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# Trans-Selective Conversions of γ-Hydroxy-α,β-Alkynoic Esters to γ-Hydroxy-α,β-Alkenoic Esters

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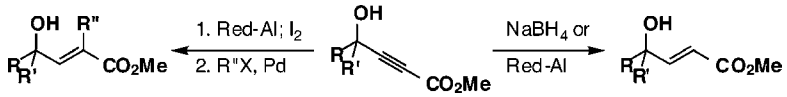
## ABSTRACT




**γ-Hydroxy-α,β-acetylenic esters are used as precursors to prepare γ-hydroxy-α,β-alkenoic esters by means of trans-selective additions of two hydrogen atoms or one hydrogen atom and one iodine atom across the triple bonds. These methods allow for the preparation of β-substituted and α,β-disubstituted alkenoic esters in highly stereoselective manners.**

Stereoselective alkene synthesis is an important topic in organic synthesis.[1] Of particular interest are the preparation of α,β-alkenoic esters because these compounds are versatile synthetic intermediates[2,3] and are contained in many natural products.[4] This class of compounds has been prepared by several different methods,[3,5,6] among which the most common method is the Wittig approach. The shortcomings of the Wittig approach are that α-alkoxy (or hydroxy) aldehydes are prone to epimerization and that an α-alkoxy group often influences the *E*:*Z* selectivity of the Wittig reactions, often generating a mixture of stereoisomers.[6,7]

Alternatively, γ-hydroxy-α,β-acetylenic esters **A**, which can be prepared enantioselectively by known methods[8] in several steps from the corresponding aldehydes, have potential to be excellent precursors for **B** (Scheme 1). However, the conversion of **A** to **B** is extremely rare,[9] presumably due to the lack of a general method for achieving trans addition of two hydrogen atoms across the triple bond in a kinetically controlled manner. (*E*)-selective reductions of propargylic

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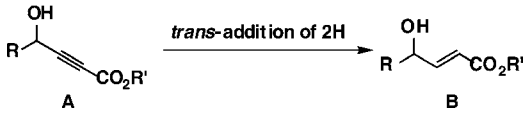
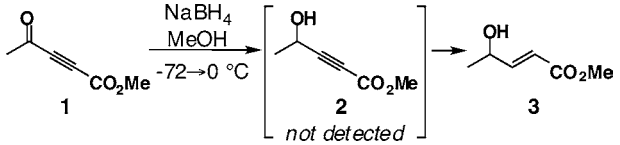
**Scheme 1.** Trans-Selective Reduction of Acetylenic Esters




alcohols are known, calling for $LiAlH_4$−NaOMe in THF at reflux[10] or $NaAlH_2(OCH_2CH_2OCH_3)_2$ (Red-Al) at room temperature.[11] However, these reaction conditions are not compatible with many functional groups. Herein, we report a general method for preparing **B** from **A** by a simple procedure using readily available sodium borohydride or Red-Al at lower temperatures.

Recently, we reported the reduction of ketone **1** to form (*E*)-enoate **3** (Scheme 2).[12] We hypothesized that this

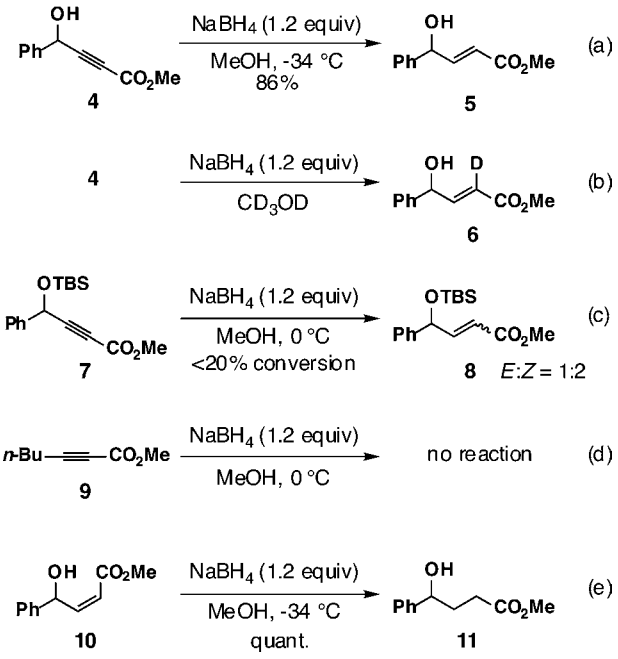
**Scheme 2.** Trans-Selective Reduction of $\gamma$-Keto-$\alpha,\beta$-acetylenic Ester **1**




unexpected stereoselective reduction of the ynoate proceeded through intermediate **2**.

