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HIGHLY ENANTIOSPECIFIC AND ERYTHRO-SELECTIVE [2,3]-WITTIG REARRANGEMENT OF ENANTIOMERICALLY-ENRICHED ALLYLIC BENZYL ETHERS. A NEW, FORMAL CHIRAL SYNTHESIS OF *l*-EPHEDRINE

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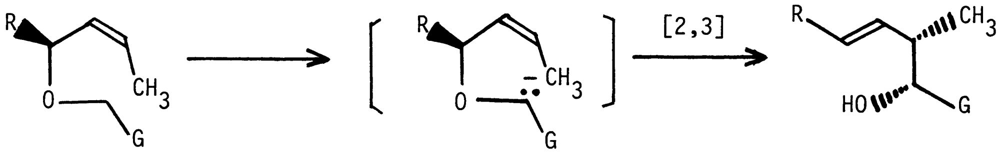
The [2,3]-Wittig rearrangement of chiral (*Z*)-allylic benzyl ethers provides 94-97% of asymmetric transfer (enantiospecificity), along with 90-96% of erythro-selectivity. Its synthetic potential is illustrated through the stereocontrolled synthesis of an optically-active precursor of *l*-ephedrine.

One of the most challenging problems for the synthetic chemists today is the control of *both* diastereo- and enantioselection over the two newly created chiral centers.[1] In an effort to develop the [2,3]-Wittig sigmatropic rearrangement into a new, basic strategy for acyclic stereocontrol,[2] we have been investigating the diastereo- and enantioselection in the [2,3]-Wittig process of enantiomerically-enriched allylic ethers as illustrated by Eq. 1.

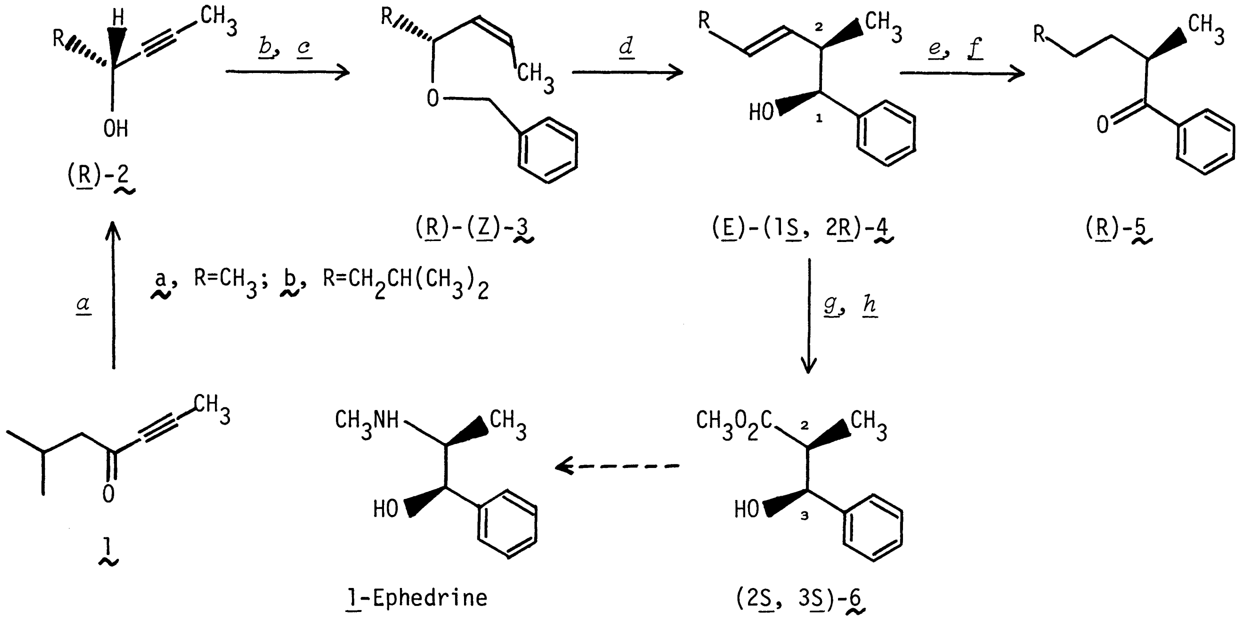


(1)

