

Larger Scale Preparation of Optically-active Allylic Alcohols

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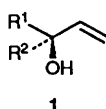
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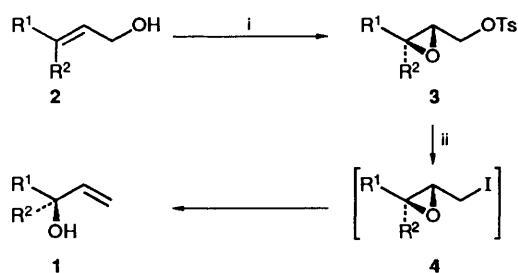
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An efficient and practical synthesis of optically-active allylic alcohols from 2,3-epoxytoluene-*p*-sulfonates by the *in situ* formation of the epoxy iodides and their subsequent reduction with zinc-copper couple has been established. Application of this procedure to the larger-scale synthesis of (*S*)-(+)-but-3-en-2-ol from (2*S*,3*S*)-3-methylglycidyl toluene-*p*-sulfonate has also been investigated.

Optically-active allylic alcohols **1** may be used as chiral building blocks for the preparation of optically pure compounds.¹ For example, the olefin may be coupled with aryl halides,² or functionalised by directed epoxidation,³ while the hydroxy function may be elaborated in various ways including inversion processes involving the Mitsunobu reaction.⁴



There are at present various methods for the synthesis of optically active allylic alcohols including the kinetic resolution of racemic allylic alcohols,⁵ reduction of chlorinated ketones,⁶ titanocene mediated deoxygenation of 2,3-epoxy alcohols⁷ and the sonochemical cleavage of 2,3-epoxyalkyl halides with zinc-copper couple.⁸ However the majority of these methods suffer from various difficulties such as expense, the need for high dilution and difficulties on scale-up. With a view to large-scale synthesis, we have developed a practical approach to the synthesis of chiral allylic alcohols, starting from the 2,3-epoxytoluene-*p*-sulfonates, readily available in a single step *via* Sharpless asymmetric epoxidation⁹ (Scheme 1).



Scheme 1 Reagents: i, (+)-DIPT, Bu'O₂H, 4 Å sieves, Ti(OPr)₄; (MeO)₃P; TsCl, Et₃N, 4-dimethylaminopyridine; ii, Zn(Cu), NaI

In this scheme, the epoxytoluene-*p*-sulfonate is converted *in situ* into the corresponding epoxy iodide with sodium iodide, which then undergoes reductive elimination by reaction with zinc-copper couple,¹⁰ to give the allylic alcohol. We have examined this process on a range of substrates (Table 1).

As can be seen from the Table, the reductive ring opening works well for a range of different substrates, but several points are worth noting. In all the cases examined, *cis*-allylic alcohols (entries 4, 5) gave poorer overall yields than the corresponding *trans* systems. This is a consequence of lower yields in the Sharpless asymmetric epoxidation step rather than in the

elimination process. This does not represent a limitation to the procedure, since the products obtained from *cis*-allylic alcohols are exactly the same as those obtained from the corresponding *trans* systems using (–)-DIPT (diisopropyl tartrate) in the asymmetric epoxidation. In the case of volatile alcohol products (entry 7) lower yields were obtained because of the problem of separating the products from reaction solvents. An additional point worth noting is that this procedure allows the preparation of tertiary allylic alcohols in good overall yields (entries 1, 2), which are not readily available *via* kinetic resolution methods.

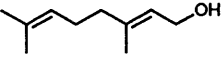
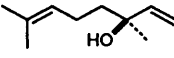

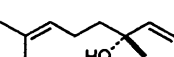
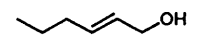
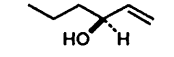

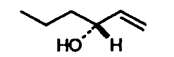
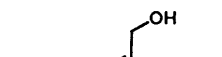
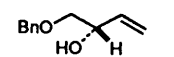



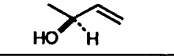
We found that the reductive elimination reaction is compatible with a range of solvents, and can be successfully carried out in acetonitrile, ethanol, and THF (tetrahydrofuran), all at reflux temperatures. Acetone can also be used, however significant amounts of diacetone alcohol are obtained in this reaction which can lead to difficulties in the purification of products. The reaction was not successful in diethyl ether or toluene.

