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Substrate Modification to Increase the Enantioselectivity of Hydrolases. A Route to Optically-Active Cyclic Allylic Alcohols.

Ajay K. Gupta and Romas J. Kazlauskas*

Department of Chemistry, McGill University, 801 Sherbrooke St. W., Montréal, Québec H3A 2K6 CANADA

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Abstract: The esterase-catalyzed resolution of the cyclic allylic acetates - 1-acetyloxy-2-cyclopentene, 1-acetyloxy-2-cyclohexene, and 1-acetyloxy-2-cycloheptene - was not enantioselective. We hypothesized that this inefficiency stems from the similarity in size of the substituents at the stereocenter (CH_2-CH_2 vs. CH=CH). To increase the enantioselectivity, we resolved precursors to these cyclic allylic alcohols: esters of *trans*-2-bromocycloalkanols (C_5, C_6, C_7). These esters had a larger difference in the size of the substituents (CH_2 vs CHBr) at the stereocenter and were efficiently resolved by both cholesterol esterase and lipase from *Pseudomonas cepacia* (Amano P, PCL). A synthetic-scale resolution with PCL yielded the (1S,2S)-1-butanoyloxy-2-bromocycloalkanes in >98% ee. Heating with DBU to eliminate HBr, followed by reduction with $LiAlH_4$ to cleave the ester, yielded the allylic alcohols: (S)-(-)-2-cyclopenten-1-ol (65% ee), (S)-(-)-2-cyclohexen-1-ol (>99% ee), and (S)-(-)-2-cyclohepten-1-ol (>98% ee).

Enzymes, especially hydrolases, have simplified the synthesis of enantiomerically-pure materials.[1] Hydrolases are inexpensive, simple to use, and show high enantioselectivity for a broad range of substrates. To identify a suitable enzyme, it is usually sufficient to screen a dozen commercially-available hydrolases.

If the initial screening does not identify a suitable enzyme, then the next step is, unfortunately, not well-defined. Screening more enzymes or microorganisms may yield the desired enzyme, but it may also prove fruitless. Modification of the substrate may increase the enantioselectivity of the available enzymes. In some cases, changing from an acetate to a butyrate ester,[2] modifying sustituents close to,[3] as well as remote from,[4] the stereocenter have increased enantioselectivity. In other cases, these substrate modifications had no effect. Our goal is to develop rational and reliable strategies to convert poorly-resolved substrates into well-resolved substrates.

One redesign strategy is based on a rule for secondary alcohols. The rule, Figure 1, predicts which enantiomer reacts faster by comparing the size of the substituents at the stereocenter. The preferred enantiomer of more than twenty secondary alcohols can be predicted for five hydrolases: cultures of *Rhizopus nigricans*,[5] lipase from *Candida rugosa*,[6] lipase from *Pseudomonas* sp. (Amano lipase AK),[7] lipase from *P. cepacia* (Amano P or PS),[6, 8] and *P. fluorescens* (SAM-2).[9] For six other hydrolases, fewer substrates have been tested, but the same rule seems to apply: cholesterol esterase,[6] lipase from *Mucor miehei*,[10] lipase from *Arthrobacter* sp.,[11] porcine pancreatic lipase,[12] *Mucor* esterase (Gist-brocades),[12] and cultures of *B. subtilus* var. *Niger*.[13]

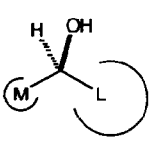
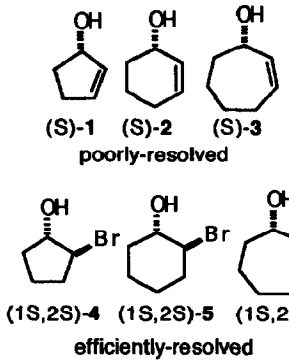


Figure 1. Eleven hydrolases favor the enantiomer of a secondary alcohol with the shape shown. M is a medium substituent (e.g., CH_3); L is a large substituent (e.g., phenyl). This rule suggests that symmetrical substrates may be difficult to resolve and that adding a large substituent may increase the enantioselectivity.

This rule suggests that hydrolases distinguish between enantiomers based on the size of the substituents at the stereocenter. Thus, increasing the difference in size of the substituents may help the hydrolase distinguish between the two enantiomers. Several groups have converted poorly-resolved secondary alcohols into efficiently-resolved ones by adding large substituents.[6, 8b, 14] In this paper we apply this



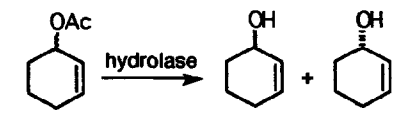
strategy to the synthesis of cyclic allylic alcohols: (S)-(-)-**1**, (S)-(-)-**2**, and (S)-(-)-**3**.

The cyclic allylic alcohols **1** and **2** serve as chiral starting materials. Compound **1** has been converted to cis-fused cyclopentanes[15] and precursors of prostaglandin $F_{2\alpha}$,[16] whereas **2** has been converted to (4S)-*trans*-β-elemenone,[17] leukotriene B_4,[18] and conformationally-restricted leukotriene antagonists.[19] Stereoselective functionalization of **2** by metal-catalyzed hydroboration[20] or bromomethoxylation[21] may further extend its usefulness.

