

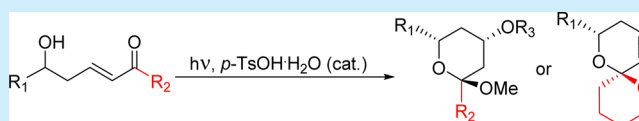
# A Mild, Diastereoselective Construction of Cyclic and Spirocyclic Ketals Employing a Tandem Photoisomerization/Cyclization Tactic

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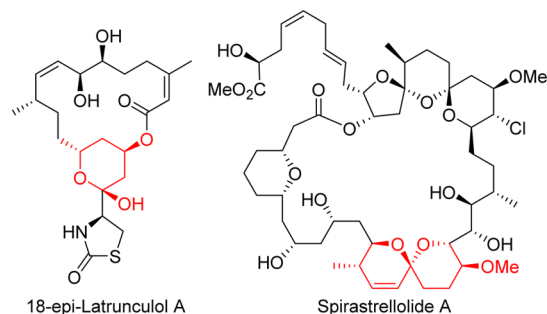
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**S** Supporting Information

**ABSTRACT:** The cyclization of *trans*- $\delta$ -hydroxy enones to cyclic mixed ketals routinely requires superstoichiometric strong acid. By operating under a photoisomerization regime, the cyclization of *trans*- $\delta$ -hydroxy enones proceeds under catalytic Brønsted acid to provide cyclic ketals or unsaturated spiroketals in a highly diastereoselective fashion. A one-pot, two-step protocol was thus developed to provide cyclic methoxy ketals with a free  $\beta$ -hydroxy group for future functionalization.



Cyclic and spirocyclic ketals comprise ubiquitous structural motifs in polyketide natural products (Figure 1).<sup>1</sup> Often decorated with substituents and a rich array of stereochemistry, the synthesis of such ketals within a natural product framework demands high functional group tolerance and diastereoselectivity.



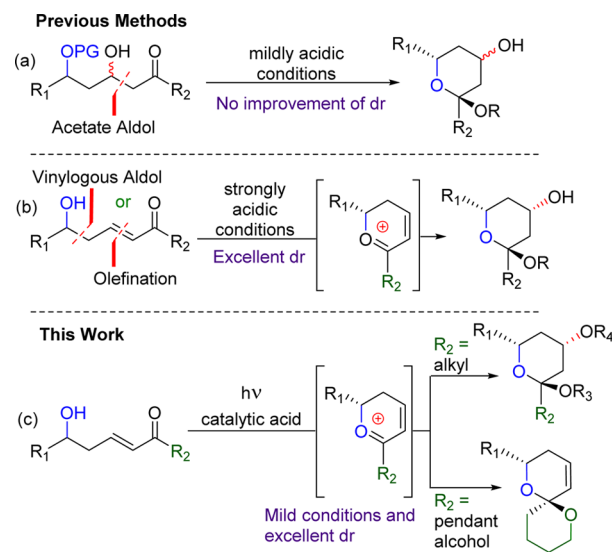
**Figure 1.** Natural products containing a cyclic hemiacetal and unsaturated spiroketal.

Dihydroxy ketones are commonly employed as precursors to cyclic ketals (Scheme 1a).<sup>2</sup> Such aldol products typically undergo cyclization upon exposure to catalytic acid in alcoholic or aqueous solvents. Synthesis of the requisite dihydroxy ketones necessitates tedious protecting group manipulations and the handling of sensitive intermediates. Moreover, the stereogenicity of the requisite  $\delta$ -hydroxy- $\alpha$ -unsubstituted ketones often arises from an acetate aldol reaction.<sup>2b,c</sup> While major advances have been achieved,<sup>3</sup> in many cases the acetate aldol reaction remains modestly diastereoselective. Alternatively,  $\delta$ -hydroxy enones have also been recognized as viable precursors to cyclic ketals (Scheme 1b).<sup>4</sup> These enones are of interest as they can be readily constructed through olefination<sup>5</sup> or vinylogous aldol reactions,<sup>6</sup> which effectively telescope the synthesis of cyclic ketals. Notably, the cross-metathesis reaction has also been employed to prepare *trans*- $\delta$ -hydroxy enones without the requirement for protecting

groups.<sup>4c,d</sup> However, broad utilization of *trans*- $\delta$ -hydroxy enones as cyclic ketal precursors in natural product synthesis has been limited due to the harsh conditions required to achieve cyclization. We became interested in developing a mild protocol for the cyclization of *trans*- $\delta$ -hydroxy enones during our total synthesis of (+)-18-*epi*-latrunculol A.<sup>4c,d</sup> The strategy level cyclization in the synthesis was highly diastereoselective yet moderate in yield due to competitive decomposition pathways under the strongly acidic conditions.

