Highly Stereoselective Oxy-Michael Additions to β,γ-Unsaturated α-Keto Esters: Rapid Enantioselective Synthesis of 3-Hydroxybutenolides
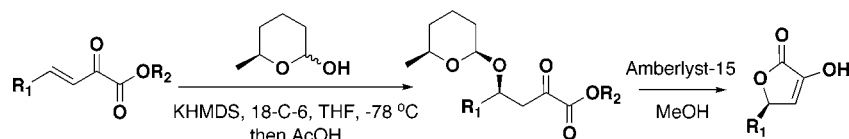
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ABSTRACT

The highly diastereoselective oxy-Michael addition of the "naked" anion of (6*S*)-methyl δ-lactol to γ-substituted β,γ-unsaturated α-keto esters leading to the direct formation of THP*-protected γ-hydroxy α-keto ester derivatives is described. Subsequent acid-mediated deprotection affords the 3-hydroxybutenolides in high yields.

The stereoselective addition of oxygen-centered nucleophiles is an emerging area in the Michael addition field.[1] Our group[2] and others[3] have been involved with the development of

chiral water equivalents for the addition to reactive nitro olefin-[4] and malonate-derived acceptors.[5] Although useful for the asymmetric synthesis of 1,2-amino alcohols and protected β-hydroxy esters, we believed an extension of this chemistry to incorporate other types of Michael acceptors, while maintaining reaction efficiency and diastereoselectivity, would expand significantly the utility and scope of the reaction.

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Table 1. Stereoselective Oxy-Michael Addition of the "Naked" Anion of **1** to a Range of β,γ-Unsaturated α-Keto Ester Acceptors

adduct[a]	R₁	R₂	yield/%	de/%[b]
3a	phenyl	Et	76	>95
3b	phenyl	Me	68	>95
3c	Br–C₆H₄	Me	80	>95
3d	Cl–C₆H₄	Me	73	>95
3e	naphthyl	Me	67	>95
3f	methyl	Et	60	>95
3g	n-butyl	Me	69	>95
3h	cyclohexyl	Me	77	>95
3i[c]	tert-butyl	Me	81	>95

[a] Adducts are prone to retro-Michael decomposition during chromatography; elution with chilled solvents is necessary (see the Supporting Information). [b] The minor diastereomer cannot be detected by analysis of the 300 or 500 MHz ¹H NMR spectra of the crude reaction product. [c] Isolated as a mixture of keto/enol isomers.

Herein, we wish to describe a highly diastereoselective oxy-Michael reaction of a chiral water equivalent to γ-substituted β,γ-unsaturated α-keto esters.[6] β,γ-Unsaturated α-keto esters are readily prepared by the condensation of pyruvate esters with aldehydes[7] and have been identified as reactive substrates in diastereo- and enantioselective Michael addition reactions.[6,8] We believed a stereoselective addition of a chiral water equivalent to such acceptors would constitute a powerful extension to the field as the adducts would have considerable synthetic utility; the high density and placement of functional groups and the abundance of β-hydroxy ketones in natural products[9] all supported the underlying need for the development of such methodology.[10]

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To provide an initial proof of principle study, γ-phenyl-substituted acceptor **2a** was chosen as a test substrate. The initial conditions adopted were identical to those previously established for the addition to β-substituted nitro olefin acceptors.[2] Thus, deprotonation of the diastereomeric mixture of (6S)-methyl δ-lactol **1** with KHMDS in THF at −78 °C and addition of 18-crown-6 (1.0 equiv) generated the "naked" chiral lactol alkoxide nucleophile (Table 1). Addition of **2a** (0.67 equiv) to this mixture, stirring for 2 h, and quenching with acetic acid (2.0 equiv) at −78 °C afforded, after aqueous workup, the crude oxy-Michael adduct **3a** in a pleasing >95% de and, after purification by flash column chromatography, in 76% yield. The necessity for 18-crown-6 in the reaction was confirmed by repeating the above protocol in its absence; **3a** was formed in a much diminished 33% de. The stereochemistry was assigned by analogy with previous oxy-Michael reactions using the naked anion of (6S)-methyl δ-lactol.[2]

Having identified **2a** as a suitably reactive substrate, the scope of the oxy-Michael addition to a range of γ-substituted β,γ-unsaturated α-keto esters was probed. Acceptors were chosen to contain simple esters and the γ-substituent varied between both aromatic and aliphatic groups (Table 1), the oxy-Michael addition products (**3a–i**) were obtained with consistently excellent diastereoselectivities (>95% de) and good yields (60–81%).

As well as inducing excellent levels of stereocontrol on addition to the electron poor alkenes, the tetrahydropyranyl ether moiety (THP*) is easily removed to reveal the parent alcohol functionality. To demonstrate the readiness of this removal, a range of adducts were subjected to methanol containing Amberlyst-15 resin (Table 2).

Table 2. Acid-Mediated Deprotection, Cyclization, and Enolization of Oxy-Michael Adducts

product	R¹	yield/%	ee[a]/%
4a	phenyl	87	>95[a]
4b	cyclohexyl	97	>95[b]
4c	tert-butyl	93	>95[b]
4d	n-propyl	97	>95[c]

[a] Enantiomeric excesses were determined by chiral HPLC using a Chiralcel AS column eluting with [a]hexane/IPA 98:2, 254 nm, 1 mL/min; [b]hexane/IPA 90:10, 220 nm, 1 mL/min; [c]hexane/IPA 97:3, 220 nm, 1 mL/min.

In all reactions, the hydroxybutenolide products **4** were isolated from the reaction mixture in excellent yields. Thus, the acid facilitated a smooth three step process; THP*

removal, lactonization, and enolization. The enantiomeric excesses of **4a**−**d** were measured as >95% ee by chiral HPLC analysis and confirmed that no racemization was occurring in the sequence.

In summary, the naked anion of enantiopure 6-methyl δ-lactol undergoes highly diastereoselective oxy-Michael additions to a range of γ-substituted β,γ-unsaturated α-keto esters. The reactions provide a new approach to γ-hydroxy α-keto ester compounds complimentary to aldol strategies. The products may be converted efficiently to butenolide compounds using a polymer-supported acid in methanol. Owing to the abundance of the butenolide motif in natural products, this chemistry should provide a solid synthetic basis for their asymmetric synthesis, and applications toward these goals will be reported in due course.

Supporting Information Available: Experimental procedures, NMR spectra (**3a**−**i** and **4a**−**d**), and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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