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SYNTHESIS AND STRUCTURE–ACTIVITY RELATIONSHIPS OF SOME NOVEL OXETANE CARBAPENEMS

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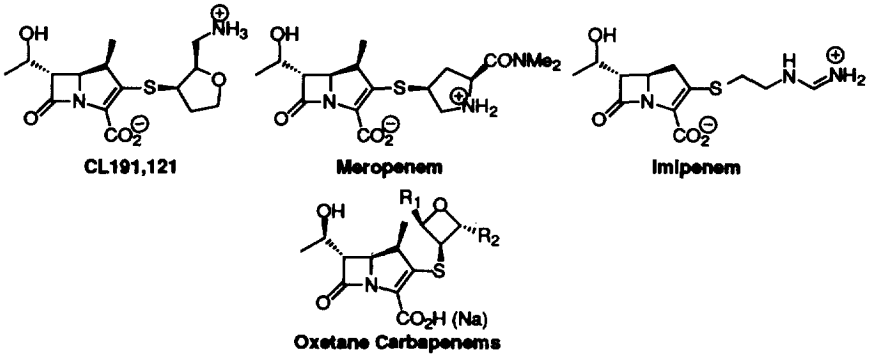
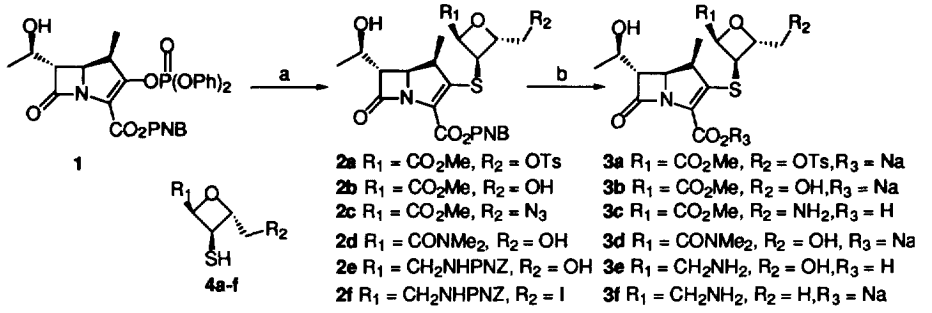
Abstract: Six disubstituted oxetane carbapenems were synthesized and their antibacterial profile compared with the lead amino methyl THF carbapenem as well as imipenem. The oxetane carbapenems had comparable or less activity against the Gram(-) bacteria and had reduced activity against Gram(+) bacteria in comparison with imipenem and the THF carbapenem CL 191,121, but were highly stable to hydrolysis by hog kidney dehydropeptidase (DHP). © 1997 Elsevier Science Ltd.

Introduction

The discovery of thienamycin[1] in 1976 has promoted a great deal of research into the synthesis of carbapenem antibiotics.[2] Until recently, however, there was only one carbapenem, imipenem,[3] in the US market. It is a broad spectrum antibiotic with activities against both Gram(+) and Gram(-) bacteria, including many resistant clinical isolates. Imipenem is also highly stable against serine ß-lactamases. However, it is not stable to renal dehydropeptidase and thus has to be coadministered with the kidney dehydropeptidase inhibitor cilastatin. In addition, it has been shown to have convulsive potential against patients with impaired renal function and underlying CNS disease.[4] A second generation carbapenem, meropenem,[5] has recently been approved for the US market. Meropenem has a similar antibacterial profile as imipenem and is stable to hydrolysis by kidney dehydropeptidase. The chemical and DHP stability of the second generation carbapenems have been attributed to the 1ß-methyl group on the carbapenems.[4,5] However, both imipenem and meropenem have short half lives and are not orally active. Our objective has been to find the next generation of carbapenems with equal or better activity than imipenem and meropenem, but having pharmacokinetic property advantages such as oral activity and longer half life.

