

Practical Enzymatic Resolution of Chiral Auxiliaries – Enantiomerically Pure *trans*-2-Phenylcyclohexanol and *trans*-2-(α -Cumyl)cyclohexanol**

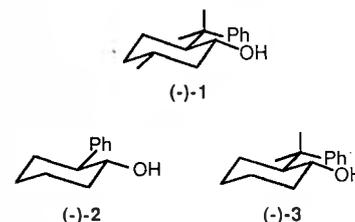
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Abstract: Commercially available, crude pig liver material (Pig Liver Acetone Powder, PLAP) is demonstrated to be effective for the preparation of enantiomerically pure alcohols that are, in turn, effective chiral auxiliaries for asymmetric induction. Resolution of the title alcohols in large scale is effected by selective enzymatic cleavage of the corresponding acetic acid esters.

Recent efforts in the area of asymmetric induction have been rewarded by a range of chemical transformations that can be carried out with high levels of absolute stereochemical control. All such methods of current practical significance rely upon the energetic difference between transition states which are made diastereomeric rather than enantiomeric through association

of the reacting species with a chiral auxiliary. Thus, whether the auxiliary is used in a stoichiometric or a catalytic fashion, the source of the bulk dissymmetry in the reaction products is imparted by this agent. The chiral pool (those species easily obtained from natural sources) has been extensively drawn upon in the past as the source of the dissymmetry of the auxiliary and thus the ultimate source of stereochemical direction. However, it has become increasingly apparent in recent years that the combination of both high selectivity and broad generality in asymmetric induction is often met by inducing agents that are specifically designed for the task at hand as opposed to being those efficaciously derived from natural sources.

In our own research, we have found the auxiliary (-)-8-phenylmenthol [(-)-1] to be extraordinarily powerful in a variety of transformations^[1-5]. Nonetheless, there are difficulties associated with the preparation of (-)-1 from natural (+)-pulegone that make its large scale application less than practical^[6]. In addition, the only sequences to date used for the preparation of the antipode (+)-1 are not at all practical^[7]. In a concerted effort to replace the auxiliary 8-phenylmenthol with a species more readily available yet just as efficacious in absolute stereochemical control, we uncovered the very powerful auxiliary *trans*-2-phenylcyclohexanol (**2**)^[8]. Furthermore, we have been able to duplicate the stereochemical directing features of 8-phenylmenthol with *trans*-2-(α -cumyl)cyclohexanol (**3**), the analogous structure lacking only the methyl substituent on the cyclohexane ring.



Both of these materials **2** and **3** are conveniently available in racemic form, the former by copper catalyzed, phenyl Grignard reagent opening of cyclohexene oxide^[9] and the latter by reduction of the ketone formed by reaction of the silylenol ether of cyclohexanone with cumyl chloride in the presence of zinc chloride. The application of these alcohols as auxiliaries for control of absolute stereochemistry re-

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quired a practical, large scale method for their separation into individual, pure enantiomers. We have found that the crude mixture of esterase enzymes present in pig liver acetone powder (PLAP⁽¹⁰⁾) is highly effective in carrying out selective hydrolysis of one of the enantiomeric acetates in each case. Indeed, the crude powdered pig liver appears to be as effective as pure pig liver esterase (PLE).

Thus, the racemic acetate of *trans*-2-phenylcyclohexanol [(±)-4] on treatment with a suspension of PLAP in water-acetone buffered to pH 8.0 is transformed over a period of six days to a nearly 1:1 mixture of the (-)-alcohol and (+)-acetate. Isolation of this mixture from the aqueous medium and simple chromatographic separation produced separated acetate (+)-4 and alcohol (-)-2. The latter was transformed into material of high optical and enantiomeric purity by simple recrystallization. Alkaline hydrolysis of the acetate afforded alcohol (+)-2 which, again, was transformed into material of high optical purity by simple recrystallization.

analysis of the monoester 5 formed concurrently with the bisester 7⁽¹²⁾.

