Lipase-Catalyzed Enantioselective Synthesis of Methyl (*R*)- and (*S*)-2-Tetradecyloxiranecarboxylate through Sequential Kinetic Resolution

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Among a variety of lipases tested, *Pseudomonas fluorescens* lipase has been found to induce enantioselective acylation of methyl (*R*,*S*)-2-hydroxy-2-(hydroxymethyl)hexadecanoate (**3**), affording, through sequential kinetic resolution, both enantiomers in good optical yields. Efficiency of the process has been compared to the Sharpless asymmetric dihydroxylation of alkene **2** using $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ as chiral ligands. The (*R*)- and (*S*)-**3** enantiomers have been cyclized to afford both enantiomers of methyl 2-tetradecyloxiranecarboxylate (**1**), a potent hypoglycemic agent and inhibitor of long-chain fatty acid oxidation.

Introduction

Methyl 2-tetradecyloxiranecarboxylate (**1**) (methyl palmoxirate, methyl 2-tetradecylglycidate) is a potent oral hypoglycemic and antiketogenic agent in mammals including humans.[1] The compound has been reported to be specific inhibitor of long-chain fatty acid oxidation.[2] From the two enantiomers only the *R* is active while the *S* is practically inactive.[3] Nonenzymatic preparation of chiral (*R*)-**1** has been carried out by resolution of the corresponding racemic 2-tetradecyloxiranecarboxylic acid (TDGA) or by Sharpless chiral epoxidation of an oxirane carbinol precursor.[3] More recently, 2-alkylglycidic acid derivatives have been synthesized by cyclization of diastereomerically pure β-sulfenyl hydroxy esters.[4]

Enzyme-catalyzed reactions constitute a great potential for the synthesis of enantiomerically pure compounds.[5] However, to our knowledge, only two enzymatic approaches to the synthesis of (*R*)-**1** and the parent TDGA have been found in the literature, i.e. by enantiotopic differentiation of prochiral 2-substituted glycerols with porcine pancreatic lipase (PPL)[6] and by resolution of racemic TDGA through a rat liver microsomal enzyme preparation.[7] Continuing our efforts directed to the enzyme-mediated chiral resolution of secondary alcohols,[8] we present herein a new, short, and straightforward enantioselective synthesis of both enantiomers of **1** through enzymatic sequential kinetic resolution of racemic diol **3** followed by cyclization. Comparison with the results obtained through Sharpless asymmetric dihydroxylation of the same diol using chiral ligands $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ is also presented.

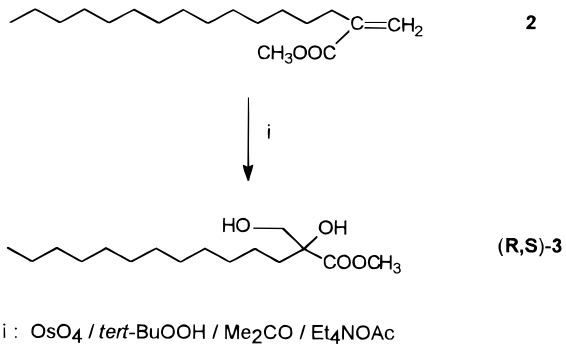

Figure 1.

Results and Discussion

The required racemic diol **3** was obtained by osmium-catalyzed dihydroxylation of methyl 2-methylenehexadecanoate (**2**), prepared from methyl malonate and 1-bromotetradecane as previously reported.[9] The reaction was carried out with *tert*-butyl hydroperoxide in acetone, osmium in catalytic amount, and "in situ" prepared tetraethylammonium acetate in order to avoid hydrolysis of the ester group.[10] Under these conditions, diol **3** was obtained in 73% isolated yield (Figure 1).

