Efficient Synthesis and Resolution of *trans*-2-(1-Aryl-1-methylethyl)cyclohexanols: Practical Alternatives to 8-Phenylmenthol

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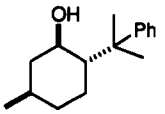
A short synthesis and resolution of effective chiral auxiliaries of the 8-arylmenthol-type were achieved using inexpensive materials, a recyclable lipase, and easily applied procedures that are amenable to large-scale preparation. A variety of isopropylarenes were α-metalated with *n*-butyllithium/potassium *tert*-pentoxide and treated with cyclohexene oxide to provide racemic *trans*-2-(1-aryl-1-methylethyl)-cyclohexanols **6a–f** in fair to high yield. *Candida rugosa* lipase and lauric acid were used to resolve these racemic alcohols by converting the (−)-enantiomer to its laurate ester. The enzymatic resolutions were carried out at 40 °C and were faster in cyclohexane than in hexanes. The synthesis and resolution of racemic *trans*-2-(1-methyl-1-phenylethyl)cyclohexanol (**6a**) were performed on a 1 mol scale in 68% overall yield, requiring three steps for (+)-**6a** and five steps for (−)-**6a**.

Ever since Corey and Ensley first reported its synthesis in 1975, a variety of ester and ether derivatives of the chiral auxiliary (−)-8-phenylmenthol (**1**) have been shown to undergo Diels–Alder,[2] [2 + 2] cycloaddition,[3] ene,[4] 1,2-addition,[5] 1,4-addition,[6] and cyclopropanation[7] reactions with high diastereoselectivity (de > 90%).



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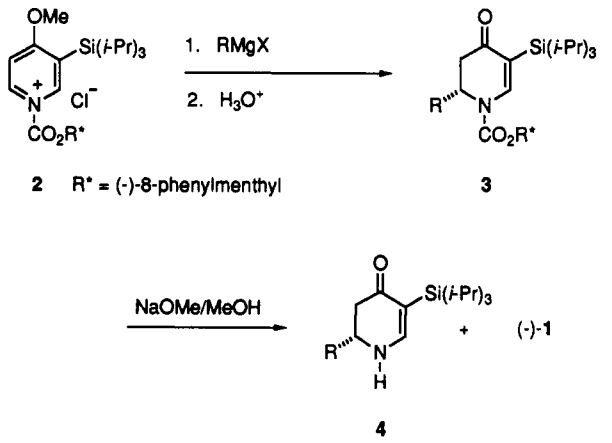
Recently, we have shown that the reaction of (−)-8-phenylmenthyl-derived 1-acylpyridinium salts **2** and Grignard reagents gives *N*-acyl-2-alkyl-2,3-dihydro-4-pyridones **3** with high diastereoselectivity. Following the removal of the minor diastereomer of **3** by recrystallization or chromatography, treatment with NaOMe/MeOH provides enantiomerically pure 2-alkyl-2,3-dihydro-4-pyridones **4** and recovered **1** (Scheme I).[8] In contrast, other chiral auxiliaries such as *trans*-2-phenylcyclohexanol[9] or *trans*-2-benzylcyclohexanol[10] were not as effective in this reaction.

Scheme I



For part of a program directed at using dihydropyridones **4** as chiral building blocks to synthesize enantiomerically pure alkaloids,[11] we needed easy access to both enantiomers of **1** or an equivalent which still retains the essential *trans*-2-α-cumyl functionality. Unfortunately, (+)-8-phenylmenthol, the least used enantiomer of **1**, requires eight steps to synthesize from optically enriched (−)-citronellol,[12] and the (−)-enantiomer requires five steps from optically pure (+)-pulegone.[13] An alternative to **1**, optically enriched (+)- or (−)-*trans*-2-(1-methyl-1-phenylethyl)cyclohexanol (**6a**), is equivalent in its stereochemical directing ability and has been made from 1-[(trimethylsilyl)oxy]cyclohexene in five or six steps, respectively.[14] The preparations of **1** and **6a** are lengthy and complicated by the need to use chromatography or derivatization to remove the epimers formed after sodium reduction of their respective 2-α-cumyl cyclohexanone precursors. We now report a

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Table I. Addition of α-Metalated Isopropylarenes to Cyclohexene Oxide

entry	isopropylarene[a] (equiv)	K-*t*-OR (equiv)	time[c] (d)	yield[d] (%)	product (mp; bp (°C))
a	cumene (1)	butoxide (3)	1	29	**6a**
b	(1)	(3)	2	44	
c	(1.4)	pentoxide (3)	1	46	
d	(1.4)	(3)	2	69	
e	(2)	(1.5)	2	41	
f	(2)	(2)	2	31	
g	(2)	(5)	2	40	
h	(2)	(1.2)	2	68	
i	(3)	(1.2)	2	93	
j	(4)	(1.2)	2	94	
k	(4)[b]	(1.2)	2	84	(mp 49.5–51.5)
l	1,4-diisopropylbenzene (1)	(1.2)	1	26[e]	**6b** (bp 130 (1.3 mmHg))
m	(4)	(1.2)	1	85[e]	
n	1,3,5-triisopropylbenzene (1)	(1.2)	1 h	31[e]	**6c** (bp 122 (0.55 mmHg))
o	(4)	(1.2)	1	92[e]	
p	4-*tert*-butylcumene (4)	(1.2)	1	48	**6d** (mp 74.5–77)
q	4-isopropylbiphenyl (4)	(1.2)	2	49	**6e** (mp 91–92)
r	2-isopropylnaphthalene (3)	(1.2)	2	33	**6f** (mp 70–71)
s	(4)	(1.2)	1 h	55[f]	

