Specific Hydromagnesiation of Prop-2-ynylic Alcohols. A Simple and Specific Route to Terpenoids

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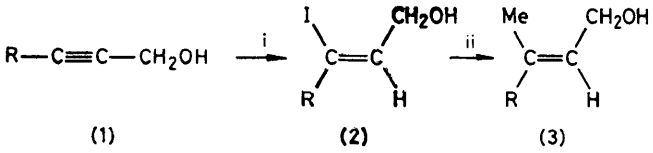
Summary Hydromagnesiation of prop-2-ynylic alcohols proceeds with stereo- and regio-specificity, affording, under mild conditions, the alkenylmagnesium halides (**5**) in almost quantitative yields, thus providing a novel and simple route to terpenoids.

REDUCTION of prop-2-ynylic alcohols (**1**) with lithium aluminium hydride in the presence of sodium methoxide and subsequent treatment with iodine yields the (*Z*)-3-iodoalk-2-en-1-ols (**2**). Treatment with lithium dimethylcuprate then gives the (*E*)-3-methylalk-2-en-1-ols (**3**)

(Scheme 1).[1] This reduction–alkylation sequence has been used in an elegant synthesis of C-18 cecropia juvenile hormone.[2] We report here a novel method for the specific one-pot conversion of (**1**) into the stereoisomers of (**2**) or (**3**), and its application in the isoprenoid field.

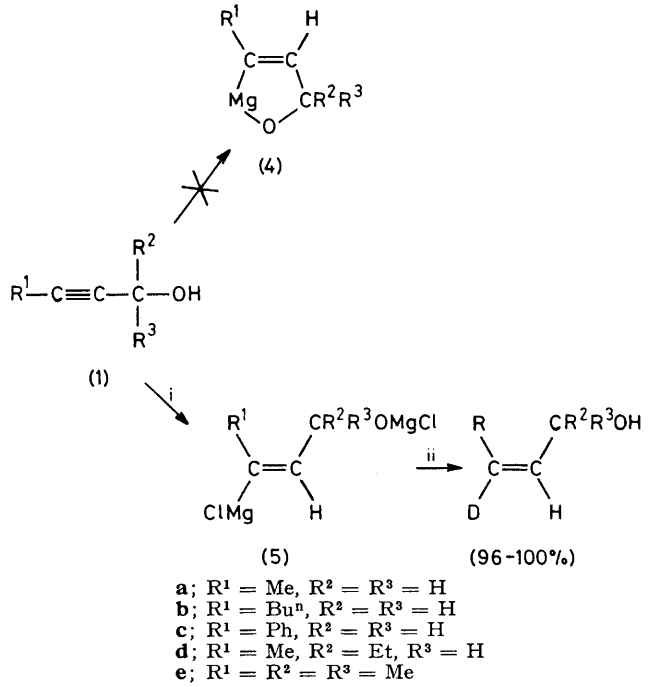


SCHEME 1. *Reagents*: i, $LiAlH_4$, NaOMe, then I_2; ii, $LiCuMe_2$.

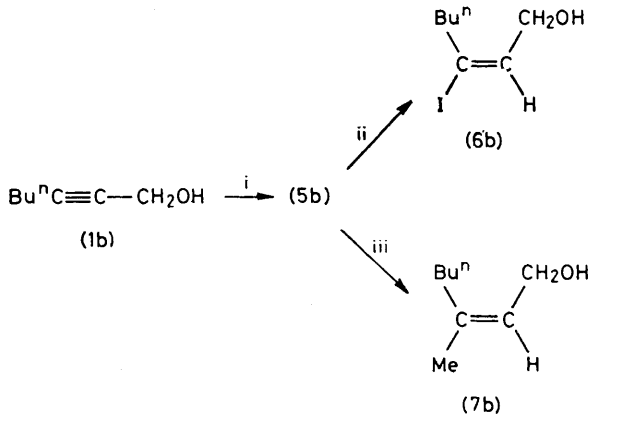
We recently reported that disubstituted acetylenes are readily hydromagnesiated by isobutylmagnesium halides in the presence of a catalytic amount of $(\eta^5\text{-}C_5H_5)_2TiCl_2$ affording *E*-alkenylmagnesium halides exclusively. The regiochemistry is strongly influenced by the substituent and the regiospecificity is high for alkylarylacetylenes and silylacetylenes.[3]

