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A Facile Route to Acyclic Substituted α,β-Unsaturated Aldehydes: The Allene Claisen Rearrangement

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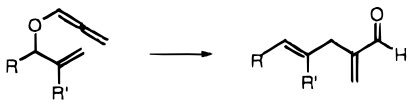
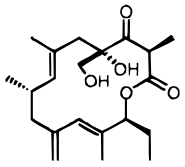
ABSTRACT



Sigmatropic rearrangement of allenyl ethers furnishes α,β-unsaturated aldehydes in good yield.

In our synthetic approach to the antifungal agent galbonolide B[1] (**1**) we required the highly substituted unsaturated aldehyde **2**. Retrosynthetic analysis of **2** revealed that an



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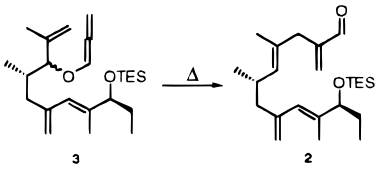
allene variant of the Claisen rearrangement[2] should provide the unsaturated aldehyde moiety in one synthetic operation (Scheme 1).

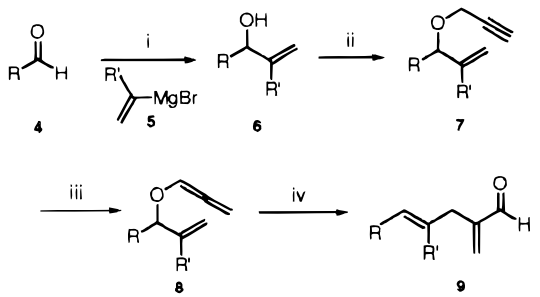
Scheme 1



The literature revealed that Sleeman[3] and co-workers had synthesized highly substituted allenyl ethers as suicide substrates for chorismate mutase enzymes. Dulcère et al have reported a cyclic variant of the allene Claisen rearrangement,[4] but to our knowledge no work has appeared on the rearrangement of acyclic allenyl ethers such as **3** for the formation of α,β-unsaturated aldehydes. In this paper we describe a convenient route to α,β-unsaturated aldehydes from a range of aldehydes selected as part of our model study work.

The allenyl ethers[5] were synthesized according to the general route outlined in Scheme 2. A range of aldehydes (**4**) were reacted with propenylmagnesium bromide (**5**) to form, after aqueous workup, the expected allylic alcohols

Scheme 2[a]



[a] (i) vinyl/propenylmagnesium bromide/THF/−78 °C. (ii) NaH/propargyl bromide/THF/reflux. (iii) KO^{t}Bu/THF; (iv) Δ.

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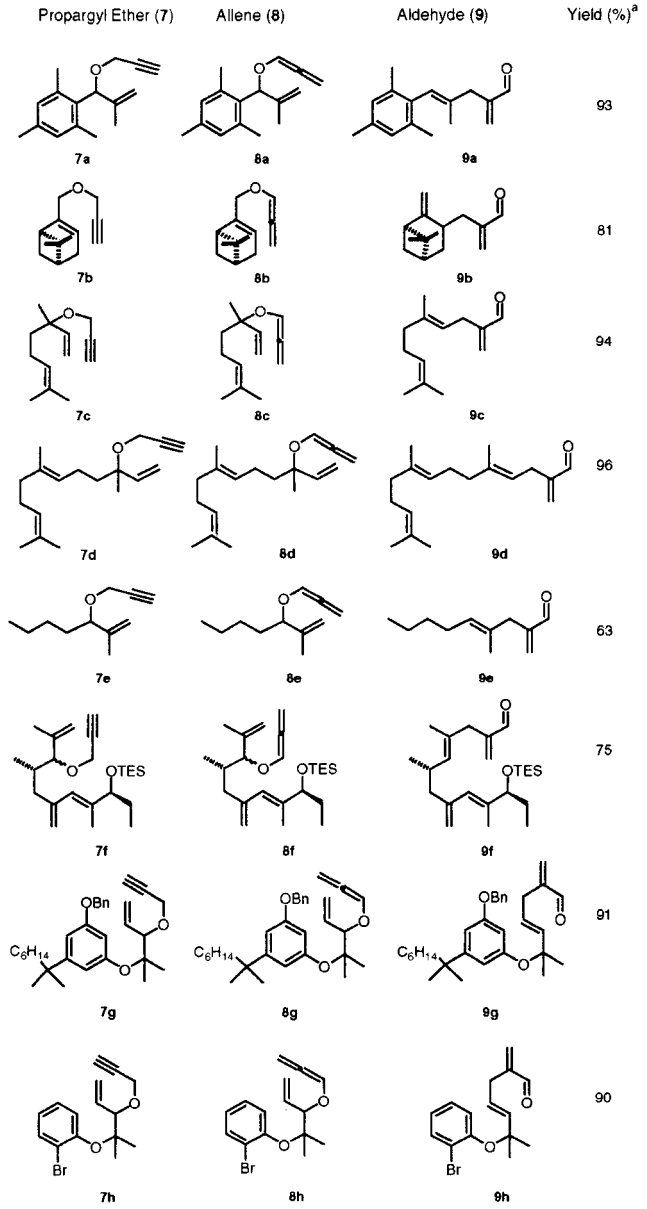
Table 1. Transformation from Propargyl Ethers to α,β-Unsaturated Aldehydes via the Allenyl Ether



