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Novel Chemoenzymatic Strategy for the Synthesis of Enantiomerically Pure Secondary Alcohols with Sterically Similar Substituents

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A novel chemoenzymatic strategy for the synthesis of enantiomerically pure secondary alcohols with sterically similar substituents is described. The key step is the kinetic lipase-catalyzed resolution of racemic mixtures of substituted propargylic alcohols. The efficiency of this new approach was tested in the preparation of the corresponding enantiomers of 1,11-hexadecandiol derivatives ((*R*)-**5** and (*S*)-**5**). Two strategies were tested. In the first one, the racemic intermediate 1-octyn-3-ol (**1**) was resolved enzymatically and then elongated with 1-bromo-9,11-dioxadodecane. Alternatively, the racemic **1** can be elongated to the corresponding racemic 17,19-dioxa-7-eicosyn-6-ol (**3**) first and then resolved biocatalytically. Twelve commercially available lipases were screened for the kinetic resolution of these intermediates. Among them, *Candida antarctica* lipase (CAL-B) and *Humicola lanuginosa* lipase (HLL) were the best biocatalysts for the resolution of **1** (*S* enantiomer 90% ee, $E = 35$), and **3** (*R* enantiomer 90% ee, $E = 34$), respectively.

Introduction

Our ongoing research interest in the study of the stereospecificities of insect desaturases involved in the sex pheromone biosynthesis[1−3] requires the preparation of chiral deuterium-labeled fatty acids as probes. For preparation of pure enantiomers of the monodeuterated acids, we have used chiral alcohols as intermediates with subsequent replacement of the hydroxyl group by the deuterium label. Chiral alcohols were obtained by kinetic enzymatic resolution of the corresponding racemic precursors with lipases[1] or from HPLC-purified diastereomeric α-methoxy-α-trifluoromethylphenyl (MTPA), (*S*)-(+)-acetoxyphenylacetate ((*S*)-(+)-APA) or α-methoxy-α-(9-anthryl)-acetate esters ((*R*)-(−)-9-AMA).[3] However, biocatalytic and/or chromatographic racemic resolutions became more difficult when the hydroxyl group was displaced toward the middle position of the aliphatic chain and the chain length was enlarged, making both approaches completely useless for preparation of the required enantiomerically pure compounds.

In a series of experiments on the lipase-catalyzed resolution of C-13 aliphatic secondary alcohols, we reported that when the ratios of the lengths of both aliphatic secondary alcohol substituents were 4/8 or 3/9, the enzymatic enantiomeric resolution was almost negligible.[3] Hence, the preparation of these type of enantiomerically pure aliphatic secondary alcohols and their derivatives cannot be achieved directly from the resolution of the corresponding racemates.

To solve this problem we have developed a general methodology by combining the reduced steric requirements of the acetylenic moiety for enzymatic chiral discrimination and the chemical versatility of this group for its easy conversion to aliphatic chains. The synthetic strategy we propose starts with commercially available racemic mixtures of substituted secondary propargylic alcohols. The approach is based on the previous experimental evidence that unsaturated substituents in the hydroxymethine functionality enhanced the enantioselectivity of some lipases.[4−8]

The efficiency of this new approach was tested in the preparation of the corresponding enantiomers of 1,11-hexadecandiol derivatives ((*R*)-**5** and (*S*)-**5**). This chiral alcohol represents a challenge for resolution due to the steric similarity of the two aliphatic moieties. Moreover, its preparation is also of our current interest for the stereo- and cryptoregiochemical (i.e., initial side of oxidation) studies on Δ^{11} and Δ^{13} desaturases of the pine processionary moth (*Thaumetopoea pityocampa*). The

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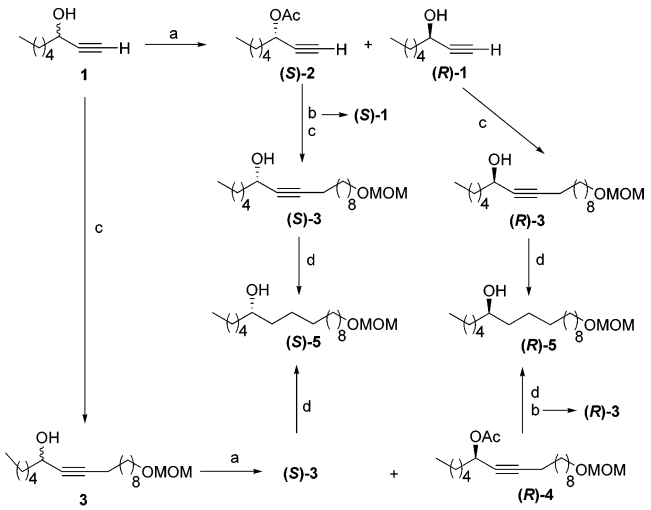
SCHEME 1[a]



[a] (a) Lipase adsorbed onto EP100, vinyl acetate, diisopropyl ether, 25 °C; (b) K_2CO_3/MeOH; (c) BuLi/Br$(CH_2)_8$OMOM/THF/HMPA; (d) H_2, Rh/Al_2O_3, EtOH.

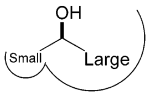


FIGURE 1. Schematic representation of the empirical Kazlauskas rule to predict which enantiomer of the secondary alcohol reacts faster in enzymatic resolution by lipases.

results obtained with this novel methodology were compared with those of the direct lipase-catalyzed resolution of the corresponding saturated alcohol.