[a] The reactions were generally performed on a 10–100 mmol scale. [b] This reaction was carried out on a 1 mol scale. [c] The time used for the metalation step prior to the addition of cyclohexene oxide. [d] Yield of product based on 1 equiv of *n*-butyllithium or cyclohexene oxide. Unless indicated the products were purified by distillation followed by recrystallization from petroleum ether. [e] Yield is of distilled product. [f] This reaction was performed in THF; see text.

Scheme II

5

6a. Ar = Ph
b. Ar = 4-*i*-PrPh
c. Ar = 3,5-di-*i*-PrPh
d. Ar = 4-*t*-BuPh
e. Ar = 4-PhPh
f. Ar = 2-Naph

new, practical synthesis and resolution of racemic *trans*-2-(1-aryl-1-methylethyl)cyclohexanols **6a–f**.[15]

Results and Discussion

We investigated the direct formation of racemic alcohols **6a–f** by the addition of α-metalated isopropylarenes **5** to cyclohexene oxide (Scheme II, Table I). As in the synthesis of 2-substituted cyclohexanols from cyclohexene oxide and Grignard reagents, this approach would avoid the formation of *cis*-isomers.

Since α-metalating cumene with alkylpotassium (56%),[16] [(trimethylsilyl)methyl]potassium (46%),[17] or more conveniently with a mixture of alkyllithium and potassium *tert*-alkoxides (50%)[17a,b,18] is shorter and more practical than synthesizing α-cumyllithium or the sodium derivative,[19] α-cumylpotassium was chosen for our initial study. It was also hoped that α-cumylpotassium might open an epoxide[20] by SN_2 substitution without the activation sometimes required for lithium[21] or magnesium[22] organometallics.

n-Butyllithium was added to a mixture of cumene and either potassium *tert*-butoxide or potassium *tert*-pentoxide at room temperature, forming a deep purple suspension. After the suspension was stirred for 1 or 2 days, cyclohexene oxide was added leading to a black solution. After quenching, **6a** was isolated by distillation and recrystallization in the yields shown in Table I (entries a–k).

Because Lockmann and Petranek[23] showed that 3 equiv of a bulky potassium *tert*-alkoxide to alkyllithium are required to metalate toluene and ethylbenzene efficiently, the same stoichiometry was initially used to metalate cumene. Upon varying the amount of potassium *tert*-pentoxide, however, the yield of **6a** did not change proportionally (entries d–h). Using 1.2 equiv proved just as effective as 3 equiv with anything in between or above giving a lower yield of **6a**. This may be because in addition to promoting the metalation of cumene, potassium *tert*-alkoxides can act as strong bases and also promote other reactions with epoxides.[24]

Having found conditions for forming **6a** in fair yield using a more favorable alkoxide stoichiometry (entry h), the same metalation–addition reaction was run with 1,4-diisopropylbenzene (entry l) and 1,3,5-triisopropylbenzene (entry n) to make cyclohexanols **6b** and **6c**, respectively. Because these isopropylarenes were more expensive starting materials than cumene, only 1 equiv of each was used in the initial runs. Ring metalation[25] was expected to be less favored for both substrates as compared to cumene, so the time period before adding cyclohexene oxide was also shortened. Surprisingly, the yield for these reactions was about half that of the reaction using cumene (entry h). Presuming that the major difference among these reactions was the amount of the isopropylarene used, the number of equivalents of isopropylarenes was increased to three and four. As has been observed in similar metalations using the substrate as the solvent,[26] efficient

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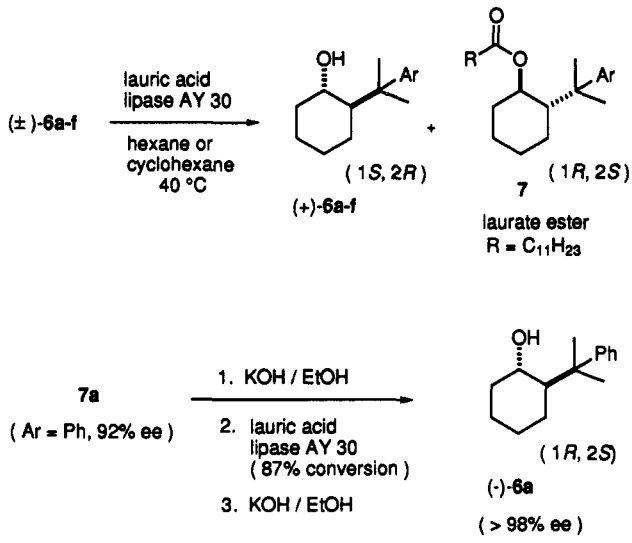
Scheme III



organometallic formation ensued, and high yields of alcohols **6a–c** (entries i, j, m, o) and unreacted isopropylarenes (97% mass balance) were obtained. Using 4 equiv of cumene, **6a** was also isolated in high yield when run on a 1 mol scale (entry k).

