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A Practical Synthetic Route to Enantiopure 3-Aryloxy-1,2-propanediols from Chiral Glycidol

Jian Chen and Wilfred Shum*
ARCO Chemical Company, Newtown Square, PA 19073

Abstract: Chiral 3-aryloxy-1,2-propanediols of >98% ee can be obtained in high yield by the nucleophilic addition of substituted phenols to chiral glycidol in the presence of triethylamine catalyst followed by recrystallization in absolute ethanol. Several enantiopure compounds of pharmaceutical significance are presented as examples.

Many racemic 3-aryloxy-1,2-propanediols and their derivatives are pharmaceutically important compounds.[1] In view of the recent emphasis on the commercialization of chiral drugs, it is highly desirable to develop a practical synthetic scheme for enantiopure 3-aryloxy-1,2-propanediols. We report here a facile epoxide-opening reaction on chiral glycidol which allows the isolation of these compounds in high enantiopurity.

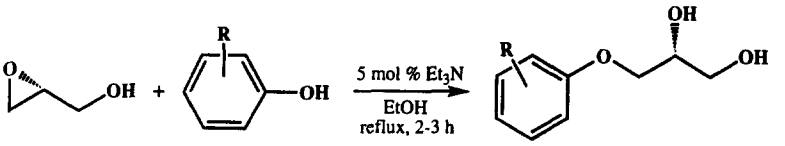
Although the $Ti(O\text{-}i\text{-}Pr)_4$-mediated epoxide-opening reaction has been demonstrated to provide excellent regioselectivity for the nucleophilic opening of chiral 2,3-epoxy alcohols,[2] the isolation of 3-aryloxy-1,2-propanediols made by this route was found to be problematic in the work-up due to the moderate solubility of these compounds in water. We therefore selected alkali alcoholates and organic amines as catalysts for the nucleophilic opening of the sterically-unhindered glycidol.[3] Excellent product yields can be obtained under the optimal reaction conditions as shown in Scheme 1. The yield loss to 1,3-propanediols is only 3-4%, and the desired 1,2-diols in the reaction mixtures have enantiomeric excesses of 86-87% based on chiral HPLC analyses. Although base catalysts have been used on glycidol for the synthesis of racemic 3-aryloxy-1,2-propanediols,[4] to our knowledge, this approach has not been reported for chiral synthesis.

The simplicity of our methodology is best illustrated by the synthesis of enantiopure guaifenesin (**1**). A mixture containing (R)-glycidol of 89% ee (4.0 g, 54.1 mmol), 2-methoxyphenol (6.7 g, 54.1 mmol), triethylamine (0.27 g, 2.7 mmol), and absolute ethanol (10 mL) was refluxed for one hour. On cooling to ambient temperature, 8.8 g of crude product (97.0% ee) crystallized out. This was recrystallized in 16 mL of hot ethanol to afford 7.1 g of purified (R)-guaifenesin (99.0% ee). Further recrystallization in 13 mL of hot ethanol gave 5.9 g of enantiopure (R)-guaifenesin (99.8% ee).

Our results are summarized in Table 1. Enantiopure guaifenesin (**1**), mephenesin (**2**), and 3-(2-chlorophenoxy)-1,2-propanediol (**3**) can be obtained in high yield after recrystallizations in absolute ethanol. These compounds, with substituents in the *ortho*-position of the phenoxy group, have been obtained only in low enantiomeric purity by the lipase-catalyzed sequential transesterification route[5] and the Sharpless asymmetric dihydroxylation route.[6] Enantiopure 3-(4-phenoxyphenoxy)-1,2-propanediol (**4**), recently prepared by the more elaborate routes for the synthesis of insect growth regulators,[7] can be readily obtained from chiral glycidol. Chiral 3-(1-naphthoxy)-1,2-propanediol (**5**) has been used for the synthesis of enantiopure propranolol via 3-(1-naphthyloxy)-1,2-epoxypropane.[8] Not all chiral 3-aryloxy-1,2-propanediols are effectively enriched to enantiopure level by carrying out multiple recrystallizations on the crude products. Although the enantiomeric purity of chlorphenesin (**6**) and 3-(3,5-dimethylphenoxy)-1,2-propanediol (**7**) can be slightly improved, optical

purification of 2-(4-methoxyphenoxy)-1,2-propanediol (**8**) by multiple recrystallizations in absolute ethanol and methylene chloride has not been effective. These compounds have unfavorable melting point phase diagram characteristics that inhibit their enantiomeric enrichment by the recrystallization method.

Scheme 1.



(1:1 stoichiometry)
89 % ee (R)-glycidol

(2R)-3-aryloxy-1,2-propanediol
>90% yield

Table 1. Synthesis and Characterization of Chiral 3-Aryloxy-1,2-propanediols

Compound	R	% EE[a]	Melting Point (°C)[b]
1	2-Methoxy	99.8	99.8
2	2-Methyl	99.0	92.9
3	2-Chloro	99.6	91.8
4	4-Phenoxy	99.0	90.9
5	1-Naphthoxy	98.9	112.4
6	4-Chloro	93.4	83.0
7	3,5-Dimethyl	93.8	71.8
8	4-Methoxy	87.2	80.0

[a]The enantiomeric excesses were determined by chiral HPLC method on a Chiralcel OD column obtained from Chiral Technologies, Inc. [b]The melting points were obtained by differential scanning calorimetry.

In summary, we have demonstrated that many enantiopure 3-aryloxy-1,2-propanediol compounds of pharmaceutical and agrochemical significance can be efficiently prepared from the chiral glycidol made by the Sharpless Asymmetric Epoxidation process.

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