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# A Short Efficient Preparation of (+) and (-)-*trans*-2-Phenylcyclohexanol

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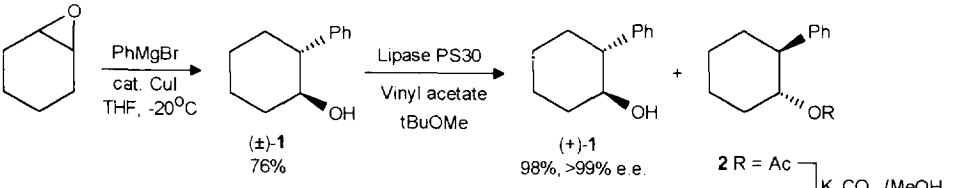
***Abstract:*** Both enantiomers of *trans*-2-phenylcyclohexanol (1) (Whitesell's auxiliary) have been prepared in a facile three step sequence starting from phenylmagnesium bromide and cyclohexene oxide using Lipase PS30 to facilitate the resolution of the racemic alcohol (10g) by a kinetic acetylation reaction on a preparative scale. Copyright © 1996 Elsevier Science Ltd

Enantiomerically pure substituted cyclohexanols are important chiral materials for asymmetric synthesis.[1] Interest in these types of systems was initiated by Corey and Ensley in 1975 with (-)-8-phenylmenthol which can be made in 5 steps from (+)-pulegone.[2] Although this auxiliary is probably one of the most powerful available to the synthetic organic chemist, it is hampered by a less than satisfactory synthesis resulting in the high cost of these materials. This limitation prompted Whitesell and co-workers[3] to develop *trans-2*-phenylcyclohexanol (**1**) as a more practical alternative. (**1**) has proved to be a very effective chiral auxiliary in a variety of organic reactions.[1] Several synthetic routes to enantiomerically pure (**1**) via either asymmetric synthesis or resolution methods have been reported. The key steps of the asymmetric syntheses are hydroboration,[4] epoxidation[5] or osmium catalyzed dihydroxylation[6] of phenylcyclohexene. Resolution of racemic (**1**) has been achieved by preparation of diastereomeric salts[7] and enzymatic hydrolytic kinetic resolution of racemic acetate or chloroacetate derivatives.[8] Herein, we report a quick and efficient synthesis that provides *both* antipodes of (**1**) in *a total* of only *three* steps by utilising a user friendly preparative scale kinetic acetylation of racemic (**1**) as the key resolution step (Scheme 1).




**Scheme 1**

Racemic (**1**) was synthesized according to Whitesell's procedure[9] via a copper catalyzed addition of phenylmagnesium bromide to cyclohexene oxide. Using Ogasawara's[10] recently reported procedure for resolving *trans*-2-(1-naphthyl)cyclohexanol, racemic (**1**) was treated with vinyl acetate and Lipase PS30 on Celite[11] in *t*-butyl methyl ether. This methodology has proved to be very satisfactory for the following reasons: i. the enzyme is used in an organic solvent and needs no careful buffering or temperature control, ii. the progress of the acetylation can be monitored by chiral HPLC,[12] iii. the enzyme can be removed and recovered for reuse by simple filtration, and iv. is applicable to a large scale reaction.[13] Chromatography provided unreacted alcohol (+)-(**1**) in 98% yield (>99% e.e.[12]) and acetate (**2**) in 100% yield, which on methanolysis gave (-)-(**1**) in 90% yield (>99% e.e.[12]).

As such, this route provides a short, efficient preparative scale route to both (+) and (-)-(**1**) in high yield and with high optical purity. Preliminary studies suggest that the Lipase PS30 on Celite can easily be recovered and reused with minimal loss of activity or resolving power.

***Typical Experimental***

Kinetic Acetylation: A suspension of racemic (**1**) (10.00 g, 56.7 mmol), vinyl acetate (52.3 mL, 567 mmol) and Lipase PS30 on Celite (5.67 g) in *t*-butyl methyl ether (250 mL) was stirred at room temperature. After 2 days when the reaction was judged to be complete by chiral HPLC, the lipase was removed by vacuum filtration, washed with ether, and the volatile organics removed *in vacuo* to give a yellow oil. Column chromatography[15] provided 6.25 g of acetate (**2**) as a yellow oil (100%, Rf = 0.41, 5:1 hexanes : ethyl acetate) and 4.89 g of the unreacted alcohol (+)-(**1**) as white crystals (98%, mp 64-65 °C,[14] Rf = 0.18, >99% e.e.[12])

Methanolysis: A suspension of acetate (**2**) (6.17 g, 28.3 mmol) and $K_2CO_3$ (11.72 g, 84.8 mmol) in methanol (124 mL) was stirred at room temperature for 23 hours. After removing the solvent *in vacuo*, the residue was taken up into water (150 mL) and extracted with ethyl acetate (2 x 75 mL). After washing with brine (100 mL) and drying over $MgSO_4$, the solvent was removed *in vacuo* to give 4.50 g of (-)-(**1**) as a white crystalline solid (90%, mp 64-65 °C,[14] >99% e.e.[12])

***Acknowledgments***

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11. Lipase PS30 on Celite from Amano Enzyme USA Co. Ltd., Lombard, Illinois.
12. Chiral HPLC was performed on a 25cm Chiralcel® OJ column, 98:2 hexane : isopropyl alcohol, 0.8 mL/min., retention times /min. acetate (**2**) 7.1, (+)-(**1**) 17.7, (-)-(**1**) 18.8, $\lambda$ = 254 nm. E.e. was determined by chiral HPLC.
13. To date we have not attempted this reaction on more than 10g of (±)-(**1**).
14. All compounds were in agreement with known literature values.[9]
15. A solvent gradient was used, starting with hexanes, then 20:1 to 5:1 hexanes : ethyl acetate until the alcohol eluted.

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