4-*tert*-Butylcumene, 4-isopropylbiphenyl, and 2-isopropylnaphthalene were also subjected to the same metalation–addition reaction to give fair yields of alcohols **6d–f** (entries p–r). As in prior reactions, most of the unreacted starting material was recovered along with alcohols **6d,e**. Only the metalation of 2-isopropylnaphthalene gave significant amounts of byproducts, perhaps due to its more facile ring metalation[26b] or oligomerization.[27] The yield of **6f** was improved by metalating 2-isopropylnaphthalene in THF at −78 °C and then warming to room temperature in the presence of cyclohexene oxide (entry s).

Having a practical, one-step synthesis of racemic *trans*-2-(1-aryl-1-methylethyl)cyclohexanols **6a–f** in hand, attention was turned to their optical resolution. Though Whitesell and Lawrence had partially resolved racemic **6a** by pig liver acetone powder-catalyzed hydrolysis of its acetate,[14] the less tedious and more general enzymatic esterification procedure[28] used by Triantaphylides and co-workers to resolve cyclohexanol derivatives like menthol was employed with modifications (Scheme III).[29]

To a warmed (40 °C) solution of **6a–f** and 1 equiv of lauric acid in hexanes or cyclohexane was added *Candida rugosa*[30] lipase (Amano AY30). The conversion of **6c** and **6e** to their laurate esters **7** was monitored by removing aliquots from the supernate and analyzing directly by regular-phase HPLC. The reaction's progress and the enantiomeric excess for all other alcohols were monitored by separating their enantiomers by chiral-column HPLC.

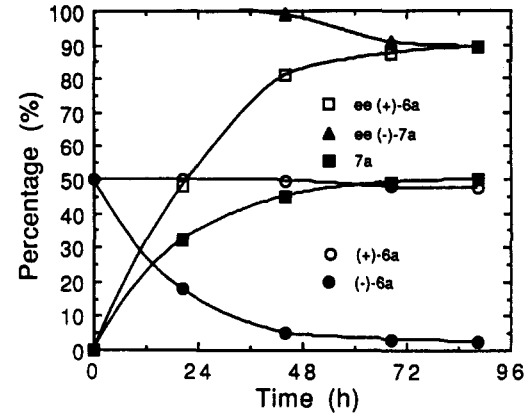


Figure 1. First esterification cycle of **6a** in hexanes.

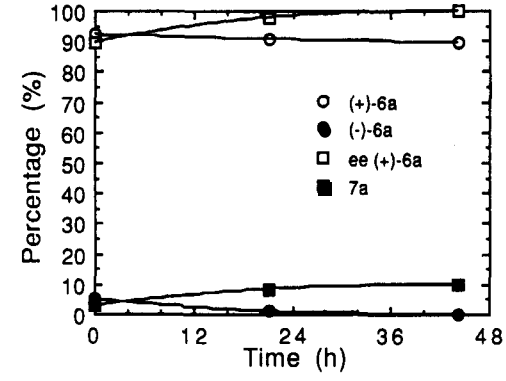


Figure 2. Second esterification cycle of enriched (+)-**6a** in hexanes.

In all cases, esterification slowed approaching 50% conversion, leaving behind predominantly the (+)-enantiomer as shown for **6a** in Figure 1. From previous work with **6a**[14] and reported resolutions using this lipase[29,30b], the absolute configuration of the (+)-enantiomer of **6a–f**, like that of (+)-1, should be *1S,2R*.

Unfortunately, pure (+)-enantiomers could not be isolated directly even by esterifying beyond 50%. In particular, when **6a** was esterified in hexanes for 15 days, its enantiomeric excess dropped to 82% (58% conversion) from a high of 89% (50% conversion). This indicates that not only after a certain point was (+)-**6a** converting to ester faster than (−)-**6a** but also some laurate ester was reverting to alcohol. With the aim of driving the equilibrium forward, the lipase was predried under vacuum leading only to its deactivation.[31]

In order to enrich (+)-**6a,b,d,f** above 90% ee, after first esterifying for 4 days (42–50% conversion in hexanes), the unreacted alcohol was isolated by distillation or chromatography and resubjected to esterification (2–4 days) with the same lipase (air dried) as shown for **6a** in Figure 2. By removing the initially formed ester, the equilibrium was shifted toward esterification of the remaining (−)-enantiomer to give enriched (+)-**6a,b,d,f** as indicated in Table II (entries 1–4).

