[2,3] Wittig Rearrangement of Nonracemic Propargyl Ethers Leading to Allenes of High Stereochemical Integrity

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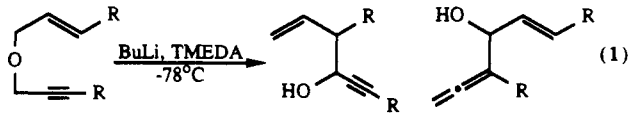
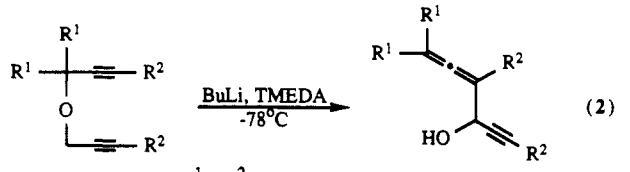
Summary: The (*R*)-propargylic tributylstannylmethyl and glycolic acid ethers **4a**, **4b**, **5a**, and **5b** rearrange to the (*R*)-allenylcarbinols **6a**, **6b**, **7a**, and **7b** of high ee upon treatment with *n*-BuLi or LDA, respectively, at low temperature.

Sir: The [2,3] Wittig rearrangement of allylic propargylic ethers constitutes an efficient route to homoallylic propargylic alcohols, often with high diastereoselectivity (eq 1).[1] Interestingly, the rearrangement affords none of the

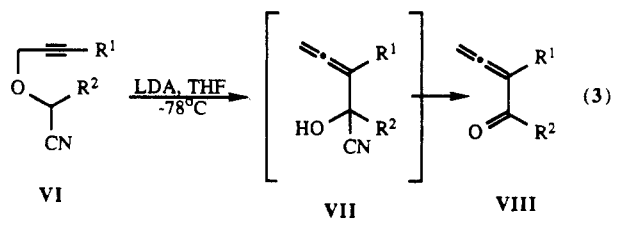


isomeric allenyl alcohols III. Presumably, propargylic anion formation is kinetically preferred over allylic anion formation. In addition, the five-membered transition state leading to propargylic alcohol II should be of lower energy than that leading to allene III.

Allenyl alcohols have been obtained from [2,3] Wittig rearrangement of bis-propargylic ethers (eq 2).[2] However, the yields are low and the reaction does not tolerate substituents at the propargylic centers.

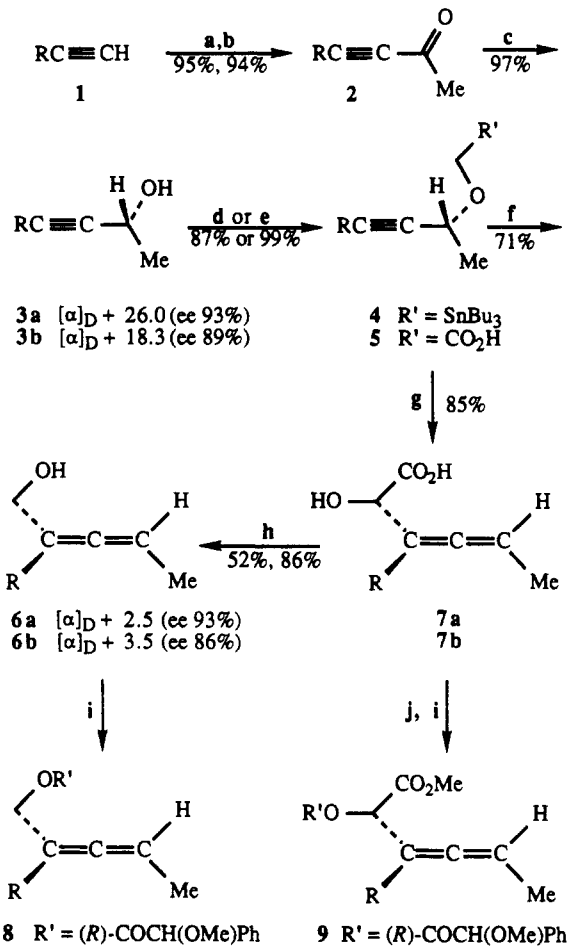


Propargylic ether derivatives of aldehyde cyanohydrins afford allenyl ketones VIII, via the cyanohydrin intermediates VII, in overall 50–60% yield upon base treatment (eq 3).[3] Thus, a five-membered allenic transition state, although strained, appears to be achievable. Of course, the foregoing allene forming reactions could also occur by a two-step dissociation–recombination pathway. To examine this possibility and to explore new routes to optically active allenes of predictable configuration we undertook the preliminary studies outlined in this report.



