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THE ISOMERIZATION OF OPTICALLY-ACTIVE PROPARGYL ALCOHOLS TO TERMINAL ACETYLENES.

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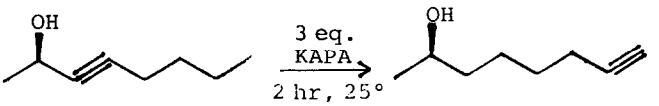
Summary: The isomerization of optically-active secondary propargyl alcohols, $RCHOHC{\equiv}C(CH_2)_nCH_3$, to terminal acetylenic alcohols, $RCHOH(CH_2)_{n+1}C{\equiv}CH$, by potassium 3-aminopropylamide (KAPA) proceeds without loss of configuration at the hydroxy center.

The isomerization of internal acetylenes to terminal acetylenes by KAPA provides a highly convenient method for the transposition of functional groups.[2] Particularly useful is the isomerization of the acetylene unit of a propargyl alcohol to the terminus remote from the hydroxy center.[2b] Since optically-active propargyl alcohols are readily available by resolution or asymmetric reduction,[3] isomerization of such compounds could provide a variety of optically-active compounds. However, the integrity of the chiral center during such isomerizations has not been demonstrated.[4] The chiral center may be racemized by deprotonation of the activated (propargylic) proton by KAPA, or by a Meerwein-Pondorf-Verley type of process if small amounts of ketone are present.[5] A ketone could arise from adventitious oxidation of the alkoxide or *via* rearrangement of the propargylic alkoxide system by KAPA.[6]

The presence of the negatively charged alkoxide - formed quantitatively upon addition of alcohols to KAPA - should decrease the acidity of neighboring protons, thus suppressing racemization *via* deprotonation. This has now been demonstrated. Isomerization[2b] of (*S*)-3-methyl-5-tetradecyne proceeds with 68% retention of configuration, while that of (*S*)-3-methyl-5-tetradecyn-1-ol proceeds with 89% retention of configuration.[7] Clearly the alkoxide, although three carbons removed from the chiral center, suppresses racemization. As seen below, the presence of the alkoxide *at* the chiral center completely suppresses racemization.

Isomerization of enantiomerically pure (*S*)-2-nonyn-4-ol (3 eq. KAPA, 2 hr,

25° [2b]) gave 1-nonyn-4-ol. Upon examination of the product with the chiral NMR shift reagent tris[3-heptafluoropropylhydroxymethylene)-d-camphorato]europium(III none of the R enantiomer could be detected. Likewise, enantiomerically enriched (R)-2-nonyn-4-ol was converted into (R)-1-nonyn-4-ol with no significant loss of enantiomeric purity. Even upon prolonged exposure to the reaction conditions (50 hr, 25°) no loss of enantiomeric purity was detected. The reaction is also applicable to longer chain propargyl alcohols in which the acetylene is moved through several methylene groups. Thus (R)-3-octyn-2-ol was converted to (R)-1-octyn-7-ol without racemization.[8,9]



In conclusion, racemization of the alcohol through a ketone or other process is unimportant since the propargyl alcohols are cleanly isomerized to optically-active terminal-acetylenic alcohols. The chiral hydroxy center can thus be placed at any position in a saturated carbon skeleton. Since the acetylene group may be converted into a number of other functionalities, such compounds are potentially useful in the syntheses of numerous products.

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References and Notes

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4. An acetylene containing a remote hydrocarbon chiral center has been isomerized (ref. 2d and K. Utimoto, M. Tanaka, M. Kitai and H. Nozaki, Tetrahedron Lett., 2301 (1978).

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6. Such rearrangement has been observed with 1-phenyl-2-alkyn-1-ols and KAPA: C. A. Brown and A. Yamashita, unpublished observations.

7. The retention of configuration was determined by hydrogenating the isomerized product and comparing the rotation at several wavelengths to the rotation of hydrogenated starting material. The samples used for rotation measurements were >99% pure by glpc on two different columns (methyl silicone, Carbowax).

8. The enantiomeric purity was confirmed with the chiral shift reagent tris(d,d-dicampholymethanato)europium(III). M. D. McCreary, D. W. Lewis, D. L. Wernick and G. M. Whitesides, J. Amer. Chem. Soc., 96, 1038 (1974).

9. Isolated yields are generally very good as reported in ref. 2b.

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