Substitution on the aromatic ring of **6** did decrease the rate of esterification of (−)-**6b,d,f**. This was shown by calculating the relative rates of esterification of (−)-enantiomers over the first 2 days of reaction. Up to this point the reactions followed pseudo-first-order kinetics

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Table II. Two-Cycle Resolution of Racemic Alcohols 6a–f

entry	6	solvent[a]	time[b] (d)	convn (%)	k_{rel}	ee[c] (%)	time[b] (d)	convn (%)	ee[c] (%)	yield[d] (%)	$[\alpha]_D$[e] (deg)mp (°C)
1	**6a**	h	4	50	1.0	89.2	2	7	99.2	46	
2	**6b**	h	4	41	0.6	69.3	4	22	92.3	33	+22.2
3	**6d**	h	4	51	0.7	87.5	4	21	98.4	31	+21.0; 76–82
4	**6f**	h	4	46	0.8	81.8	2	11	99.4	46	+12.0; 71–74
5	**6a**	c	1	45	1.8	80.5	1	11	98.5	44	
6	**6e**	c	31 h	45	1.4		1	11		48	+15.2; 79–82
7	**6c**	c	15	42	0.1						
8	**6a**	c	41 h	46	1.1	81.6	46 h	10	98.3	46	+29.6
9	(−)-**6a**[f]					92.4	2	87	98.2	36	−29.4

[a] Solvents: h = hexane, c = cyclohexane. [b] The reaction mixtures were stirred for the indicated time at 40 °C. [c] The ee was determined by chiral-column HPLC analysis. [d] The yield is based on a 50% theoretical maximum. [e] The optical rotations were taken in methanol solution. [f] Distilled (−)-**6a** obtained from hydrolysis of laurate ester **7a**.

but deviated thereafter. The overall rate of esterification of both enantiomers still remains to be studied.

The time required to resolve **6a** was reduced to two 1-day cycles by running the enzymatic esterification in cyclohexane instead of hexanes and by interrupting the first cycle at 45% conversion instead of 50% (entry 5). In cyclohexane, menthol has previously been esterified three times faster than in hexanes.[32] For other enzymes, *i.e.*, *Pseudomonas* sp. lipase, it has been observed that a cyclic versus an acyclic solvent improves the selectivity but not the rate of *trans*-esterification.[33] The first esterification cycle was interrupted at 45% conversion since the rate of esterification of the (−)-enantiomer significantly drops, whereas the rate of esterification of the (+)-enantiomer actually increases leading to little improvement in the enantiomeric excess of unreacted alcohol beyond this point (Figure 1, ee (+)-**6a**). Since a goal was also to hydrolyze the laurate esters **7** and isolate enriched (−)-**6a**, not converting past 45% also reduces its contamination (Figure 1, ee (−)-**7a**). By this method alcohol **6a** was resolved, giving 45% of the (+)-enantiomer after two esterification cycles and 35% of the (−)-enantiomer after hydrolyzing the ester **7a** from the first cycle and enriching it by another esterification–hydrolysis cycle of equal duration. Both enantiomers of **6a** had optical rotations above the literature value of ±26.3°[14] and were greater than 98% enantiomerically pure as determined by chiral column HPLC analysis. By the same method in cyclohexane (+)-**6e** was isolated, whereas **6c** failed to convert beyond 42% after 2 weeks (entries 6, 7).

As an indication of the number of times that the lipase may be reused, when 1 mol of **6a** was resolved with recovered lipase, used four times, twice the time per cycle was required to achieve the same results as using fresh lipase (entry 8). Thus, as has been previously observed in the resolution of menthol,[32] the lipase loses about half of its activity after four uses.

Overall, racemic *trans*-2-(1-aryl-1-methylethyl)cyclohexanols were easily prepared using 4 equiv of isopropylarenes and stoichiometric amounts of all other reagents. The syntheses and resolutions of these alcohols were achieved using relatively inexpensive materials and easily applied procedures that are amenable to large-scale preparation. The (+)-enantiomers were made and isolated in three steps, whereas the (−)-enantiomers can be isolated as byproducts in two more steps. In particular, (±)-**6a** was synthesized and resolved at a 1 mol scale in 68% overall yield. Equivalent diasteroselectivities are observed when **6a** is used in place of 8-phenylmenthol during the asymmetric addition of Grignard reagents to chiral 1-acylpyridinium salts (Scheme I). Since a variety of analogs of **1** have already been shown to give even better asymmetric induction in certain stereoselective reactions,[14b,34] work is in progress to make other *trans*-2-(1-aryl-1-methylethyl)cyclohexanols and to study their effectiveness as chiral auxiliaries in asymmetric reactions of 1-acylpyridinium salts.

Experimental Section

Melting points are uncorrected. Elemental analyses were performed by MicroLabs Inc. (Norcross, GA). Optical rotations were taken at ambient temperature in methanol. All materials were commercially available except for 4-*tert*-butylcumene and 4,4′-isopropylbiphenyl, which were prepared as described below.

