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Acid-mediated coupling of γ-hydroxybutenolides and aldehydes: synthesis of a new class of spirocyclic ketal-lactones

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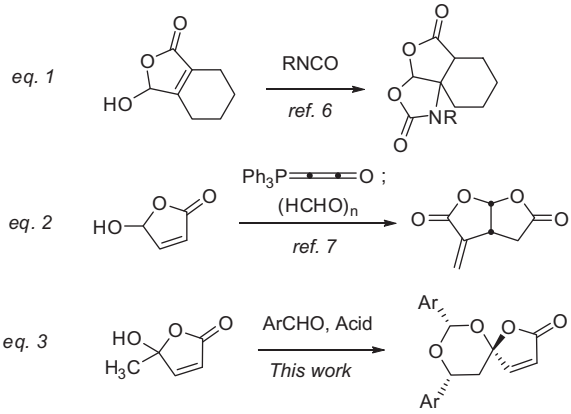
ABSTRACT

In the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), γ-methyl-γ-hydroxybutenolide reacts with aromatic aldehydes to generate a new class of stereochemically rich spirocyclic ketal-lactones in good yields and with excellent stereoselectivities. We believe that this process takes place through the in situ generation of protoanemonin followed by a Prins reaction. Herein, we describe this discovery, along with substrate scope and preliminary mechanistic studies.

γ-Hydroxybutenolides are heterocyclic structures found in a variety of natural products[1] that can be synthesized readily through the oxidation of furan.[2–4] While underexplored as synthons, they have also found some utility as synthetic precursors to complex lactone-containing compounds. For example, upon acylation of γ-hydroxybutenolides, it has been demonstrated that the resulting compounds can be used in dynamic kinetic asymmetric palladium-catalyzed coupling reactions.[5] In addition, γ-hydroxybutenolides can react in cascade reactions with molecules such as isocyanates (Scheme 1, Eq. 1)[6] and ketenes (Scheme 1, Eq. 2)[7] to generate complex bicyclic lactones, and have been implicated as synthons in natural product biosynthesis.[8,9] Given their convenient preparation and bond-forming potential, our group has been interested in further exploration of the reactivity of γ-hydroxybutenolide-containing molecules. In the course of our studies it was revealed that aromatic aldehydes react with γ-methyl-γ-hydroxybutenolides under strongly acidic conditions to generate novel spirocyclic ketal-lactones (Scheme 1, Eq. 3).

Optimization of this reaction was performed with 3-nitrobenzaldehyde as the carbonyl source (Table 1). The reaction works best with triflate acids, as both trimethylsilyltriflate and triflic acid provided comparably high yields (Table 1, entries 1 and 2). The optimal amount of acid is 2 equiv, as lowering the equivalency to 1 brings the reaction yield down significantly (Table 1, entry 3). In addition, the optimal amount of aldehyde was found to be 6 equiv (Table 1, entry 4). The excess aldehyde was easily separable from our product by silica gel chromatography. Other Lewis acids such as chlorotrimethylsilane or zirconium tetrachloride did not lead to product, nor did the Bronsted acid, toluenesulfonic acid (Table 1, entries 5–7). In these instances the acids isomerized the γ-hydroxybutenolide to the open, *trans* form (**4**).

A substrate scope study revealed that the nitro group can be put at either the *ortho* or *para* positions while still providing moderate yields (**3b** and **3c**). Other electronically poor aryl aldehydes, such as *meta*-chloro and *meta*-trifluoromethylbenzaldehyde work as well (**3d** and **3e**). When benzaldehyde was used, we saw a significant decrease in yield (**3f**). Increasing the amount of aldehyde to 20 equiv, however, led to an increase in yield from 18% to 48%.



Scheme 1. Examples of γ-hydroxybutenolide cascade reactions.

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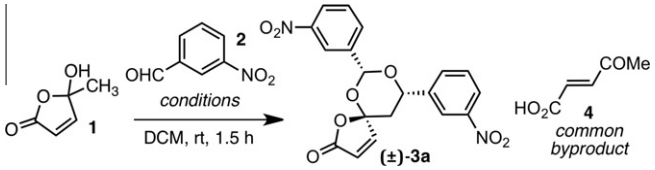
Table 1
Select examples from optimization studies

