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An Efficient Preparation of (+)-*trans*-2-(α-Cumyl)cyclohexanol ((+)-TCC): A Practical Alternative to (+)-8-Phenylmenthol[1]

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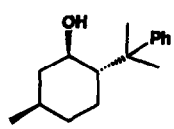
Abstract: *An efficient synthesis and resolution of trans-2-(α-cumyl)cyclohexanol gives the (+)-enantiomer in three steps from cyclohexene oxide.*

The importance of chiral, nonracemic structural units in a number of biologically active compounds has led to intensive efforts to develop efficient methods for their assemblage. Chiral auxiliary mediated asymmetric synthesis has played an important role in the development of a range of chemical transformations that can be carried out with a high degree of absolute stereocontrol. Enantiopure (-)-8-phenylmenthol (**1**) is a highly efficient chiral auxiliary which has been demonstrated to have powerful stereochemical directing influences in several types of synthetically useful reactions.[3] The main limitation of 8-phenylmenthol as a chiral auxiliary is that both enantiomers are not readily available. Chiral auxiliary **1** is commercially available (Aldrich Chemical Co.), or it can be prepared from (+)-pulegone in five synthetic steps.[4] Unfortunately, (+)-8-phenylmenthol is very expensive (Merck Schuchardt) or requires eight steps to synthesize from optically enriched (-)-citronellol.[5] Whitesell developed *trans*-2-phenylcyclohexanol (**2**)[6] and *trans*-2-(α-cumyl)cyclohexanol (TCC) (**3**)[7] as alternatives to 8-phenylmenthol. Although **2** can be prepared as either enantiomer, it is, in general, not as effective a chiral auxiliary as **1** or **3**.[8] Optically enriched (+)- and (-)- **3** were prepared from 1-trimethylsilyloxycyclohexene and cumyl chloride in five and six steps, respectively.[7] This preparation is complicated by the need to use chromatography to remove the epimer formed from sodium reduction of the 2-(α-cumyl)cyclohexanone precursor. There is a clear need for an inexpensive practical route to (+)-TCC (**3**).



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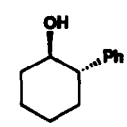

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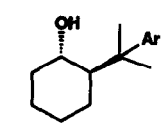

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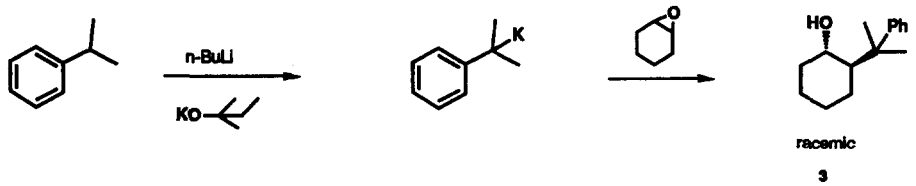
Prompted by our own need for chiral auxiliaries of this type to support our recently developed asymmetric synthesis of 2,3-dihydro-4-pyridones,[9] we investigated a short route to (+)- and (-)-TCC.

A one-step formation of racemic TCC via the addition of an α-cumyl anion to cyclohexene oxide was attractive because, as in the synthesis of alcohol 2[6], the formation of a *cis*-isomer is avoided. Since α-metalating cumene with alkylpotassiums (56%)[10], trimethylsilylmethylpotassium (46%)[11], or more conveniently with a mixture of alkyllithium and potassium *tert*-alkoxide (50%)[11a-b, 12] is shorter and more practical than preparing α-cumyllithium or the corresponding organosodium, α-cumylpotassium was chosen for our initial study. It was hoped that α-cumylpotassium would open cyclohexene oxide cleanly without the additional activation sometimes required for lithium[13] or magnesium[14] organometallics.

After considerable study, conditions were found which gave the desired transformation in high yield. A hexane solution of *n*-butyllithium (1.0 equiv) was added to a mixture of cumene (4.0 equiv) and potassium *tert*-pentoxide[15] (1.1 equiv) in cyclohexane (25°C). After stirring for 2 d at room temperature, neat cyclohexene oxide (1.0 equiv) was added slowly dropwise (<30°C, 30 min) to the dark purple suspension. After 3 h and careful quenching (0°C) with saturated aqueous ammonium chloride (dropwise, 30 min), standard workup provided the crude product as a light-green oil. After Kugelrohr distillation (80-120°C, 0.5 mmHg) and recrystallization from petroleum ether (bp 30-60°C), racemic TCC was obtained as white crystals, mp 49.5-51.5°C (lit.[7b] 45.5-47.5°C) in 84-94% yield. This reaction was carried out on a one-mole scale to provide 183 g (84%) of racemic **3**.



