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A simple procedure for the synthesis of γ-hydroxy-α,β-(*E*)-alkenoic esters: formal synthesis of (+)-macrosphelides A and B☆

K. Srinivasa Rao,[a,b] K. Mukkanti,[b] D. Srinivasa Reddy,[a] Manojit Pal[a] and Javed Iqbal[a,*]

[a]*Discovery Research, Dr. Reddy's Laboratories Ltd, Bollaram Road, Miyapur, Hyderabad 500 049, AP, India*
[b]*Chemistry Division, Institute of Science and Technology, JNT University, Kukatpally, Hyderabad 500 072, AP, India*

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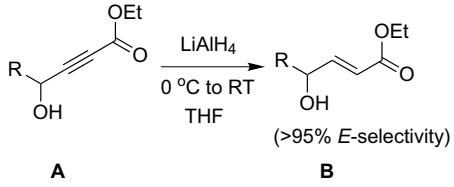
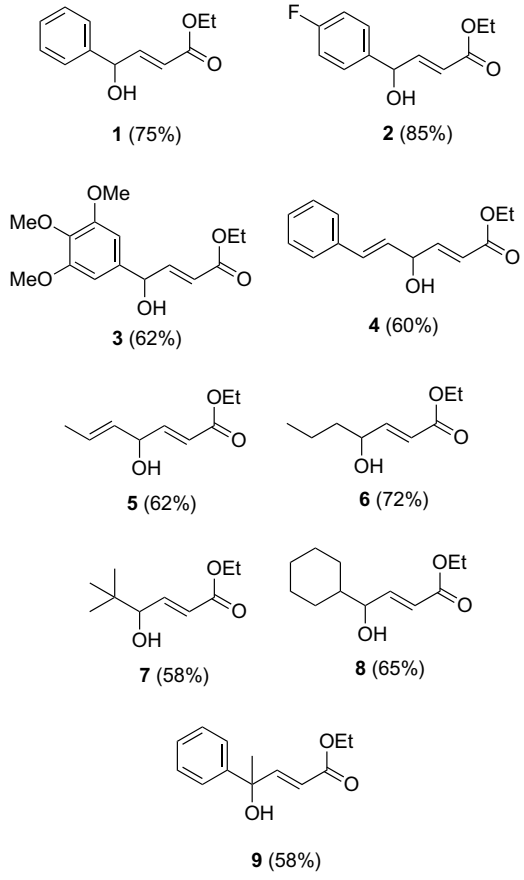
Abstract—A highly *trans*-selective conjugate reduction of γ-hydroxy-α,β-alkynoic esters to produce γ-hydroxy-α,β-(*E*)-alkenoic esters using $LiAlH_4$ is reported. The application of this methodology is demonstrated by a formal synthesis of the potent cell–cell adhesion inhibitors (+)-macrosphelides A and B.

γ-Hydroxy-α,β-alkenoic esters are versatile building blocks in the synthesis of complex natural products and heterocycles.[1] However, there are only limited methods available to access this important group of compounds.[2] The most popular is the Wittig method for the synthesis of γ-hydroxy-α,β-alkenoic esters but it suffers from the limitation that the starting α-hydroxy aldehydes are prone to epimerization under basic conditions.[2]

In this letter, we disclose a general method for the efficient and highly *trans*-selective conjugate hydride addition on γ-hydroxy-α,β-alkynoic esters using $LiAlH_4$ as the hydride source (Scheme 1).[3,4] The potential use of



Scheme 1.



Scheme 2.

Keywords: Conjugate reduction; γ-Hydroxy-α,β-alkenoic esters; Macrosphelide.

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* Corresponding author. Tel.: +91 40 2304 5439; fax: +91 40 2304 5438; e-mail: javediqbaldrf@hotmail.com

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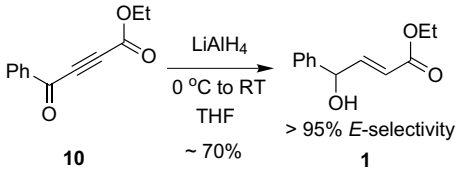
the resulting γ-hydroxy-α,β-alkenoic esters in complex natural product synthesis was demonstrated by a formal synthesis of (+)-macrosphelides A and B, which are potent, orally bioavailable, inhibitors of cell–cell adhesion.

