Studies on Chirality Transfer in the [2,3] Sigmatropic Rearrangement

of Anions Derived from Trialkylstannylmethyl Allylic Ethers.

Stereospecific Synthesis of (2R)-3-Benzyloxy-2-methylpropanol.

M. Mark Midland* and Young C. Kwon
Department of Chemistry, University of California
Riverside, CA 92521, USA

Abstract: Virtually complete chirality transfer is observed in the
[2,3] sigmatropic rearrangement of the anion derived from trialkyl-
stanylmethyl (E)- or (Z)-allylic ethers.

The recent focus of attention on the [2,3] sigmatropic rearrange-
ment has substantially reinforced the arsenal of stereocontrol for
acyclic systems.[1] The scope of the [2,3] sigmatropic (Wittig)
rearrangement was considerably expanded by Still's discovery that
anions derived from transmetallation of trialkylstannylmethyl allylic
ethers can undergo a facile rearrangement. Still examined the olefin
geometry of the resulting homoallylic alcohols.[2] Recent attention has
focused on the stereochemistry of the migrating termini as well as
the olefin geometry. Substitution patterns at the anion center as
well as on the allylic ether can have profound effects on the stereo-
chemistry of the rearranged product. It was not clear what effect
would be exhibited by the parent anion. Because of the synthetic
potential of these transformations[3] we have explored the stereo-
chemistry of this reaction. Herein we report our results and the
application of the reaction for the preparation of (2R)-3-benzyloxy-2-
methylpropanol.

Our starting material 1 (92% e.e. by analysis with NMR shift
reagent) was obtained by the reduction of 5-methyl-2-hexyn-4-one with
B-3-pinanyl-9-BBN (R-Alpine Borane, from 92% e.e. (+)-α-pinene).[4]
(Scheme I). Partial hydrogenation of 1 using Lindlar catalyst provided
(Z)-allylic alcohol 2 (92% e.e.), which was then deprotonated with NaH
and the resulting alkoxide reacted with trimethylstannylmethyl iodide
to afford ether 3. Treatment of 3 with n-BuLi at -78° followed by
warming to 0° provided only (E)-homoallylic alcohol 4, [a]D + 28.4 (c 1,

CHCl$_3$). The enantiomeric purity of **4** was determined to be 92% by NMR shift studies (Eu(hfc)$_3$). Since the starting material was also 92% e.e. the reaction proceeds with complete chirality transfer. The absolute configuration of **4** was verified as follows. Ozonolysis of benzyl-protected **4** and subsequent reduction of the ozonide provided (2R)-3-benzyloxy-2-methylpropanol[5], [α]$_D$ -3.39, (c 1.68, EtOH), lit.,[5a] [α]$_D$ -4 (c 1.076, EtOH), and [α]$_D$ +10.7 (c 3.10, CHCl$_3$), lit.[5b] [α]$_D$ +11.2 (c 16, CHCl$_3$). This route not only verifies the absolute configuration of **4**, but also represents an asymmetric synthesis of (2R)-3-benzyloxy-2-methylpropanol (**5**) which has been commonly produced by microbial oxidation of isobutyric acid with pseudomonas putida.[5] This chiral unit has been extensively used in the synthesis of more complex molecules.

In the case of the (E)-allylic system (readily available by LAH reduction of **1**) treatment of ether (**7**) with n-BuLi afforded a mixture of (E)- and (Z)-homoallylic alcohols (**8** and **9**) in a 53:47 ratio. The two products (**8** and **9**) were isolated by HPLC. The optical rotation of **8** was of the same magnitude but opposite sign of **4** ([α]$_D$ -28.1 (c 1, CHCl$_3$)). Analysis by NMR (Eu(hfc)$_3$) indicated a 92% e.e.. Hence, the absolute configuration of **8** and its enantiomeric excess were confirmed. Analysis of **9** by NMR indicated a 92% e.e. of the opposite configuration at C-2. Hydrogenation of **8** and **9** provided **10** and **11** respectively. (**10**, [α]$_D$ -3.75 (c 0.8, CHCl$_3$) and **11** [α]$_D$ +3.64 (c 0.77, CHCl$_3$)).

The stereochemistry and selectivity of the transformation may be rationalized by consideration of the possible 5-membered ring transition states (Scheme II). In the case of isomerization of the R,Z isomer only the transition state leading to the R,E isomer (**4**) is favorable. The transition state leading from the R,Z starting material to the S,Z product is destabilized by the methyl-isopropyl interaction. However, in the case of the R,E isomer, neither transition state is destabilized by the methyl-isopropyl interaction. Of course one must be cautioned that these pictures are greatly over-simplified. For example, they do not take into account the nature of the carbanion or the position of the counter ion.

