described. Carbapenems having a 1'-substituted vinyl moiety at the 2 position were found to be very stable toward DHP-1, displaying comparable stability to compounds with a 1 $\beta$ -methyl functionality.

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### Introduction

Since the discovery of thienamycin in 1976,<sup>1</sup> extensive efforts have been devoted to the development of new synthetic carbapenem antibiotics. These efforts have produced compounds that can be divided into two main categories; 1) natural-type carbapenems, possessing an alkylthio side chain at the 2 position and, 2) unnatural-type carbapenems, that have alkyl, alkenyl, or aryl side chains directly attached to the 2 position. Carbapenems are known to be unstable toward the renal dehydropeptidase DHP-1, leading to low urinary recovery, and occasionally, renal toxicity. This has been overcome in type-1 derivatives by chemical modification at the 1-position (introduction of 1 $\beta$ -methyl, as in meropenem,<sup>2</sup> and biapenem<sup>3</sup>) or by co-administration with an additive (cilastatin, a DHP-1 inhibitor with imipenem,<sup>4</sup> or betamipron, an organic anion transport inhibitor with panipenem<sup>5</sup>). In the case of type-2 derivatives, Shionogi researchers have described a "1 $\beta$ -methyl" strategy,<sup>6</sup> whilst the Glaxo compound GV104326 (**1**) has a rigid tricyclic ring system which makes this compound particularly stable toward DHP-1.<sup>7</sup> L-695,256 (**2**), with an aryl system and a quaternary ammoniomethyl side chain is also very stable.<sup>8</sup>



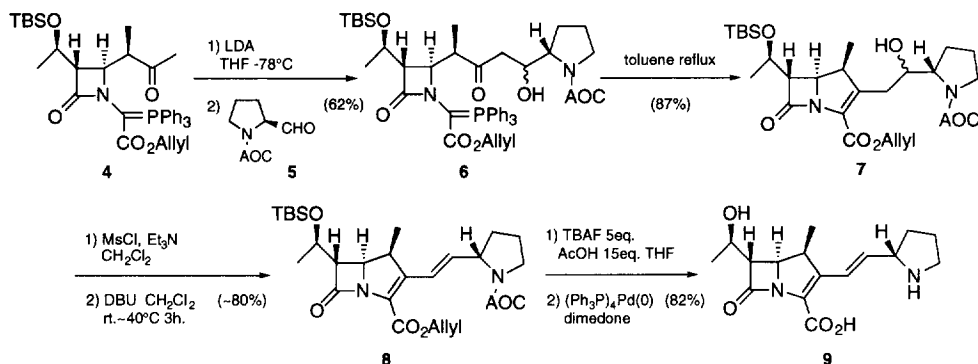
As a part of our continuing investigations in this field,<sup>9</sup> we were interested in introducing vinyl substituents at C2, since; 1) a vinyl moiety is known to be a bioisostere of sulfur, 2) a sp<sup>2</sup> carbon can bear substituents whilst sulfur can not, and thus may allow fine tuning of antibacterial activity and stability against DHP-1, and 3) carbon substituted analogs have been shown to be potent against Gram-positive bacteria, such as MRSA, which are of clinical importance. In this communication, we wish to report the synthesis and preliminary biological evaluation of novel 2-vinyl carbapenems (**3**) and in particular the discovery that 1'-substituted vinyl analogs possess comparable levels of stability to DHP-1 to the 1 $\beta$ -methyl carbapenems.

## Chemistry

### a) Synthesis of 1 $\beta$ -Methyl Derivative (9)

Scheme 1 summarizes the synthetic approach to the 1 $\beta$ -methyl derivative (9). Coupling of the lithium enolate derived from **4**<sup>10</sup> and LDA in THF, with allyloxycarbonyl-protected L-proline **5** gave a mixture of epimers **6**, which was then submitted to intramolecular Wittig-type cyclization without separation of the two isomers. Ring closure was effected by heating **6** in toluene at reflux to give a 2:1 mixture of isomers **7**, which were easily separated by silica gel column chromatography. Two step dehydration gave the same vinyl derivative **8** from either isomer of **7**. Desilylation, followed by a palladium-catalyzed deprotection of both the AOC and allyl ester<sup>9</sup> gave **9** after purification by HP-20 column chromatography and lyophilization.

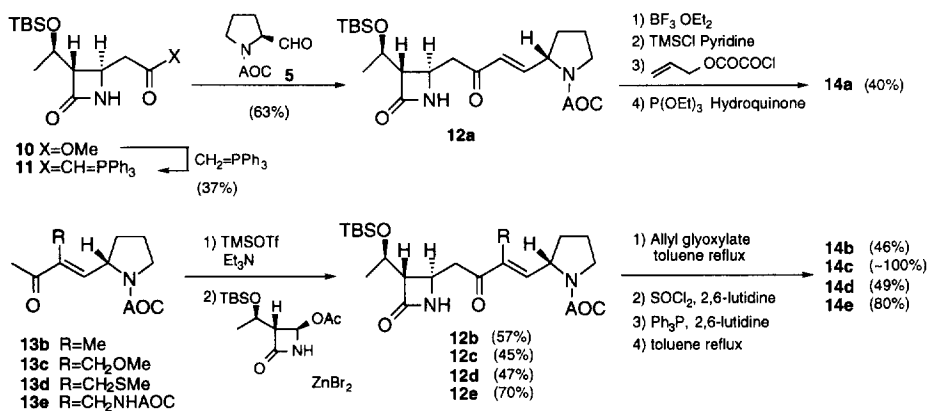
Scheme 1



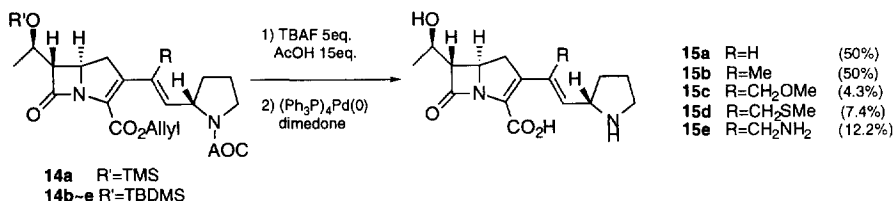
### b) Synthesis of 1-Non-Substituted Derivatives (15a~e)

