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Synthesis of oxetane-3-carboxaldehyde and methyl oxetane-3-carboxylate via homologation of oxetane-3-one

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ABSTRACT

A 4-pot telescoped procedure to prepare oxetane-3-carboxaldehyde and methyl oxetane-3-carboxylate was developed using readily available starting materials. Classical homologation methods applied to oxetane-3-one proved challenging due to the sensitivity of the oxetane ring toward strongly oxidative, basic and acidic conditions. Subsequently, a mild homologation sequence was developed. The key steps involve a Tsuji hydrogenolysis of an allylic acetate, osmium-free dihydroxylation and oxidative cleavage. Although methyl oxetane-3-carboxylate is marketed by a small number of specialty chemical companies, this work represents the first published preparation of this vital building block.

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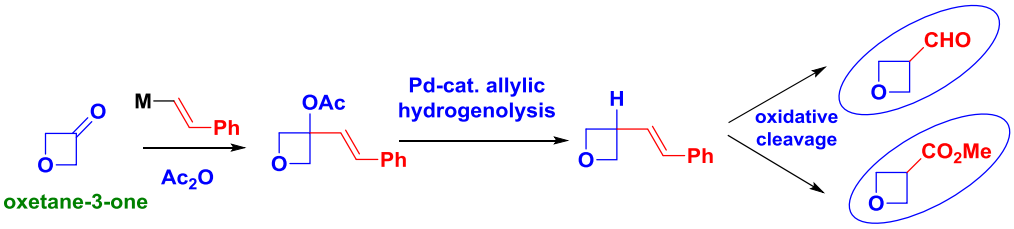

1. Introduction

Oxetanes are important heterocycles for drug discovery as demonstrated by Carreira[1–14] and others.[15,16] Modification of a lipophilic or poorly soluble lead compound by the incorporation of an oxetane can positively impact the physiochemical properties of that lead. For example, improved aqueous solubility and metabolic stability were gained by judicious substitution of an oxetane in place of larger cyclic ethers in a program focused on γ-secretase inhibitors.[17] Oxetanes have also appeared in natural products with biological activity, the Taxane family being the most well-known (Fig. 1).

Because of their symmetry, 3-substituted oxetanes are particularly important since they do not introduce the complexity of a new chiral center. A large body of excellent synthetic work has focused on 3,3-disubtituted and 2-substituted oxetanes but fewer literature reports describe methods to prepare 3-monosubstituted oxetanes. Due to ring strain and the basicity of the oxygen, oxetanes can undergo ring opening reactions under acidic conditions to form allylic and homo-allylic alcohols.[18–20] Strategic ring opening, ring expansion and C2 functionalization of oxetanes can afford a variety of oxygen containing heterocycles. For oxetane containing lead compounds, the ring opening reaction is an undesired event complicating synthesis of these important heterocyclic compounds.[21] To circumvent these complications, synthesis of 3-monosubstituted oxetanes tend to be lengthy. For example, the synthesis of oxetane-3-methanol takes 7 steps with an overall yield of 12%.[22] This process is stymied by four protection/deprotection steps and a low yielding oxetane ring formation step. The targets of this report have a 3-carbonyl group and 3-hydrogen making ring opening reactions via beta-elimination a facile process, due to activation of beta-elimination by the carbonyl. This

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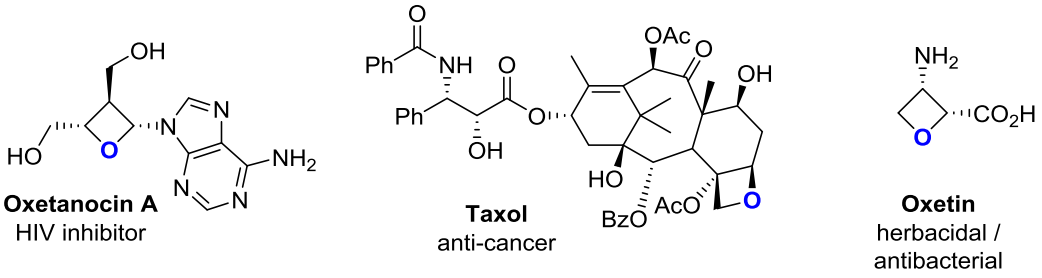
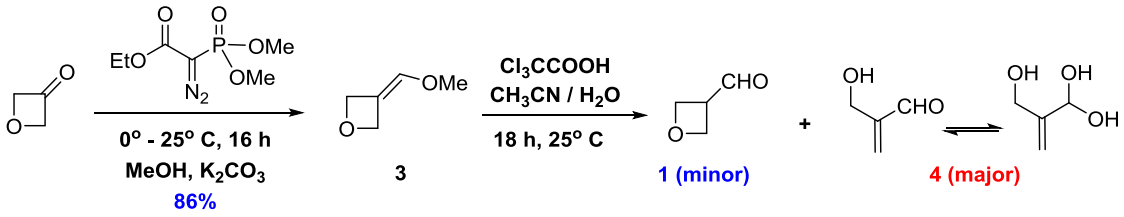