For the enzymatic resolution of **3** a number of commercially available lipases, i.e. *Pseudomonas cepacia* (PS, Amano), *Candida cylindracea* (CC, Sigma), porcine pancreatic lipase (PPL, Sigma), *Pseudomonas fluorescens* lipase (PFL, Fluka), and *Candida antarctica* lipase (CA, Novo Nordisk), were screened. The enzymes were used as received from commercial sources, but some of them

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Table 1. Chiral Resolution of (*R,S*)-3 through Several Lipases

lipase	lipase:alcohol	time	convn (%)	$[\alpha]^{20}_D$ (*R*)-**3**	yield (*R*)-**3** (%)[a]	ee (*R*) (%)	yield (*S*)-**3** (%)[a,b]	$[\alpha]^{20}_D$ (*S*)-**3**	ee (*S*) (%)	*E*[c]
PS immob	2	10 min	55	9.4	53	83[d] (81[e])	35		69[e]	14
PPL immob	2	25 min	46	1.1	43	10[e]	*f*			
CC immob	2	>350 h								
CA	2	20 min	56	6.9	35	59[e]				
PS	0.5	8 h	35	5.2	58	41[d] (45[e])	31	−8.9	75[d] (77[e])	11
PFL	0.5	6.5 h	39	6.2	52	54[e]	25		83[d]	19
PFL	0.5	8 h	53	9.8	38	81[d] (84[e])	33	−8.3	71[d] (71[e])	15

[a] Yields refer to pure isolated products after column chromatography purification. [b] Overall yield of alcohol derived from hydrolysis of the initially formed chiral acetate (*S*)-(+)-**4**. [c] Enantiomeric ratio (*E*) values were determined from the ee of the residual substrate and the extent of conversion (Chen, Ch.-Sh.; Fujimoto, Y.; Girdaukas, G.; Sih, Ch. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294). [d] ee based on $[\alpha]^{20}_D$ values in comparison to that of the enantiomerically pure compound. [e] ee based on ^{19}F NMR analysis of the corresponding Mosher ester.[14] [f] The corresponding acetate (*S*)-**4** was not hydrolyzed due to a disappointingly low specific rotation value.

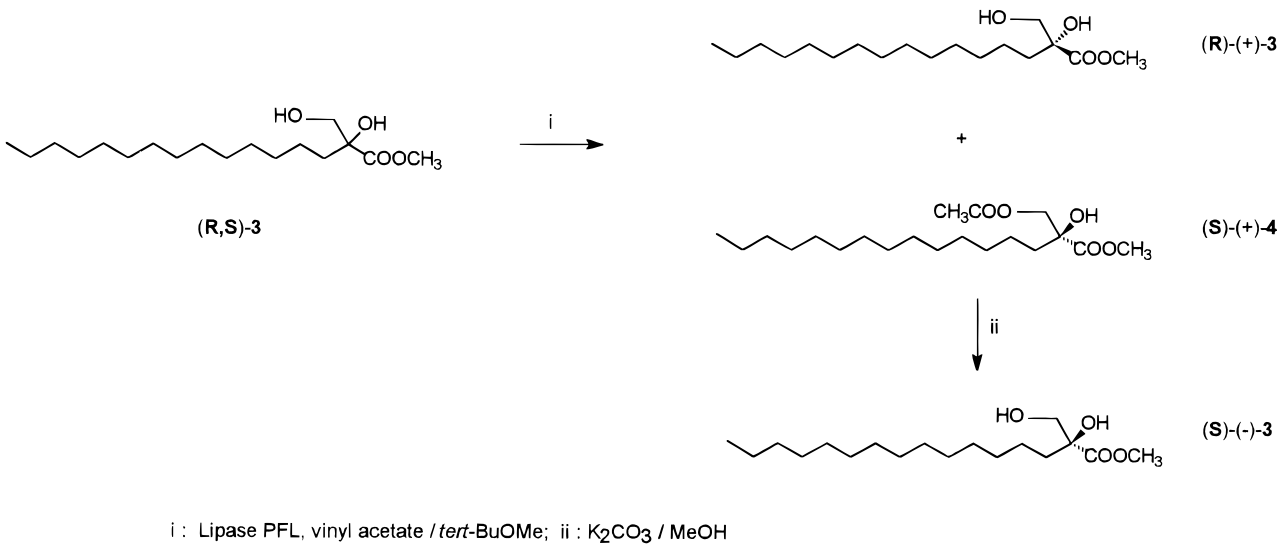

Figure 2.