[a]Yields quoted are for the transformation of the allene to the α, β-unsaturated aldehyde.

(**6**). Conversion of the alcohols (**6**) into the propargyl ethers (**7**) was achieved using propargyl bromide in the presence of sodium hydride. Reaction of the ethers (**7**) with potassium *tert*-butoxide gave the allenes (**8**) in high yield.[6] Thermolysis of the allenes (**8**) in dry dimethylformamide at 120 °C (**9a**−**f**, method A) or in dry benzene at 80 °C (**9g,h**, method B), gave the desired aldehydes in good yield (Table 1).[7]

Although the di- and trisubstituted double bonds in **9a** and **9e**−**h** were formed predominantly (97%) as the *E* isomers, **9c** and **9d** were isolated as mixtures of geometric isomers (60:40 *E*/*Z*).

This simple rearrangement sequence offers a one-step alternative to the Mannich reaction and a useful route to allylic alcohols for further iterative elaboration by allene Claisen rearrangements.

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(7) A typical experimental procedure is as follows: (ii) Formation of propargyl ether; sodium hydride 95% (0.061 g, 2.4 mmol) was added to alcohol **7h** (0.540 g, 2.0 mmol) with stirring in THF (15 cm^3), and the reaction mixture was then refluxed for 1 h under nitrogen to give a yellow solution. Propargyl bromide was added (0279 g, 2.1 mmol), and the reaction mixture was refluxed for a further 8 h, allowed to cool, and then partitioned between diethyl ether (20 mL) and water (30 mL). The aqueous phase was then extracted with diethyl ether (2 × 20 mL), and the organic phases were combined, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash silica chromatography, eluting with 5% diethyl ether in petroleum ether, afforded the product as a colorless oil (0.585 g, 95% yield). (iii) Isomerization to the allenyl ether; potassium *tert*-butoxide (0.181 g, 162 mmol) was added in one portion to a stirred solution of the propargyl ether **8h** (0.500 g, 1.62 mmol) in dry THF (30 mL) to give immediately a dark brown solution. The reaction mixture was stirred for 4 h at room temperature before being passed through a silica plug to remove the color impurity, yielding the allenyl ether as a colorless oil (0.491 g, 98%). (iv) Claisen rearrangement Method A: to the allenyl ether (typically around 1−2 mmol) was added dry dimethylformamide (30 mL), and the reaction mixture was heated to 120 °C for 1 h and then cooled to room temperature. The reaction mixture was partitioned between diethyl ether (100 mL) and water (300 mL), and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo to afford the desired aldehydes as amber oils. Method B: to the allenyl ether (typically around 1−2 mmol) was added dry benzene (30 mL). The reaction mixture was heated to reflux for 10 h, cooled to room temperature, and concentrated in vacuo to afford the desired aldehydes as amber oils.