Fig. 1. Examples of oxetane rings in natural products.

structural feature makes synthesis of these simple looking building blocks more complicated than one might anticipate. The basic form 2-(hydroxymethyl)acrylaldehyde **4** as a mixture of aldehyde and hydrate as observed by ^{1}H NMR.



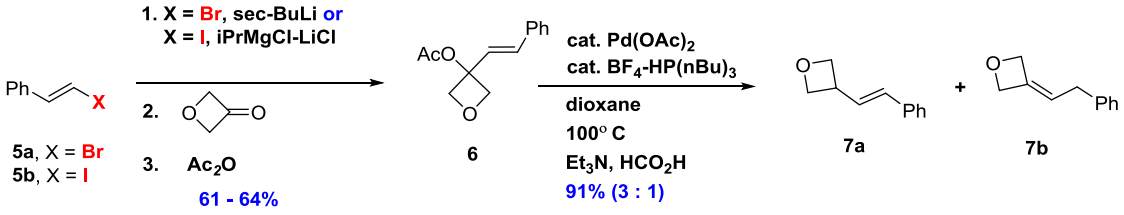
Scheme 1. Unsuccessful one carbon homologation of oxetane-3-one.

conditions required for oxetane ring closure[23] from 1,3-diol precursors are not suitable for 3-H/3-carbonyl containing oxetanes. Here, we report an alternative approach to install a carbonyl group off the 3-position of the oxetane through an unusual homologation sequence.

2. Results and discussion

Building from a strategy of avoiding oxetane ring formation, oxetane-3-one was anticipated to be a key starting material, commercially available in kilogram quantities. Homologation of this readily available ketone was the central challenge we faced. A large number of methods have been published on homologation of ketones to carbonyl compounds.[24] Our initial foray sought to use a classical homologation strategy of vinyl ether formation followed by hydrolysis to the aldehyde. Synthesis of **3** using an interrupted Ohira–Bestmann reaction[25] proceeded smoothly to provide the vinyl ether in 86% yield as a distillable liquid. Mild Brønsted and Lewis acids were then screened in an attempt to hydrolyze the enol ether. Hydrolysis reactions were monitored by running the reactions in deuterated solvents while monitoring by ^{1}H NMR. The only acid found to perform marginally as desired was trichloroacetic acid in a 1:1 mixture of CH_3CN/water (Scheme 1). All other acids either gave no reaction or led to complete ring opening to form 2-(hydroxymethyl)acrylaldehyde **4** as a mixture of aldehyde and hydrate as observed by ^{1}H NMR.

Several other homologation strategies were attempted without success including furylation followed by furan cleavage by ozonolysis or treatment with Oxone,[26] hydrolysis of the α-cyanoepoxide, and hydrolysis of a ketene acetal. Then, we investigated a strategy based on regioselective Pd-catalyzed reductive cleavage of an allylic acetate.[27–29] Previous work had established the ability for regiocontrol in hydride addition to either side of a palladium-allyl species depending on the selected conditions. The more hindered side of the Pd-allyl intermediate is preferentially reduced when P(nBu)$_3$ is used as the ligand and trimethylamine/formic acid is used as the hydride source. With this knowledge in hand, we prepared allylic acetate **6** using two related procedures (Scheme 2). 1,2-addition of either (*E*)-styryllithium or the corresponding Grignard reagent to oxetane-3-one followed by quenching the alkoxide with acetic anhydride afforded **6** in 61–64% yield on a 0.5 mol scale without chromatography.



Scheme 2. Synthesis of *trans*-stryl oxetane, **7a**.

Pd-catalyzed reductive cleavage of allylic acetate **6** was accomplished under modified conditions to those reported by Tsuji, Meijere and Salaun.[28] The reaction required heating at 100 °C for initiation and short reaction time (40–50 min) to avoid over reduction to the alkane. Pd(OAc)$_2$ was found to give the same yield as Pd(dba)$_2$ and produced fewer colored impurities. A further improvement was to use the air stable tri-n-butylphosphonium tetrafluoroborate[30] to generate the free phosphine ligand in-situ using

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