The optically active propargylic alcohols **3** were readily prepared in high ee through reduction of the acetylenic ketones **2** with Chirald–LAH (Scheme I).[4] The absolute

Scheme I[a,b]



[a] **a** series, R = C_4H_9; **b** series, R = C_7H_{15}. [b] (a) *n*-BuLi, THF, −78 °C; CH_3CHO; (b) PCC, CH_2Cl_2; (c) Chirald, $LiAlH_4$, Et_2O, −78 °C; (d) KH, Bu_3SnCH_2I, THF; (e) NaH, $ClCH_2CO_2H$, THF; (f) *n*-BuLi, THF, −78 °C; (g) LDA, THF, −78 °C; (h) $NaIO_4$, MeOH; $NaBH_4$, EtOH; (i) (*R*)-PhCH(OMe)CO_2H, DCC, CH_2Cl_2; (j) CH_2N_2, Et_2O.

configuration of the alcohol products was assigned by analogy[5] and from analysis of the ^1H NMR spectrum of the *O*-methylmandelates.[6] These diastereomeric derivatives could also be analyzed by capillary gas chromatography thereby allowing an accurate evaluation of the enantiomeric excess (ee).

Still found that (tributylstannyl)methyl ethers of allylic alcohols undergo smooth [2,3] rearrangement upon transmetallation with *n*-BuLi.[7] The corresponding stan-

(1) Cf.: Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.
(2) Huchi, M.; Cresson, P. *Tetrahedron Lett.* **1975**, 367.
(3) Cazes, B.; Julia, S. *Synth. Commun.* **1977**, *7*, 273.
(4) Aldrich Chemical Co., Milwaukee, WI. Chirald is a trade name for Darvon alcohol. For the use of this ligand in asymmetric reductions, see: Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870.
(5) Cf.: Cohen, N.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 582.
(6) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. D. *J. Org. Chem.* **1986**, *51*, 2370.
(7) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927. Castedo, L.; Granja, J. R.; Mourino, A. *Tetrahedron Lett.* **1985**, *26*, 4959. Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1985**, *26*, 5013, 5021. Paquette, L. A.; Sugimura, T. *J. Am. Chem. Soc.* **1986**, *108*, 3841. Castedo, L.; Mascareñas, J. L.; Mouriño, A. *Tetrahedron Lett.* **1987**, *28*, 2099. Broka, C. A.; Hu, L.; Lee, W. J.; Shen, T. *Tetrahedron Lett.* **1987**, *28*, 4993.

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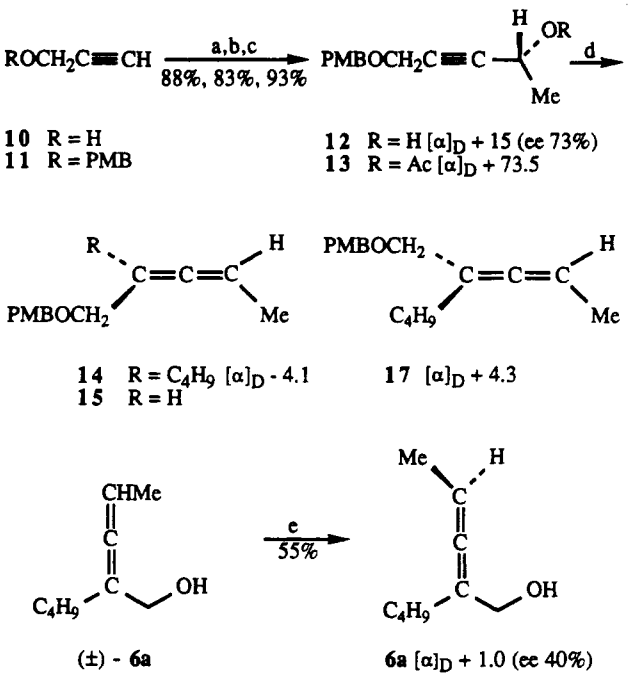
Scheme II[a]



[a] (a) *n*-BuLi, THF, −78 °C; CH_3CHO; (b) PCC, CH_2Cl_2; Chirald, $LiAlH_4$, Et_2O, −78 °C; (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (d) Bu_2CuLi, Et_2O, −30 °C; (e) D-(−)-DIPT, TIP, TBHP, CH_2Cl_2, −20 °C.

nylmethyl ethers **4** of the propargylic alcohols **3** rearranged under comparable conditions to the optically active allenylcarbinols **6**. The enantiomeric excess of these allenic alcohols was virtually identical with that of the starting alcohols **3** as judged by integration of the vinylic methyl doublets in the ^1H NMR spectra of the (*R*)-*O*-methylmandelate derivatives **8**.[6] These findings provide direct evidence in support of a nondissociative pathway for such rearrangements.