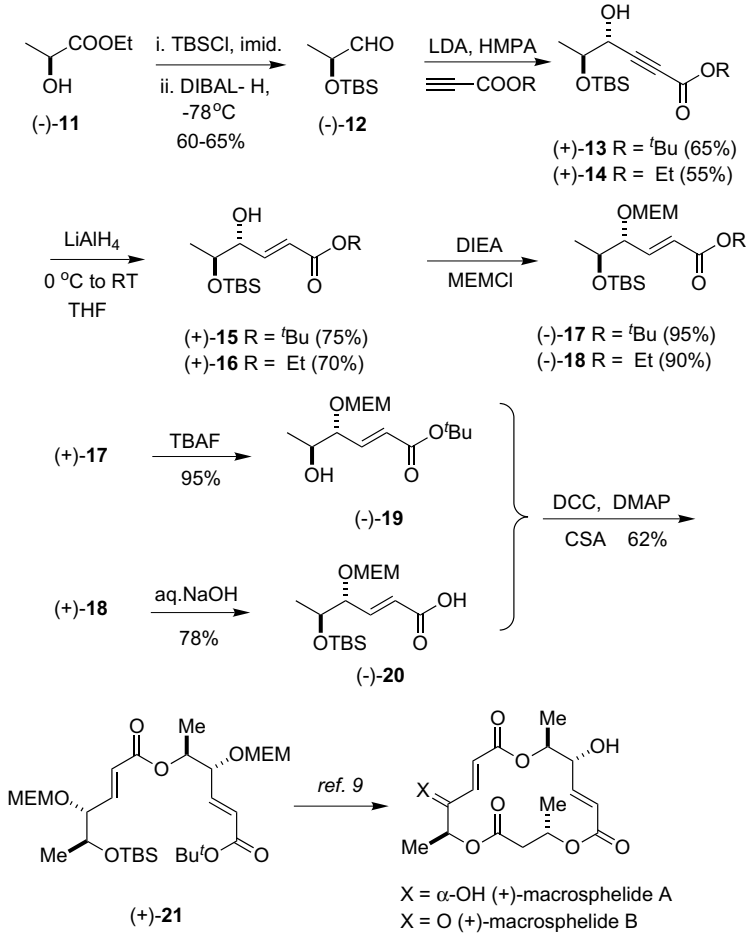
Initially, we chose a phenyl substituted acetylene substrate and carried out $LiAlH_4$ reduction to produce the corresponding (*E*)-alkenoic ester **1** in 75% yield with >95% (*E*)-selectivity. After a few attempts, we found that the use of one equivalent of $LiAlH_4$ in dry THF or diethyl ether at 0 °C to rt were the optimum conditions for this method.[5] Next we generalized the method for other substrates. All the starting γ-hydroxy-α,β-alkynoic esters (**A**) were synthesized from the corresponding aldehydes by coupling with ethyl propiolate in the presence of LDA as previously described.[6] We found that our procedure worked well with a variety of R groups, which include phenyl, alkyl, and vinyl groups (see **2**–**8** in Scheme 2). Stereoelectronic factors had little or no effect on this reaction and it is worth mentioning that the product **9** could be readily obtained from the corresponding tertiary alcohol in good yield (Scheme 2). In spite of the moderate yields in these reactions, we did not observe significant amounts of over-reduced by-products.

The excellent *E*-stereoselectivity (>95%) in these reactions may arise due to reasons reported earlier by others in a similar hydride mediated reduction.[3,4] In another example (conversion of **10** to **1**), we showed that γ-keto-α,β-alkynoic esters[7] can be directly reduced to γ-hydroxy-α,β-alkenoic esters without effecting the selectivity (Scheme 3).

The utility of the γ-hydroxy-α,β-alkenoic esters was readily demonstrated by a formal synthesis of (+)-macrosphelides A and B via Omura's advanced intermediate (+)-**21**. Macrosphelides are novel 16-membered macrolides isolated from *Microspheraeropsis* sp. FO-5050 and have been reported to inhibit strongly the adhesion of human leukemia HL-60 cells to human-umbilical-vein endothelial cells (HUVETC). Thus, these macrolides may serve as valuable leads for the development of anticancer drugs.[8] In addition to their biological profile, the presence of three lactone moieties along with four stereogenic centers offers an attractive synthetic



Scheme 3.



Scheme 4.