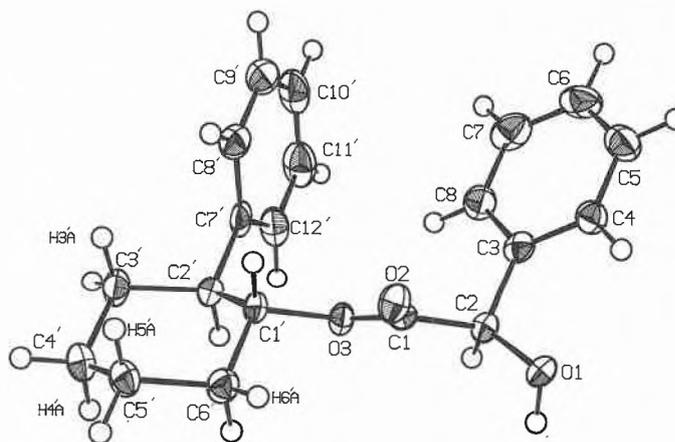
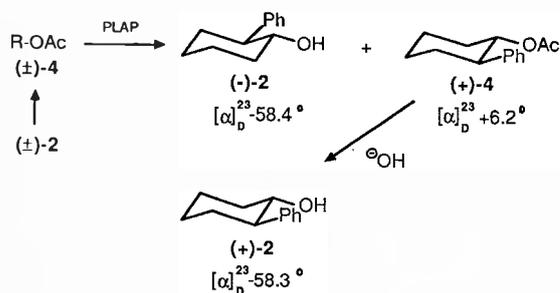


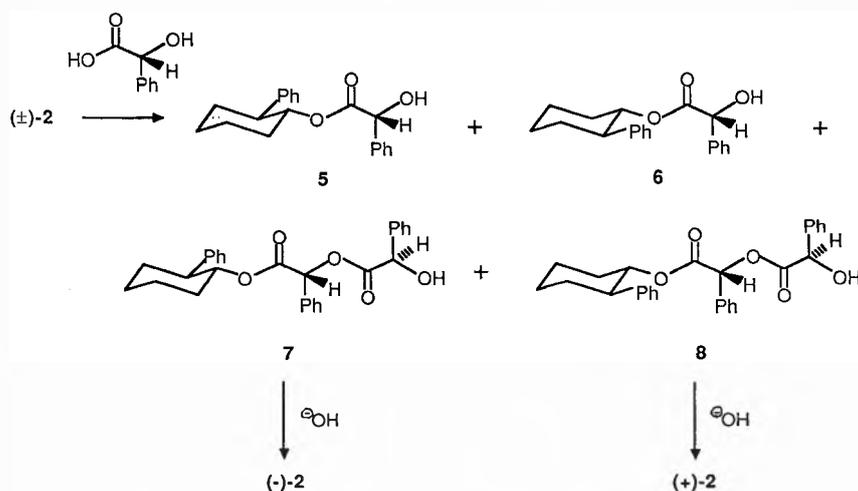
Fig. 1. Structure of the monoester 5 in the crystal.

Resolution of *trans*-2-(α -cumyl)cyclohexanol [(±)-3] proceeded essential as described above for 2. However, the resulting purified enantiomers (unlike the racemic

ated and resubmitted to an enzymatic hydrolysis that was interrupted before all of the (-)-acetate was consumed. The optical rotation of the resulting alcohol was equal



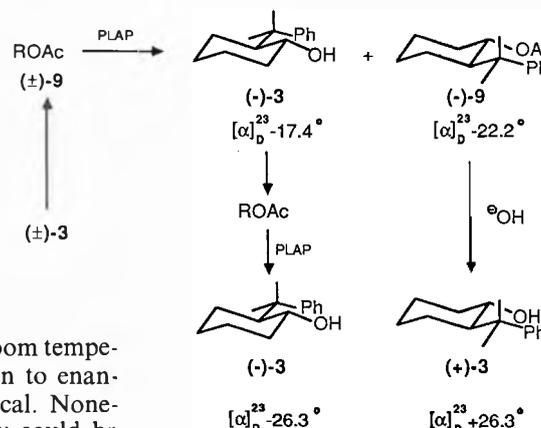
The correspondence between optical rotation, and therefore optical purity and enantiomeric excess for this material was established by HPLC analysis of the diastereomeric mandoylmandelic acid esters (7 and 8) formed by acid catalyzed esterification with excess mandelic acid⁽¹¹⁾.



