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Custom synthesis of substituted butenolides, dihydropyranones, and α-*E*-alkylidenelactones via alkenylalumination

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ABSTRACT

Alkenylalumination of aldehydes with [α-(ethoxycarbonyl)-β-(*t*-butyldimethylsilyloxyalkyl)alkenyl]diisobutylaluminum provides the corresponding α-*Z*-alkylidene-β′-hydroxy esters, which upon protection and treatment with trifluoroacetic acid lactonizes to furnish α-acetoxyalkyl butenolides ($n = 1$) and dihydropyranones ($n = 2$) in 40% overall yield. Conjugate addition to these lactenones and concurrent acetate elimination constitute a general and stereospecific synthesis of the corresponding α-*E*-alkylidene lactones.

α,β-Unsaturated carbonyl moieties, such as butenolides, pyranones, α-alkylidene-γ-butyrolactones, and -δ-valerolactones, are structural motifs found in a multitude of natural products.[1] α-Alkylidene-γ-lactones display a variety of biological activities,[2] including COX-2 inhibition, nuclear factor κB inhibition,[3] and increased cellular resistance to oxidant injury in HepG2 cells.[4] Accordingly, there has been considerable interest in the development of efficient protocols for the preparation of α-alkylidene butyrolactones, during the past three decades.[5] These include free-radical annelation of phenyl selenocarbonates,[6] Horner-Wadsworth-Emmons condensations of α-phosphono lactones,[7] the Wittig reaction of α-(triphenylphosphoranylidene)lactones[8] or Wittig-Horner condensation of α-(dimethoxyphosphonyl)lactones,[9] the α-formylation of lactones, followed by aldol type condensation,[10] etc. Recently, the Cossy[11] and Howell[12] groups independently reported a cross metathesis protocol for the synthesis of β,γ-unsubstituted-α-*E*-alkylidene-γ-butyrolactones. In contrast, there are only few reports on the preparation of α-alkylidene valerolactones.[13]

Inefficient, multi-step protocols, poor yields, and or poor *E*/*Z* selectivity currently encountered in α-alkylidene lactone syntheses call for new and improved methods.[14] As part of an ongoing project in the pursuit of anti-inflammatory and anti-cancer molecules,[15] we recently reported several protocols for the synthesis of α-methylene and *E*- and *Z*-alkylidene-γ- and δ-lactones. These involved the alkenylalumination of aldehydes as the first step (Scheme 1).[16–19] The syntheses of a variety of α-*Z*- or *E*-alkyl(aryl)idene-β,γ-disubstituted-γ-butyrolactones were achieved via either a crotylboration-cyclization[16] or a crotylboration-oxonia-Cope rearrangement-cyclization[17] of aldehydes and alkenylalumination-cyclization of oxiranes.[18] A simple synthesis of α-alkylidene-δ-valerolactones was achieved via the conjugate addition of ketone enolates to functionalized allyl acetates.[19]

In continuation, we sought a more versatile, tailored process for α-alkylidene lactones of varying ring sizes and substitutions. We envisioned a general synthesis of β′-substituted-γ-unsubstituted-α-*E*-alkylidene-γ-butyrolactones, and -δ-valerolactones via the alkenylalumination of aldehydes using customized reagents. These latter reagents were formed through the hydroalumination of TBS-protected hydroxy alkynoates (Scheme 2). This process was also meant to provide a general route for the synthesis of functionalized butenolides and dihydropyranones. The results of our study are presented herein.

The required alkynoates were prepared in 90–92% yield from the TBS-protected alkyn-1-ols via deprotonation with *n*-butyllithium at −78 °C, followed by a treatment with ethyl chloroformate in tetrahydrofuran (THF). Ethyl 4-(tert-butyldimethylsilyloxy)but-2-ynoate and ethyl 5-(tert-butyldimethylsilyloxy)pent-2-ynoate were transformed to the corresponding alkenylaluminum reagents **1** and **2** via hydroalumination with DIBAL-H/NMO complex in THF at 0 °C.[20] Reagent **1** was mixed with benzaldehyde (**3a**) and stirred for 8 h at 0 °C. Acidic workup provided the α-alkylidene-β-hydroxy-β-phenyl ester (**4a**) in 58% overall yield (Scheme 2).[21] The generality of this process was then demonstrated by carrying out the reaction with 4-NO_2PhCHO, (**3b**) as well as an aliphatic aldehyde,