Our efforts in the THF carbapenem series have produced some remarkably active carbapenems possessing amino methyl and hydroxy methyl side chains.[6,7] CL 191121 is the most active carbapenem in the THF carbapenem series. As an extension of this THF carbapenem program, synthesis of the oxetane carbapenems was initiated. Here we report our effort in the synthesis and structure–activity relationship studies of some aminomethyl and hydroxymethyl oxetane carbapenems, in line with the most active THF carbapenems.





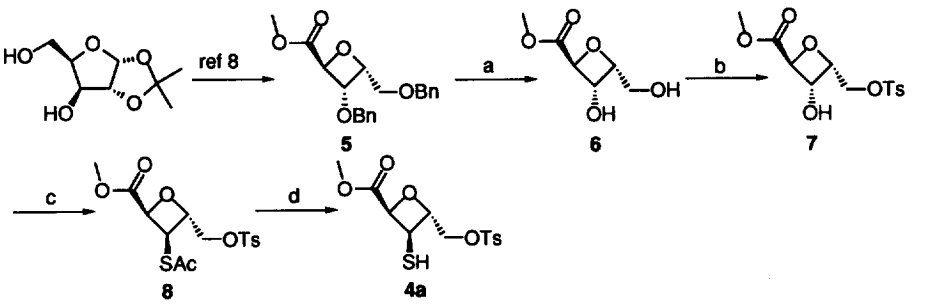
Scheme 1. (a) 4/i-Pr_2NEt/CH_3CN; (b) H_2/10%Pd on C/pH 6.5

Chemistry

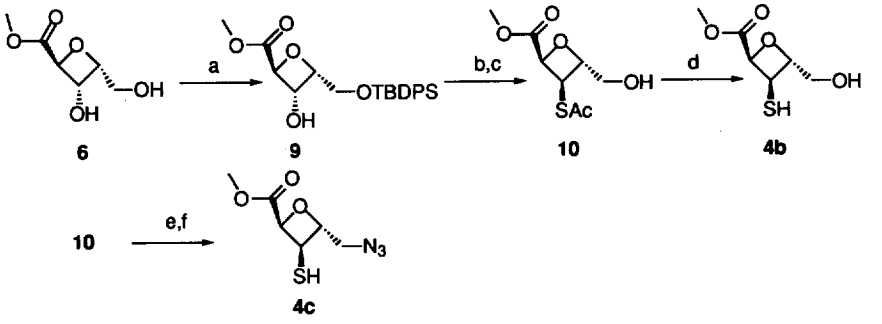
The oxetane carbapenems **3** were prepared according to established conditions as shown in Scheme 1. The oxetane thiols **4** were synthesized and reacted with the phosphate ester **1**[3] in the presence of Hunig's base to give the 1ß-methyl carbapenem esters **2**. For obtaining zwitterionic carbapenems (**3c, 3e**), the hydrogenation was performed with 10% palladium on charcoal in a pH 6.5 phosphate buffer and dioxane mixture. In the case of **3e**, the p-nitrobenzyloxycarbonyl (PNZ) group on the amine is deprotected simultaneously. The sodium salt (**3a, 3b, 3d, 3f**) was obtained by hydrogenation in the presence of one equivalent of sodium bicarbonate in aqueous dioxane. Both the PNZ protecting group and the iodide is reduced during the hydrogenation step for the preparation of **3f**.

The key oxetane intermediate **5** was synthesized according to literature conditions and is shown in Scheme 2.[8] Following debenzylation of the dibenzyl ethers **5**, the primary alcohol was activated as a tosylate to be displaced with a nitrogen nucleophile. Unfortunately, mostly retroaldol products or decomposition products

were isolated when reacted with azides or amines. The secondary alcohol **7** was thus transformed into a thioacetate via the triflate and potassium thioacetate and the resulting thioacetate was deprotected with sodium methoxide to obtain the thiol **4a**.