In addition, the correspondence between absolute configuration and optical rotation was established unambiguously by internal comparisons between alcohol and acid residues in a single crystal X-ray

mixture) are not crystalline at room temperature and thus recrystallization to enantiomeric purity was not practical. Nonetheless, material of high purity could be obtained by carrying the enzymatic hydrolysis past the point where the ratio of acetate to alcohol was 1:1⁽¹³⁾.

Hydrolysis of the unconsumed acetate (-)-9 afforded (+)-alcohol of high optical purity. The alcohol produced directly by the enzymatic cleavage was enriched in the (-)-enantiomer. This material was reacyl-



in magnitude but opposite in sign to that obtained from the acetate (-)-9.

The absolute configurational assignment for these enantiomers was established by correspondence of the sign of rotation with that for 8-phenylmenthol and, more rigorously, by establishing the sense of asymmetric induction of this auxiliary. Effecting the ene reaction between the glyoxylate of (-)-3 and 1-hexene followed by ester reduction (LiAlH₄) and double bond saturation (H₂/Pd) afforded (*S*)-(-)-1,2-octanediol. Thus, the sense of asymmetric induction for (-)-3 is the same as that for (-)-8-phenylmenthol.

Experimental

Materials: Diethyl ether and tetrahydrofuran (THF) were distilled prior to use from a deep-blue solution resulting from benzophenone and sodium. Hexane was stirred with H₂SO₄ and solid Na₂CO₃ and distilled before use. CH₂Cl₂ was distilled from CaH₂. All other solvents and reagents were used as obtained from commercial sources.

Procedures: Reactions were routinely run under dry N_2 with magnetic stirring. Organic solutions of products were dried with molecular sieves (unless otherwise noted) before concentrating in vacuo. Reference to purification by preparative chromatography refers to the use of a Waters Prep-500 system with two silica gel cartridges. Analytical LC was performed on a Waters 6000A pump with a refractive index detector and one microporasil column.

Spectra: ^{13}C -NMR spectra were obtained using a Nicolet NT-360 spectrometer at 90 MHz or where noted a Varian FT-80 at 20 MHz. 1H -NMR spectra were obtained using a Nicolet NT-360 at 361 MHz. Both 1H - and ^{13}C -NMR were obtained with $CDCl_3$ as solvent and values are reported in ppm downfield from TMS as an internal standard. IR spectra were obtained on dilute (5%) CH_2Cl_2 solutions using a Perkin-Elmer 298 instrument with polystyrene 1601 cm^{-1} as reference. Low-resolution mass spectra in EI mode were recorded using a Bell and Howell Model 21-491 spectrometer at 70 eV and those in CI mode using a Finnigan-MAT 4023 GC/MS with CH_4 . High-resolution mass spectra were recorded with a CEC 21-110B instrument in EI mode.