Direct resolution of alcohols (±)-**1**-**3** by hydrolysis of the corresponding acetates showed low enantioselectivity (E = 1.4-2.1).[22] We hypothesized that the resolution was inefficient because two substituents at the stereocenter (CH_2-CH_2 vs. CH=CH) were similar in size. To increase the enantioselectivity, we resolved precursors to cyclic allylic alcohols, *trans*-2-bromocycloalkanols ((±)-**4**, (±)-**5**, and (±)-**6**). These precursors had a larger difference in the size of the two substituents (CH_2 vs. CHBr). This paper describes the efficient resolution of **4**-**6** and their conversion to cyclic allylic alcohols. While this work was in progress the resolution of **5** was also reported by others.[23]

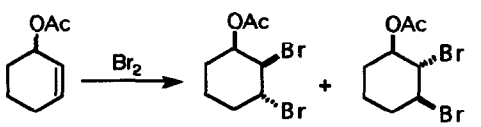
RESULTS

All enzymes tested showed low enantioselectivity (E<1.4) in the hydrolysis of (±)-1-acetyloxycyclohexene, (±)-**2** acetate, eq 1, Table 1.



(±)-2-acetate (1)

To create a more efficiently-resolved substrate, we added bromine across the carbon-carbon double bond, eq 2, which increased the size of one of the substituents at the stereocenter. Bromine added with *anti* stereochemistry, giving a 4: 1 ratio of two diastereomers, (±)-**7** and (±)-**8**, which were separated by chromatography.



(±)-2-acetate (±)-7 (±)-8 (2)

The enantioselectivity of the hydrolases increased for these new substrates. The enzymes CE and PCL showed moderate and low enantioselectivity for (1R)-**7** (E = 10 and 1.5, respectively) and high enantioselectivity for (1R)-**8** (E >100). The enzyme CRL showed the reverse behavior: high enantioselectivity for (1R)-**7** (E >100), but moderate enantioselectivity for (1R)-**8** (E = 7.7). Thus, CE and PCL were more enantioselective when the bromine at the 2-position was oriented trans to the hydroxyl group, whereas CRL was more enantioselective when this bromine was cis. Regardless of the orientation, introducing a bromine substituent increased the enantioselectivity.

However, none of the enzymes was highly enantioselective for both substrates. Thus, none of the enzymes could resolve a mixture of the **7** and **8**. Because the separation of the two diastereomers was tedious, a synthesis

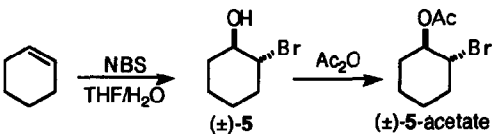
Table 1. Enantioselectivity of Hydrolase-Catalyzed Resolution of (±)-**2**-acetate, (±)-**7**, and (±)-**8**.

Substrate	Enzyme[a]	Activity (units/g)	conv[b] (%)	ee_s[c] (%)	ee_p[d] (%)	E[e]
(±)-**2**-acetate	CE	1400	47	nd	8	1.3
(±)-**2**-acetate	PCL	700	46	nd	5	1.2
(±)-**2**-acetate	CRL	18	44	nd	9	1.4
(±)-**2**-acetate	ANL	5.3	46	nd	10	1.4
(±)-**7**	CE	2.4	44	56	71	10
(±)-**7**	PCL	0.15	24	nd	5	1.5
(±)-**7**	CRL	1.3	36	52	94	54
(±)-**8**	CE	62	45	81	>98	> 100
(±)-**8**	PCL	4.9	49	93	>98	> 100
(±)-**8**	CRL	2.7	54	68	59	7.7

[a] CE = cholesterol esterase, PCL = lipase from *Pseudomonas cepacia* (Amano P), CRL = lipase from *Candida rugosa*, ANL = lipase from *Aspergillus niger*. [b] The % conversion was calculated either from the amount of base consumed during hydrolysis or from the enantiomeric excess of the starting material (ee_s) and product (ee_p) using %conv = $ee_s/(ee_s + ee_p)$. [c] Determined by ^{1}H NMR in the presence of (+)-Eu(hfc)3. nd = not determined. [d] After acetylation, the enantiomeric excess was determined by ^{1}H NMR in the presence of (+)-Eu(hfc)3. [e] Enantiomeric ratio measures the preference of the enzyme for one enantiomer over the other (See reference 1b).

of allylic alcohols based on the resolution of **7** and **8** would not be practical.

An alternate substrate, (±)-**5** acetate, was prepared as a single diastereomer via the bromohydrin, eq 3. Both

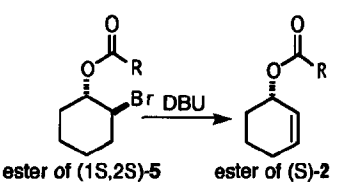


(3)

CE and PCL resolved (±)-**5**-acetate with high enantioselectivity (E >100); CRL resolved (±)-**5** acetate with moderate enantioselectivity (E = 30), Table 2. Hönig and Seufer-Wasserthal reported similar results for (±)-**5**-butyrate with PCL and CRL.[23]

The same enzymes also resolved the corresponding five- and seven-membered bromocycloalkanols, **4** and **6**, Table 2. Both CE and PCL showed high enantioselectivity for **4**-acetate (E = 60 and 80, respectively), whereas CRL showed low enantioselectivity (E = 2.5). For **6**-acetate, BPAP (a crude preparation containing CE activity) showed good enantioselectivity (E = 30), whereas both PCL and CRL showed high enantioselectivity (E >100).