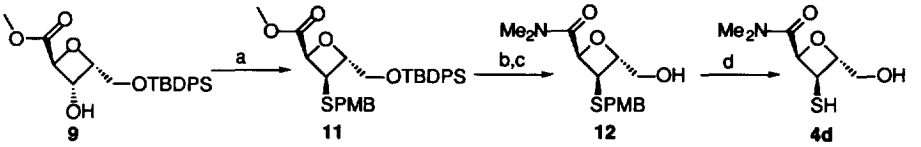
Scheme 2. (a) $H_2/Pd(OH)_2$, >90%; (b) pyridine/TsCl, 68%; (c) i. pyridine/Tf_2O; ii. KSAc, 71%; (d) NaOMe, THF, 52%.



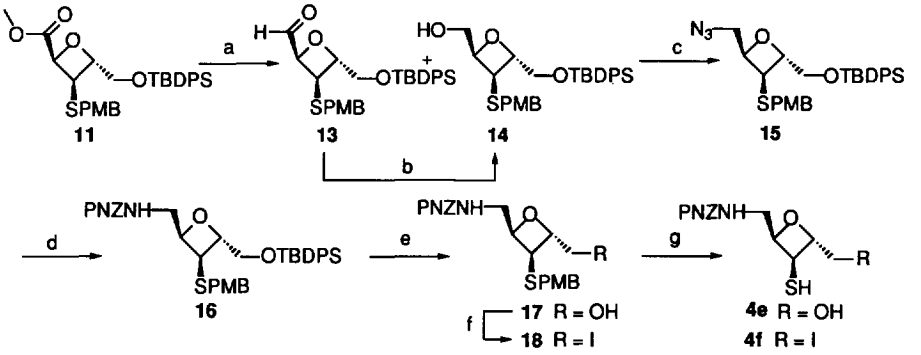
Scheme 3. (a) imidazole/TBDPSCl, 84%; (b) i. pyridine/Tf_2O; ii. KSAc, 54%; (c) TBAF/HOAc, 92%; (d) NaOMe, THF, 92%(crude); (e) i. pyridine/Tf_2O; ii. LiN_3, 47%; f) NaOMe,THF,100% (crude).

It was decided to introduce the thiol group prior to substituting the primary alcohol in **6**. As shown in Scheme 3, the primary alcohol in **6** was protected selectively with *t*-butyldiphenyl silyl chloride (TBDPSCl) to give **9** and the secondary alcohol transformed into a thioacetate by displacement of the triflate. Use of mesylate instead of the triflate failed to give any desired product. The silyl group was removed with tetrabutylammonium fluoride (TBAF) in the presence of acetic acid to give the alcohol **10**, which was subsequently converted to the thiol **4b**. The alcohol **10** was also transformed into the azide in two steps and the thioacetate was deprotected to give the desired thiol **4c**, which, after aqueous work up, was carried to the next step without further purification.

In order to modify the methyl ester, it became necessary to choose a different protecting group for the thiol. Thus, **9** was converted to the *p*-methoxybenzyl thioether **11** in an analogous manner to the thioacetate case. The methyl ester was hydrolyzed to the acid and converted to the dimethyl amide via the anhydride approach (Scheme 4), followed by two sequential deprotections to give the desired thiol **4d**.



Scheme 4. (a) i. pyridine/Tf_2O; ii. PMBSH/K_2CO_3/18-crown-6, 80%; (b) NaOH, 84%; (c) i. i-Pr_2NEt / isobutyl chloroformate; ii. dimethyl amine hydrochloride/i-Pr_2NEt, 65%; TBAF/HOAc, 98%; (d) $Hg(OCOCF_3)_2$, anisole, HOAc/H_2O, rt, 96%.



Scheme 5. (a) DIBAL, THF, -78 to -20 °C;**13**, 15-100%;**14**, 0-45%; b) $NaBH_4$, 82%; (c) i. pyridine/Tf_2O; ii. LiN_3, 81%; (d) i. Ph_3P; ii. PNZCl/NaOH, 78%; (e) TBAF, 82%; (f) i. pyridine/Tf_2O; TBAI, 93%; (g) $Hg(OCOCF_3)_2$, anisole, HOAc/H_2O, rt, 92%.

