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Copper-Catalyzed Methylenation Reaction: Total Synthesis of (+)-Desoxygaliellalactone

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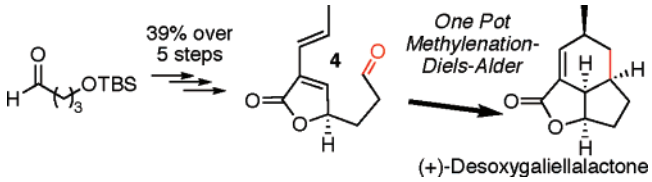
ABSTRACT



The enantioselective total synthesis of (+)-desoxygaliellalactone was achieved in six steps starting from 4-*tert*-butyldimethylsilyloxybutanal. This synthesis featured a one-pot copper-catalyzed methylenation–Diels–Alder cyclization. The challenging methylenation of aldehyde 4 was studied under various reaction conditions. Whereas Wittig reaction conditions led to byproducts resulting from decomposition of the sensitive butenolide moiety, the mild copper-catalyzed methylenation reaction produced the desired triene in good yield.

Alkenes are predominant functional groups, found in a large range of biologically important products.[1] They serve as precursors for numerous reactions, including many C−C bond-forming reactions. Terminal alkenes are ideal substrates for processes such as Heck cross-coupling, metathesis, or cyclization reactions. The synthesis of such terminal alkenes is typically achieved by the methylenation reaction of carbonyl derivatives.[2] Although the Wittig reaction is a suitable method to afford the transformation,[3] it possesses several drawbacks, including low reactivity of the reagent when hindered carbonyl derivatives are employed as well as the potential decomposition of base-sensitive substrates. Several stoichiometric *gem*-dimetallic reagents have subsequently been developed to overcome these problems.[4] Recently, our group developed a mild rhodium- and copper-catalyzed methylenation method with trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol to further address the challenges of synthesizing terminal alkenes from aldehydes and ketones containing base-sensitive functional groups.[5,6] In this paper, we present the total synthesis of (+)-desoxygaliellalactone (**2**) using a one-pot copper-catalyzed methylenation−Diels−Alder cascade with sensitive butenolide aldehyde **4**.

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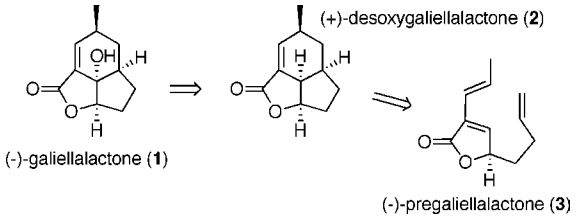
(−)-Galiellalactone (**1**) was first isolated from ascomycetes *Galliela rufa* in 1990.[7] Since then, various biological activities have been associated with (−)-galiellalactone (**1**) including the inhibition of interleukin-6 signaling in HepG2 cells[8] and of prostate cancer cell xenografts.[9] Sterner and co-workers were the first to establish the absolute stereochemistry of **1** by synthesizing (+)-galiellalactone (*ent*-**1**) from (*R*)-(+)-pulegone in 3.4% overall yield.[10] The biosynthesis of (−)-galiellalactone **(1)** presumably involved an intramolecular Diels−Alder cyclization of pregaliellalactone (**3**) to give (+)-desoxygaliellalactone (**2**), followed by an enzymatic hydroxylation (Scheme 1).[11] Sterner and co-

Scheme 1. Proposed Biosynthesis of (−)-Galiellalactone (**1**)

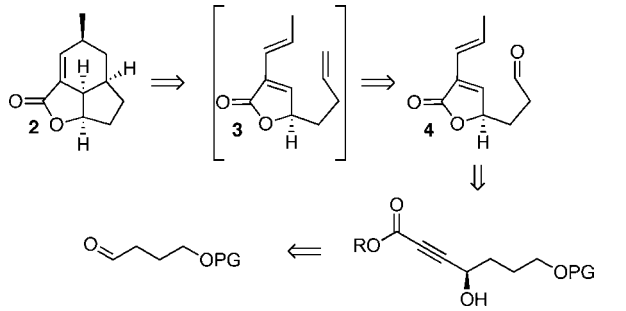


workers showed that indeed **2** was the biosynthetic precursor of **1**. Furthermore, they synthesized **2** from **3** via a Diels−Alder reaction, while **3** was prepared from 4-pentenal in 16% yield over six steps. The stereogenic alcohol was obtained with 83% ee using an enantioselective reduction with stoichiometric amounts of (*R*)-Alpine-Borane.