Base-catalyzed elimination of HBr converted esters of **5** to esters of **2**, eq 4. Heating **5**-butyrate (70-75°C,



(4)

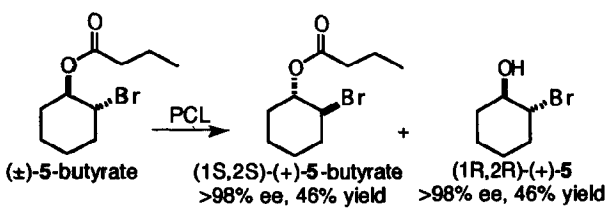
18 h) or **5**-benzoate (90°C, 5 h) in a hindered base, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) gave the highest yields: 91% and 84%, respectively. The acetate ester gave a lower yield (43%), perhaps due to difficulty in isolating the volatile **2**-acetate.

Table 2. Enantioselectivity of Several Hydrolases for Esters of (±)-**4**, (±)-**5**, and (±)-**6**.

Substrate	Enzyme[a]	Activity (units/g)	conv[b] (%)	ee_s[c] (%)	ee_p[c] (%)	E[d]
(±)-**4**-acetate	CE	6.6	31	43	>95	60
(±)-**4**-acetate	PCL	0.5	41	66	>95	80
(±)-**4**-acetate	CRL	0.2	44	26	32	2.5
(±)-**4**-butyrate	PCL	2.6	53	94	84	40
(±)-**5**-acetate	CE	41	43	75	>98	> 100
(±)-**5**-acetate	PCL	1.6	51	>98	94	> 100
(±)-**5**-acetate	CRL	5	57	>98	74	30
(±)-**5**-acetate	BPAP[a]	1.4	31	44	>98	> 100
(±)-**5**-benzoate[b]	CE	61	44	24	30	2.3
(±)-**5**-butyrate	PCL	17	50	>98	>98	>100
(±)-**6**-acetate	PCL	0.7	50	96	96	> 100
(±)-**6**-acetate	CRL	0.1	40	67	98	> 100
(±)-**6**-acetate	BPAP	1	43	67	88	30
(±)-**6**-butyrate	PCL	5	50	>98	>98	>100

[a]BPAP = bovine pancreas acetone powder. This crude extract is an inexpensive source of cholesterol esterase. [b]Enantiomers were separated by HPLC using Chiralcel OD column eluted with hexane at 0.5 mL/min, $\alpha = 1.30$, the (1S,2S)-enantiomer eluted first.

Because (±)-**5**-butyrate was efficiently resolved (PCL, E >100), but the (±)-**5**-benzoate was not (CE, E = 2.3), Table 2, we chose the butyrate to demonstrate a practical synthetic procedure. We resolved 10 g of (±)-**5**-butyrate with PCL, eq 5, and converted the remaining starting material, (1S,2S)-(+)-**5**-butyrate, into enantiomerically-pure (S)-**2**, eq 6.



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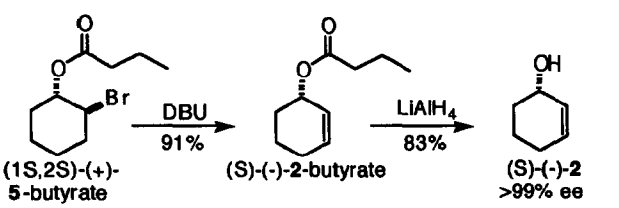
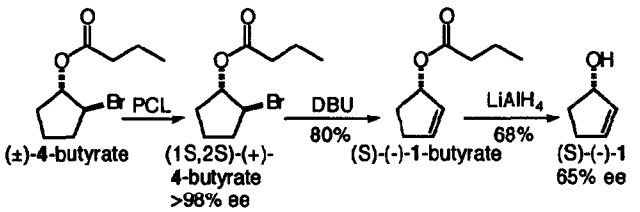


(6)

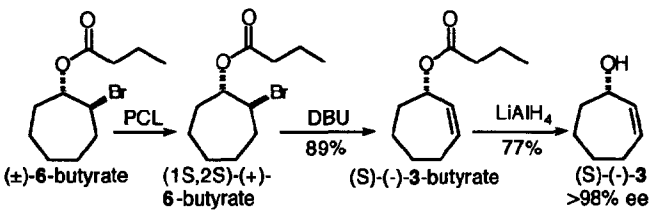
Reduction with $LiAlH_4$ was used to cleave the ester because base-promoted hydrolysis (NaOH/THF/reflux) was slow. This reaction sequence yielded (S)-(-)-**2** with >99% ee as shown by ^{1}H-NMR of the Mosher's ester of **2**. The high ee was established by comparison of the ^{13}C-satellite peak of the major diastereomer (0.55%) to the peak for the minor diastereomer.

