



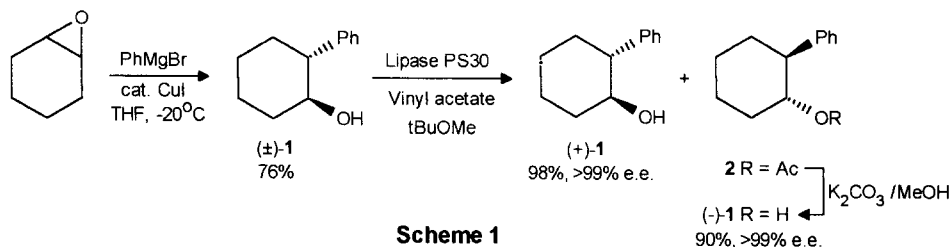
A Short Efficient Preparation of (+) and (-)-*trans*-2-Phenylcyclohexanol

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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-workers³ 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 epoxidation⁵ or osmium catalyzed dihydroxylation⁶ of phenylcyclohexene. Resolution of racemic (**1**) has been achieved by preparation of diastereomeric salts⁷ 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 procedure⁹ via a copper catalyzed addition of phenylmagnesium bromide to cyclohexene oxide. Using Ogasawara's¹⁰ recently reported procedure for resolving *trans*-2-(1-naphthyl)cyclohexanol, racemic (**1**) was treated with vinyl acetate and Lipase PS30 on Celite¹¹ 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 chromatography¹⁵ provided 6.25 g of acetate (2) as a yellow oil (100%, *R*_f = 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 *R*_f = 0.18, >99% e.e.¹²)

Methanolysis: A suspension of acetate (2) (6.17 g, 28.3 mmol) and K₂CO₃ (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 MgSO₄, 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)

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- Lipase PS30 on Celite from Amano Enzyme USA Co. Ltd., Lombard, Illinois.
- 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, λ = 254 nm. E.e. was determined by chiral HPLC.
- To date we have not attempted this reaction on more than 10g of (±)-(1).
- All compounds were in agreement with known literature values.⁹
- 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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