Racemic trans-2-phenylcyclohexanol (2): A solution of phenylmagnesium bromide in 1.4 L of THF was prepared from 35.3 g (1.47 mol) of magnesium and 155.0 mL (1.47 mol) of bromobenzene using standard procedures. The Grignard reagent solution was cooled to $-30^\circ C$ and 6.53 g (0.066 mol) of purified copper(I) chloride was added. The resulting solution was allowed to stir for 10 min and then a solution of 101 mL (1.0 mol) of cyclohexene oxide in 100 mL of THF was added dropwise. The reaction mixture was allowed to warm to $0^\circ C$ and stir for 2 h before quenching by the addition of 500 mL of saturated $(NH_4)_2SO_4$. The organic layer was washed with saturated $(NH_4)_2SO_4$ solution until the aqueous layer was no longer blue. The combined aqueous layers were no longer blue. The combined aqueous layers were extracted with Et_2O . The organic layers combined, dried ($MgSO_4$), and concentrated to afford 169.5 g (96% crude) of the desired racemic alcohol 2, as a light yellow solid. Recrystallization from pentane afforded 130.2 g (80%) of a white solid, *m.p.* 56.5–57.0 $^\circ C$ (lit.¹⁹ 57–58 $^\circ C$). ^{13}C -NMR: 143.4 (s, C7), 128.7 (d, C9), 127.9 (d, C8), 126.7 (d, C10), 74.3 (d, C1), 53.3 (d, C2), 34.6 (t, C6), 33.4 (t, C3), 26.1 (t, C4), 25.1 (t, C5); 1H -NMR: 7.35–7.17 (m, 5 H), 3.64 (ddd, $J = 5.4, 10.8, 10.8\text{ Hz}$, 1 H), 2.42 (ddd, $J = 5.4, 10.8, 16.5\text{ Hz}$, 1 H), 2.11 (m, 1 H), 1.84 (m, 2 H), 1.76 (m, 1 H), 1.62 (s, 1 H), 1.53–1.25 (bm, 4 H); IR: 3592, 3461, 2941, 2863, 1604, 1497, 1451 cm^{-1} ; MS (EI): 176 (M^+), 158, 143, 130, 117, 104, 91 (base).

Resolution of (\pm)-2:

a) Racemic trans-2-phenylcyclohexyl acetate (4): To a solution of 4.2 g (34.0 mmol) of 4-dimethylaminopyridine and 171.0 mL (2.1 mol) of pyridine in 600 mL of CH_2Cl_2 was added dropwise with stirring a solution of 176.0 g (1.0 mol) of racemic 2 in 250 mL of CH_2Cl_2 . After 10 min, 188.2 mL (2.0 mol) of acetic anhydride in 150 mL of CH_2Cl_2 was added dropwise over 1.5 h. After 2 h, the reaction mixture was poured into a mixture of 500 mL of 6 N HCl, 750 mL of ice, and 1.5 L of Et_2O . The organic layer was washed with 2 N HCl (4 \times 300 mL), the combined aqueous layers were extracted with Et_2O , the combined organics were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Concentration afforded 213.6 g (98%) of 4 as a slightly viscous liquid. ^{13}C -NMR: 169.9 (s, C1), 143.1 (s, C7), 128.2 (d, C9), 127.5 (d, C8), 126.4 (d, C10), 75.7 (d, C1), 49.8 (d, C2), 33.9 (t, C3), 32.4 (t, C6), 25.9 (t, C4), 24.8 (t, C5), 20.7 (q, C2); 1H -NMR: 7.30–7.15 (m, 5 H), 4.97 (ddd, $J = 5.4, 11.0, 11.0\text{ Hz}$, 1 H), 2.65 (ddd, $J = 5.4, 11.0, 16.5\text{ Hz}$, 1 H), 2.13 (m, 1 H), 1.93 (m, 1 H), 1.84 (m, 1 H), 1.78 (m, 1 H), 1.74 (s, 3 H), 1.56 (m, 1 H), 1.46 (m, 1 H), 1.41 (m, 1 H), 1.35 (m, 1 H); IR: 3070, 2940, 2860, 1730, 1604, 1497 cm^{-1} ; LRMS (EI): 175, 158 (base), 130, 91; (CI): 219 ($[M + H]^+$), 159 (base).