A similar sequence of reactions to prepare the corresponding five-membered cyclic allylic alcohol, (S)-**1**, was less efficient for two reasons. First, the imperfect enantioselectivity of PCL for the enantiomer of **4**-butyrate (E = 40) resulted in a low yield (20%, a maximum of 50% is possible with a kinetic resolution) of (1S,2S)-**4**-butyrate (>98% ee). Second, partial racemization of (1S,2S)-**4**-butyrate during the elimination reaction with DBU lowered the enantiomeric purity of the final product. Thus, at the end of the reaction sequence, the allylic alcohol, (S)-**1**, had only 65% ee.



(7)

We used a similar sequence of reactions to prepare the corresponding seven-membered cyclic allylic alcohol, (S)-**3**, eq 8. Resolution of (±)-**6**-butyrate (10 g) with PCL gave (1S,2S)-(+)-**6**-butyrate (45% yield, >98% ee) and (1R,2R)-(-)-**6** (41% yield, >98% ee). The (1S,2S)-(+)-**6**-butyrate was heated in DBU to eliminate HBr (89% yield) and treated with $LiAlH_4$ to remove the butanoyl group (77% yield) giving (S)-**3** in 98.5% ee.



(8)

DISCUSSION

The rule for secondary alcohols suggested a way to modify substrates **1**-**3**. Introduction of bromine to make one substituent substantially larger, increased the enantioselectivity of the three enzymes: CE, PCL, and CRL. This rule did not predict the more subtle effects of the orientation of the added bromine. The degree of increase in enantioselectivity depended on the enzyme and the orientation of the bromine at the 2-position. Enzymes CE and PCL were usually more enantioselective when the bromine was trans to the hydroxyl group, whereas CRL was more enantioselective when it was cis. Enzymes CE and PCL also catalyzed the hydrolysis of the (1R)-**8**, (2-Br trans to OAc) thirty times faster than (1R)-**7** (2-Br cis to OAc). These enzymes may be useful in separating diastereomeric cyclohexanols that differ in the orientation of the substituent at the 2-position.

Using the well-resolved substrate **5**-butyrate, we have demonstrated a practical synthesis of enantiomerically-pure (S)-**2**. The advantages of this synthesis are that it yields **2** in high enantiomeric purity and that it is easy to carry out on a multi-gram scale. Further, because the synthesis uses a kinetic resolution, both enantiomers are accessible. A disadvantage of this synthesis is the extra step needed to remove the bromine substituent.

Alternative routes to **2** in >90% ee include three asymmetric syntheses: reduction of 2-cyclohexenone with $LiAlH_4$ modified by chiral amines,[24] isomerization of epoxycyclohexane with chiral lithium amide,[25] and hydroboration of 1,3-cyclohexadiene.[26] In addition, kinetic resolution of **2** by asymmetric hydrogenation gave 96% ee (E = 62),[27] but resolution by asymmetric epoxidation gave only 30% ee.[28] When high enantiomeric purity is crucial, we recommend using our enzymic route.

For allylic alcohols **1** and **3**, no syntheses in >90% ee have been reported;[16, 22, 24-28] thus, our synthesis of (S)-**3** in high enantiomeric purity is the only one available. Our synthesis of (S)-**1** yielded only 65% ee due to partial racemization of (1S,2S)-**4**-butyrate. One possible mechanism involves loss of bromide via neighboring group participation of the butanoyloxy substituent to form a butanoyloxonium ion. Return of bromide would give either (1S,2S)-**4**-butyrate or (1R,2R)-**4**-butyrate. A less labile substituent in place of bromine may eliminate this racemization.

EXPERIMENTAL SECTION

General. Lipase from *Mucor miehei* (MML, 52 units/g solid with olive oil), *Aspergillus niger* (ANL, 2 units/g solid with olive oil), *Pseudomonas cepacia* (PCL, Amano P30, 190 units/g solid with olive oil). *Candida rugosa* (CRL, also known as *C. cylindracea,* 160 units/g with olive oil) were purchased from Amano Enzyme Co., Troy, VI. Bovine pancreas acetone powder (BPAP) was purchased from Sigma Chemical Co., St. Louis, MO. Cholesterol esterase (CE) from porcine pancreas was purchased from Genzyme, Boston, MA. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. Ammonia was used as the reagent gas for chemical ionization mass spectra. Silica gel 70-230 mesh, 60Å (Aldrich, Milwaukee, WI) was used for flash chromatography. Pyridine was dried over solid KOH and distilled.[29] Mosher's esters,[30] acetates of (±)-**1**-**3**, and (±)-**5**-butyrate[23] were prepared by standard procedures.

Screening of enzymes. Substrate (0.5 mmol) dissolved in diethyl ether (8 mL) was added to a stirred mixture of diethyl ether (2 mL) and phosphate buffer (10 mM, 10 mL) containing enzyme (100 mg). The pH maintained at 7.00 by automatic titration with NaOH (0.103 N). Sodium taurocholate (30 mg) was added to hydrolyses where CE or BPAP was used as the catalyst. The initial rates listed in Table 1 indicate the rate of consumption of NaOH over the first 5% of the reaction. After the consumption of base indicated 30-55% conversion the reaction mixture was extracted with ethyl acetate (4 x 10 mL). The combined extracts were dried over anhydrous sodium sulfate, concentrated under vacuum and the resulting oil was purified by chromatography on silica gel.

