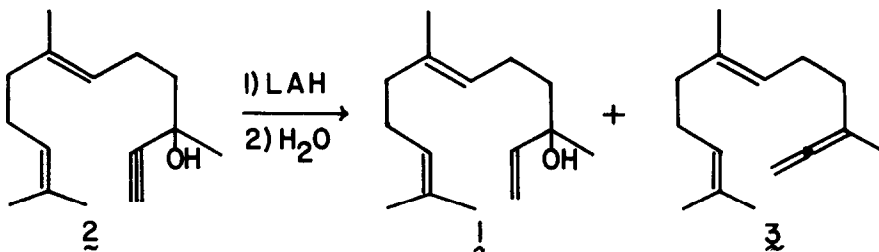


CARBON-CARBON BOND CLEAVAGE DURING LITHIUM ALUMINUM
HYDRIDE REDUCTION OF A TERMINAL PROPARGYL ALCOHOL

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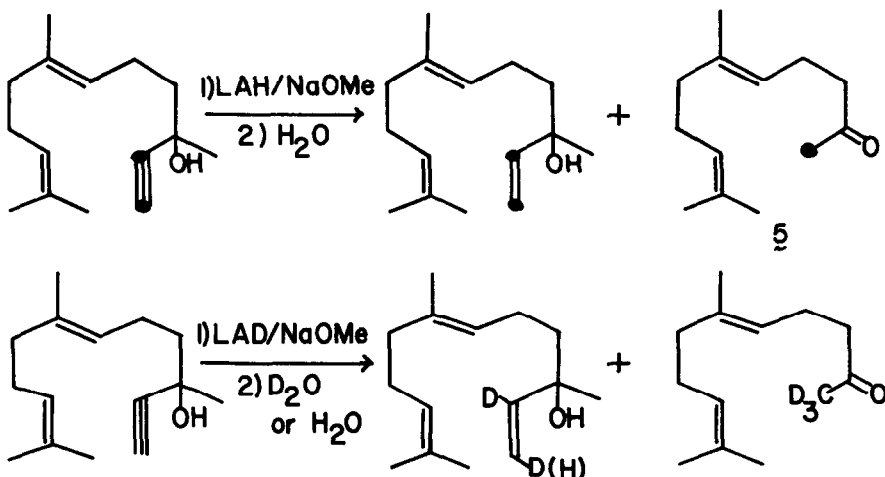
ABSTRACT: Reduction of dehydronerolidol with lithium aluminum hydride in the presence of sodium methoxide gave, in addition to the expected nerolidol, geranyl acetone. Labeling experiments established that the C-1 methyl of geranyl acetone is derived from one of the carbons of the acetylene.

The preparation of trans-disubstituted double bonds by reduction of propargyl alcohols with lithium aluminum hydride is a frequently used synthetic procedure.² In connection with studies of the biochemical conversion of farnesyl to nerolidyl pyrophosphate, we wished to apply this reduction to the preparation of nerolidol(1) from the corresponding terminal acetylenic alcohol, dehydronerolidol(2).³ In the course of these investigations we have encountered a previously unobserved side product of the methoxide-assisted reduction. We report below our results as well as some surprising observations from a series of labeling experiments designed to establish the details of this unusual side reaction.



Treatment of dehydronerolidol with 3 equiv. of LAH for 18 h in refluxing THF gave a 37% yield of the desired nerolidol as well as 38% of the allene 3.⁴ Since it had previously been found that added methoxide increased the proportion of reduction products formed from five-membered ring intermediates such as 4,^{2c} it was felt that addition of sodium methoxide to the reaction mixture might suppress

formation of the undesired allene.⁴ Indeed reduction of **2** with 3.2 equiv. of LAH in the presence of 6.4 equiv. of freshly prepared sodium methoxide in THF for 18 hr at reflux gave a 60% yield of nerolidol accompanied by <5% of allene. Unexpectedly, however, the product also contained a new substance in 20% yield, identified unequivocally by ¹H and ¹³C nmr, i.r., mass spectrometry, and gas chromatography as geranyl acetone (**5**). The survival of the ketone is apparently due to depletion of the reducing agent since addition of excess LAH gave the corresponding alcohol. It was initially assumed that the geranyl acetone had been formed by a sodium methoxide catalyzed elimination of acetylene from **2**. In fact this assumption received circumstantial support in the finding that treatment of **2** with excess NaOMe at reflux overnight in THF gave a 17% yield of geranyl acetone. Further experiments, however, conclusively eliminated this simple explanation.

