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PREPARATION OF CRYSTALLINE *P*-NITROBENZYL 2-FORMYL CARBAPENEMS BY OXIDATIVE CLEAVAGE

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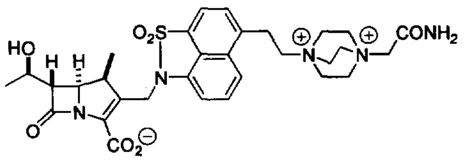
Abstract: Crystalline 1β-methyl-2-formyl carbapenem pNB esters were prepared by osmium-mediated oxidative cleavage of the corresponding 2-vinyl derivatives. Reduction of the 2-formyl compounds gave the corresponding 2-hydroxymethyl derivatives, which are key intermediates for the anti-MRS carbapenem candidate (**1**).

Recently, many 2-carbon substituted carbapenems have been studied in the search for new antibiotics. Among them, compound **1** is an attractive candidate not only from its very potent activity against gram-positive pathogens, including resistant strains such as MRS, VRE, and VISA, but also from its drug design based on a new releasable pharmacophore concept.[1–3] Previously, **1** was prepared from 1β-methyl-2-hydroxymethyl carbapenem (**2**) as the key intermediate.[4] However, preparation of this intermediate required 3.5 equiv of Bu_3SnCH_2OH and HMPA. To avoid these reagents, we wished to employ 2-formyl carbapenems (**3**) as alternative intermediates. Previously, lengthy preparations of allyl or *p*-methoxybenzyl protected 2-formyl carbapenems have been reported for studies of biologically active 2-functionalized-carbon substituted carbapenems.[5–7] Here, we report the preparation of stable crystalline *p*-nitrobenzyl (pNB) protected 2-formyl carbapenems in two steps from a commercially available intermediate.



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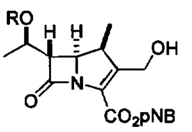

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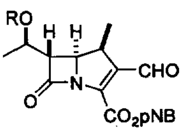

3

a: R = TBS
b: R = TES

As a starting point, to determine the feasiblity of a synthesis of the 2-formylcarbapenems, the stability of aldehydes **3** (**a** and **b**), which were prepared by oxidation of 2-hydroxymethyl carbapenems **2** (**a** and **b**), was examined at various pH's using reverse phase HPLC to monitor degradation (Figure 1). Crystalline **3a** and **3b** are stable in solution under mildly acidic and neutral conditions. Under strong acidic conditions, however, moderate decomposition triggered by desilylation at C-8 position (especially **3b**) was observed. Under basic conditions, **3** is extremely unstable, expelling *p*-nitrobenzyl alcohol (pNBOH).

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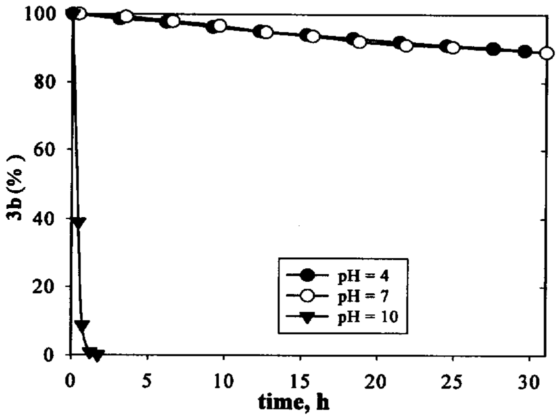


Figure 1. Stability of aldehyde (**3b**) in acetonitrile-H_2O at 25 °C.

Using the stability data for guidance, oxidative cleavage of 2-vinyl carbapenems **4** and **5** was investigated. The starting materials **4** and **5** were readily prepared from a commercially available β-methyl intermediate in one step in high yields using palladium-mediated cross-coupling reactions.[8–12]

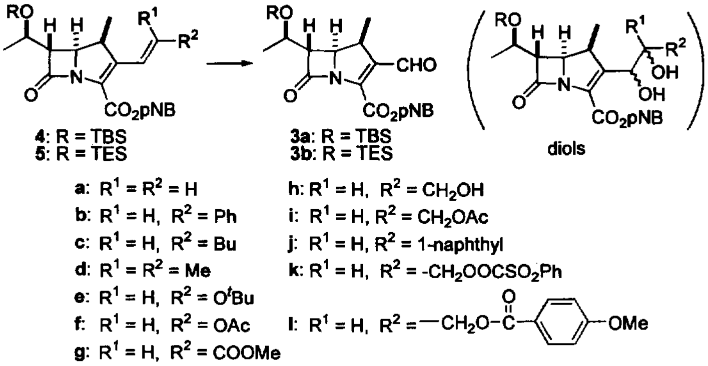
Of the many oxidative-cleavage methods that have been reported,[13] the most common is ozonolysis. Ozonolysis of **5a** was carried out in acetone, methanol or CH_2Cl_2 at −78 °C. Although a 50% assay yield of the desired aldehyde was observed on HPLC analysis when ozonolysis was stopped at 80% conversion, the reaction was very hard to control, as the aldehyde was not stable in the presence of ozone even at −78 °C.

Oxidative cleavage with sodium periodate in the presence of OsO_4/K_2OsO_4, $RuO_2/RuCl_3$, or $KMnO_4$ is another common method.[14] We applied this method to 2-vinyl carbapenems and optimized the reaction conditions such that an 88% yield of the aldehyde was realized. Some of the key results are summarized in the table below.

Regarding catalyst, OsO_4 proved to be the best. When $KMnO_4$ was used as catalyst, only trace amounts of aldehyde **3a** were observed. With $RuCl_3$, somewhat better results were obtained, but in both cases, over oxidation was a major problem.