b) Enzymatic Hydrolysis: (–)-trans-2-phenylcyclohexanol [(–)-2]: To 8.0 L of 0.5 M, pH 8.0 KH_2PO_4/K_2HPO_4 aqueous buffer at $31^\circ C$ was added with rapid stirring a solution of 218.0 g (1.0 mol) of racemic 4 in 1.1 L (15.0 mol) of acetone. The heterogeneous mixture was stirred for 1 h before adding 33.0 g of PLAP. The reaction was monitored by quenching aliquots with 2 N HCl and extracting with CH_2Cl_2 . HPLC analysis (5:1 hexane/EtOAc) was used to determine the ratio of acetate to alcohol. After 115 h the ratio was 68:32 (pH 7.55). After 140 h the ratio had changed to 61:39 (pH

7.50)¹⁴. Additional PLAP (10.0 g) was added and after 240 h (ratio 55:45)¹⁵ the reaction was quenched by acidification to pH 4.0 with 2 N HCl. To the acidic solution 1 kg of sodium chloride and 500 mL of CH_2Cl_2 were added and the mixture was stirred for 1 h before allowing to stand until all the PLAP residue had settled. The aqueous supernatant was carefully removed and filtered through cotton leaving the product containing, PLAP residue behind. The aqueous layers were then extracted twice with 500 mL portions of CH_2Cl_2 . The residue was poured into large centrifuge tubes, shaken with CH_2Cl_2 , and centrifuged to break the emulsion. The organic layer was removed, filtered through cotton, and concentrated. This extraction process was repeated until no additional product was obtained. A total of 190.7 g of a yellow liquid was obtained. Preparative chromatography afforded 77.0 g (88% crude) of the (–)-alcohol and 107.5 g (97% of the (+)-acetate (yields based on 55:45 ratio). The (–)-alcohol was recrystallized from pentane. Four recrystallizations afforded 63.0 g (82%) of optically pure (–)-2, $[\alpha]_D^{25} -58.4^\circ C$ ($c = 10.0$, MeOH), *m.p.* 64–65 $^\circ C$ [lit.¹⁶ $[\alpha]_D^{25} -55.5^\circ C$ ($c = 0.10$, MeOH), *m.p.* 64–65 $^\circ C$] and 4.3 g of (–)-2, $[\alpha]_D^{25} -56.4^\circ C$ (98% ee).

c) (+)-trans-2-phenylcyclohexanol [(+)-2]: To a solution of 107.5 g (0.49 mol) of the acetate obtained above (cf. b)) in 500 mL of MeOH was added 69.0 g (1.23 mol) of 85% KOH. The resulting solution was heated to $50^\circ C$ for 3 h, cooled to ambient temperature, and concentrated. The resulting solid residue was partitioned between EtOAc and H_2O . The aqueous layer was extracted with EtOAc (5 \times 100 mL) and the combined organics were filtered through cotton and concentrated to afford 84.0 g (97%) of (+)-2. Recrystallization afforded 46.0 g (55%) of optically pure (+)-2 with $[\alpha]_D^{25} +58.3^\circ C$ ($c = 10.0$, MeOH), *m.p.* 64–65 $^\circ C$, 7.2 g with $[\alpha]_D^{25} +57.3^\circ C$ (99% ee), and 27.1 g of optically enriched material.