were also immobilized on Celite.[11] The resolution was carried out on a thermostatized bath at 37 °C in *tert*-butyl methyl ether as solvent and using vinyl acetate as acylating agent. The lipase:alcohol ratio ranged from 0.5 to 2, and the reaction was stopped when ca. 50% conversion was achieved, which occurred for most enzymes in a reasonable reaction time (20 min to 8 h) (Table 1). The most promising results were obtained with PFL in a lipase:alcohol ratio of 0.5:1. After 8 h of transformation (53% conversion), the mixture was filtered and the nonreactive alcohol (*R*)-**3** (38%, 84% ee) separated from the acetate (*S*)-**4**, which was hydrolyzed under basic conditions to yield the corresponding (*S*)-**3** enantiomer (33% overall yield from the racemic alcohol, 71% ee) (Figure 2). The enantiomeric ratio was only moderate ($E = 15$). Immobilized lipase PS afforded also similar chemical and optical yields of both enantiomers, but the reaction was too fast to be controlled. When immobilized PPL was used, the nonreacting enantiomer (*R*)-**3** and the corresponding acetate (*S*)-**4** were obtained in poor ee, as shown by their $[\alpha]^{20}_D$ values, suggesting that both enantiomers may easily enter into the catalytic active site of the enzyme leading to no enantiodifferentiation by the enzyme. No transesterification occurred with CC lipase after more than 350 h reaction (Table 1). The absolute configuration assignment of the alcohols was based on the sign of the specific rotation of the samples in comparison with that previously reported.[3]

In order to improve the enantiomeric purity of the enantiomers, a sequential kinetic resolution with PFL was undertaken[12,13] (Scheme 1). Thus, racemic (*R,S*)-**3** was subjected to a first enzymatic resolution for 4 h using a lipase:alcohol ratio 0.6:1. After hydrolysis of the acetate (*S*)-$\mathbf{4}_1$, the resulting diol (*S*)-$\mathbf{3}_1$ was subjected to a new enzymatic resolution at 47% conversion to afford acetate (*S*)-$\mathbf{4}_3$ (38%). Subsequent hydrolysis of this acetate furnished alcohol (*S*)-$\mathbf{3}_3$ (32%) with a 94% ee, based on ^{19}F NMR analysis of the corresponding Mosher ester.[14] The slow-reacting enantiomer (*R*)-$\mathbf{3}_2$, obtained in the first enzymatic process, needed 19 h to accomplish ca. 50% conversion under the same conditions, yielding unreacted alcohol (*R*)-$\mathbf{3}_4$ in 38% yield and >99% ee (Table 2). Once a good to excellent optical purity of both (*R*)- and (*S*)-**3** was attained, we optimized the corresponding chemical yields in the following manner. A batch of alcohol (*S*)-**3** (60% ee) and (*R*)-**3** (80% ee), obtained in a separate experiment with a lipase:alcohol ratio of 0.15:1 and 18 h reaction, was subjected to a new sequential biocatalytic resolution. In this case, the fast-reacting enantiomer (*S*)-$\mathbf{3}_1$ was almost completely transformed after 22 h reaction into acetate (*S*)-$\mathbf{4}_3$ (80% isolated yield), which was hydrolyzed to enantiomer (*S*)-$\mathbf{3}_3$ in 73% yield and 93% ee. In turn, the slow-reacting enantiomer (*R*)-$\mathbf{3}_2$ was allowed to react only to 27% conversion to give 69% yield of remaining unreactive (*R*)-$\mathbf{3}_4$ of 94−96% ee (Table 2).