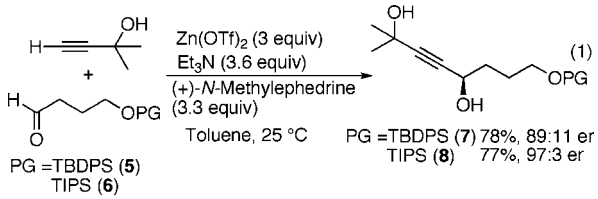
Given the moderate yields and selectivities previously reported for the synthesis of triene **3**, we investigated the mild methylenation of aldehyde **4** to produce **3** (Scheme 2) in hope of improving the overall yield. Furthermore, our goal was to develop a one-pot method involving direct access to desoxygaliellalactone (**2**) from aldehyde **4** without isolating the triene **3**. Our strategy involved the synthesis of butenolide **4** from the corresponding propargylic alcohol, which could be derived from the readily available silyl-protected 4-hydroxybutanal via an enantioselective addition of an alkyne derivative.

High yields and selectivities for the enantioselective alkynation of aldehydes were reported recently. This included a new method by Carreira et al.,[12] who used zinc acetylide derivatives in the presence of (*R*)- or (*S*)-*N*-methylephedrine to access propargylic alcohols.[13] For the purposes of our

Scheme 2. Retrosynthetic Analysis of (+)-Desoxygaliellalactone (**2**)



study, the addition of 2-methyl-3-butyn-2-ol[14] to readily available silyl-protected 4-hydroxybutanal[15] produced the desired propargylic alcohol in 77−78% yield (eq 1). Surprisingly, the remote protecting group affected the enantioselectivity such that 97:3 er was obtained with TIPS, while TBDPS led to only 89:11 er. We assume the deleterious π-stacking between the chiral moiety of the catalyst and the protecting group is responsible for this effect, although further experiments are required to confirm this.



The propargylic alcohol **11** was obtained from **8** in three steps (Scheme 3). Protection of the secondary alcohol was required prior to liberation of the terminal alkyne, which was subsequently acylated to give substituted propiolate **10**. Selective deprotection of the secondary TBS-protected alcohol versus the primary TIPS-protected alcohol was challenging.[16] A number of reaction conditions were tested, and the best yield for the formation of **11** (57%) was obtained using TMSOTf at −50 °C.[17]

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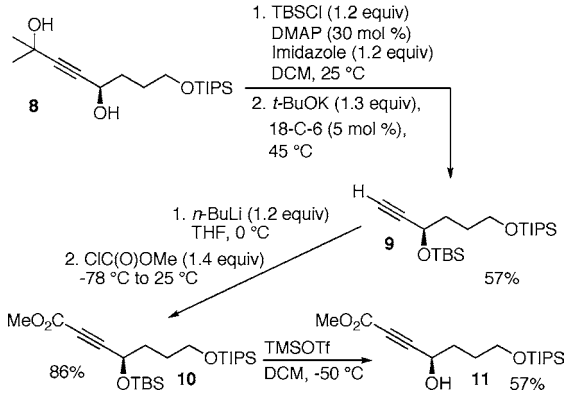
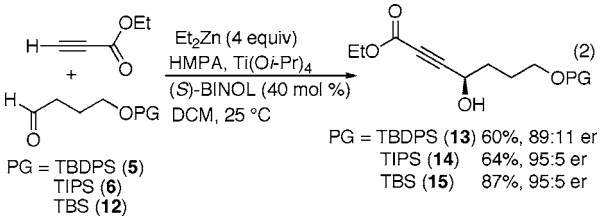
Scheme 3. Synthesis of Alcohol **11**