(±)-(1α,2α,3β)-1-acetyloxy-2,3-dibromocyclohexane, (±)-7, and (±)-(1α,2β,3α)-1-acetyloxy-2,3-dibromocyclohexane, (±)-8 were prepared by bromination of (±)-**2**-acetate (0.36 g, 2.6 mmol) using a procedure for the bromination of **2**.[31] The two isomers were separated by flash chromatography on TLC silica gel (Merck Kieselgel 60 GF254) eluted with hexane: ethyl ether (7: 3): (±)-**7** (0.27 g, 35%) and (±)-**8** (0.25 g, 33%). (±)-**7**: ^{1}H NMR (C_6D_6, 200 MHz): δ 1.0-2.0 (m, 6H), 1.65 (s, 3H, CH_3), 4.17 (br m, 1H, H-3), 4.46 (br m, 1H, H-2), 5.26 (dt, 1H, H-1, $J_{1,2} = J_{1,6eq} = 3.6$ Hz, $J_{1,6ax} = 9.4$ Hz); IR (neat): 1742 (C=O), 1458, 1448, 1048 cm^{-1}; MS (CI, CH_4) *m/z* (rel int): 303, 301, 299 (49, 100, 51, M+H$^+$ cluster), 241 (16), 219 (14), 177 (13), 159 (45). (±)-**8**: mp 49-51°C, uncor; ^{1}H NMR (C_6D_6, 300 MHz): δ 0.5-1.4 (m, 6H), 1.72 (s, 3H, CH_3), 3.54 (ddd, 1H, H-3, $J_{2,3} = 9.7$ Hz, $J_{3,4ax} = 11$ Hz, $J_{3,4eq} = 4.5$ Hz), 3.81 (t, 1H, H-2, $J_{1,2} = J_{2,3} = 9.7$ Hz), 4.85 (ddd, 1H, H-1, $J_{1,6ax} = 10$ Hz, $J_{1,6eq} = 4.5$ Hz); IR (Nujol): 1734 (C=O), 1458, 1448, 1036 cm^{-1}; MS (EI) *m/z* (rel int): 302, 300, 298 (0.1, 0.05, 0.1, M$^{+\cdot}$ cluster), 240 (11), 159 (48), 97 (31), 79 (26), 43 (100).

(±)-trans-2-bromocyclohexanol, (±)-5, was prepared by bromination of cyclohexene (1.0 g, 12 mmol) in tetrahydrofuran: water (1:1) following a literature procedure.[32] After workup, column chromatography on silica gel eluted with hexane: ethyl ether (7: 3) gave a colorless oil (1.7 g, 78%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.10-2.40 (m, 8H, $(CH_2)_4$), 2.75 (br s, 1H, OH, exchanged with D_2O), 3.67 (br ddd, 1H, -CHOH, $J_{1,6ax} = 10$ Hz, $J_{1,6eq} = 4.7$ Hz), 3.87 (ddd, 1H, -CHBr, $J_{1,2} = 12$ Hz, $J_{2,3ax} = 9.4$ Hz, $J_{2,3eq} = 4.3$ Hz); IR (neat): 3383 (OH), 2938, 1074 cm^{-1}, MS (EI) *m/z* (rel int): 180, 178 (5, 5, M$^{+\cdot}$ cluster), 81 (100).

(±)-trans-2-bromocyclopentanol, (±)-4, was prepared in the same manner as (±)-**5**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.44-2.41 (m, 6H, $(CH_2)_3$), 3.20 (br s, 1H, OH, exchanged with D_2O), 4.01 (br q, 1H, -CHOH, $J_{1,2} = 10$ Hz), 4.29 (br q, 1H, -CHBr); IR (neat): 3399 (OH), 2973, 1071 cm^{-1}; MS (EI) *m/z* (rel int): 166, 164 (3, 3, M$^{+\cdot}$ cluster), 148

(6), 146 (6), 57 (100), 55 (32).

(±)-trans-*2-bromocycloheptanol, (±)-6*, was prepared in the same manner as (±)-**5**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.20-2.40 (m, 10H, $(CH_2)_5$), 2.60 (br s, 1H, OH, exchanged with D_2O), 3.74 (br ddd, 1H, -CHOH, $J_{1,7eq}$ = 3.2 Hz, $J_{1,7ax}$ = 8.5 Hz), 4.00 (ddd, 1H, -CHBr, $J_{1,2}$ = 13 Hz, $J_{2,3ax}$ = 8.8 Hz, $J_{2,3eq}$ = 3.7 Hz); IR (neat): 3399 (OH), 2937, 1458, 1031 cm^{-1}; MS (EI) *m/z* (rel int): 194, 192 (0.1, 0.1, $M^{+\cdot}$ cluster), 113 (16), 95 (100), 71 (12), 57 (45).