We have now investigated the hydromagnesiation of prop-2-ynylic alcohols. We were initially interested in determining the effect of the prop-2-ynylic hydroxy-group on the stereo- and/or regio-chemistry. Organocopper or Grignard reagents and a catalytic amount of a copper(I) salt have been shown to add to prop-2-ynylic alcohols *via* an *anti*-pathway in contrast with the *syn*-addition usually observed with terminal acetylenes.[4,5] It has also been shown that $(\eta^5\text{-}C_5H_5)_2TiCl_2$-catalysed hydromagnesiation of allylic alcohols affords chelated magnesium compounds.[6] These results indicated the possibility of forming such a chelated structure (**4**); however, we have found that the hydromagnesiation of (**1**) clearly follows the *syn*-pathway usually observed with disubstituted acetylenes, to yield the alkenylmagnesium halides (**5**) in almost quantitative yields regiospecifically. The stereo- and regio-chemistry of compounds (**5**) have been unequivocally established by conversion into (*Z*)-γ-deuterio-allylic alcohols† by deuteriolysis (Scheme 2).

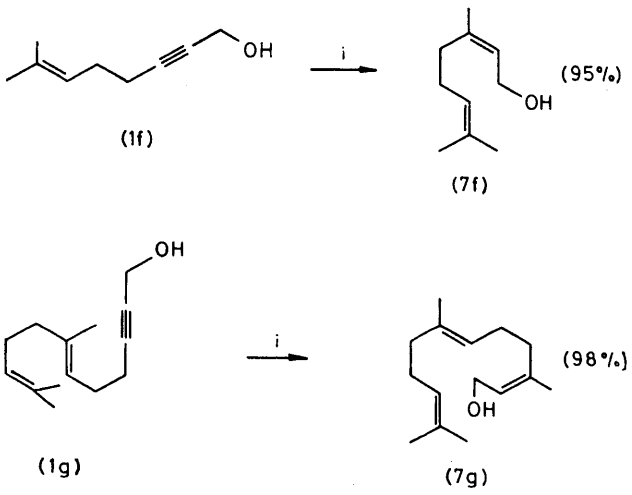
Because of the high reactivity of the Grignard reagent, the reaction promises to provide a novel, specific, and operationally simple route for the preparation of γγ′-disubstituted alk-2-en-1-ols, which are of widespread occurrence among natural products. Scheme 3, which shows the one-pot conversion of hept-2-yn-1-ol (**1b**) into (*E*)-3-iodohept-2-en-1-ol (**6b**) or (*Z*)-3-methylhept-2-en-1-ol (**7b**), illustrates the applicability of our methodology. Hydromagnesiation of (**1b**) followed by treatment with iodine (at −70 °C) afforded (**6b**)† specifically. The overall yields of the alcohol (**6b**) after purification by column chromatography on silica gel were in the range 78—86%. Methylation of (**5b**) was effected by reaction with methyl iodide in tetrahydrofuran (THF) (at 0 °C and then room



SCHEME 2. *Reagents*: i, $2Bu^tMgCl$, $(\eta^5\text{-}C_5H_5)_2TiCl_2$; ii, D_2O, then HCl–H_2O.



SCHEME 3. *Reagents*: i, $2Bu^tMgCl$, $(\eta^5\text{-}C_5H_5)_2TiCl_2$; ii, I_2; iii, MeI.



SCHEME 4. *Reagents*: i, $2Bu^tMgCl$, $(\eta^5\text{-}C_5H_5)_2TiCl_2$, then MeI.

† No detectable amounts of the stereo- and regio-isomers were detected by g.l.c. and/or ^1H n.m.r. spectroscopy.

temperature). After chromatography on silica gel, (**7b**)† was obtained in 88—92% yields with 3—4% of the hydrolysis product of (**5b**) (*Z*)-hept-2-en-1-ol.

The methodology reported here is of particular interest in connection with the possibility of preparing natural products and related compounds the stereochemistry of which is opposite to that resulting from the Corey procedure starting with the same material (**1**). We have synthesized‡ nerol (**7f**) and (*E,Z*)-farnesol (**7g**) from (**1f**) and (**1g**), respectively, as shown in Scheme 4. The products (**1f**) and (**1g**) were identified by spectroscopic and g.l.c. comparison with an authentic sample, and were free from the stereo- and regio-isomers.

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‡ The following procedure is representative. To a solution of isobutylmagnesium chloride in ether (8·0 ml of a 0·88 M solution; 7·0 mmol) was added (η^5-$C_5H_5)_2TiCl_2$ (0·29 mmol) at 0 °C, and the mixture was stirred for 5 min at that temperature. To this solution was added (**1f**) (3·0 mmol), and the mixture was stirred for 2 h at 20 °C. After removal of the ether under reduced pressure, the residue was dissolved in THF (10 ml) and treated with methyl iodide (7·7 mmol) at 0 °C for 10 min and then at room temperature for 2 h. The usual work-up and column chromatography on silica gel gave nerol (**7f**) (98% pure by g.l.c.) in 95% yield.

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