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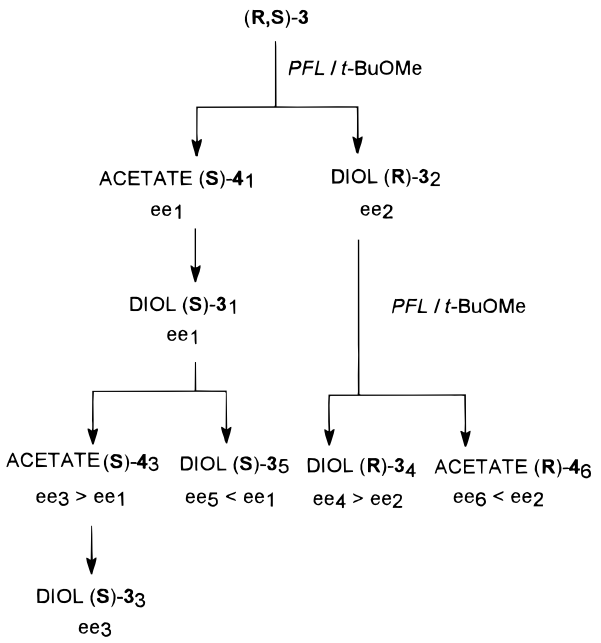
Table 2. Sequential Kinetic Resolution of (*R,S*)-3 with Lipase PFL

substrate	lipase:alcohol	time (h)	convn (%)	yield **3** (%)[a]	ee (%)	yield **4** (%)[a]	yield **3** (%)[a,b]	ee (%)
(*R,S*)-**3**	0.6	4	51	42 (*R*)-$\mathbf{3}_2$		46 (*S*)-$\mathbf{4}_1$	44 (*S*)-$\mathbf{3}_1$	
diol (*S*)-$\mathbf{3}_1$	0.6	2	47	41 (*S*)-$\mathbf{3}_5$	43[c] (*S*)-$\mathbf{3}_5$	38 (*S*)-$\mathbf{4}_3$	32 (*S*)-$\mathbf{3}_3$	94[d] (91[c]) (*S*)-$\mathbf{3}_3$
diol (*R*)-$\mathbf{3}_2$	0.6	19	50	38 (*R*)-$\mathbf{3}_4$	>99[d] (*R*)-$\mathbf{3}_4$	34 (*R*)-$\mathbf{4}_6$		
(*R,S*)-**3**	0.15	18	45	46	60[c]	32	30	80[c]
diol (*S*)-$\mathbf{3}_1$	0.5	22	85			80 (*S*)-$\mathbf{4}_3$	73 (*S*)-$\mathbf{3}_3$	93[d] (93[c]) (*S*)-$\mathbf{3}_3$
diol (*R*)-$\mathbf{3}_2$	0.5	6	27	69 (*R*)-$\mathbf{3}_4$	94[d] (96[c]) (*R*)-$\mathbf{3}_4$			

[a] Yields refer to pure isolated products after column chromatography purification. [b] Overall yield of alcohol derived from hydrolysis of the initially formed chiral acetate (*S*)-(+)-**4**. [c] ee based on $[\alpha]^{20}_D$ values in comparison to that of the enantiomerically pure compound. [d] ee based on ^{19}F NMR analysis of the corresponding Mosher ester.[14]

Scheme 1



Chiral alcohols (*R*)- and (*S*)-**3** were also alternatively prepared by osmium tetraoxide-catalyzed asymmetric dihydroxylation of ester **2** using $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ as chiral ligands.[15] After running several experiments, the best conditions found for optimum ee values implied utilization of 1.6 equiv of $K_3Fe(CN)_6$ at 0−5 °C for 15−23 h. The presence of the dihydroquinidine as ligand led, as expected, to the *R* enantiomer (62%) (95% ee based on the $[\alpha]^{20}_D$ value), while when the dihydroquinine derivative was used the *S* enantiomer (72%) resulted in somewhat lower enantiomeric purity (91% ee based on the $[\alpha]^{20}_D$ value)[16] (Figure 3). The Sharpless procedure provides, therefore, better isolated yields of the desired enantiomer in comparison with the enzymatic acylation, since the latter can only afford a maximum 50% yield of either enantiomer. However, the enzymatic process allows preparation of both enantiomers in a *single* operation, and by a judicious selection of experimental conditions it is possible to attain ee >99%, particularly of the active *R* enantiomer.