To develop mild cyclization conditions, we first examined the accepted reaction mechanism.<sup>7</sup> Importantly, the cyclization of *trans*- $\delta$ -hydroxy enones to cyclic ketals initiates through protonation of the enone carbonyl, which enables the subsequent

## Scheme 1. Synthesis of Cyclic Ketals

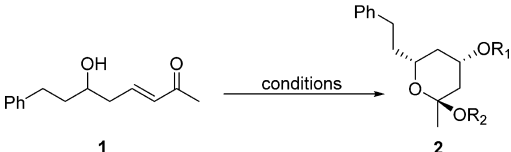


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intermolecular addition of water. The overall requirement for strong acidic conditions is presumably due both to the low basicity of the carbonyl oxygen and to the poor nucleophilicity of water. To circumvent this constraint, we envisioned that the photoisomerization of *trans*- $\delta$ -hydroxy enones in acidic media<sup>8</sup> held promise for the formation of a dynamic equilibrium, in which the *cis*-enone would cyclize and hydrate under milder conditions (Scheme 1c). We were encouraged by early reports from Snider et al. on their elegant synthesis of peroxy ketals.<sup>9</sup> Moreover, during the development of our work, Rueping<sup>10</sup> and Rovis<sup>11</sup> reported cyclization reactions utilizing tandem photoisomerization/cyclization strategies. Herein, we report a mild, acid-catalyzed photoisomerization/cyclization sequence that permits the cyclization of *trans*- $\delta$ -hydroxy enones to cyclic ketals or unsaturated spiroketals.

The development of the envisioned photoisomerization/cyclization protocol began with racemic *trans*-enone **1** as a substrate (Table 1). As expected, no cyclization occurred when **1** was exposed to catalytic toluene sulfonic acid monohydrate (*p*-TsOH·H<sub>2</sub>O) in methanol. Irradiation of **1** at 355 nm for 30 min (without acid) quickly demonstrated the proposed effective isomerization of the enone geometry. Indeed, irradiation of **1** in methanol with 10 mol % of *p*-TsOH·H<sub>2</sub>O provided quantitative conversion, as measured by <sup>1</sup>H NMR, to bis-methoxy ketal **2** as a single observable diastereomer.

**Table 1. Evaluation of a Photoisomerization-Assisted Cyclization**



entry	conditions	yield (%)
1	MeOH, <i>p</i> -TsOH·H <sub>2</sub> O (10 mol %), rt, overnight	NR
2	MeOH, <i>hν</i> (355 nm), rt, 4 h	4:1 <i>E/Z</i>
3	MeOH, <i>p</i> -TsOH·H <sub>2</sub> O (10 mol %), <i>hν</i> , rt, 4 h	100; <sup>a</sup> R <sub>1</sub> , R <sub>2</sub> = Me
4	THF/H <sub>2</sub> O, <i>p</i> -TsOH·H <sub>2</sub> O (10 mol %), <i>hν</i> , rt, 4 h	— <sup>b</sup>
5	allyl alcohol, <i>p</i> -TsOH·H <sub>2</sub> O (10 mol %), <i>hν</i> , rt, 4 h	— <sup>b</sup>
6	BnOH (25 equiv), THF <i>p</i> -TsOH·H <sub>2</sub> O (10 mol %), <i>hν</i> , rt, 4 h	94, <sup>a</sup> 5:1 dr R <sub>1</sub> , R <sub>2</sub> = Bn
7	(i) BnOH (25 equiv), THF, <i>p</i> -TsOH·H <sub>2</sub> O (10 mol %), <i>hν</i> , rt, 4 h (ii) Pd/C, H <sub>2</sub> (600 psi), MeOH, rt, 1.5 h	83%, ≥20:1 dr R <sub>1</sub> = H, R <sub>2</sub> = Me