4-*tert*-Butylcumene. To a cooled (0 °C), stirred mixture of cumene (140 mL, 1.0 mol) and sulfuric acid (200 mL) was added dropwise 2-methyl-2-propanol (135 mL, 1.4 mol). After 1 h, the mixture was poured into ice–water (0.5 L), and the layers were separated. The organic layer was diluted with hexanes (300 mL), washed with water and saturated aqueous sodium bicarbonate, and dried ($MgSO_4$). After filtration, concentration of the filtrate, and distillation of the residue (80–88 °C, 4.65 mmHg), 110.59 g (63%) of 4-*tert*-butylcumene was isolated as a clear oil. The ^1H NMR spectrum of this product was in agreement with the literature data.[35]

4-Isopropylbiphenyl. To a cooled (0 °C), stirred solution of methylmagnesium bromide in ether (3.0 M, 205 mL, 0.62 mol) was added a suspension of 4-acetylbiphenyl (100 g, 0.51 mol) in anhydrous ether (1 L). The suspension was stirred at room temperature for 3 d, followed by quenching with saturated aqueous ammonium chloride. The aqueous layer was separated and extracted with ether. The combined organic layers were dried (K_2CO_3), filtered, and concentrated to give 105.91 g of a yellow solid. The ^1H NMR data were consistent with that of known 1-(4′-biphenyl)-1-methylethanol.[36]

A mixture of the crude carbinol, 10% Pd/C (10 g), and aluminum chloride (3 g) in cyclohexene (0.5 L) was heated at reflux for 3 d.[37] The mixture was filtered, the solvent was evaporated, and the remaining residue was distilled (122 °C, 0.5 mmHg) to give a 4:1 mixture (85.89 g) of 4-isopropylbiphenyl and 4-isopropenylbiphenyl. This mixture was hydrogenated overnight (100 mL EtOH, 4 g of 10% Pd/C, 40 psi H_2), filtered, and evaporated, and the residue was distilled (94–105 °C, 0.15–0.17 mmHg) to give 79.28 g (79% overall) of 4-isopropylbiphenyl as a clear oil. The ^1H NMR data and GC retention time matched that of the minor component of Tanacol CG (2:1 *o*-/*p*-isopropyl-1-1′-biphenyl) generously supplied by Sybron Chemicals Inc., Wellford, SC.

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Racemic *trans*-2-(1-Methyl-1-phenylethyl)cyclohexanol (6a). To an oven-dried 3-L three-neck flask equipped with addition funnel, mechanical stirrer, argon inlet, and a circulating bath (25 °C) was added 18 wt % potassium *tert*-pentoxide in cyclohexane (925 mL, 1.1 mol) and cumene (555 mL, 4.0 mol). Dropwise addition (<30 °C) of 2.06 M *n*-butyllithium in hexanes (485 mL, 1.0 mol) was carried out over 2 h. The resulting dark purple suspension was stirred for 2 d before dropwise addition (<30 °C) of cyclohexene oxide (105 mL, 1.0 mol). After 3 h, the black solution was cooled (0 °C) and carefully quenched with saturated aqueous ammonium chloride (750 mL). The organic layer was separated and washed with water (3 × 100 mL) and saturated aqueous sodium chloride (2 × 100 mL). The combined aqueous layers were back-extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried (K_2CO_3) and decanted. The solvent was evaporated under aspirator pressure (90 °C), and the remaining light-green oil (235 g) was distilled (80–120 °C, 0.5 mmHg) using a Kugelrohr apparatus to give 213 g of crude product as a viscous oil. The oil was crystallized and recrystallized by cooling (−20 °C) its solution in petroleum ether (200 mL, bp 30–60 °C) with seeding to give 183 g (84%) of racemic **6a** as white crystals: mp 49.5–51.5 °C (lit.[14] mp 45.5–47.5 °C).

Resolution of 6a. To a stirred, heated (40 °C) solution of racemic **6a** (218.35 g, 1.0 mol) and lauric acid (200 g, 1.0 mol, 98%, Aldrich) in cyclohexane (4 L) was added recycled (4×) lipase (655 g, Amano AY30, 35 800 U/g fresh).[38] The progress of the formation of laurate ester **7a** and the enantiomeric excess of unreacted alcohol were monitored by allowing the reaction suspension to settle for 5 min and removing aliquots from the supernate for direct analysis on a chiral HPLC column (Chiracel-OJ, J.T. Baker, 10% 2-propanol/hexanes, 0.4 mL/min). After 45% conversion to ester (41 h), the lipase was filtered and air dried (4 d, 666 g). The solvent was removed from the filtrate under reduced pressure and recovered for reuse, and the remaining oil was bulb-to-bulb distilled (90–160 °C, 0.5 mmHg) to give a mixture of lauric acid and (+)-**6a** (225.63 g, 54% w, 82% ee (1*S*,2*R*)). The pot residue contained the laurate ester **7a** (180.71 g, 45%).

The mixture of alcohol and lauric acid was resubjected to the above esterfication procedure (4 L of cyclohexane (freshly distilled), 40 °C, 666 g of air-dried lipase, 2 d, 10% conversion). The lipase was again filtered and air dried (5 d, 650 g). The solvent was evaporated from the filtrate, and the remaining oil was stirred with potassium carbonate (138 g, 1.0 mol) in hexanes (0.5 L). After 1 h, the precipitate (potassium laurate) was filtered and washed with hexanes (3 × 500 mL). The solvent was evaporated from the filtrate, and the remaining oil was distilled as before to give 100.06 g of (+)-**6a** (45.8% overall, $[\alpha]^{22}_D$ +29.6° (*c* 1.7, MeOH), 98.4% ee (1*S*,2*R*)).