Finally, cyclization of both enantiomers of (*R*)-**3** and (*S*)-**3** was independently and easily achieved by tosylation of the primary alcohol function followed by NaH treatment in THF at 0 °C for 4 h. The overall yield of (*R*)-(+)-**1** was 69% and the enantiomeric purity 96%, based on the optimum $[\alpha]^{20}_D$ value from the literature.[3] In the same manner, (*S*)-(−)-**1** was obtained in 61% overall yield and 87% ee, based on the optimum $[\alpha]^{20}_D$ value of the *R* enantiomer (Figure 4).

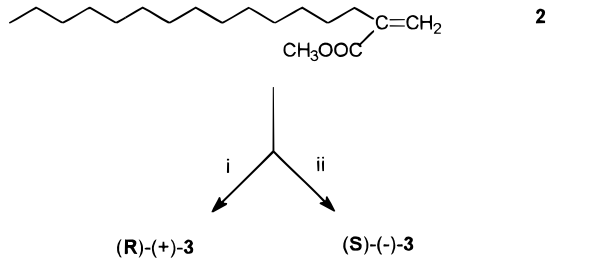


Figure 3.

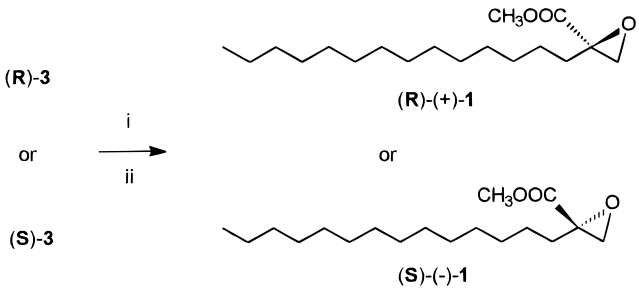


Figure 4.

Conclusions

In conclusion, a new and convenient way to prepare both enantiomers of methyl 2-tetradecyloxiranecarboxylate (**1**) has been developed through PFL-mediated sequential kinetic resolution. The procedure affords both enantiomers in good optical yields and efficiently complements the very scarce methods readily available for the synthesis of the *R* enantiomer, a very potent inhibitor of fatty acid oxidation. The sequential kinetic resolution has been confirmed as an effective tool to markedly enhance the enantioselectivity of a biocatalytic process.

Experimental Section

Melting points are uncorrected. Elemental analyses were performed in our Department. IR spectra were recorded on film or in $CHCl_3$ solution. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions and recorded at 200 or 300 MHz for ^{1}H and 50 and 75 MHz for ^{13}C. The values are expressed in δ scale relative to internal Me_4Si. ^{19}F NMR spectra were

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recorded at 282 or 470 MHz, and the values are reported in δ scale relative to trifluoroacetic acid as external standard. Low-resolution mass spectra were run using a HP-5 25 m × 0.20 μm i.d. fused silica capillary column. Optical rotations were measured in $CHCl_3$ at 20 °C using a sodium lamp.

C. cylindracea, porcine pancreatic lipase, and *P. fluorescens* lipase were commercially available. Analytical-grade reagents were obtained from commercial suppliers and were used directly without further purification.