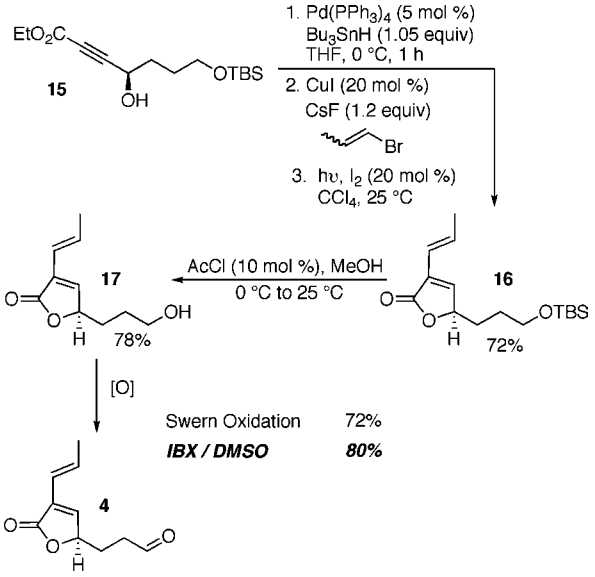
Alternatively, direct addition of the corresponding propiolate to silyl-protected 4-hydroxybutanal is a more convergent approach to access the desired propargylic alcohol. However, addition of ethyl propiolate under Carreira's conditions failed to provide the desired adduct. Only a few enantioselective methods are known to produce propargylic alcohols from aldehydes and propiolate derivatives in good yields and selectivities. Unfortunately, these methods apply exclusively to aromatic and unsaturated aldehydes.[18] We therefore used the recent method of Rajaram and Pu because it can be applied to aliphatic aldehydes such as **5** and **6**.[19] Their reaction conditions were tested to form the desired propargylic alcohol (eq 2).



The slow addition of 4-*tert*-butyldimethylsilyloxybutanal (**12**)[20] to a solution containing 4 equiv of diethylzinc and ethyl propiolate, 40 mol % of BINOL, 2 equiv of HMPA, and 1 equiv of Ti(O*i*-Pr)$_4$ led to the desired product **15** in 87% yield with 95:5 er. Lower yields were obtained with the TBDPS- and the TIPS-protected aldehydes (**5** or **6**), while the former also gave a lower er.

Hydrometalation followed by the cross-coupling reaction to provide the corresponding substituted butenolide by spontaneous lactonization was studied using the propargylic alcohol **15** (Scheme 4). Initially, we used the recently developed hydrostannylation reaction by Chiu et al. using

Scheme 4. Synthesis of Aldehyde **4**



Stryker's catalyst[21] in a one-pot process such that the tin intermediate was not isolated.[22] Stoichiometric amounts of tributyltin hydride and 10 mol % of Stryker's catalyst, however, afforded the desired product in only 22% yield. The incompatibility of Stryker's catalyst with the alcohol group is probably responsible for the failed reaction. Consequently, palladium-catalyzed hydrostannylation was used to obtain the desired vinyltin, which was subsequently used without isolation. The desired butenolide was obtained as a mixture of *Z* and *E* isomers in 72% yield via Stille cross-coupling using copper iodide, cesium fluoride, and 1-bromopropene.[23] Quantitative photoisomerization with iodine gave **16**. Deprotection of the primary TBS-protected alcohol with acetyl chloride in methanol[24] provided alcohol **17**, which was then oxidized. Unfortunately, Sigman oxidation[25,26] failed to produce aldehyde **4**, as the butenolide is sensitive to heating. Consequently, **4** was obtained in 72% by Swern oxidation[27] and in 80% yield using 3 equiv of IBX in DMSO.

With aldehyde **4**, we investigated its methylenation with methylenetriphenylphosphorane to produce triene **3**. We first examined standard Wittig reaction conditions with **4** using methyltriphenylphosphonium bromide and NaHMDS. Un-

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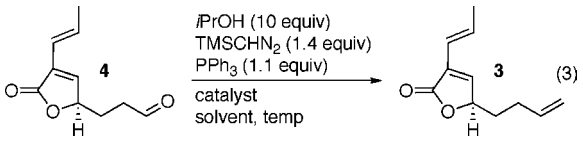
(26) Reaction conditions: Pd(IPr)(OAc)$_2$·H$_2$O (10 mol %), Bu$_4$NOAc (15 mol %), MS 3A, O$_2$, 60 °C, PhMe. This method was tried first, as it was used in the one-pot oxidation−methylenation process we recently developed. See: Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 11152−11153.