The initially isolated laurate ester **7a** (180.71 g, 0.45 mol) was refluxed (3 h) with potassium hydroxide (56.11 g, 85%, 0.85 mmol) in 95% ethanol (200 mL), and then the solvent was evaporated by heating the mixture (90 °C) and gradually increasing the aspirator vacuum to avoid foaming and bumping. The remaining solid mass was bulb-to-bulb distilled (up to 160 °C, 0.5 mmHg) to give 95.44 g of (−)-**6a** (97%, 92.4% ee (1*R*,2*S*)).

This alcohol was resubjected to the above enzymatic esterification (100 g of lauric acid, 650 g of lipase, 4 L of cyclohexane, 40 °C, 2 d, 87% conversion), the lipase was filtered, the solvent was evaporated from the filtrate, and the remaining oil was distilled as before to give a mixture of alcohol and lauric acid (33.46 g). The distillation pot contained 147.97 g (84%) of ester **7a**. The ester was hydrolyzed in an identical fashion as above to give 78.27 g (97%, 35.8% overall) of (−)-**6a**: $[\alpha]^{27}_D$ −29.4° (*c* 2.0, MeOH), 98.2% ee.

Racemic *trans*-2-[1-(4-(1-Methylethyl)phenyl)-1-methylethyl]cyclohexanol (6b). Following the same procedure as for **6a**, potassium *tert*-pentoxide (18 wt % in cyclohexane, 30 mL, 36 mmol), 1,4-diisopropylbenzene (23 mL, 121 mmol), *n*-butyllithium (2.06 M in hexanes, 15 mL, 31 mmol) and, after 18 h, cyclohexene oxide (3.0 mL, 30 mmol) were combined to give after distillation 14.95 g (76%) of starting isopropylarene and 6.57 g (85%, 130 °C at 1.3 mmHg) of racemic **6b** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.33, 7.18 (ABq, 4 H, *J* = 8.4 Hz), 3.55 (ddd, 1 H, *J* = 4.1, 9.5, 13.6 Hz), 2.87 (dq, 1 H, *J* = 6.8, 6.8 Hz), 2.06–1.45 (m, 5 H), 1.40 (s, 3 H), 1.27 (s, 3 H), 1.23 (d, 6 H, *J* = 7.3 Hz), 1.19–1.07 (m, 3 H), 1.04 (d, 2 H, *J* = 3.7 Hz); ^{13}C NMR 148.1, 145.7, 126.1, 125.4, 72.9, 54.2, 39.3, 36.4, 33.2, 28.2, 26.6, 26.0, 24.8, 23.7, 23.7; IR (film) 3560, 2960, 2930, 2860, 1510, 1460, 1445, 1410, 1385, 1360, 1050, 825 cm^{-1}. Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.04; H, 10.89.

Resolution of 6b. Following the same procedure as for **6a**, racemic **6b** (4.68 g, 18 mmol), lauric acid (3.60 g, 18 mmol), fresh lipase AY30 (11.77 g, 35 800 U/g), and hexanes (72 mL) were heated (40 °C) for 4 d to convert 41% of **6b** to its laurate ester. Unreacted **6b** and lauric acid (4.52 g, 55 wt %) were isolated by distillation (107–160 °C, 0.75 mmHg) and subjected to the same esterification procedure for 4 d (22% conv) with the same lipase (11.67 g after air drying 3 d) to give 1.55 g (33%) of (+)-**6b**: $[\alpha]^{24}_D$ +22.2° (*c* 1.7, MeOH), 92.3% ee by chiral HPLC analysis (Chiracel-OJ, hexanes, 0.3–0.4 mL/min).

Racemic *trans*-2-[1-(3,5-Bis(1-methylethyl)phenyl)-1-methylethyl]cyclohexanol (6c). Following the same procedure as for **6a**, potassium *tert*-pentoxide (18 wt % in cyclohexane, 30 mL, 36 mmol), 1,3,5-triisopropylbenzene (29 mL, 120 mmol), *n*-butyllithium (2.06 M in hexanes, 15 mL, 31 mmol) and, after 18 h, cyclohexene oxide (3.0 mL, 30 mmol) were combined to give after distillation 18.07 g (74%) of starting isopropylarene and 8.26 g (92%, bp 122 °C at 0.55 mmHg) of racemic **6c** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.07 (s, 2 H), 6.92 (s, 1 H), 3.50 (m, 1 H), 2.88 (dq, 2 H, *J* = 7.0, 7.0 Hz), 1.89–1.66 (m, 5 H), 1.41 (s, 3 H), 1.27 (s, 3 H), 1.24 (d, 12 H, *J* = 7.3 Hz), 1.21–0.99 (m, 5 H); ^{13}C NMR 150.7, 148.5, 121.6, 121.4, 73.1, 54.5, 39.7, 36.4, 34.2, 28.6, 26.7, 26.2, 24.8, 24.0, 23.8; IR (film) 3560, 2960, 2930, 2860, 1600, 1460, 1445, 1380, 1360, 1050, 865, 715 cm^{-1}. Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.26; H, 11.33.