The methyl ester **11** could also be reduced with DIBAL-H to give either the aldehyde **13** or the alcohol **14**. At low temperatures (-78 to -20 °C), only the aldehyde **13** was isolated. Increasing the temperature (0 °C to rt) and prolonging the reaction resulted in further reduction to the alcohol. Under optimized conditions (-20 °C to 0 °C), DIBAL-H reduction gave the alcohol in only 45% yield. Longer reaction time or warming above 0°C resulted in silyl migration. Aldehyde **13** was reduced with sodium borohydride to give the alcohol **14** in good yield, which was subsequently converted to the azide **15** in two steps. The azide was reduced and protected with the p-nitrobenzyloxycarbonyl (PNZ) group in a two step, single pot reaction by converting it to the iminophosphorane with triphenylphosphine and then treating sequentially with p-nitrobenzyl chloroformate and sodium hydroxide.[9] Water instead of sodium hydroxide gave mixtures of the free amine and the desired

product. The silyl group was removed without incident and converted to the iodide. Deprotection of **17** and **18** using mercuric trifluroacetate in aqueous acetic acid gave **4e** and **4f**. [10]

Table 1. In Vitro Activity of the Oxetane Carbapenems

Organism	Strains	CL191121	Imipenem	3a	3b	3c	3d	3e	3f
		MIC*	MIC*	MIC*	MIC*	MIC*	MIC*	MIC*	MIC*
E.coli	ATCC 25922	≤ 0.06	0.12	>128	0.50	0.25	0.50	0.12	0.12
E.coli	GC 2205	≤ 0.06	0.12	2	0.25	0.50	0.50	0.25	0.25
E.coli	GC 1792	≤ 0.06	0.12	> 128	1	0.50	1	0.25	0.12
E.cloacae	GC 2209	≤ 0.06	≤ 0.06	> 128	4	0.25	2	0.25	0.50
C.freundii	GC 2211	0.12	0.50	> 128	16	1	8	1	1
M.morganii	GC 2213	0.50	2	> 128	4	16	4	2	4
A.calcoaceticus	GC 756	2	0.50	> 128	32	16	32	4	16
P.aeruginosa	ATCC 27853	4	2	> 128	> 128	128	> 64	16	64
P.aeruginosa	GC 1544	16	16	> 128	> 128	> 128	> 64	32	128
X.maltophilia	GC 562	>128	>128	> 128	> 128	> 128	> 64	> 128	> 128
S.aureus	ATCC 29213	≤ 0.06	≤ 0.06	4	2	1	4	0.12	0.12
S.aureus	GC 2220	2	1	64	32	32	> 64	8	8
E.faecalis	GC 842	1	1	64	16	32	32	4	4
E.faecium	GC 1182	64	128	> 128	> 128	> 128	> 64	> 128	> 128
Relative hydrolysis to hog DHP		8.5	100	<1	<1	<1	NT**	NT	NT

*MIC in μg/mL

**Not Tested

Results and Discussion

The oxetane carbapenem **3e** was the most active among these carbapenems against both Gram(+) as well as Gram(-) bacteria (Table 1). The tosylate containing carbapenem **3a** showed no activity against the Gram(-) bacteria presumably due to lack of or reduced permeability. Against Gram(+), it was the least active. The structural isomer **3f** of the lead THF carbapenem, **CL 191,121**, was almost as active as the best compound in the series, **3e**, but none were better than the lead THF carbapenem. In addition, none of the compounds showed any activity against *Pseudomonas aeruginosa* or the resistant organisms. The oxetane carbapenems were almost as active as the reference compound, imipenem, against the Gram(-) bacteria but were less active against the Gram(+) bacteria. Against the Gram(+) bacteria, the difference in activity among the oxetane carbapenems were only two to four fold. This class of compounds, however, showed excellent stability towards the hog kidney dehydropeptidases (Table 1), almost hundred times more stable than imipenem.

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