The stereochemistry of allenylcarbinols **6** was initially assigned from transition-state considerations, assuming that the pathway from ether **4** involves a five-centered cyclic array. As an independent check on this assignment we examined an alternative synthesis of the *p*-methoxybenzyl (PMB) derivative **17** of alcohol **6a** through S_N2' displacement of the propargylic acetate **13**, as outlined in Scheme II.[8] Thus, the PMB ether **11** of propargyl alcohol was lithiated and condensed with acetaldehyde to afford racemic alcohol **12**. Oxidation and reduction with the Chirald–LAH complex afforded the (*R*)-alcohol **12** of 73% ee.[4,5] Addition of the Gilman butyl cuprate in ether at −78 °C yielded the optically active allene **14** along with a small amount of separable protonolysis product **15**.[9] Surprisingly, allene **14** was enantiomeric to the sample **17** prepared by *p*-methoxybenzylation of the [2,3] Wittig alcohol **6a**. Thus, either the Gilman cuprate effects syn S_N2' displacement of acetate **13** or the [2,3] Wittig rearrangement of stannane **4** proceeds by an anti pathway. Of the two possibilities, the former seems more likely.

To resolve this stereochemical dilemma we subjected a sample of racemic allenylcarbinol (±)-**6a** to Sharpless kinetic resolution with the D-(−)-DIPT derived reagent.[10]

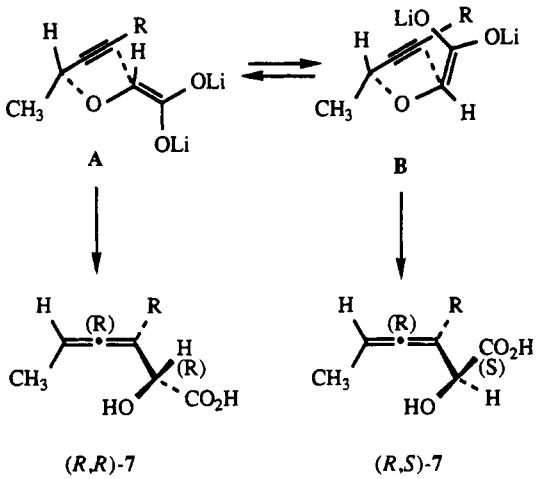


Figure 1. Transition-state conformers for [2,3] Wittig rearrangement of lithiated acid **5**.

The recovered alcohol showed a positive optical rotation in accord with the sample obtained by [2,3] rearrangement of stannane **4a**. Thus, the cuprate displacement of acetate **13** must proceed by a syn S_N2' pathway.[11]

We also examined the base initiated [2,3] Wittig rearrangement of the propargylic glycolic acid ether **5**. Related allylic glycolic acid ethers rearrange with high to moderate diastereoselectivity, depending on the substitution pattern of the allylic grouping.[12] Ether **5** rearranged analogously to afford the optically active α-hydroxyallenylacetic acid **7** of high (~90%) diastereomeric purity as judged by the ^1H NMR spectrum and gas chromatogram of the methyl ester. The configuration and enantiomeric excess of the allenyl moiety was established through conversion to the previously obtained carbinol **6b** by oxidative cleavage and reduction (Scheme I). It was thereby ascertained that the rearrangement proceeds through the expected cyclic transition state with high asymmetric transfer. The configuration at the carbinyl center was not proved but, based on inspection of the probable transition states, steric factors should favor the *S* isomer (Figure 1). Additional studies on this point are in progress.

Our findings show that the [2,3] Wittig rearrangement can be employed for the synthesis of chiral allenes of high optical purity and predictable absolute configuration. These allenyl alcohols are potentially valuable intermediates for the synthesis of nonracemic carbocyclic and heterocyclic compounds through intra- and intermolecular cycloadditions.[13] Further work along those lines is underway.

Acknowledgment. Support for this work was provided by the National Science Foundation (Grant CHE-8615569) and the National Institutes of Health (Grant GM 29475).

(8) Cf.: Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726. Pirkle, W. H.; Boeder, C. W. *J. Org. Chem.* **1978**, *43*, 1950.

(9) Cf.: Luche, J. L.; Barreiro, E.; Dollat, J. M.; Crabbé, P. *Tetrahedron Lett.* **1975**, 4615.

(10) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Applied Chem.* **1983**, *55*, 589 (see Table I, entry 7).

(11) Syn S_N2' displacements of certain allylic derivatives by organocopper reagents have been observed but all S_N2' displacements on propargylic systems by cuprates reported to date proceed by an anti pathway. We are unable to explain the apparent preference of proparagylic acetate **13** for syn S_N2' displacement by the Gilman butyl cuprate. Additional studies on this point are in progress. An addition–elimination mechanism has been proposed for syn additions to propargylic ethers by Grignard reagents and copper salts (Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1989**, *30*, 2387).

(12) Nakai, T.; Mikami, K.; Taya, S.; Kimura, Y.; Mimura, T. *Tetrahedron Lett.* **1981**, *22*, 69. Mikami, K.; Kawamoto, K.; Nakai, T. *Tetrahedron Lett.* **1986**, *27*, 4899. Koreeda, M.; Recca, D. J. *J. Org. Chem.* **1986**, *51*, 4090.

(13) For a comprehensive review of allene chemistry, see: Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; John Wiley and Sons: New York, 1984. Smadja, W. *Chem. Rev.* **1983**, *83*, 263.