(±)-trans-*1-acetyloxy-2-bromocyclohexane, (±)-5-acetate.* Acetic anhydride (1.7 mL, 20 mmol) was added to a stirred solution of (±)-**5** (1.7 g, 10 mmol) in dry pyridine (5 mL) at 0°C. After 18 h, the reaction mixture was diluted with ether (10 mL), washed with HCl (1 N, 3 x 5 mL) and satd $NaHCO_3$ (2 x 5 mL), dried over anhydrous sodium sulfate and concentrated to a pale yellow oil by rotary evaporation. Column chromatography on silica gel eluted with hexane: ethyl ether (9: 1) yielded a colorless oil (1.8 g, 86%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.10-1.95 (m, 7H,), 2.10 (s, 3H, CH_3), 2.30 (m, 1H), 3.91 (ddd, 1H, -CHBr, $J_{2,3eq}$ = 4.3 Hz, $J_{2,3ax}$ = 9.4 Hz, $J_{1,2}$ = 14 Hz), 4.83 (ddd, 1H, -CHOAc, $J_{1,6eq}$ = 4.6 Hz, $J_{1,6ax}$ = 9.3 Hz); IR (neat): 1741 (C=O), 1236, 1038 cm^{-1}; MS (EI) *m/z* (rel int): 222 , 220 (0.2, 0.2, $M^{+\cdot}$ cluster), 180 (5), 178 (5), 162 (22), 160 (22), 99 (17), 81 (100).

(±)-trans-*1-acetyloxy-2-bromocyclopentane, (±)-4-acetate.* Using the procedure for (±)-**5** acetate, but starting with (±)-**4** (1.1 g, 6.7 mmol) gave a colorless oil (1.06 g, 77%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.59-2.37 (m, 6H, $(CH_2)_3$), 2.01 (s, 3H, $-OCOCH_3$), 4.18 (m, 1H, -CHBr), 5.22 (m, 1H, -CHOAc); IR (neat): 1741 (C=O), 1233, 1018 cm^{-1}; MS (EI) *m/z* (rel int): 208, 206 (0.1, 0.1, $M^{+\cdot}$ cluster), 148 (97), 146 (98), 85 (26), 67 (83), 43 (100).

(±)-trans-*1-acetyloxy-2-bromocycloheptane, (±)-6-acetate.* Using the procedure for (±)-**5** acetate, but starting with (±)-**6** (1.0 g, 5.2 mmol) gave a colorless oil (1.07 g, 88%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.40-2.40 (m, 10H, $(CH_2)_5$), 2.04 (s, 3H, $-OCOCH_3$), 4.12 (ddd, 1H, -CHBr, $J_{1,2}$ = 12 Hz, $J_{2,3ax}$ = 8.1 Hz, $J_{2,3eq}$ = 3.9 Hz), 5.06 (ddd, 1H, -CHOAc, $J_{1,7eq}$ = 3.1 Hz, $J_{1,7ax}$ = 7.8 Hz); IR (neat): 1738 (C=O), 1252, 1028 cm^{-1}; MS (EI) *m/z* (rel int): 236, 234 (0.1, 0.1, $M^{+\cdot}$ cluster), 194 (3), 192 (3), 176 (16), 174 (16), 113 (28), 95 (100).

(±)-trans-*1-(benzoyloxy)-2-bromocyclohexane, (±)-5-benzoate.* A solution of benzoyl chloride (1.0 mL, 8.6 mmol) and (±)-**5** (1.0 g, 5.6 mmol) in dry pyridine (5 mL) was stirred at room temperature for 24 h. Work-up as for **5**-acetate above followed by column chromatography on silica gel eluted with hexane: ethyl ether (7: 3) afforded a colorless oil, (1.5 g, 95%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.26-2.44 (m, 8H, $(CH_2)_4$), 4.15 (m, 1H, -CHBr), 5.13 (m, 1H, -CHOBz), 7.41-8.09 (m, 5H, Ph); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 23.1, 25.2, 30.9, 35.4, 52.5, 76.2, 128.2, 129.5, 130.1, 132.9, 165.4; IR (neat): 2938, 1733 (C=O), 1685, 1316 cm^{-1}; MS (CI) *m/z* (rel int): 283, 285 (100, 98, $M+H^+$ cluster), 203 (17), 123 (29).

(±)-1-(benzoyloxy)-2-cyclohexene, (±)-2-benzoate. A solution of (±)-**5** benzoate (0.50 g, 1.8 mmol) in DBU (2 mL) turned light brown while it was heated to 120°C for 3 h. The solution was cooled to room temperature, diluted with ethyl acetate (10 mL), washed HCl (1 M, 2 x 5 mL), dried over anhydrous $MgSO_4$ and concentrated to a light brown oil (0.30 g, 84%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.6-2.3 (m, 6H, $(CH_2)_3$), 5.5 (m, 1H, -CHOBz), 5.7-6.1 (m, 2H, olefin), 7.3-8.2 (m, 5H, Ph); IR (neat): 2360, 1716 (C=O), 1653, 1270 cm^{-1}; MS (EI) *m/z* (rel int) 202 (21, $M^{+\cdot}$), 157 (3), 105 (100), 97 (13), 81 (26), 77 (26).

(±)-trans-*2-bromo-1-(butanoyloxy)cyclopentane, (±)-4-butyrate.* ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.96 (t, 3H, $-(CH_2)_2CH_3$), 1.56-2.37 (m, 10H), 4.22 (m, 1H, -CHBr), 5.27 (m, 1H, -CHOCOR); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 13.5, 18.4, 21.6, 29.4, 34.4, 36.1, 53.1, 81.8, 172.6; IR (neat): 1736 (C=O), 1252, 1094 cm^{-1}.