Quite recently we have demonstrated that the [2,3]-Wittig process of a chiral (*Z*)-allylic propargyl ether system ($G = C{\equiv}C\text{-}SiMe_3$, $R = CH_3$) exhibits an extremely high degree of asymmetric transfer (enantiospecificity) and erythro-selectivity within the context of the chiral synthesis of insect pheromones.[3] In a continuation of these studies, we now report that the [2,3]-Wittig process of chiral (*Z*)-allylic benzyl ethers ($G = C_6H_5$)[4] also provides a high degree of enantiospecificity and erythro-selectivity, and illustrate its potential through the chiral synthesis of a precursor of *l*-ephedrine.

In this work, we investigated the stereoselections in the [2,3]-Wittig process of the two enantiomerically-enriched benzyl ethers, (*R*)-(*Z*)-**3a** ($R = CH_3$) and (*R*)-(*Z*)-**3b** ($R = CH_2CH(CH_3)_2$), for the chiral synthesis of the α-methyl-β-hydroxy ester (2*S*, 3*S*)-**6** that is a well-secured[5] precursor of *l*-ephedrine, a famous adrenergic drug[6] (see Scheme 1).

Scheme 1.



(a) Darvon alcohol-$LiAlH_4$ complex, Et_2O, -85 °C; (b) H_2/Lindlar cat., MeOH; (c) $PhCH_2Br$, n-Bu_4NI (cat.), 75% aq. NaOH; (d) n-BuLi (5 equiv.), THF, -85 °C; (e) H_2/PtO_2 (cat.), AcOEt; (f) CrO_3, H_2SO_4; (g) $NaIO_4$-$KMnO_4$, t-BuOH; (h) CH_2N_2, Et_2O

First, we examined the [2,3]-Wittig process[7] of (R)-(Z)-**3a** (>99% Z)[8] which was derived from an optically-resolved[9] propargylic alcohol (R)-**2a** with 95% ee ($[\alpha]_D$ +46.1° (c 1.05, dioxane)). The carbanion rearrangement was best carried out by using a large excess of butyllithium[10] to afford a 70% yield of alcohol **4a** in an extremely high geometric purity (>99% E).[11] Unfortunately, however, the diastereomeric excess of (E)-**4a** was found to be only 80% (erythro-rich)[4] by NMR analysis.[12] In order to determine the sense and degree of asymmetric transfer along the allylic array, the diaseteromixture of (E)-**4a** was converted to ketone **5a** in 62% yield via hydrogenation followed by oxidation. We found that ketone **5a** was the (R)-enantiomer with 92% ee ($[\alpha]_D$ -26.1° (c 0.31, EtOH), as judged from the highest $[\alpha]_D$-value (-28.0°) reported for (R)-**5a**.[7] Thus, it is proved that the rearrangement of (R)-(Z)-**3a** proceeds with at least 97% of suprafacial transfer of chirality along the allylic array,[13] although the erythro-selectivity is not so high (90%). Oxidative cleavage of the double bond in **4a** followed by esterification afforded a 58% yield of an erythro-rich mixture[14] of the desired hydroxy-ester **6** ($[\alpha]_D$ -15.2° (c, 0.81, $CHCl_3$). Thus, the major erythro-**6** is assignable to the desired (2S, 3S)-**6** based on the reported configuration of (-)-(2S, 3S).[15]