To test this hypothesis, we treated alcohol **4** with $NaBH_4$ at −34 °C in methanol and found that (*E*)-enoate **5** was formed in 86% isolated yield (Scheme 3, eq a). We were

**Scheme 3.** Control Experiments to Elucidate the Mechanism of the Trans-Selective Reduction of Acetylenic Esters




not able to detect any other byproducts even when this reaction was performed in an NMR tube in $CD_3OD$ (from −72 to 20 °C) in an attempt to detect minor products.

To gain insight into the mechanism of this stereoselective reduction, this reaction was carried out in $CD_3OD$ (eq b). Subsequently, the deuterated compound **6** was isolated as a sole product, suggesting the conjugate addition of a hydride at C-3 of **4**. To address the role of the hydroxy group at the $\gamma$-position in this stereoselective reduction of **4**, the TBS-protected derivative **7** was subjected to the same reaction conditions (1.2 equiv of $NaBH_4$ in MeOH at −30 °C), which resulted in the recovery of the starting material in a quantitative yield. When this reduction was carried out at 0 °C for 1 h, the NMR spectrum of the resulting crude mixture showed the presence of approximately 15% enoates **8** (*E*:*Z* = 1:2) together with 80% of the starting material (eq c). We also treated acetylenic ester **9** with $NaBH_4$ in methanol at 0 °C, which resulted in the recovery of the starting material in nearly quantitative yield (eq d). These results suggest that the reduction of **4** to **5** is facilitated by the $\gamma$-hydroxy group, and this hydroxy group is involved in *E*/*Z* stereocontrol. To determine whether this reduction was a thermodynamic or a kinetic process, $NaBH_4$ was added to a solution of (*Z*)-enoate **10** in methanol at −34 °C. The olefin was reduced to the saturated methyl ester **11**, and no trace of (*E*)-olefin **5** was detected (eq e). This result indicates that *the reduction of* **4** *to* **5** *is kinetically controlled*.

This (*E*)-selective reduction of acetylenic esters appears to be general, as shown in Table 1. Upon treatment of the acetylenic esters **2** and **4** with $NaBH_4$ in methanol (condition **a**), the corresponding (*E*)-enoates **D** were obtained in good to excellent yields with little **E**. The base-sensitive *N*-Fmoc group of alcohol **12**[13] was found to be compatible with this method, providing the corresponding (*E*)-enoate in quantitative yield with excellent (*E*)-selectivity ((*Z*)-isomer was not detectable). Sterically more hindered alcohols **13** and **14** gave somewhat compromised stereoselectivities.

To further improve the (*E*)-selectivities of the sterically hindered alcohols **13** and **14**, we turned our attention to other reducing agents. After screening various reducing agents,[14] we found that Red-Al showed excellent (*E*)-selectivities in the reduction of alcohols **13** and **14** to form the corresponding $\alpha,\beta$-alkenoic esters (Table 1, condition **b**). It is noteworthy that the $^1H$ NMR analyses of the crude mixtures of these two reactions indicate that neither formations of the corresponding (*Z*)-enoates or saturated compounds nor reduction of the methyl esters occurred. To test the compatibility of this Red-Al reduction with an epoxide, compound **15**[11] was treated with Red-Al at −72 °C for 25 min to afford the

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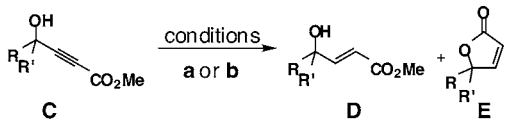
(14) Besides $NaBH_4$ and Red-Al, we tested $NaBH_3CN$, *n*-$Bu_4NBH_4$, and $BH_3$, none of which afforded the desired product.