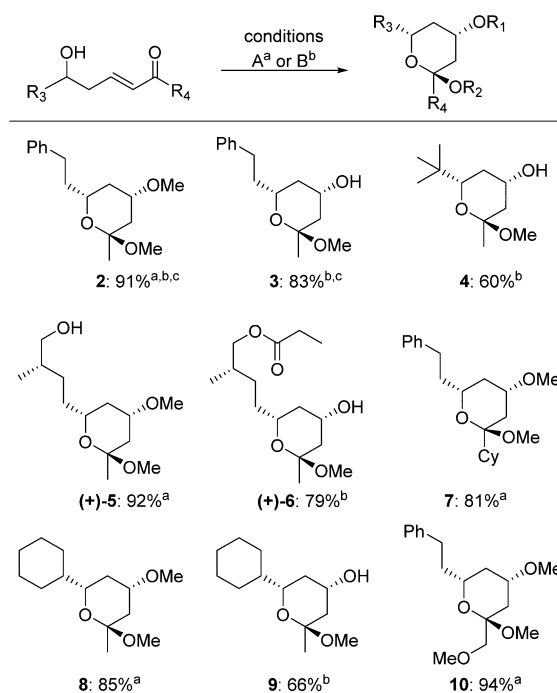
<sup>a</sup>Determined by <sup>1</sup>H NMR analysis using hexamethyldisilane as an internal standard. <sup>b</sup>A complex mixture was obtained.

While chiral methyl ethers are indeed prevalent in nature,<sup>1a</sup> we were cognizant that obtaining a free secondary hydroxyl from this cyclization would enable greater diversification of the cyclized products. Toward this end, **1** was irradiated in the presence of aqueous acid; unfortunately, a complex mixture of products was obtained. We turned to alcohol solvent with potentially removable alkyl groups, such as allyl alcohol and benzyl alcohol. Allyl alcohol provided substantial decomposition upon irradiation; alternatively, employing a mixture of benzyl alcohol and THF delivered bis-benzylated ketal **2** (R<sup>1</sup> and R<sup>2</sup> = Bn) in a 94% yield (5:1 dr). To obtain a ketal with a free secondary hydroxyl (**2**; R<sup>1</sup> = H) from the reaction, the development of a two-step, one-pot cyclization/hydrogenation procedure was then ex-

plored. The subsequent investigation revealed that the bis-benzyloxy ketal (**2**; R = OBn) could be converted in situ to a methoxy ketal containing a free secondary alcohol after a solvent swap for a methanol/THF mixture and hydrogenation employing catalytic palladium on carbon (Table 1, entry 7).

The scope of the devised photoisomerization/cyclization to provide bis-methoxy ketals, as well as the two-step, one-pot reaction, was next evaluated with several *trans*- $\delta$ -hydroxy enones (Scheme 2). Enones containing various functional groups were subjected to the cyclization protocol to provide methyl ketals with a  $\beta$ -methoxy group in high yields. The two-step, one-pot protocol also provided several ketals with a free  $\beta$ -hydroxyl group as a functional group handle in high yields. Excellent diastereoselectivities were obtained for all reactions (>20:1 dr, via <sup>1</sup>H NMR). Additionally, the optimized reaction conditions can tolerate sterically encumbering groups adjacent to the secondary alcohol (Scheme 2, **4** and **8**), although diminished yields were obtained. Interestingly, while steric bulk next to the carbonyl is tolerated in the cyclization, the ensuing hydrogenation is significantly slower.