In conclusion, the rearrangement of these anions is stereospecific. However, the stereochemistry of the new chiral center is intimately related to the geometry of the olefinic product. The Z starting
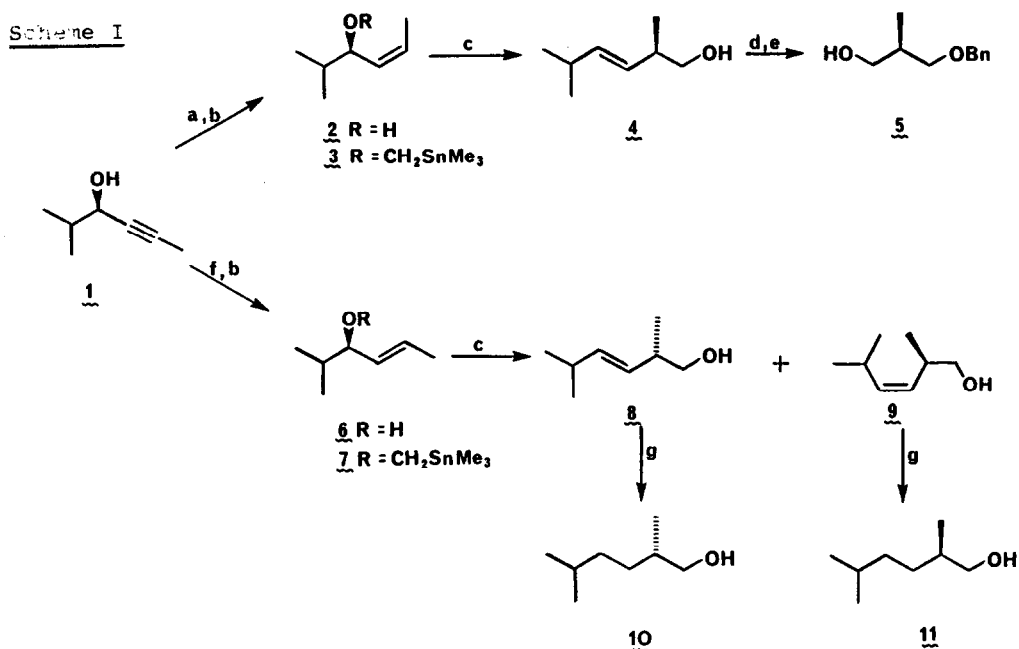
Scheme I

(a) H$_2$, Lindlar cat. 98%. (b) 1.4 eq. NaH, 1 eq. ICH$_2$SnMe$_3$, THF reflux, 17 h, 75%. (c) 2 eq. n-BuLi, -78°, 40 min, 0°, 40 min, 72% (d) 1.8 eq. NaH, 2.2 eq. benzyl chloride, THF, reflx, 15 h, 87%. (e) Ozone, -78°, NaBH$_4$, -78° → RT, 15 h, 78%. (f) 8 eq. LAH, THF, reflux, 4 h, 74%. (g) H$_2$, 5% Pd/C, 100%.

Scheme II
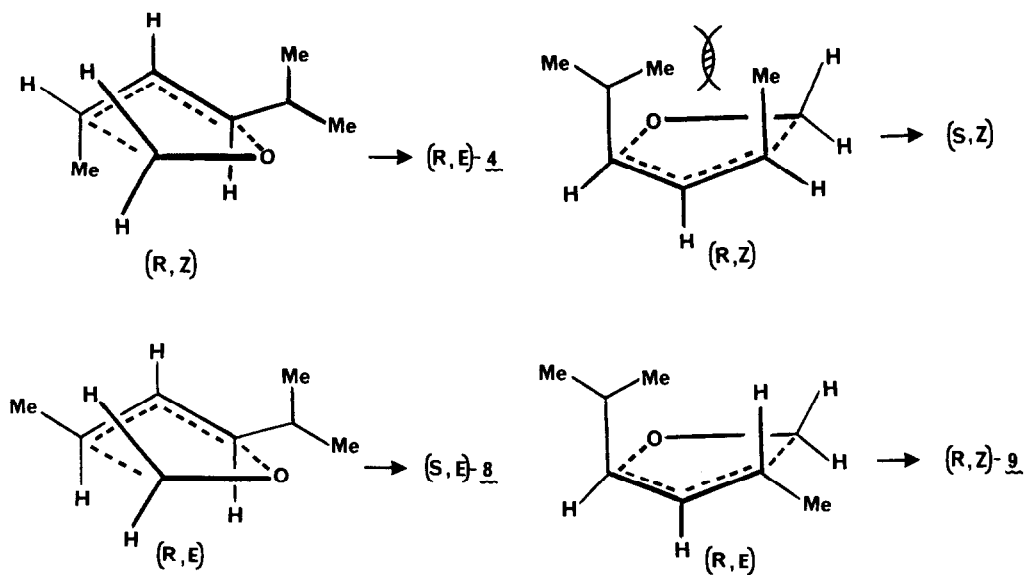
material provides a single product which may be converted into the chiral unit **5**. Either enantiomer of **5** may be prepared by the appropriate asymmetric reduction of the starting propargyl ketone.

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