**Table 1.** Scope of $NaBH_4$ and Red-Al Reductions of Acetylenic Esters C[a]



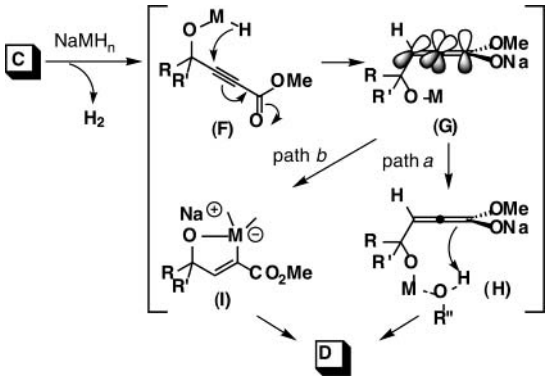

| substrate | conditions | isolated yield (%) | D:E |
|---|---|---|---|
| **2** | a | 70 | **2D** only (**2D** = **3**) |
| **4** | a | 86 | **4D** only (**4D** = **5**) |
| FmocHN (**12**) | a | quant. | **12D** only |
| *c*-Hex (**13**) | a | 75 | 5.5:1 |
| | b | 80 | **13D** only |
| (**14**) | a | 60 | 4:1 |
| | b | 77 | **14D** only |
| (**15**) | b | 80 | >40:1 |

[a] Reagents and conditions: (a) $NaBH_4$ (1.2−4 equiv), MeOH, −34 to 0 °C, 15−50 min; (b) Red-Al (2 equiv), THF, −72 °C, 25 min.

corresponding (*E*)-alkenoate in 80% yield. Therefore, the $NaBH_4$- or Red-Al-mediated (*E*)-selective reductions of acetylenic esters are compatible with both the base-sensitive *N*-Fmoc group and the electrophilic epoxide.

We speculate that this unusual trans addition of two hydrogen atoms across the C−C triple bond can be accounted for by either of the following mechanisms (Scheme 4). First, both Red-Al and $NaBH_4$ react with alcohol **C** to form intermediate **F**. Then, a hydride is delivered intramolecularly

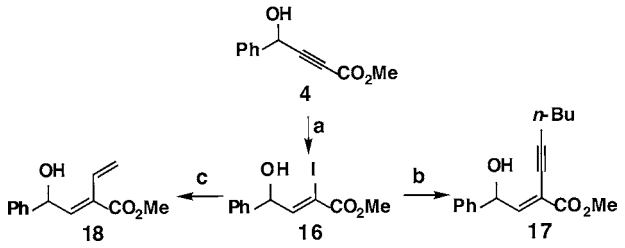
**Scheme 4.** Plausible Mechanisms




to form allenolate **G**. We postulate two possible pathways from this point. Either allenolate **G** reacts with MeOH or $H_2O$ acidified by the Lewis acid formed at the bottom face of the allenolate as shown in **H** (path *a*) or ate complex **I** reacts with MeOH or $H_2O$ to form compound **D**. These working hypotheses imply wide applications of this method by using other electrophiles.

To extend the application of the trans-selective Red-Al-promoted conjugate addition toward acetylenic esters, the Red-Al reduction of **4** was quenched with $I_2$ rather than water (Scheme 5). Subsequently, we isolated vinyl iodide **16** in

**Scheme 5.** Preparations of Highly Functionalized, α,β-Disubstituted Alkenoates[a]




[a] Reagents and conditions: (a) Red-Al (1.5 equiv), −72 °C, 25 min; then $I_2$ (5.0 equiv), −72 → −10 °C, THF, 2 h, 78%; (b) 1-hexyne (2.0 equiv), $Pd(Ph_3P)_4$ (10 mol %), CuI (5 mol %), *i*-$Pr_2NH$ (excess), 23 °C, 6 h, 64%; (c) $CH_2$=$CHSnBu_3$ (1.2 equiv), $Pd(Ph_3P)_2Cl_2$ (2 mol %), DMF, 23 °C, 48 h, 45%.

78% yield.[15] This vinyl iodide could be transformed into disubstituted alkenoates **17** (64% yield; not optimized) and **18** (45% yield; not optimized) by means of Sonogashira coupling and Stille coupling, respectively. These two-step schemes have potential for the preparation of highly conjugated disubstituted alkenoates in a trans-selective manner.

In conclusion, we have developed a general method for preparing synthetically versatile (*E*)-enoates **D** and (*Z*)-enoate **16** from acetylenic esters **C** under mild conditions. The working hypothesis depicted in Scheme 4 indicates that it is possible to further functionalize intermediate **G** or **I** with other electrophiles.

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**Supporting Information Available:** $^1H$ NMR, $^{13}C$ NMR, IR, and HRMS data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (*Z*)-geometry of vinyl iodide **16** was determined by means of a NOESY experiment after the DIBALH reduction of a closely related compound (see Supporting Information for details).