trans-2-phenylcyclohexyl mandoylmandelate (7 and 8): A solution of 7.48 g (42.5 mmol) of racemic 2, 0.83 g (4.4 mmol) of *p*-toluenesulfonic acid monohydrate, and 12.9 g (85.1 mmol) of (*R*)-(–)-mandelic acid in 200 mL of benzene was heated at reflux with azeotropic removal of water for 18 h. The cooled solution was washed with 2 N Na_2CO_3 (2 \times 100 mL) and the combined organics were washed with 100 mL of brine and dried ($MgSO_4$). Concentration afforded 13.2 g of a viscous oil. Preparative chromatographic separation of 5.0 g of this material afforded 2.85 g of a 1:1 mixture of monoesters 5 and 6, along with 1.16 g of bisester 7 and 0.87 g of bisester 8. For 5: ^{13}C -NMR: 172.8 (s, C1), 142.3 (s, C7), 137.9 (s, C3), 128.3 (d, C5 and C9), 127.7 (d, C6), 127.1 (d, C4), 126.3 (d, C10), 126.2 (d, C8), 78.2 (d, C1') 72.9 (d, C2), 49.5 (d, C2') 34.1 (t, C3'), 32.3 (t, C6'), 25.6 (t, C4'), 24.7 (t, C5'). For 6: ^{13}C -NMR: 172.7 (s, C1), 142.6 (s, C7), 138.6 (s, C3), 128.5 (d), 128.4 (d), 128.1 (d), 127.5 (d), 126.7 (d), 126.6 (d), 78.0 (d, C1'), 72.9 (d, C2), 49.5 (d, C2') 33.6 (t, C3'), 32.1 (t, C6'), 25.6 (t, C4'), 24.5 (t, C5'). For 7: ^{13}C -NMR: 172.5 (s, C1), 167.0 (s, C1'), 142.4 (s, C7), 137.7 (s, C3), 133.0 (s, C3'), 128.8 (d, C6), 128.5 (d, C5, C5', C9'), 128.2 (d, C6'), 127.1 (d, C8', C4'), 126.9 (d, C4), 126.3 (d, C10'), 77.6 (d, C1'), 75.6 (d, C2'), 73.0 (d, C2), 49.4 (d, C2'), 34.3 (t, C3'), 32.1 (t, C6'), 25.7 (t, C4'), 24.7 (t, C5'); 1H -NMR: 7.55–6.82 (m, 15 H), 5.74 (s, 1 H), 5.22 (s, 1 H), 4.96 (ddd, $J = 5.4, 12.6, 12.6\text{ Hz}$, 1 H), 2.51 (ddd, $J = 5.4, 12.6, 12.6\text{ Hz}$, 1 H), 2.12 (m, 1 H), 1.90–1.65 (bm, 3 H), 1.50–1.22 (bm, 4 H); IR: 3530, 3030, 2940, 2860, 1740, 1604 cm^{-1} ; LRMS (EI): 294, 204, 176, 158 (base), 136, 129, 118, 107, 91; (CI): 445 ($[M + H]^+$), 159 (base). For 8: ^{13}C -NMR: 172.6 (s, C1), 166.9 (s, C1'), 142.7 (s, C7), 138.1 (s, C3), 133.1 (s, C3'), 129.1 (d, C6), 128.6 (d, C5, C5', C6'), 128.3 (d, C9'), 127.8 (d, C4'), 127.5 (d, C8'), 127.0 (d, C4), 126.4 (d, C10'), 77.6 (d, C1'), 76.3 (d, C2'), 72.7 (d, C2), 48.9 (d, C2'), 33.9 (t, C3'), 31.4 (t, C6'), 25.7 (t, C4'), 24.5 (t, C5'); 1H -NMR: 7.59–6.65 (m, 15 H), 5.72 (s, 1 H), 5.22 (s, 1 H), 4.84 (ddd, $J = 5.4, 12.6, 12.6\text{ Hz}$, 1 H), 3.42 (bs, 1 H), 2.16 (ddd, $J = 5.1, 12.6, 12.6\text{ Hz}$, 1 H), 1.97–1.87 (m, 1 H), 1.86–1.60 (bm, 3 H), 1.47–1.13 (bm, 3 H), 0.94 (m, 1 H); IR: 3530, 3030, 2940, 2860, 1740, 1604 cm^{-1} ; LRMS (EI): 294, 158, 136, 118, 107 (base), 91, 79; (CI): 445 ($[M + H]^+$), 159 (base), 119.