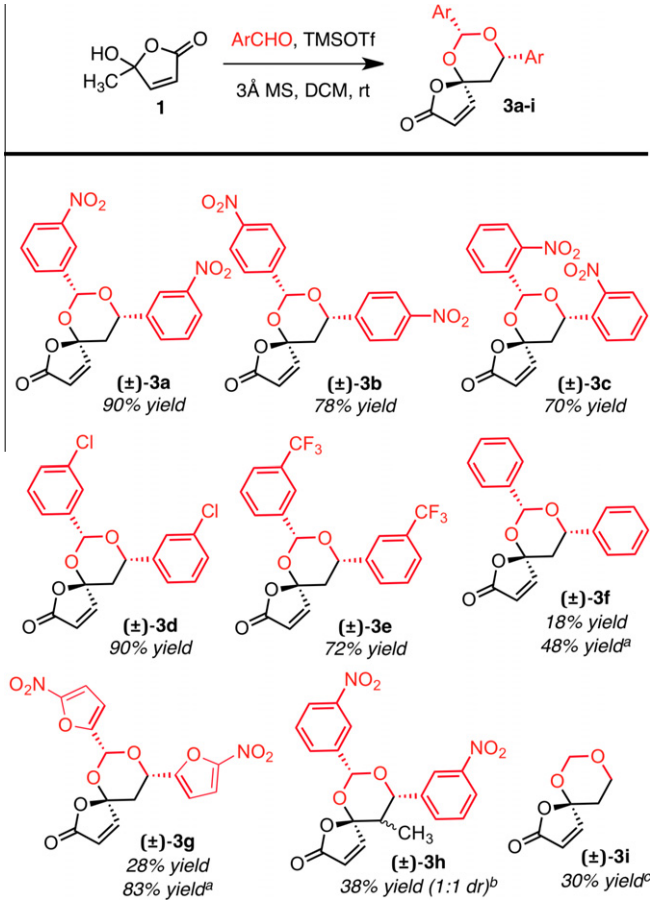


Entry	Acid	Equiv of acid	Equiv **2**	% Yield **3a**[a]
1	TMSOTf	2	6	90
2	TfOH	2	6	90
3	TMSOTf	1	6	53
4	TMSOTf	2	3	47
5	$ZrCl_4$	2	6	0
6	TMSCl	2	6	0
7	TsOH	2	6	0

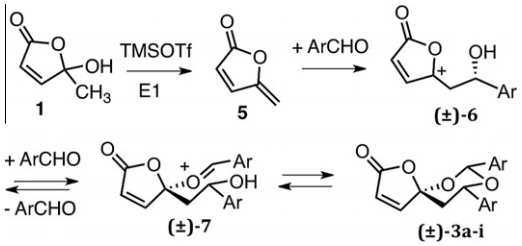
[a] Isolated yields following silica gel chromatography.

Aldehydes toward the more electronically rich extremes, such as 4-anisaldehyde and 2-furaldehyde, did not lead to any noticeable amounts of product (results not shown). However, attenuating the electronics of the furan by introducing a nitro group did allow for furans to be incorporated (**3g**). Taken together, these reactions indicate that electronically poor aldehydes work best under the reaction conditions.

γ-Ethyl-γ-hydroxybutenolide can also be used in place of γ-methyl-γ-hydroxybutenolide, and generate a molecule with 4



Scheme 2. Substrate scope studies. (a) Reactions were run with 20 equiv of aldehyde; (b) γ-ethyl-γ-hydroxybutenolide was used as butenolide, and products were isolated as a mixture of diastereomers; (c) 5.25 mass equivalents of paraformaldehyde were used as carbonyl source.



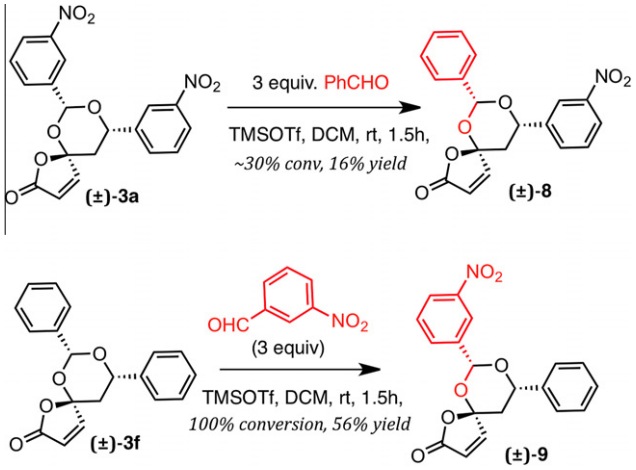
Scheme 3. Proposed mechanism for formation of **3a–i**.

stereocenters (**3h**). In this instance, reaction yields were lower, and the additional stereocenter was introduced without any selectivity. Finally, while aliphatic aldehydes did not work, paraformaldehyde could be used as the source of carbonyl. The product in this instance, **3i**, was significantly less stable than other substrates made, and the lower yield obtained is believed to be at least in part due to the instability to chromatographic conditions.