In the case of TBS-protected 2-vinyl carbapenems **4**, addition of HIO_4 considerably increased the reaction rate as well as the yield of aldehyde **3a**. Since aldehyde **3a** could also be slowly oxidized by $NaIO_4$, shorter reaction times gave higher yields of **3**. Introducing substitutions on the olefin decreased the rate of oxidative cleavage (Entries 4–7). This suggests that steric hindrance around the double bond plays a more important role, than electron density. After optimization, the yield of aldehyde **3a** was improved to 88% (Entry 3) when the reaction was carried out at room temperature in a THF-H_2O solution using a mixture of $NaIO_4$ and HIO_4 as oxidant. At lower reaction temperatures (5 °C), the reaction was sluggish; while, at higher temperatures, it was difficult to control. Other solvents, such as *t*BuOH-H_2O, ethyl acetate, acetonitrile, acetonitrile-water, and acetone, gave aldehyde **3a** in low yield along with decomposition byproducts.

Table 1. Oxidative cleavage of 2-vinyl carbapenems[a]



Entry	substrate	catalysts-oxidants	°C	time, h	results[b]
1	**4a**	$KMnO_4$-$NaIO_4$	40	4	**3a** (trace)
2	**4a**	$RuCl_3$-$NaIO_4$/HIO_4	24	5	**3a** (30%)
3	**4a**	OsO_4-$NaIO_4$/HIO_4	24	4	**3a** (88%)
4	**4b**	OsO_4-$NaIO_4$/HIO_4	24	4	**3a** (24%)
5	**4d**	OsO_4-$NaIO_4$	24	20	**3a** (10%)
6	**4e**	K_2OsO_4-NMO/MOPS	0	1	Decomposition
7	**4f, 4g**	K_2OsO_4-NMO/MOPS	24	4	no reaction
8	**5a**	K_2OsO_4-$NaIO_4$/MOPS	24	5	**3b** (43%)
9	**5a**	K_2OsO_4-NMO/MOPS	24	3	diol (62%)
10	**5h**	K_2OsO_4-NMO/MOPS/$NaIO_4$	24	2	**3b** (60%, isolated 55%)
11	**5i**	K_2OsO_4-NMO/MOPS/$NaIO_4$	24	6	trace
12[c]	**4b, 5j, 5l**	AD-mix-α or β	24	4	decomposition

[a] All reactions were carried out in THF/H_2O (1/1) at room temperature. Concentration: 0.13 M; Os: 5–7.5 mol%. [b] Assayed by reversed-phase HPLC, Inertsil ODS-3. [c] These reactions were carried out in *t*-BuOH-H_2O.[15]

In many carbapenem syntheses, TES is favored over TBS as the protecting group due to its ease of removal. Unfortunately, oxidative cleavage of TES-protected compounds **5** did not proceed well under the above optimized conditions due to the acidic conditions (pH 2.5) which caused desilylation. Therefore, buffer was employed to control the pH between 4 and 6.5. Among buffers, MOPS and MES were found to be the better choices (Entry 8). The oxidative cleavage reaction was slower than under non-buffered conditions; the best yield of **3b** was 43%.

Given the poor yield for the TES-protected substrate, alternate strategies for the oxidative cleavage were investigated. Since oxidative cleavage of a 1,2-dihydroxy moiety is significantly milder and faster than that of a carbon-carbon double bond, dihydroxylation of **5** was studied. Dihydroxylation of **5** proceeded with *N*-methylmorpholine *N*-oxide (NMO) in the presence of K_2OsO_4. However, the pH of the reaction mixture increased to >7 as the reaction progressed due to generation of *N*-methylmorpholine, and cleavage of the pNB ester resulted. Using MOPS as a buffer solved this problem, giving a diol yield of 62% (Entry 9).

It is well known that introduction of an acidic proton to olefinic substrates which have coordination ability to osmium, such as allylic alcohol or homoallylic alcohol, enhances dihydroxylation.[15] We screened several 2-vinyl derivatives and found that 2-allyl alcohol (**5h**), prepared by Suzuki–Miyaura cross-coupling in almost quantitative yield,[16] was the best substrate (72% assay yield for the dihydroxylation). After dihydroxylation and oxidative workup ($NaIO_4/H_2O$-THF, 10 min), the desired aldehyde **3b** was isolated in 55% overall yield (Entry 10; 60% assay yield). Reaction of compound **5i** ($R^2 = CH_2OAc$) which has no coordination ability was sluggish and low yielding (Entry 11).

Since Sharpless reported a strong ligand acceleration effect on dihydroxylation of aromatic olefins,[17] compounds **4b**, **5j**, and **5l** were prepared. Unfortunately, dihydroxylation of **4b**, **5j**, and **5l** under Sharpless' conditions gave predominately pNBOH without the desired product, which may be unstable under the basic reaction conditions (Entry 12).

Finally, reduction of aldehydes **3** was straightforward using borane•THF in THF at −15 °C, providing the 2-hydroxymethyl carbapenem (**2**) in 94% assay yield and 89% isolated yield.

In conclusion, crystalline TBS and TES protected 1β-methyl-2-formyl carbapenem pNB esters (**3**) were prepared in 88 and 60% yields, respectively, by osmium-mediated oxidative cleavage of the corresponding 2-vinyl derivatives. Aldehydes **3** are very versatile intermediates not only for the preparation of anti-MRS carbapenem candidate **1** via 2-hydroxymethyl derivatives but also for investigation of new antibacterial reagents including KR-21012.[7]

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