Acylation of Methyl (*R,S*)-2-Hydroxy-2-(hydroxymethyl)hexadecanoate (3) with *Pseudomonas fluorescens* Lipase through Sequential Kinetic Resolution. Synthesis of (*R*)-(+)-3 and (*S*)-(+)-4. In a 50 mL Erlenmeyer flask was placed a mixture of 350 mg (1.10 mmol) of (*R,S*)-**3** (see preparation and spectroscopic data in Supporting Information) in 15 mL of *tert*-butyl methyl ether, 50 mg of *P. fluorescens* (PFL) lipase and 0.952 g (11.0 mmol) of vinyl acetate. The Erlenmeyer flask was capped, placed in a thermostatized bath at 37 °C, and shaken at 80 units/min. The reaction was monitored by TLC, and when the transformation was 45% (18 h reaction), the mixture was filtered off and the enzyme washed with diethyl ether. The solvent was stripped off and the resulting crude purified by column chromatography on silica gel eluting with hexane:ether mixtures to furnish 125 mg (32%) of acetate (*S*)-(+)-**4** and 162 mg (46%) of unreactive alcohol (*R*)-(+)-**3**. Acetate (*S*)-(+)-**4** was hydrolyzed to the corresponding alcohol (*S*)-(−)-**3** (see below), and both alcohols were subjected to a second enzymatic resolution. Thus, 60 mg (0.189 mmol) of diol (*R*)-(+)-**3** was treated with 30 mg of PFL, 163 mg (1.89 mmol) of vinyl acetate and 5 mL of *tert*-butyl methyl ether for 6 h (27% conversion) to yield alcohol (*R*)-(+)-**3** (42 mg, 69% yield), $[\alpha]^{20}_D = 11.2°$ (*c* 4.1, $CHCl_3$) (96% ee, based on the α value). Diol (*S*)-(−)-**3** (60 mg) was also treated with PFL (30 mg) under similar conditions for 22 h (85% conversion) to afford 55 mg (80%) of acetate (*S*)-(+)-**4**. This compound was hydrolyzed under standard conditions to give 44 mg (91%) of the desired alcohol (*S*)-(−)-**3**, $[\alpha]^{20}_D = -10.8°$ (*c* 4.4, $CHCl_3$) (93% ee, based on the $[\alpha]_D$ value). Spectroscopic data of racemic **4**: mp 71−72 °C; IR (ν) 3467, 2914, 1745, 1727, 1231 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.20 (d, J = 11.1 Hz, 1H), 4.13 (d, J = 11.1 Hz, 1H), 3.78 (s, 3H), 3.33 (s, 1H), 2.03 (s, 3H), 1.7−1.52 (m, 2H), 1.23 (b, 24H), 0.86 (t, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.72, 170.51, 76.57, 68.91, 53.0, 35.16, 31.89, 29.64−29.33, 22.95, 22.66, 20.69, 14.08 ppm; MS (EI) *m*/*z* 61 (2), 55 (100). Anal. Calcd for $C_{20}H_{38}O_5$: C, 67.00; H, 10.68. Found: C, 67.11; H, 10.82.

Hydrolysis of Acetate (*S*)-(+)-4. Acetate (*S*)-(+)-**4** (125 mg) was dissolved in 3 mL of analytical grade methanol and mixed with 72 mg of K_2CO_3. The mixture was stirred for 1 h and 15 min at room temperature, quenched with water, and extracted with CH_2Cl_2 (6 × 10 mL). The organic phases were combined and washed with brine and dried. Evaporation of the solvent afforded a crude, which was purified by column chromatography on silica gel, eluting with hexane:ethyl acetate mixtures to give 102 mg (93%) of alcohol (*S*)-(−)-**3**.