**Scheme 2. Scope of Photoisomerization/Cyclization**



<sup>a</sup>Condition A: *hν* (355 nm), MeOH, *p*-TsOH·H<sub>2</sub>O (10 mol %), rt, 4 h

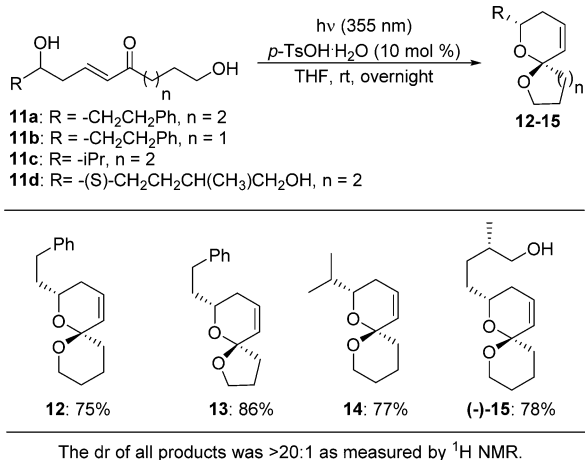
<sup>b</sup>Condition B: 1) *hν* (355 nm), BnOH (25 equiv), *p*-TsOH·H<sub>2</sub>O (10 mol %), THF, rt, 4 h 2) 10% Pd/C (5 wt % to BnOH), H<sub>2</sub> (600 psi), MeOH:THF = 1:1, rt, 1.5 h <sup>c</sup>The dr of all products was >20:1 as measured by <sup>1</sup>H NMR

Having developed an approach to cyclic ketals with varying functionality, we turned to the possibility of utilizing enones with two free hydroxyl groups, in what appears to be an unprecedented method to construct unsaturated spiroketals. Moreover, given our interest in the total synthesis of spirastrellolide (Figure 1),<sup>12</sup> we were familiar with the requirement for mild conditions to perform such spirocyclizations.

Toward this end, subjecting diol **11a** (Scheme 3) to catalytic *p*-TsOH·H<sub>2</sub>O in THF under irradiation (355 nm) resulted in the smooth formation of the unsaturated spiroketal **12** in 75% yield as a single diastereomer. Exploration of the scope of this transformation yielded 6,5- and 6,6-unsaturated spiroketals (**12**—

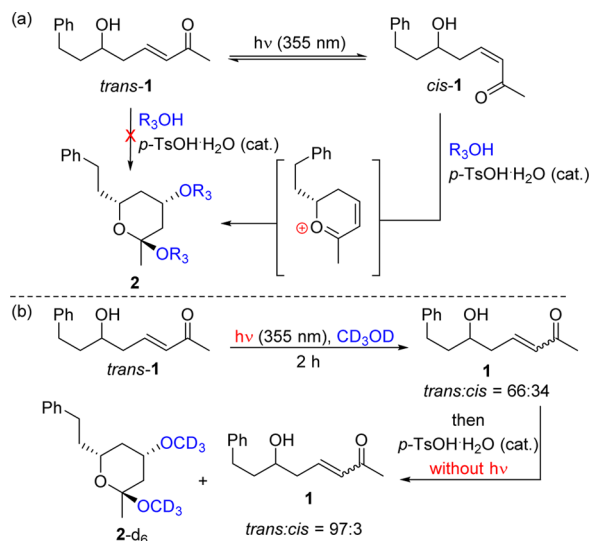
15) in good yields with varying steric constraints next to the secondary alcohol. The reaction also tolerated the use of an additional unprotected hydroxyl group to provide spiroketal (–)-15.

**Scheme 3. Photoisomerization/Spirocyclization Sequence**



Finally, to explore the mechanism of this protocol (vide supra), *trans*-enone **1** (Scheme 4a) was irradiated (355 nm) to give the expected mixture of olefin isomers (Scheme 4b). This mixture was then treated with 10 mol % of *p*-TsOH·H<sub>2</sub>O and stirred in the dark. In accordance with our proposal, the *cis*-isomer preferentially underwent cyclization, thus enriching the remaining enone mixture with the *trans*-isomer.

**Scheme 4. (a) Rationale for Facile Cyclization under Photochemical Conditions and (b) <sup>1</sup>H NMR Monitoring of the Photoisomerization/Cyclization Sequence**



In summary, we have developed a mild photochemical protocol for the cyclization of  $\delta$ -hydroxy enones to cyclic ketals or unsaturated spiroketals. The reaction proceeds with high functional group tolerance, requires only catalytic acid, and provides cyclic products in moderate to high yields with high diastereoselectivities. Efforts directed at the expansion of this work, employing alternative nucleophiles, is currently underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Author Contributions

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### Notes

The authors declare no competing financial interest.

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