Racemic trans-2-(1-methyl-1-phenylethyl)cyclohexanone: To 2.36 g (13.8 mmol) of 1-trimethylsilyloxy-1-cyclohexene and 2.58 g (16.6 mmol) of 1-methyl-1-chloroethylbenzene in 50 mL of CH_2Cl_2 was added 0.189 g (1.37 mmol) of anhydrous zinc chloride. The mixture was stirred at room temperature for 1 h and poured into cold water. The aqueous layer was separated and ex-

tracted with two 50 mL portions of ether. The organic layers were combined, washed with saturated $NaHCO_3$ and brine, dried, and concentrated to afford 3.12 g of a liquid, which was distilled at $108^\circ C$ under 0.45 mmHg vacuum to give 2.50 g (84%) of the desired ketone. ^{13}C -NMR (20 MHz): 211.4 (s, C1), 149.7 (s, C10), 127.9 (d, C12), 125.7 (d, C11), 125.4 (d, C13), 60.2 (d, C2), 44.0 (t, C6), 39.2 (s, C7), 30.2 (t, C3), 28.4 (t, C4), 26.8 (q, C8), 25.9 (t, C5), 23.8 (q, C9); 1H -NMR: 7.35–7.16 (m, 5 H), 2.73 (dd, $J = 4.1, 12.2\text{ Hz}$, 1 H), 2.35–2.21 (m, 2 H), 2.02 (m, 1 H), 1.79 (m, 2 H), 1.70–1.40 (bm, 3 H), 1.47 (s, 3 H), 1.41 (s, 3 H); IR: 2940, 2866, 1709, 1496, 1446, 1377, 1314, 1136 cm^{-1} ; LRMS (EI): 216 (M^+), 201, 183, 119 (base), 98, 91.

Racemic trans-2-(1-methyl-1-phenylethyl)cyclohexanol (3) (trans-2-cumylcyclohexanol): A solution of 7.45 g (324.0 mmol) of sodium metal and 300 mL of toluene was refluxed until all the sodium had become molten. A solution of 10.0 g (46.0 mmol) of 2-(1-methyl-1-phenylethyl)cyclohexanone in 34.7 mL (460.0 mmol) of isopropyl alcohol was then added dropwise over a 2 h period. After 21 h at reflux, the reaction was cooled and the large pieces of excess sodium were removed before adding 50 mL of MeOH to quench the remainder of the sodium. After dilution with 250 mL of toluene, the solution was washed with saturated NaH_2PO_4 (3 \times 300 mL) and the aqueous layers were extracted with toluene (2 \times 100 mL). Concentration afforded 9.84 g (98% crude) of a mixture of *cis*- and *trans*-diastereomers. Preparative chromatography (22:1 hexane/EtOAc) afforded 7.93 g (79%) of pure equatorial alcohol, *m.p.* 45.5–47.5 $^\circ C$ and 0.45 g (4%) of the axial alcohol, *m.p.* 68.0–70.0 $^\circ C$. For racemic 3: ^{13}C -NMR: 151.4 (s, C10), 128.4 (d, C12), 125.9 (d, C11), 125.7 (d, C13), 73.4 (d, C1), 54.8 (d, C2), 40.2 (s, C7), 37.0 (t, C6), 28.3 (q, C8), 27.1 (t, C3), 26.4 (t, C4), 25.1 (t, C5), 25.0 (q, C9); 1H -NMR: 7.43–7.15 (m, 5 H), 3.50 (ddd, $J = 5.4, 10.8, 10.8\text{ Hz}$, 1 H), 1.87 (m, 1 H), 1.82–1.57 (m, 1 H), 1.44 (s, 3 H), 1.29 (s, 3 H), 1.27–1.08 (m, 3 H), 1.07–0.92 (m, 1 H); IR: 3585, 3020, 2935, 2860, 1597, 1497 cm^{-1} ; LRMS (EI): 218 (M^+), 200 ($M - H_2O$), 119 (base), 91; HRMS (EI): calc. for $C_{15}H_{22}O$ 218.1670, found 218.1665. For the *cis*-diastereomer: ^{13}C -NMR: 149.9 (s, C10), 128.0 (d, C12), 126.3 (d, C11), 125.5 (d, C13), 67.7 (d, C1), 52.8 (d, C2), 40.5 (s, C7), 35.3 (t, C6), 27.5 (q, C8), 27.0 (t, C4), 25.8 (q, C9), 21.5 (t, C3), 20.0 (t, C5); 1H -NMR: 7.41–7.14 (m, 5 H), 3.85 (bs, 1 H), 1.76 (m, 1 H), 1.64 (m, 1 H), 1.60–1.11 (bm, 7 H), 1.39 (s, 3 H), 1.37 (s, 3 H), 1.01 (m, 1 H); IR: 3609, 2937, 2860, 1600, 1497 cm^{-1} .