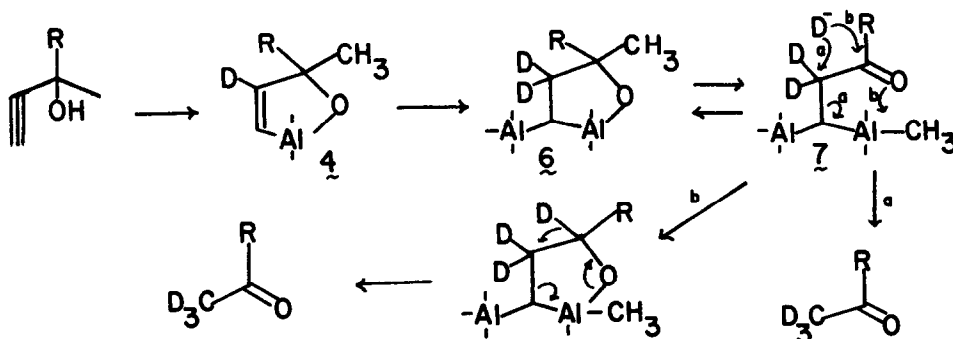


Repetition of the reduction using 3.2 equiv. lithium aluminum deuteride plus 6.4 equiv. of NaOMe, followed by quenching with D₂O gave, in addition to E-[1,2-²H₂]-nerolidol, geranyl acetone labeled with three deuterium atoms at C-1! (Mass spect 98.1% d₃, 0.8% d₂, 0.6% d₁, 0.5% d₀.) The presence of a fully deuterated methyl was supported by the absence of the usual methyl protons at δ2.10 in the ¹H nmr, as well as the appearance of a septuplet, J = 19 Hz, centered at 28.8 ppm, in the ¹³C nmr spectrum in place of the normal singlet at 29.4 ppm. No evidence was found for the presence of any deuterium at C-3 of **5** or in the C-3 methyl of nerolidol. Furthermore control experiments established that geranyl acetone did not exchange under the conditions of work-up nor did the corresponding enolate, prepared

by treatment of geranyl acetone with lithium diisopropylamide, undergo reaction with LAD/NaOMe under the reaction conditions. Even more surprising, reduction of dehydronerolidol with LAD/NaOMe followed by quenching with unlabeled water gave once again (100% d_3)-geranyl acetone. The corresponding experiment with LAH/NaOMe followed by D_2O quench gave unlabeled product.

The formation of (100% d_3)-geranyl acetone appeared inconsistent with any exchange process and strongly suggested that the new methyl of geranyl acetone was derived from C-2 of dehydronerolidol, which initially carries no hydrogens. In support of this notion it was found that when $[1,2-^{13}C_2]$ -dehydronerolidol was treated with LAH/NaOMe, the geranyl acetone obtained was essentially completely labeled with ^{13}C in the C-1 methyl carbon.

While further experiments will be required to conclusively establish a mechanism for this novel fragmentation, we would like to tentatively suggest the following explanation for the demonstrated loss of a methyl group and one of the acetylenic carbons: It is well established that under forcing conditions allylic alcohols will undergo reduction to saturated derivatives.⁵ A second equivalent of deuteride may therefore be delivered to C-2 following initial reduction with formation of the bis-alanate 6. The ate-complex 6 may be in equilibrium with the corresponding methyl aluminum species 7.⁶ This latter substance either undergoes direct displacement with deuteride at C-2 or is reduced to a d_3 -ate complex which suffers fragmentation and rearrangement to geranyl acetone. The role of methoxide in the reaction under discussion as well as in propargyl reductions in general remains unexplained.^{7,8}



References and Notes

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7. See B. B. Molloy and K. H. Hauser, Chem. Commun., 1017 (1968) for a proposed explanation of the role of methoxide.
8. This work was supported by the National Science Foundation, PCM 74-07924.

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