(±)-trans-*2-bromo-1-(butanoyloxy)cycloheptane, (±)-6-butyrate.* ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.98 (t, 3H, $-(CH_2)_2CH_3$), 1.28-2.36 (m, 14H), 4.19 (ddd, 1H, -CHBr, $J_{1,2}$ = 8.1 Hz, $J_{2,3ax}$ = 12 Hz, $J_{2,3eq}$ = 3.8 Hz), 5.13 (ddd, 1H, -CHOCOR, $J_{1,7ax}$ = 11 Hz, $J_{1,7eq}$ = 3.1 Hz); IR (neat): 1736 (C=O), 1383, 1252, 1079 cm^{-1}; MS (CI) *m/z* (rel

int): 265, 263 (19, 21, M+H$^+$ cluster), 194 (32), 192 (35), 177 (67), 175 (70), 112 (100).

(1S,2S)-(+)-trans-*2-bromo-1-(butanoyloxy)cyclohexane, (1S,2S)-(+)-5-butyrate.* Lipase (PCL, 1.5 g) was added to a vigorously stirred suspension of (±)-**5**-butyrate (10.0 g, 40.2 mmol) in phosphate buffer (10 mM, pH 7.0, 50 mL). A pH stat regulated the addition of NaOH (0.49 N). After 76 h, 41.7 mL of base had been consumed, 51% conversion. The mixture was extracted with ethyl acetate (5 x 100 mL), dried over anhydrous $MgSO_4$ and concentrated to an oil. Column chromatography on silica gel eluted with hexane: ethyl ether (7: 3) gave (1S,2S)-(+)-**5**-butyrate (4.54 g, 46%, a maximum of 50% is possible in a kinetic resolution) and the alcohol (1R,2R)-(-)-**5** (3.25 g, 46%). (1S,2S)-(+)-**5**-butyrate: >98% ee by ^{1}H-NMR with Eu(hfc)$_3$; $[\alpha]_D$ = +45.3 (*c* 10.1, CH_2Cl_2), lit.[23] $[\alpha]_D$ = +43.6 (*c* 2, CH_2Cl_2). (1R,2R)-(-)-**5**: >98% ee by ^{1}H-NMR with Eu(hfc)$_3$ of the acetate; $[\alpha]_D$ = -27.5 (*c* 11.2, CH_2Cl_2), lit.[23] $[\alpha]_D$ = -33.2 (*c* 2, CH_2Cl_2).

(S)-(-)-1-(butanoyloxy)-2-cyclohexene, (S)-(-)-2-butyrate. A solution of (1S,2S)-(+)-**5**-butyrate (2.0 g, 8.0 mmol) in DBU (5 mL) was heated to 70-75°C for 18 h. The solution was cooled to room temperature, diluted with ethyl acetate (10 mL), washed with HCl (1 M, 5 mL), dried over anhydrous $MgSO_4$ and concentrated to a light brown oil. Column chromatography on silica gel eluted with hexane: ethyl ether (7: 3) gave a colorless oil: (1.17 g, 91%), $[\alpha]_D$ = -174° (*c* 9.6, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.96 (t, 3H, -$(CH_2)_2C\underline{H}_3$), 1.57-2.32 (m, 10H), 5.29 (m, 1H, -CHOCOR), 5.67-6.01 (m, 2H, olefin H); IR (neat): 1746 (C=O), 1698, 1380, 1368 cm^{-1}; MS (EI) *m/z* (rel int): 168 (17, M$^{+\cdot}$), 140 (7), 125 (11), 98 (20), 81 (80), 71 (100), 53 (10); HRMS (EI) M$^{+\cdot}$ measured: 168.1149 Da; $C_{10}H_{16}O_2$ requires 168.11502 Da.

(S)-(-)-2-cyclohexenol, (S)-(-)-2. To a solution of (S)-(-)-**2** butyrate (0.50 g, 2.98 mmol) in dry THF (2 mL) was added $LiAlH_4$ (1.6 mL of 1.0 M suspension in THF) and the resulting mixture was stirred at room temperature for 0.5 h. Dilute HCl (1 M) was added dropwise until the solution was acidic to litmus paper. Concentration of the resulting solution under vacuum produced a white paste, which was dissolved in a mixture of ethyl acetate (5 mL) and water (2 mL). The ethyl acetate layer was separated, dried over anhydrous $MgSO_4$ and concentrated under vacuum. Column chromatography on silica gel eluted with hexane: ethyl ether (7: 3) yielded a colorless liquid: (0.242 g, 83%), >99% ee by ^{1}H NMR (C_6D_6, 300 MHz) of the (R)-Mosher ester, ^{13}C satellite peak (0.55%) was used as an internal standard, $[\alpha]_D$ = -125 (*c* 6.4, $CHCl_3$), lit.[19] $[\alpha]_D$ = -97 (*c* 1.4, $CHCl_3$).