In order to examine the applicability of this method to the larger scale synthesis of allylic alcohols, we examined the preparation of (*S*)-(+)-but-3-en-2-ol (entry 7) in more detail. The starting epoxy toluene-*p*-sulfonate may be prepared in moderate yields (50–68%) from crotyl alcohol using Sharpless methodology⁸ and is also commercially available in optical purity of 84% ee.† This material could not be prepared in large quantities using THF for the reductive elimination due to problems with separation of the product from the solvent. It was envisaged that the use of a higher boiling solvent may well be advantageous since this should facilitate separation of the production alcohol. To this end, it was found that treatment of the epoxy toluene-*p*-sulfonate with sodium iodide and zinc-copper couple at 60 °C for 2 h in ethylene glycol allowed isolation of the resulting allylic alcohol *via* fractional distillation directly from the high boiling solvent in 85–92% yield. It was found that the alcohol contained 15–20% w/w water the origin of which has not been established. The water can be removed by drying a solution of the alcohol with molecular sieves prior to use, for example, the water content was lowered to an acceptable level of < 2% by stirring the alcohol in THF with 3 Å molecular sieves for two days. The (*S*)-(+)-but-3-en-2-ol obtained by this method had a chemical purity of > 92%. The optical purity was lowered only slightly to 76% ee from that of the starting epoxytoluene-*p*-sulfonate as determined by Mosher ester formation.¹¹

Consequently this method represents an efficient and practical synthesis of an important class of chiral molecules, that is amenable to the preparation of substantial quantities of material.

† Available from ARCO Chemical Co., recrystallisation of the toluene-*p*-sulfonate can improve optical purity to ≥ 90%.

Table 1 Yields and approximate enantiomeric excesses for allylic alcohols

Entry	Starting alcohol 2	Yield of 3 (%)	Product alcohol 1	Yield of 1 ^a (%)	ee of 1 ^b (%)
1	 geraniol	95	 (+)-linalool	78	> 90
2	 nerol	96	 (-)-linalool	82	> 90
3	 3-penten-2-ol	70	 3-penten-2-ol	76	> 90
4	 3-penten-2-ol	56	 3-penten-2-ol	73	> 85
5	 3-penten-2-ol	45	 3-penten-2-ol	73	> 80
6	 3-phenyl-2-propen-1-ol	38	 3-phenyl-2-propen-1-ol	53	> 95
7	 3-penten-2-ol	68	 3-penten-2-ol	67	> 90

^a Yields quoted are for reactions carried out in the presence of Zn(Cu) (3.5 equiv.), NaI (3 equiv.) in refluxing THF, and are for isolated materials after purification. ^b The enantiomers drawn are those obtained using (+)-DIPT and the enantiomeric excesses are estimated based on the measured enantiomeric excess of the corresponding crude epoxy alcohols.⁸ We have demonstrated in a number of cases that the enantiomeric excess of the final alcohols is at similar to these intermediates, and in some cases higher due to optical enrichment on crystallisation of the epoxytoluene-*p*-sulfonates.

Experimental

Materials.—(2*S*,3*S*)-3-Methylglycidyl toluene-*p*-sulfonate was obtained from ARCO Chemical Co. and contained a 5% impurity of *cis*-2,3-epoxybutyl toluene-*p*-sulfonate and had an optical purity of 86% ee. All anhydrous solvents were obtained from Aldrich Chemical Co. and used as received. The sodium iodide was oven dried overnight at 100 °C prior to use.

Procedure for the Formation of Non-volatile Alcohols.—(+)-Linalool. The epoxytoluene-*p*-sulfonate⁹ derived from geraniol (10.24 g, 32 mmol) in dry THF (30 cm³) was added to a stirred suspension of zinc-copper couple (5.12 g) and sodium iodide (10.04 g) in dry THF (150 cm³). The resulting mixture was heated at reflux for 2 h, then cooled and filtered through a silica pad. The pad was washed with fresh THF and the combined organic solution evaporated under reduced pressure. Distillation of the residue gave (+)-linalool (3.84 g, 24.9 mmol, 78%) as a colourless oil. The optical purity of this material was estimated as 92% ee by optical rotation measurement.

Procedure for the Formation of Volatile Alcohols.—(*S*)-(+)-But-3-en-2-ol. (2*S*,3*S*)-3-Methylglycidyl toluene-*p*-sulfonate (150 g, 0.62 mol) in anhydrous ethylene glycol (750 cm³) was added to a stirred suspension of zinc-copper couple (75 g) and sodium iodide (278.4 g, 1.86 mol) in anhydrous ethylene glycol (1.5 dm³). A slight exotherm of approximately 5–10 °C occurred and the resulting mixture was heated to 70 °C for 2 h. After cooling, the mixture was filtered through a silica pad. The pad was washed with fresh ethylene glycol and the filtrate fractionally distilled, under atmospheric pressure using a glass helical packed column and a reflux head. The fraction between 86–94 °C was collected as (*S*)-(+)-but-3-en-2-ol (40.08 g, 90%), chemical purity >92%, water content v/v 16.3% (as

determined by GC analysis). Optical purity determined by Mosher ester formation was 74% ee.

Removal of Water.—(*S*)-(+)-But-3-en-2-ol (38.36 g) in anhydrous THF (60 cm³) was stirred over 3 Å molecular sieves (19.18 g) at room temperature for 3 days. The sieves were then filtered off and the water content of the filtrate determined (known water content of the solvent). The water content of the solution was 2.6% v/v.

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