racemic

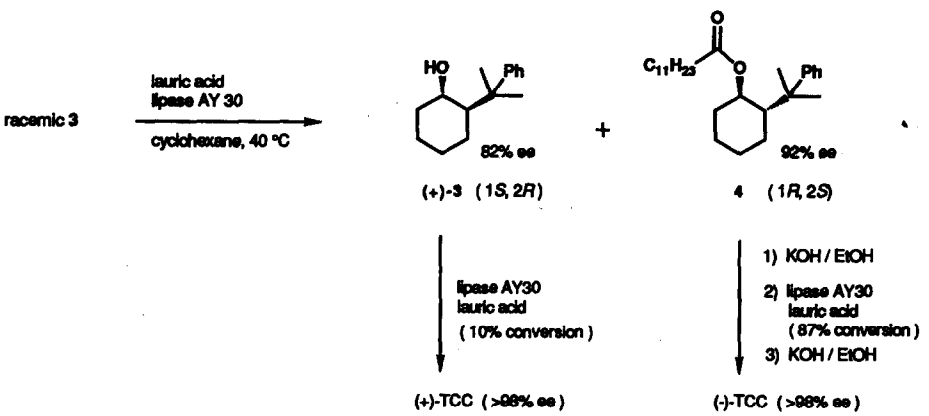
3

With a practical, one-step synthesis of racemic TCC in hand, attention was directed to its resolution. Although a resolution of **3** via a pig liver acetone powder catalyzed hydrolysis of its acetate has been reported,[7b] the less tedious enzymatic esterification procedure developed by Triantaphylides and coworkers[16] was employed with modifications.

To a stirred and warmed (40°C) solution of racemic **3** (1.0 mol) and one equivalent of lauric acid in cyclohexane was added *Candida rugosa*[17] (Amano AY30, 655 g)[18]. The progress of laurate ester formation and the enantiomeric excess of unreacted alcohol was monitored by chiral column HPLC (Chiracel-OJ, J.T. Baker, 10% isopropanol/hexanes, 0.4 mL/min). After 45% conversion to ester (24-41 h), the lipase was

collected by filtration and air dried (4 d, 666 g). The filtrate was concentrated, and the remaining oil was Kugelrohr distilled (90-160°C, 0.5 mmHg) to give a mixture (226 g) of lauric acid and (+)-TCC 3 (82% ee). The pot residue contained laurate ester (181 g). The mixture of alcohol and lauric acid was resubjected to the above esterification procedure (4 L of cyclohexane, 666 g of air dried lipase, 40°C, 2 d, 10% conversion). The lipase and crude product were isolated as before. The residual oil was stirred with K_2CO_3 (138 g) in hexanes (0.5 L) for 1 h to precipitate potassium laurate. Filtration, concentration, and Kugelrohr distillation gave 100.1 g (46%) of (+)-TCC (98.4% ee); $[\alpha]_D^{22}$ + 29.6 (*c* 1.7, MeOH) [lit.[7b] $[\alpha]_D^{23}$ + 26.3 (*c* 2.05, MeOH)].

The initially isolated laurate ester can be saponified (KOH/EtOH), and the resulting alcohol distilled to give (-)-TCC (95 g, 92.4% ee). Resubjecting this alcohol to the above enzymatic esterification (100 g lauric acid, 650 g of lipase, 4 L of cyclohexane, 40°C, 2 d, 87% conversion) gave, after Kugelrohr distillation, 148 g of laurate ester as pot residue. Hydrolysis and distillation gave 78.3 g (36% overall) of (-)-TCC as an oil: $[\alpha]_D^{27}$ - 29.4 (*c* 2.0, MeOH); 98.2% ee (by HPLC analysis).



The synthesis and resolution of 8-phenymenthol equivalent 3 (TCC) has been achieved using relatively inexpensive materials, a recyclable lipase, and easily applied procedures that are amenable to large scale preparation. The (+)-enantiomer, (+)-TCC (> 98% ee), is prepared in three steps, and (-)-TCC (> 98% ee) can be isolated as a byproduct in two additional steps. Work is in progress to prepare other *trans*-2-(1-aryl-1-methylethyl)cyclohexanols and to study their effectiveness as chiral auxiliaries.

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