(S)-(+)-trans-*2-bromo-1-(butanoyloxy)cyclopentane, (S)-(+)-4-butyrate.* Following the procedure for **5**-butyrate, but starting with (±)-**4**-butyrate (10.0 g, 38 mmol) gave a colorless oil (19 h to reach 53 % conversion with 2.5 g lipase) (S)-(+)-**4**-butyrate (3.53 g, 37% yield), 94% ee by ^{1}H-NMR with Eu(hfc)$_3$ as the shift reagent, $[\alpha]_D$ = +72.1° (*c* 10.2, CH_2Cl_2) and the alcohol (R)-(-)-**4** (2.97 g, 41% yield); 84% ee by ^{1}H-NMR with Eu(hfc)$_3$ of the acetate derivative; $[\alpha]_D$ = -32.1 (*c* 12.2, CH_2Cl_2). A further hydrolysis of this sample of (S)-(+)-**4**-butyrate catalyzed by PCL to 6.7% conversion followed by chromatography yielded (S)-(+)-**4**-butyrate (2.05 g, 20% overall, a maximum of 50% was possible); >98% ee, $[\alpha]_D$ = +75.6 (*c* 10.7, CH_2Cl_2). The product slowly racemized. After 20 d at room temperature, the $[\alpha]_D$ had decreased to +68.5 (*c* 3.87, CH_2Cl_2).

(S)-(-)-1-(butanoyloxy)-2-cyclopentene, (S)-(-)-1-butyrate. Heating (S)-(+)-**4** butyrate (1.5 g, 6.4 mmol, ~90% ee) with DBU (65-70°C 10 h) followed by workup as for **2**-butyrate gave a colorless oil: (0.80 g, 80%), $[\alpha]_D$ = -114° (*c* 10.6, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.94 (t, 3H, -$(CH_2)_2C\underline{H}_3$), 1.56-2.70 (m, 8H), 5.68 (m, 1H, -CHOCOR), 5.69-6.11 (m, 2H, olefin H); IR (neat): 1733 (C=O), 1359, 1257, 1182 cm^{-1}; MS (EI) *m/z* (rel int): 154 (7, M$^{+\cdot}$), 84 (5), 71 (57), 67 (100), 43 (25); HRMS (EI) M$^{+\cdot}$ measured: 154.0994 Da; $C_9H_{14}O_2$ requires 154.09937 Da.

(S)-(-)-2-cyclopentenol, (S)-(-)-1. Cleavage of the ester group in (S)-(-)-**1**-butyrate (0.50 g, 3.25 mmol) with $LiAlH_4$ as above for **2**-butyrate gave a colorless oil: (0.185 g, 68%); 65% ee by ^{1}H NMR (C_6D_6, 300 MHz) of the (R)-Mosher ester; $[\alpha]_D$ = -91 (*c* 3.89, CCl_4) lit.[24] $[\alpha]_D$ = -105.8 (*c* 1.14, $CHCl_3$, 82% ee).

(S)-(+)-trans-*2-bromo-1-(butanoyloxy)cycloheptane, (S)-(+)-6-butyrate.* Following the same procedure as for **5**-butyrate, but starting with (±)-**6**-butyrate (10.0 g, 38 mmol), (120 h reaction to reach 50% conversion using 1.5 g of lipase) gave (S)-(+)-**6**-butyrate (4.5 g, 45% yield): >98% ee ^{1}H-NMR with Eu(hfc)$_3$; $[\alpha]_D$ = +26.4 (*c* 10.9, CH_2Cl_2) and the alcohol (R)-(-)-**6** (3.03 g, 42% yield): 99% ee by ^{1}H-NMR with Eu(hfc)$_3$ of the acetate; $[\alpha]_D$ = -4.6 (*c* 10.8, CH_2Cl_2).

(S)-(-)-1-(butanoyloxy)-2-cycloheptene, (S)-(-)-3-butyrate. Heating (S)-(+)-**6**-butyrate (2.0 g, 7.6 mmol) with DBU (75-80°C for 20 h) in a manner similar to **5**-butyrate gave a colorless oil after workup: (1.23 g, 89%), $[\alpha]_D$ = -31.4° (*c* 10.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.95 (t, 3H, -$(CH_2)_2C\underline{H}_3$), 1.20-2.32 (m, 12H), 5.42 (m, 1H, -CHOCOR), 5.59-5.87 (m, 2H, olefin H); IR (neat): 1733 (C=O), 1653, 1458, 1179 cm^{-1}; MS (EI) *m/z* (rel int): 182 ($M^{+\bullet}$, 9), 154(12), 139 (17), 112 (20), 95 (28), 79 (100), 43 (36), HRMS (EI) $M^{+\bullet}$ measured: 182.1305 Da; $C_{11}H_{18}O_2$ requires 182.13067 Da.

(S)-(-)-2-cycloheptenol, (S)-(-)-3. Treatment of (S)-(-)-**3**-butyrate (0.50 g, 2.75 mmol) with $LiAlH_4$ as above for **5**-butyrate gave a colorless oil (0.24 g, 77%); >98.5% ee by ^{1}H NMR (C_6D_6, 300 MHz) of the (R)-Mosher ester; $[\alpha]_D$ = -24.9 (*c* 7.8, CH_3OH), lit.[22] $[\alpha]_D$ = -7.5 (*c* 2, CH_3OH, <20% ee).

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