(27) Reaction conditions: DMSO (4 equiv), (ClCO)$_2$ (2 equiv), Et$_3$N (6 equiv)/DCM.

fortunately, an unwanted degradation byproduct of the butenolide moiety was exclusively obtained. Transition-metal-catalyzed methylenation using trimethylsilyldiazomethane, 2-propanol, and triphenylphosphine, which also produces methylenetriphenylphosphorane[5] using milder reaction conditions, was subsequently used to transform **4** into **3** (Table 1). No reaction occurred with Wilkinson's catalyst

Table 1. Transition-Metal-Catalyzed Methylenation of Aldehyde **4** (eq 3)



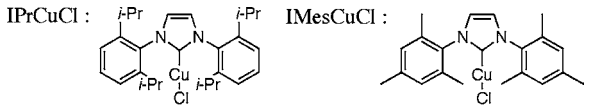
entry	catalyst (mol %)	solvent, T (°C)	yield[a] (%)
1	$RhCl(PPh_3)_3$ (3)	THF, 25	-
2	$RhCl(PPh_3)_3$ (3)	dioxane, 60	-
3	CuCl (10)	THF, 60	<5
4	IPrCuCl (5)	dioxane, 60	9
5	IMesCuCl (5)	THF, 60	<5
6	IMesCuCl (5)	dioxane, 60	70
7	**IMesCuCl (10)**	**dioxane, 60**	**77**

[a] Isolated yield after flash chromatography.

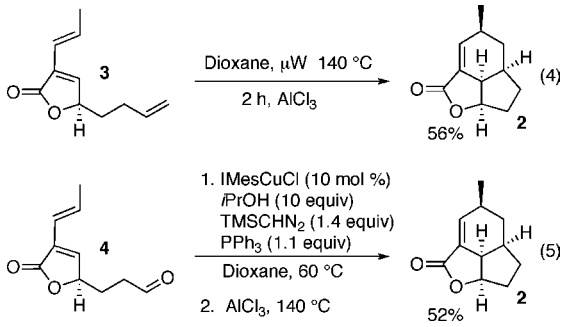
at room temperature, and the aldehyde **4** was recovered (entry 1). Decomposition of the starting material occurred with Wilkinson's catalyst at 60 °C in dioxane (entry 2), while copper(I) chloride and IPrCuCl[28] led to low conversions (entries 3 and 4). Conversely, the desired triene **3** was isolated in 77% using IMesCuCl[28] in dioxane at 60 °C (entry 7).

We then tested the Diels–Alder reaction with triene **3** in dioxane to produce (+)-desoxygaliellalactone (**2**). After considerable investigation, the desired product (**2**) was obtained in 56% yield using aluminum trichloride at 140 °C under microwave for 2 h in a sealed tube (eq 4).[29]

(28) Structures of IPrCuCl and IMesCuCl:



Gratifyingly, the one-pot copper-catalyzed methylenation–Diels–Alder reaction afforded (+)-desoxygaliellalactone (**2**) from aldehyde **4** in 52% yield. NMR data, optical rotation and spectroscopic properties were identical for both the synthetic and the natural product.



In conclusion, the total synthesis of (+)-desoxygaliellalactone (**2**) in seven steps in 20% overall yield has been reported. The synthetic strategy featured the enantioselective addition of propiolate anion to 4-*tert*-butyldimethylsilyloxybutanal, one-pot formation of butenolide via a palladium-catalyzed hydrostannylation–cross-coupling reaction, and a one-pot copper-catalyzed methylenation–Diels–Alder reaction to afford the final product. Our synthesis clearly illustrates the usefulness of transition-metal-catalyzed methylenation reactions over classic methods.

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Supporting Information Available: Experimental procedures, compound characterization data, and ^1H spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) Sterner and co-workers reported the Diels–Alder reaction with triene **3** to produce **2** in 80% yield in toluene at 140 °C (see ref 11a). However, in our hands, we could not repeat this result and the desired product could not be isolated under these reaction conditions. We tested other Lewis acids as well as the addition of chloride salts and water, but with less success than the use of aluminum trichloride.