Determination of the Enantiomeric Excess of Alcohols (*R*)-(+)-3 and (*S*)-(−)-3. (*R*)-(+)-α-Methoxy(trifluoromethyl)phenylacetic acid was converted into the acid chloride as previously described.[17] A sample of the alcohol (ca. 2 mg) was mixed with 150 μL of a 8.4×10^{-2} M solution of (*S*)-(+)-MTPA chloride in anhydrous CH_2Cl_2 and one crystal of DMAP. The mixture was stirred for 2 h at room temperature, and after this time no starting material was detected on TLC. After evaporation of the solvent, direct ^{19}F NMR spectrum of the crude diastereomeric esters allowed calculation of the ee by integration of the CF_3 signals. *R,R* diastereomer: ^{19}F NMR (470 MHz, $CDCl_3$) δ −72.555 (s). *R,S* diastereomer: ^{19}F NMR (470 MHz, $CDCl_3$) δ −72.580 (s). The calculated enantiomeric purity of the alcohols was 93% ee for (*S*)-(−)-**3** and 94% ee for (*R*)-(+)-**3**. From their $[\alpha]^{20}_D$ values the enantiomeric purity of both alcohols was 93% for (*S*)-(−)-**3** and 96% for (*R*)-(+)-**3**.

Methyl (*R*)-2-Tetradecyloxiranecarboxylate [(*R*)-1]. To an ice-cooled solution of alcohol (*R*)-**3** (37 mg, 0.12 mmol) in anhydrous pyridine (1 mL) was added *p*-toluenesulfonyl chloride (67 mg, 0.35 mmol) and the mixture allowed to stand at 4 °C for 23 h. The reaction mixture was quenched with 3 mL of 1 N HCl, extracted with CH_2Cl_2 (5 × 5 mL), and washed with 1 N HCl, $NaHCO_3$ saturated solution, and brine. The solvent was evaporated off and the residue purified by column chromatography on silica gel, eluting with hexane:ethyl acetate mixtures to afford the corresponding tosylate (45 mg, 82%): IR (ν) 3540, 3034, 2925, 1747, 1598, 1378, 1189 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 4.22 (d, J = 9.7 Hz, 1H), 4.00 (d, J = 9.7 Hz, 1H), 3.75 (s, 3H), 3.34 (s, 1H), 2.45 (s, 3H), 1.7−1.5 (m, 2H), 1.23 (b, 24H), 0.87 (t, J = 6.7 Hz, 3H) ppm. To an ice-cooled dispersion of NaH (2.6 mg, 0.1 mmol) in anhydrous THF (2 mL) was added 45 mg (0.096 mmol) of the tosylate dissolved in 3 mL of anhydrous THF. The reaction mixture was stirred at 0 °C for 4 h and 30 min, the solvent stripped off, and water (10 mL) added. The organic material was extracted with CH_2Cl_2 (5 × 10 mL), washed with water, and dried. The solvent was evaporated off to leave a residue, which was purified by column chromatography on silica gel, eluting with hexane: ethyl acetate mixtures to afford the expected (*R*)-(+)-**1** (24 mg, 69%): $[\alpha]^{20}_D = 9.9°$ (*c* 2.4, $CHCl_3$), 96% ee based on the optimum $[\alpha]^{20}_D$ value;[3] mp 44−45 °C; IR (ν) 3056, 2925, 1739, 1290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.03 (d, J = 6 Hz, 1H), 2.79 (d, J = 6 Hz, 1H), 2.07 (m, 1H), 1.65 (m, 1H), 1.5−1.2 (b, 24H), 0.88 (t, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.91, 57.02, 52.45, 51.79, 31.89, 31.22, 29.65−29.32, 24.71, 22.65, 14.08 ppm; MS (EI) *m*/*z* 55 (100). Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found: C, 72.49; H, 11.50.

Methyl (*S*)-2-Tetradecyloxiranecarboxylate [(*S*)-1]. This compound was prepared in a manner similar to that of the corresponding *R* enantiomer in 61% isolated yield, $[\alpha]^{20}_D = -8.9°$ (*c* 1.85, $CHCl_3$), 87% ee, based on the optimum $[\alpha]_D$ value of the *R* enantiomer.

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Supporting Information Available: A description of experimental procedures for the synthesis of compounds **2**, **3**, (*R*)-**3**, and (*S*)-**3** through asymmetric dihydroxylation along with ^1H and ^{13}C NMR spectra of compounds **2**, **3**, (*S*)-**4**, and **1** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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