In our proposed mechanism, elimination of water and/or TMSOH takes place under the acidic conditions to generate the known molecule protoanemonin (**5**, Scheme 3).[10] Protoanemonin then undergoes a Prins reaction with 2 equiv of the aldehyde to form **3a–i**.[11] When studies were carried out in deuterated chloroform, and the reaction was monitored by ^{1}H NMR, no protoanemonin was observed. However, when γ-methyl-γ-hydroxybutenolide (**1**) was treated with triflic acid in the absence of the aldehyde, protons consistent with those reported for protoanemonin were observed.[12] Adding the aldehyde subsequently led to product, albeit with noticeably diminished efficiency.[13] We see this as evidence that the productive coupling reaction is competing with non-productive side reactions of protoanemonin. Thus, we believe that the higher equivalents of aldehyde lead to a higher yielding process by increasing the rate of the productive reaction.

We believe **3a–i** are thermodynamic products, and form via the reversible nature of our proposed transformation. As can be seen in Scheme 2, the two aryl groups on the six-membered dioxane ring sit in the equatorial position, and the butenolide is connected with its carbon–oxygen bond axial as would be predicted as thermodynamically favorable using an anomeric effect argument. This stereochemistry was solved using NOESY correlative experiments, and confirmed with crystal structure analysis. The non-selective nature of the methyl stereocenter of **3h** suggests that conversion of **5** to **6** proposed in Scheme 3 is not reversible.

We then re-subjected product **3a** to the reaction conditions in the presence of benzaldehyde to gauge the reaction's reversibility.



Scheme 4. Aldehyde exchange experiments.

This experiment yielded partial incorporation of the aldehyde, but only into the position shown (Scheme 4, **3a** → **8**), consistent with our hypothesis. In this instance, approximately 30% conversion was observed, as the starting material was isolated along with **8** in a 2:1 ratio. The partial conversion is believed to be due to the lower stability of electronically poor carbonyls, thus shifting the global equilibrium to limit nitrobenzaldehyde formation.[14] To test this hypothesis, we then subjected phenyl-containing compound **3f** to the reaction conditions with 3-nitrobenzaldehyde (Scheme 4, **3f** → **9**). In this instance, full incorporation of 3-nitrobenzaldehyde was observed, leading exclusively to **9**. Regardless of the features influencing the relative incorporation, these studies demonstrate that the reaction is reversible at the steps that lend the relative stereochemistry, and help support the hypothesis that the high diastereoselectivity is thermodynamically driven.

There are several aspects of this reaction that we find noteworthy. For one, protoanemonin (**5**) is a toxic metabolite found in a variety of plants,[12] and has demonstrated efficiency as a synthon in both Diels–Alder[15] and dipolar cycloaddition reactions.[16] In both instances, the reaction takes place exclusively with the exocyclic γ-unsaturated alkene over the internal γ-unsaturated alkene, which is consistent with the proposed Prins reaction described here-in. While synthesizing protoanemonin can be done in a two step sequence from γ-angelica lactone, handling and storing protoanemonin can be troublesome, requiring stabilizers such as hydroquinone to prevent dimerization and polmerization processes.[12] Thus, the in situ generation of protoanemonin from γ-methyl-γ-hydroxybutenolide (**1**) could have synthetic advantages.

Moreover, while the selectivity of the reaction may be expected based on prior examples of anomeric effect in spiroketal synthesis,[17] to the best of our knowledge this is the first demonstration of anomeric effect-driven stereoselectivity in 1,3-dioxane-generating Prins reactions with exocyclic enol ethers. Whether other exocyclic enol ethers may behave in a similar fashion is currently unknown, but investigations are currently underway.

Finally, the complex spirocyclic molecular architecture being generated represents a new class of ketal-lactones. Ketal-lactones are prevalent in many biologically active natural products, and often contain 'extended ketals' or ketals where one of the oxygens is part of an additional ketal or acetal, similar to the molecules being generated here-in.[18] In this regard, preliminary biological studies of these new compounds are currently underway.

In summary, we have found that γ-methyl-γ-hydroxybutenolide (**1**) reacts with aromatic aldehydes in the presence of triflate acids to generate a new class of stereochemically rich spirocyclic ketal-lactones in good yields and with high diastereoselectivities. The studies lend insight into both the reactivity of γ-hydroxybutenolides and the stereoselectivity of Prins reactions on exocyclic enol ethers.

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Supplementary data

Crystal structure cif file of **3a** can be requested from Cambridge Crystallographic Database (http://www.ccdc.cam.ac.uk/) using deposition number CCDC 899874.

Supplementary data (experimental procedures and spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.139. These data include MOL files and InChiKeys of the most important compounds described in this article.

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