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

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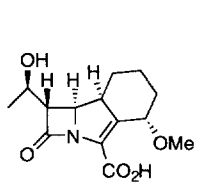
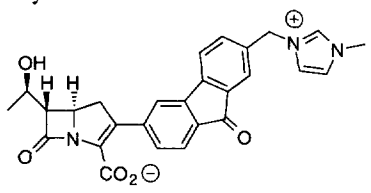
Abstract: The synthesis, antibacterial activity and DHP-susceptibility of a series of novel 2-vinyl carbapenems is described. Carbapenems having a 1'-substituted vinyl moiety at the 2 position were found to be very stable toward DHP-1, displaying comparable stability to compounds with a 1β-methyl functionality.

Introduction

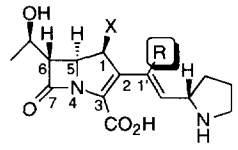
Since the discovery of thienamycin in 1976,[1] extensive efforts have been devoted to the development of new synthetic carbapenem antibiotics. These efforts have produced compounds that can be divided into two main categories; 1) natural-type carbapenems, possessing an alkylthio side chain at the 2 position 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 1β-methyl, as in meropenem,[2] and biapenem[3]) or by co-administration with an additive (cilastatin, a DHP-1 inhibitor with imipenem,[4] or betamipron, an organic anion transport inhibitor with panipenem[5]). In the case of type-2 derivatives, Shionogi researchers have described a "1β-methyl" strategy,[6] whilst the Glaxo compound GV104326 (**1**) has a rigid tricyclic ring system which makes this compound particularly stable toward DHP-1.[7] L-695,256 (**2**), with an aryl system and a quaternary ammoniomethyl side chain is also very stable.[8]



1 GV104326



2 L-695,256



3

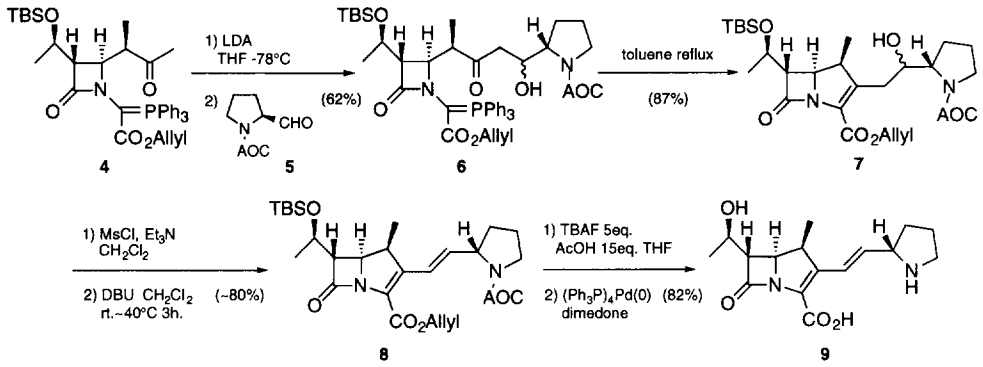
As a part of our continuing investigations in this field,[9] we were interested in introducing vinyl substituents at C2, since; 1) a vinyl moiety is known to be an bioisostere of sulfur, 2) a sp2 carbon can bear substituents whilst sulfur can not, and thus may allow fine tuning of antibacterial activity 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 1β-methyl carbapenems.

Chemistry

a) Synthesis of 1β-Methyl Derivative (9)

Scheme 1 summarizes the synthetic approach to the 1β-methyl derivative (**9**). Coupling of the lithium enolate derived from **4**[10] and LDA in THF, with allyloxycarbonyl-protected L-prolinal **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[9] gave **9** after purification by HP-20 column chromatography and lyophilization.

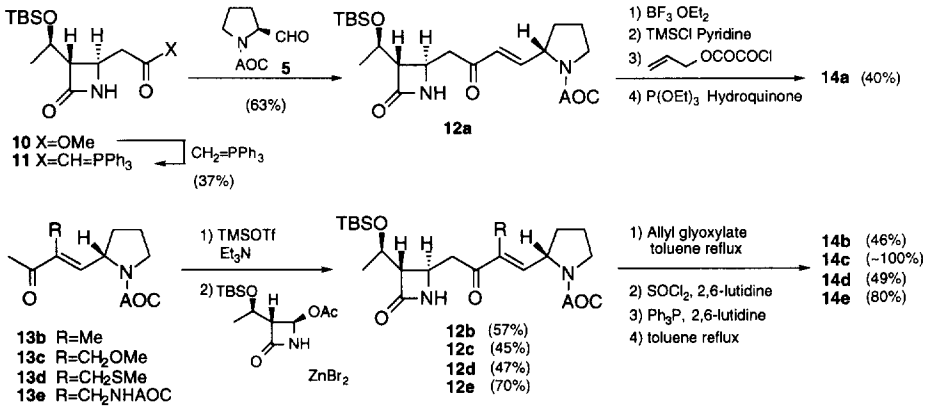
Scheme 1



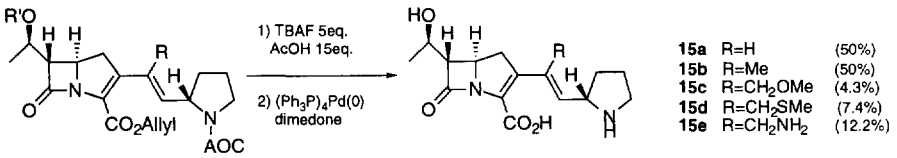
b) Synthesis of 1-Non-Substituted Derivatives (15a~e)

Scheme 2 summarizes the synthesis of 1-non-substituted derivatives. Reaction of triphenylphosphorane derivative **11**, derived from **10**,[11] with N-protected prolinal **5** afforded **12a** in 63% yield. After exchange of the silyl protecting group, cyclization afforded **14a** via the oxalimide.[12] 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,[13] and this was followed by Wittig-type cyclization to **14b~e**. Deprotection as described for **8** gave 1-non-substituted derivatives **15a~e**.[14]

Scheme 2



Scheme 2 (cont.)



14a R'=TMS
14b~e R'=TBDMS

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 1β-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[15]

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

*1 Methicillin-Resistant Staphylococcus aureus(MRSA) *2 DHP-I susceptibility is given relative to imipenem

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

Since **15b** was slightly more stable to swine DHP-1 than the 1β-methyl compound **9**, we evaluated the species variability, since it is well known that 1β-methyl compounds (e.g. meropenem[2b]) 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 1β-methyl compounds such as meropenem.

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

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

*4 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-1. These results suggest a new strategy for improving DHP-1 stability that is complementary to the "1β-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}H NMR (90MHz, D_2O) 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 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.

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