Second, we examined the [2,3]-Wittig process of (*R*)-(*Z*)-**3b** with a view to obtaining a higher level of erythro-selectivity. The notable advantage of this variant is that the requisite starting alcohol (*R*)-**2b** is easily accessible via asymmetric reduction16) of α,β-ynone **1** without the tedious optical resolution step. Thus, (*R*)-(*Z*)-**3b** (>99% *Z*)17) was derived from (*R*)-**2b** with 68% ee18) ($[\alpha]_D$ +10.28° (*c* 1.07, $CHCl_3$), which was prepared in 86% yield via reduction of **1** with Darvon alcohol-$LiAlH_4$ complex.16a) The rearrangement of (*R*)-(*Z*)-**3b** under the same conditions as described for **3a** afforded an 89% yield of (*E*)-**4b** with a higher erythro-selectivity (96%).19) A similar oxidation-esterification sequence performed on **4b** followed by column chromatography (silica gel, ether/hexane) afforded a 55% overall yield of pure erythro-**6**14) with 64% ee ($[\alpha]_D$ -14.7° (*c* 0.71, $CHCl_3$), as judged from the highest $[\alpha]_D$-value (-23.1°) reported for (2*S*, 3*S*)-**6**.15b) Thus, these stereochemical outcomes indicate that the rearrangement of (*R*)-(*Z*)-**3b** proceeds *with a higher erythro-selectivity than that of* (*R*)-(*Z*)-**3a**, along with essentially the same degree (94%) of asymmetric transfer.20) Since (±)-erythro-**6** has been elaborated to (±)-ephedrine in two simple steps,5) the present asymmetric synthesis of (2*S*, 3*S*)-**6** constitutes a new, formal asymmetric synthesis of *l*-ephedrine.

The most notable feature of the chiral syntheses outlined herein is that the enantiomeric purity of the final product is essentially the same as that of the starting propargylic alcohol. In other words, the substrate chirality is specifically transmitted to the two newly created chiral centers in the product with high efficiency (94-97%) by virtue of the combination of the high (*E*)- and erythro-selectivity with nearly complete transfer of chirality. This high stereospecificity can be explained on essentially the same mechanistic grounds used to rationalize the comparable stereospecificity previously reported for the chiral propargylic ether system.3)

In summary, the results of this work convincingly expand the synthetic potential of the asymmetric [2,3]-Wittig rearrangement of chiral substrates for the concurrent control of diastereo- and enantioselection and provides the synthetic chemist with a powerful weapon with which to attack the current problem of acyclic stereocontrol. Further synthetic applications of the present strategy are in progress.

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10) Surprisingly, the use of 1.2 equiv. of n-BuLi was found to afford only 24% of (E)-4a.

11) Confirmed by IR and ^{13}C NMR analysis: IR (film), 970 cm^{-1} (E) and 720 cm^{-1} (Z). This high (E)-selectivity is in contrast to 87% of (E)-selectivity reported for (E)-3a (Ref. 7).

12) NMR (CCl_4), δ 4.37 (d, J=5.4 Hz) for (E)-erythro-4a and δ 4.16 (d, J=7.7 Hz) for (E)-threo-4a.

13) This high degree of asymmetric transfer is in stark contrast to 62-72% of the enantiospecificity reported for (S)-(E)-3a (Ref. 7).

14) NMR (CCl_4), δ 5.04 (d, J=4.5 Hz) for erythro-6 and δ 4.71 (d, J=9.0 Hz) for threo-6. For the NMR assignments, see: Ref. 5.

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17) Prepared in 63% yield from (R)-2b: bp 105-107 °C/2 mmHg.

18) More recently, we have succeeded in improving the optical yield up to 85%.

19) NMR (CCl_4), δ 4.50 (d, J=5.4 Hz) for (E)-erythro-4b and δ 4.21 (d, J=7.7 Hz) for(E)-threo-4b.

20) In a separate experiment, the rearrangement of (R)-(Z)-3b (76% ee) was found to provide 97% of asymmetric transfer based on 74% ee at the hydroxy-chirality in (E)-4b, which was directly determined by the Mosher method using ^{19}F NMR analysis of the MTPA-ester of (E)-4b: J. A. Dale, D. L. Dull, and M. S. Mosher, *J. Org. Chem.*, 34, 2543 (1969).

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