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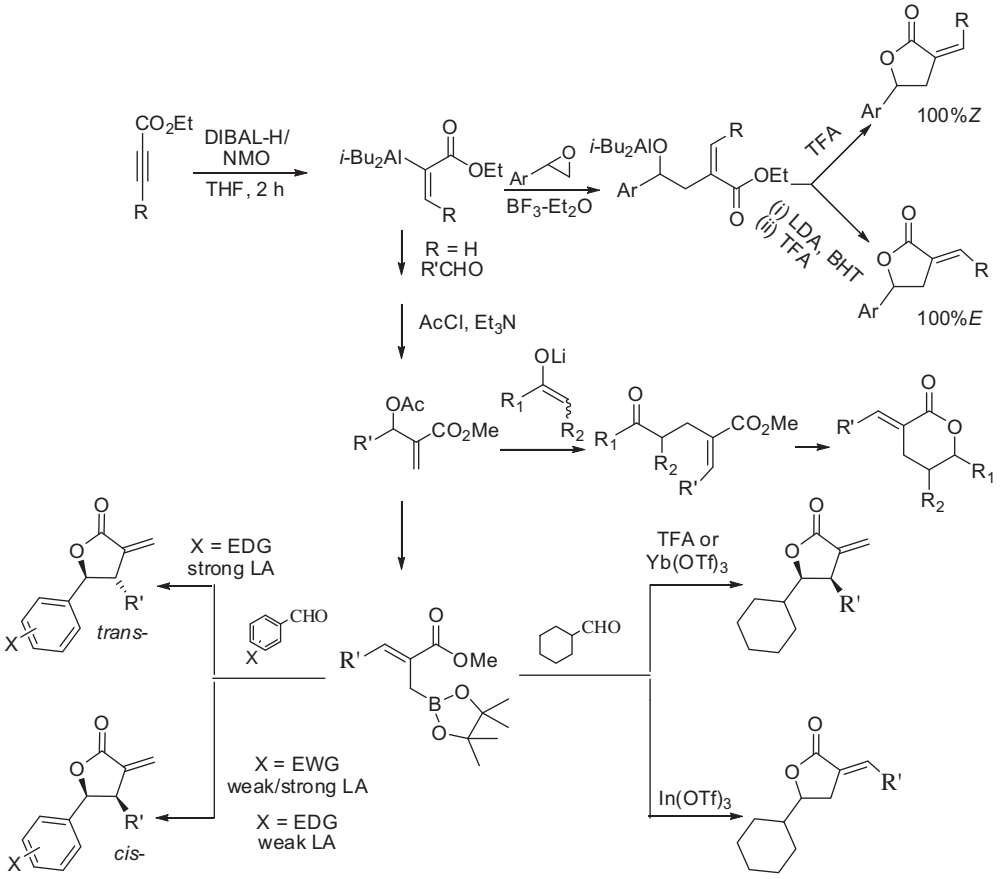
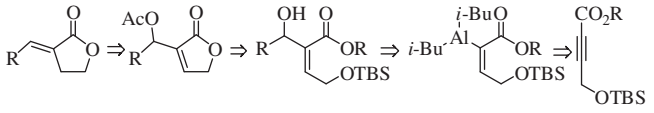


Scheme 1. Alkenylalumination route to α-alkylidene/methylene-γ- and δ-lactones.



Scheme 2. Retrosynthetic analysis of β′-substituted-γ-unsubstituted-α-*E*-alkylidene-γ-butyrolactones.

cyclohexanecarboxaldehyde (ChxCHO, **3c**). The product hydroxy esters **4b** and **4c** were obtained in 73% yield and 54% yield, respectively. The results are summarized in Table 1. These same aldehydes, when treated with reagent **2**, provided the corresponding alcohols **5a–c**, the precursors for the synthesis of pyranones and δ-valerolactones (Scheme 3, Table 1).

Table 1
Alkenylalumination of aldehydes with **1** and **2**

Entry		RCHO			
	#	#	R	#	Yield (%)
1	**1**	**3a**	Ph	**4a**	62
2	**1**	**3b**	*p*-NO_2-Ph	**4b**	73
3	**1**	**3c**	Chx	**4c**	54
4	**2**	**3a**	Ph	**5a**	72
5	**2**	**3b**	*p*-NO_2-Ph	**5b**	66
6	**2**	**3c**	Chx	**5c**	55

The preparation of butenolides and dihydropyranones from **4** was completed by the following transformation sequence: Treatment of allylic alcohol **4a** with acetyl chloride and pyridine in dichloromethane afforded the allylic acetate **6a** in 90% yield. Addition of trifluoroacetic acid (TFA), followed by heating the mixture to reflux for 2 h resulted in both the removal of the TBS group and concurrent lactonization to provide the butenolide **8a** in 88% yield—an overall yield of 50% for three steps. This protocol was then extended to allylic alcohols **4b** and **4c** to yield the corresponding acetates **6b** and **6c** and butenolides **8b** and **8c**, respectively (Scheme 4, Table 2).

The above acetylation-cyclization protocols were then utilized to prepare α-substituted dihydropyranones (**9a–c**) from the allylic acetates (**7a–c**), which were derived from the allylic alcohols **5a–c** (Table 2).

Having achieved the preparation of α-substituted butenolides and dihydropyranones, we next focused on their conversion to the corresponding α-alkylidene lactones via a conjugate addition-elimination strategy. As representative examples, the endocyclic allylic acetates **8** and **9** were treated with a hydride nucleophile[22] to achieve the preparation of β,γ-unsubstituted butyro- and valerolactones. Accordingly, the addition of $NaBH_4$ to allylic acetate **8a** in methanol at 0 °C provided the α-alkylidene-β,γ-unsubstituted-γ-butyrolactone **10a** in 92% yield within 20 min (Table 2). Examination of the PMR spectrum revealed a chemical shift of δ 6.8 ppm for the olefinic proton, thereby confirming the *E*-stereochemistry of the exocyclic olefin.[23] This was then extended to **8b** and **8c** in 86–91% yields. Preparation of the α-alkylidene-δ-lactones (**11a–c**) was similarly achieved from the dihydropyranones **9a–c** (Table 2).