Attempted Resolution of 6c. Following the same procedure as for **6a**, racemic **6c** (6.05 g, 20 mmol), lauric acid (4.01 g, 20 mmol), fresh Lipase AY 30 (13.10 g, 35 800 U/g), and cyclohexane (80 mL) were heated (40 °C) for 2 weeks to convert 42% of **6c** to its laurate ester as determined by HPLC. The ee of unreacted alcohol could not be determined by chiral HPLC analysis. The reaction was discarded without isolation of products.

Racemic *trans*-2-[1-(4-(1,1-Dimethylethyl)phenyl)-1-methylethyl]cyclohexanol (6d). Following the same procedure as for **6a**, potassium *tert*-pentoxide (18 wt % in cyclohexane, 100 mL, 120 mmol), 4-*tert*-butylcumene (70.52 g, 400 mmol), and *n*-butyllithium (2.06 M in hexanes, 53 mL, 109 mmol) were combined to give a solid black mass which was allowed to stand overnight. Cyclohexene oxide (10 mL, 99 mmol) was added, and the mass was broken with a spatula to allow stirring. Distillation gave 54.82 g (78%) of starting isopropylarene and 19.71 g (73%, bp 120–140 °C at 0.5 mmHg) of crude **6d** as a viscous oil. Recrystallizing twice from petroleum ether (bp 30–60 °C) gave 13.00 g (48%) of pure racemic **6d** as white crystals: mp 74.5–77 °C; ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 4 H), 3.50 (m, 1 H), 1.88–1.67 (m, 6 H), 1.40 (s, 3 H), 1.29 (s, 9 H), 1.27 (s, 3 H), 1.23–1.15 (m, 2 H), 1.08–1.00 (m, 2 H); ^{13}C NMR 148.4, 147.9, 125.3, 73.2, 54.4, 39.3, 36.4, 34.2, 31.2, 29.1, 26.7, 26.2, 25.0, 23.5; IR (film) 3570, 2960, 2930, 2860, 1510, 1460, 1445, 1400, 1360, 1050, 830 cm^{-1}. Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.22; H, 11.07.

Resolution of 6d. Following the same procedure as for **6a**, racemic **6d** (5.49 g, 20 mmol), lauric acid (4.01 g, 20 mmol), fresh lipase AY30 (13.1 g, 35 800 U/g), and hexanes (80 mL) were heated (40 °C) for 4 d to convert 51% of **6d** to its laurate ester. Unreacted **6d** and lauric acid (4.46 g, 47% by wt) were isolated by distillation (up to 140 °C at 0.35 mmHg) and resubjected to esterification (21% conversion) with the same lipase (12.94 g after air drying 3 d) to give 1.68 g (31%) of (+)-**6d** as an oil which solidified on standing: mp 76–82 °C; $[\alpha]^{19}_D$ +21.0° (*c* 2.0, MeOH), 98.4% ee by chiral HPLC analysis (Chiracel-OJ, J.T. Baker, hexanes, 0.3–0.4 mL/min).

Racemic *trans*-2-[1-(4'-Biphenyl)-1-methylethyl]cyclohexanol (6e). Following the same procedure as for **6a**, 4-isopropylbiphenyl (79.12 g, 403 mmol), potassium *tert*-pentoxide (18 wt % in cyclohexane, 100 mL, 120 mmol), *n*-butyllithium (2.06 M in hexanes, 60 mL, 124 mmol), and, after 2 d, cyclohexene oxide (10 mL, 99 mmol) were combined to give by distillation 64.64 g (82%, 90–110 °C at 0.25 mmHg) of starting isopropylarene

(38) A Sigma lipase may also be used accounting for a different definition of units (U); see: Lavayre, J.; Baratti, J. *J. Biotechnol.* **1982**, *24*, 1007.

and 25 g (86%, 140–200 °C at 0.5 mmHg) of crude **6e** as a viscous oil. Recrystallizing twice from hexanes gave 14.33 g (49%) of pure **6e** as white crystals: mp 91–92 °C; ^{1}H NMR ($CDCl_3$) δ 7.60–7.29 (m, 5 H), 7.51 (ABq, 4 H, J = 8.8 Hz), 3.53 (ddd, 1 H, J = 4.4, 9.5, 13.9 Hz), 1.92–1.52 (m, 5 H), 1.46 (s, 3 H), 1.33 (s, 3 H), 1.30–1.12 (m, 3 H), 1.11–1.00 (m, 2 H); ^{13}C NMR 150.2, 140.5, 138.2, 128.5, 126.9, 126.8, 126.7, 126.1, 73.2, 54.3, 39.7, 36.7, 28.0, 26.8, 26.1, 24.9, 24.8; IR (film) 3580, 3030, 2930, 2860, 1600, 1485, 1445, 1400, 1385, 1365, 1050, 835, 765, 730, 695 cm^{-1}. Anal. Calcd for $C_{21}H_{26}O$: C, 85.67; H, 8.90. Found: C, 85.74; H, 8.97.