Resolution of (\pm)-3:

a) Racemic trans-2-(1-methyl-1-phenylethyl)cyclohexyl acetate (9) (trans-2-cumylcyclohexyl acetate): This acetate was prepared in 98% yield as described above for the synthesis of racemic 4. ^{13}C -NMR: 170.2 (s, C1), 151.6 (s, C10'), 127.9 (d, C12'), 125.4 (d, C11'), 125.0 (d, C13'), 74.5 (d, C1'), 50.9 (d, C2'), 39.9 (s, C7'), 33.4 (t, C6'), 28.0 (q, C8), 27.1 (t, C3'), 26.0 (t, C4'), 24.8 (q, C9), 24.7 (t, C5'), 21.0 (q, C2); 1H -NMR: 7.31–7.24 (m, 4 H), 7.17–7.10 (m, 1 H), 4.76 (ddd, $J = 5.4, 10.8\text{ Hz}$, 1 H), 2.06 (ddd, $J = 4, 10.8, 11.7\text{ Hz}$, 1 H), 1.91–1.48 (m, 1 H), 1.77–1.57 (bm, 3 H), 1.52 (s, 3 H), 1.32 (s, 3 H), 1.31–1.00 (bm, 4 H), 1.21 (s, 3 H); IR: 2940, 2860, 1730, 1600, 1497 cm^{-1} ; LRMS (EI): 260 (M^+), 200, 158, 141, 119 (base), 105, 91; (CI): 261 ($[M + H]^+$), 201, 119 (base), 105; HRMS (EI): calc. for $C_{17}H_{24}O_2$ 260.1776, found 260.1783.

b) Enzymatic Hydrolysis: To 600 mL of 0.5 M, pH 8.0 KH_2PO_4/K_2HPO_4 aqueous buffer at $31^\circ C$, a solution of 3.0 g (12.0 mmol) of racemic 9 in 13.2 mL (180.0 mmol) of acetone and 2.0 g of PLAP were added as described above. After 98 h the ratio of acetate to alcohol was 54:46, at which point an additional 300 mg of PLAP was added. After 191 h the ratio was 45:55 and workup afforded 2.29 g. Preparative chromatography afforded 1.12 g (80%) of the acetate, $[\alpha]_D^{25} -22.3^\circ C$ ($c = 9.4$, MeOH) and 1.15 g (80%) of the alcohol, $[\alpha]_D^{25} -17.4^\circ C$ ($c = 9.3$, MeOH). Hydrolysis of the acetate (KOH/MeOH) afforded (+)-3, $[\alpha]_D^{25} +26.3^\circ C$ ($c = 2.05$, MeOH), $[\alpha]_D^{25} +25.8^\circ C$ ($c = 0.48$, MeOH). The (–)-alcohol (1.13 g, 5.2 mmol) was reacylated (affording 1.06 g, 76%) and resubmitted to enzymatic hydrolysis. The reaction was stopped after 74 h (ratio 41:59). Workup and preparative chromatography afforded 0.426 g (84% based on final ratio) of (–)-3, $[\alpha]_D^{25} -26.3^\circ C$ ($c = 2.05$, MeOH).

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