Pergamon

Tetrahedron Letters, Vol. 35, No. 31, pp. 5611-5612, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01156-7

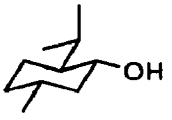
An Efficient Synthesis of Enantiomerically Pure *trans*-2-Phenylcyclohexanol

S. Bruce King and K. Barry Sharpless*

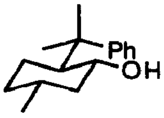
Department of Chemistry, The Scripps Research Institute,
10666 North Torrey Pines Road, La Jolla, CA 92037, U.S.A.

Abstract: *Both enantiomers of trans-2-phenylcyclohexanol (3), Whitesell's auxiliary, have been prepared in a simple two step sequence featuring a catalytic asymmetric dihydroxylation followed by stereoselective hydrogenolysis*

Cyclohexyl based chiral auxiliaries such as menthol (1), 8-phenylmenthol (2), and *trans*-2-phenylcyclohexanol (3) play an important role in asymmetric synthesis.[1] Whitesell introduced 3 as an alternative to 1 and 2,[2] and has demonstrated its effectiveness as a chiral auxiliary in a number of organic reactions.[1] Recently, Ojima has shown 3 to be the auxiliary of choice in preparing the optically pure 3-hydroxy-4-aryl-β-lactams needed for the synthesis of the taxol C-13 side chain.[3] To date, optically pure 3 has been prepared by the asymmetric hydroboration and epoxidation of 1-phenylcyclohexene (4),[4,5] the resolution of various derivatives of 3,[6,7] and the enzyme-catalyzed hydrolytic kinetic resolution of the racemic chloroacetate of 3.[8] We report here a short synthesis of enantiomerically pure 3 which depends on the osmium-catalyzed asymmetric dihydroxylation (AD) process.[9]



1



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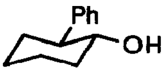


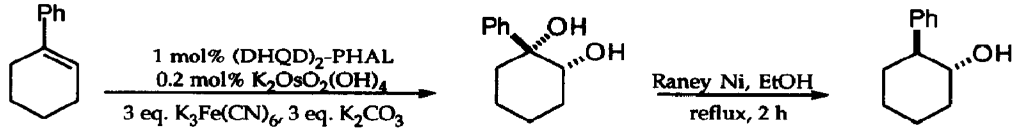
3

Using 1,4-bis-(9-O-dihydroquinidinyl)phthalazine [(DHQD)$_2$-PHAL] as the chiral ligand, commercially available 1-phenylcyclohexene (**4**, 23 g, 143 mmol) was asymmetrically dihydroxylated (Scheme 1) at room temperature to give (+)-(1R, 2R)-1-phenylcyclohexane-*cis*-1,2-diol [(+)-**5**] in 98% yield and 98% enantiomeric excess (ee).[10] Recrystallization (ethyl acetate/hexane) of crude (+)-**5** afforded enantiomerically pure (>99% ee) diol in 74% yield.[11] Reduction of (+)-**5** (10 g, 52 mmol) with Raney® Ni in refluxing ethanol occurred almost exclusively with retention to give (-)-(1R, 2S)-*trans*-2-phenylcyclohexanol [(-)-**3**] as the major product with a small amount (<5% by NMR) of the diastereomeric *cis*-2-phenylcyclohexanol. Recrystallization of this mixture from pentane afforded pure (-)-**3** as a white solid (66% yield, > 99% ee).[12] Raney® Ni reductions of chiral benzylic alcohols have been noted to proceed with retention of configuration.[13]

Similarly using 1,4-bis-(9-O-dihydroquininyl)phthalazine [(DHQ)$_2$-PHAL], 4 (20 g, 126 mmol) was converted to (-)-5 (75% yield, 99% ee) which was then reduced to (+)-3 (69% yield, >99% ee).[14]

Thus, choice of the appropriate ligand (DHQD)2-PHAL or (DHQ)2-PHAL allows the synthesis of either enantiomer of *trans*-2-phenylcyclohexanol (3) in optically pure form. As demonstrated, significant amounts of 3 can be produced by this two step sequence in good yield from a commercially available prochiral olefin. The ease and efficiency of this method make it an attractive alternative to the existing methods for preparation of optically active 3.

Scheme 1



4 (+)-5 (-)-3

Acknowledgements: Financial support was provided by the National Institutes of Health (GM-28384). SBK thanks Glaxo Inc. for a postdoctoral fellowship (1993-94).

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10. Enantiomeric excess for (+)-**5** was determined by HPLC analysis of the cyclic carbonate of (+)-**5** (Chiralcel® OD-H, 2.5% isopropanol in hexanes, 0.8 ml/min, λ = 254 nm).
11. (+)-**5**: mp 121-122 °C; $[\alpha]_D$ = +18.9° (c = 1.29, C_6H_6); ^1H NMR (250 MHz, $CDCl_3$) 7.50-7.21 (m, 5H), 3.94 (dd, 1H, J = 10.6, 3.4 Hz), 2.62 (s, 1H), 1.89-1.35 (m, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) 146.3, 128.4, 126.9, 125.1, 75.7, 74.4, 38.4, 29.1, 24.3, 21.0; MS (FAB^+/NBA/NaI) m/z 215 (M + Na).
12. (-)-(1R, 2S)-*trans*-2-phenylcyclohexanol (-)-3--In a three-necked 500 mL round bottom flask equipped with a mechanical stirrer and reflux condenser, (+)-5 (10.0 g, 52 mmol) was dissolved in EtOH (250 mL). Raney® Ni (Aldrich, 100 g) was added to this solution with the aid of EtOH (50 mL) and this stirred suspension was heated to reflux. After 2 h, the suspension was allowed to cool and then filtered through a pad of celite, and the celite was rinsed with EtOH (3 x 100 mL). The EtOH was concentrated and the crude product dried in vacuo to give a white solid (8.3 g, 91%). This solid was recrystallized from warm pentane (50 mL) at 10 °C to yield (-)-3 (6.0 g, 66%) as long white crystals: mp 64-65 °C, lit. 64-66 °C (Aldrich); Rf 0.39 (3:1 hexane:EtOAc); $[\alpha]_D$ = -56.8° (c = 1.42, CH_3OH), lit. -58° (c = 10, CH_3OH, Aldrich); ^1H NMR (250 MHz, $CDCl_3$) 7.30-7.14 (m, 5 H), 3.60 (ddd, 1 H, J = 10.0, 9.9, 4.6 Hz), 2.42 (ddd, 1 H, J = 12.0, 9.9, 3.6 Hz), 2.11 (m, 1H), 1.89-1.74 (m, 3 H), 1.55-1.29 (m, 5 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) 143.2, 128.7, 127.9, 126.8, 74.4, 53.2, 34.3, 33.2, 26.0, 25.0; MS (FAB^+/NBA/NaI) m/z 199 (M + Na). The optical purity was determined to be > 99% ee by HPLC (Chiralcel® OD-H, 2.5% isopropanol/hexane, 0.6 mL/min, λ = 254 nm).
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14. (+)-**3**: mp 64-65 °C, $[\alpha]_D$ = +58.5° (c = 1.1, CH_3OH).

(*Received in USA* 19 *April* 1994; *revised* 8 *June* 1994; *accepted* 10 *June* 1994)