Resolution of 6e. Following the same procedure as for **6a**, racemic **6e** (5.89 g, 20 mmol), lauric acid (4.01 g, 20 mmol), fresh lipase AY30 (13.10, 35 800 U/g) and hexanes (80 mL) were heated (40 °C) for 31 h to convert 45% of **6e** to its laurate ester. Unreacted **6e** (3.53 g, 60%) and laurate ester (4.44 g, 46%) were isolated by first precipitating potassium laurate (2.76 g of K_2CO_3 in hexanes) and subsequent flash-vacuum column chromatography of the organic residue (SiO_2, 0–5% EtOAc/hexanes).

Unreacted **6e** (3.53 g, 12.0 mmol) was resubjected to esterification using lauric acid (2.40 g, 12.0 mmol), air dried lipase (13.17 g, 5 d), and cyclohexane (80 mL) to convert 11% of **6e** to its laurate ester. By the same procedure as above, distillation (170–190 °C, 0.5 mmHg) gave 2.82 g (48% overall) of **6e** as a viscous oil, which solidified on standing to white crystals: mp 79–82 °C; $[\alpha]^{23}_D$ +15.2° (*c* 1.3, MeOH).

Racemic *trans*-2-[1-(2-Naphthyl)-1-methylethyl]cyclohexanol (6f). Following the same procedure as for **6e**, potassium *tert*-pentoxide (18 wt % in cyclohexane, 20 mL, 24 mmol), 2-isopropylnaphthalene (10.5 mL, 60 mmol), *n*-butyllithium (2.06 M in hexanes, 10 mL, 21 mmol), and after 2 d, cyclohexene oxide (2.0 mL, 20 mmol) were combined to give after distillation (166 °C at 0.5 mmHg) and recrystallization from petroleum ether (bp 30–60 °C) 1.75 g (33%) of racemic **6f** as white crystals.

Alternatively, to a cooled (−78 °C) solution of potassium *tert*-pentoxide (18 wt % in cyclohexane, 10 mL, 12 mmol) and 2-isopropylnaphthalene (7.0 mL, 40 mmol) in THF (90 mL) was added *n*-butyllithium (2.06 M in hexanes, 5 mL, 10 mmol), turning the solution from light-green to dark-green. After 1 h at −78 °C, cyclohexene oxide was added (1 mL, 10 mmol), and the solution was allowed to warm to room temperature. Standard workup and distillation gave 5.41 g (79%, 120 °C at 0.85 mmHg) of starting isopropylarene and 2.22 g (84%, 150–170 °C at 0.85 mmHg) of crude **6f** as a viscous light-green oil. Recrystallizing twice from petroleum ether (bp 30–60 °C) provided 1.46 g (55%) of racemic **6f** as white crystals: mp 70–71 °C; ^{1}H NMR ($CDCl_3$) δ 7.82–7.76 (m, 4 H), 7.60–7.56 (dd, 1 H, J = 2.2, 8.8 Hz), 7.48–7.25 (m, 2 H), 3.56 (ddd, 1 H, J = 4.4, 8.8, 13.2 Hz), 1.93–1.85 (m, 2 H), 1.75–1.55 (m, 3 H), 1.54 (s, 3 H), 1.37 (s, 3 H), 1.24–1.17 (m, 3 H), 1.09–1.02 (m, 2 H); ^{13}C NMR 148.7, 133.1, 131.4, 127.7, 127.6, 127.1, 125.6, 125.1, 125.0, 123.0, 73.1, 53.7, 40.0, 36.6, 27.2, 26.8, 26.0, 25.4, 24.8; IR (film) 3570, 3060, 2930, 2860, 1600, 1505, 1470, 1445, 1385, 1370, 1050, 850, 815, 740 cm^{-1}. Anal. Calcd for $C_{19}H_{24}O$: C, 85.03; H, 9.01. Found: C, 84.88; H, 9.05.

Resolution of 6f. Following the same procedure as for **6a**, racemic **6f** (5.37 g, 20 mmol), lauric acid (4.01 g, 20 mmol), fresh lipase AY30 (13.10 g, 35 800 U/g) and hexanes (80 mL) were heated (40 °C) for 4 d to convert 46% of **6f** to its laurate ester. Unreacted **6f** (3.01 g, 56%) was isolated by precipitation of potassium laurate (K_2CO_3 in hexanes), filtration, evaporation of the filtrate, and distillation (160 °C at 0.8 mmHg). Reesterification using lauric acid (2.24 g, 11.2 mmol), air-dried lipase (13.02 g, 3 d) and hexanes (80 mL) gave 11% conversion after 2 d. By the same methods as above, 2.48 g (46% overall) of (+)-**6f** was isolated as a clear oil which solidified on standing to give white crystals: mp 71–74 °C; $[\alpha]^{23}_D$ +12.0° (*c* 2, MeOH); 99.4% ee by chiral HPLC analysis (Chiracel-OJ, 10% 2-propanol/hexanes, 0.3–0.4 mL/min).

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