Scheme 2 summarizes the synthesis of 1-non-substituted derivatives. Reaction of triphenylphosphorane derivative **11**, derived from **10**,<sup>11</sup> with N-protected proline **5** afforded **12a** in 63% yield. After exchange of the silyl protecting group, cyclization afforded **14a** via the oxalimide.<sup>12</sup> The trimethylsilyl enol ether of enones **13b~e** were formed with trimethylsilyl trifluoromethanesulfonate; zinc bromide-mediated aldol condensation with the acetoxyazetidinone derivative afforded **12b~e** in moderate to good yield. Monobactams **12b~e** were then transformed to the corresponding phosphorane derivatives using Woodward's three step procedure,<sup>13</sup> and this was followed by Wittig-type cyclization to **14b~e**. Deprotection as described for **8** gave 1-non-substituted derivatives **15a~e**.<sup>14</sup>

Scheme 2



Scheme 2 (cont.)



### Biological Activity

As shown in Table 1, **15a**, having no substituent at both the 1 and 1' positions, is susceptible to swine renal DHP-1, and thus the urinary recovery is not good. However, all compounds having a substituent at the 1' position of the side chain, ie **15b-e** displayed essentially the same DHP-1 stability as **9**, which has a 1 $\beta$ -methyl substituent. Amongst these compounds, the 1'-methyl substituted vinyl compound **15b** had the best balance of antibacterial activity against Gram-positive and Gram-negative strains, but its anti-pseudomonas activity was a little weaker than that of imipenem (IMP).

Table 1. Biological evaluation of Novel 2-Vinyl Carbapenems<sup>15</sup>

	MIC ( $\mu$ g/ml)						
	<b>15a</b>	<b>9</b>	<b>15b</b>	<b>15c</b>	<b>15d</b>	<b>15e</b>	IMP
<i>S.aureus</i> 209P JC-1	0.10	$\leq 0.025$	$\leq 0.025$	0.20	0.10	0.78	$\leq 0.025$
<i>S.aureus</i> 3004 <sup>*1</sup>	>100	100	50	>100	100	>100	100
<i>E.coli</i> NIHJ JC-2	1.56	0.78	0.39	0.78	0.78	100	0.78
<i>P.vulgaris</i> IAM 1025	1.56	6.25	1.56	50	3.13	>100	3.13
<i>Ps.aeruginosa</i> 26	3.13	3.13	3.13	25	25	>100	0.78
DHP-I Susceptibility <sup>*2</sup>	0.22	0.043	0.036	<0.008	<0.006	0.004	1.0
Urinary Recovery <sup>*3</sup>	20.2	60.7	67.8	64.4	54.3	52.1	28.9

<sup>\*1</sup> Methicillin-Resistant Staphylococcus aureus(MRSA) <sup>\*2</sup> DHP-I susceptibility is given relative to imipenem

<sup>\*3</sup> Recovery (%) in mice after s.c administration (20mg/kg)

Since **15b** was slightly more stable to swine DHP-1 than the 1 $\beta$ -methyl compound **9**, we evaluated the species variability, since it is well known that 1 $\beta$ -methyl compounds (e.g. meropenem<sup>2b</sup>) display remarkable animal specificity. Table 2 summarizes the susceptibility of **15b** against DHP-1 from various species. **15b** was found to be very stable compared with 1 $\beta$ -methyl compounds such as meropenem.

Table 2. DHP-1 susceptibility of **15b**

	mouse	rat	rabbit	dog	monkey	human
DHP-I Susceptibility <sup>*4</sup>	0.45	0.11	0.015	0.249	0.032	0.45

<sup>\*4</sup> DHP-I susceptibility is given relative to meropenem

## Summary

In this communication, we have reported the discovery of 1'-substituted vinyl derivatives that are remarkably stable toward renal DHP-I. These results suggest a new strategy for improving DHP-I stability that is complementary to the "1 $\beta$ -methyl" strategy hitherto employed. Future publications will report the *in vivo* protective activity of **15b**, as well as detailed structure activity relationships.

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14. Selected spectroscopic data for **15b**:  $^1\text{H}$  NMR (90MHz,  $\text{D}_2\text{O}$ ) 1.25 (d, 3H,  $J$  = 7Hz), 1.88 (d, 3H,  $J$  = 1Hz), 1.50-2.37 (m, 4H), 2.60-3.53 (m, 5H), 3.95-4.59 (m, 3H), 5.45 (dd, 1H,  $J$  = 1 and 9Hz); IR (nujol) 3250, 1760, 1580  $\text{cm}^{-1}$ .
15. MIC's were determined by the agar dilution method using heart infusion agar after incubation at 37°C for 20 hours with an inoculum size of  $10^6$  cfu/ml. DHP-I stability was determined as the relative rate of hydrolysis compared to the control compound, imipenem or meropenem.