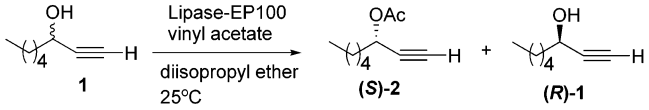
Results and Discussion

In the synthetic strategy devised (Scheme 1), the kinetic enzymatic resolution of the propargyl alcohol **1** was first attempted. Considering the structural substrate requirements for the stereoselective catalysis by a number of lipases, a medium-sized substituent (Figure 1) such as the ethynyl group can be appropriate for the enantiomeric resolution.[9,10] Furthermore, we were also interested in investigating if the racemic secondary alcohol **3**, with the acetylenic functionality near to the stereogenic center, could be effectively resolved by lipases to avoid any risk of possible racemization during the elongation of enantiopure compound (*R*)-**1** or (*S*)-**1**.

Twelve commercially available lipases from different origins were screened as catalyst for the enantioselective acylations of the substituted propargylic alcohol **1**. Lipases were adsorbed onto porous polypropylene material (EP100) to increase their catalytic efficiency in organic media.[1,11] The specific activity of each immobilized lipase was assessed using the acylation of 1-dodecanol as model reaction (see the values in Experimental Section). The amount of immobilized preparation used for each reaction (50−150 mg) was conveniently modulated to achieve 35−45% substrate conversion between 2 and 72 h of reaction time. The units (U) of lipase used in each incubation, according to the test developed in this work, are listed in Tables 1 and 2.

The results for the resolution of **1**, summarized in Table 1, revealed that all lipases tested follow the Kazlauskas

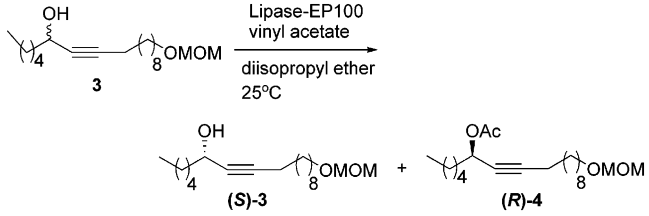
TABLE 1. Lipase-Catalyzed Enantioselective Acylation of 1-Octyn-3-ol (1)



entry	lipase[a]	units[b]	conversion (%)	(*S*)-**2** ee (%)[d]	reaction time (h)	*E*[g]
1	RML	64	35	20	72	2
2	CRL	2	25	30[e]	24	2
3	PCL	24	30	34	2	2
4	CAL-B	252	40	90[f]	2	35
5	RML-IM	27	20	64	72	5
6	PPL	3	*c*		72	
7	ANL	0.2	14	0	96	1
8	ROL	8	45	56	24	6
9	RAL	8	40	44	72	3
10	RNL	2	36	48	144	4
11	MJL	9	20	68	72	6
12	HLL	30	35	40	24	2

[a] RML: *Mucor miehei*. CRL: *Candida rugosa*. PCL: *Pseudomonas cepacia*. CAL-B: *Candida antarctica* (Novozyme 435). RML-IM: *Rhizomucor miehei* (Lipozyme IM). PPL: Porcine pancreas. ANL: *Aspergillus niger* (lipase A, Amano). ROL: *Rhizopus oryzae*. RAL: *Rhizopus arrhizus*. RNL: *Rhizopus niveus*. MJL: *Mucor javanicus*. HLL: *Thermomyces lanuginosus*. [b] Units of lipase used (see Experimental Section). [c] No activity was observed. [d] The enantiomeric excesses were calculated by ^{1}H NMR spectroscopy after derivatization with (*R*)-(−)-MPA and comparison with authentic samples of (*S*)-**7** and (*R*)-**7** (Figure 2). [e] The ee corresponds to the (*R*)-**2** enantiomer. [f] 85% ee of the recovered (*R*)-alcohol. [g] Enantiomeric ratio.

TABLE 2. Lipase-Catalyzed Enantioselective Acylation of 3



entry	lipase[a]	units[b]	conversion (%)	(*R*)-**4** ee (%)[d]	reaction time (h)	*E*[e]
1	RML	64	40	60	72	6
2	CRL	4	40	20	72	2
3	PCL	12	40	58	24	5
4	CAL-B	758	40	72	12	10
5	RML-IM	27	20	0	72	1
6	PPL	3	c		72	
7	ANL	0.2	40	50	96	4
8	ROL	8	50	40	24	3
9	RAL	8	40	62	72	6
10	RNL	2	30	46	144	3
11	MJL	9	11	38	72	2
12	HLL	30	40	90	24	34

[a] Abbreviations as indicated in Table 1. [b] Units of lipase used (see Experimental Section). [c] No activity was observed. [d] The enantiomeric excesses were calculated by ^{1}H NMR spectroscopy after derivatization with (*R*)-(−)-MPA and comparison with the authentic samples of (*S*)-**8** and (*R*)-**8** (Figure 2). [e] Enantiomeric ratio.

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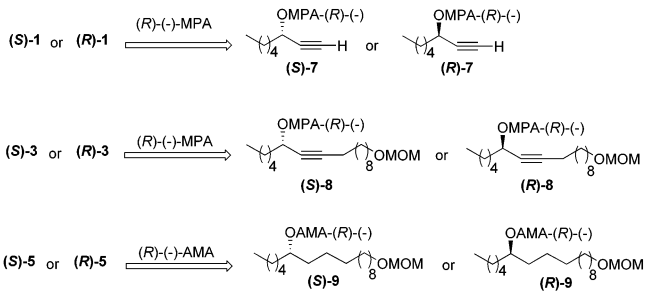
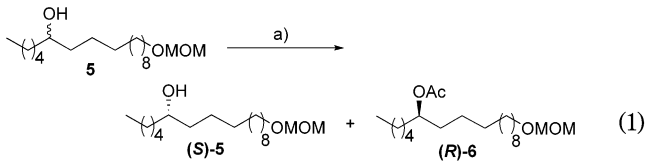


FIGURE 2. Different esters used for evaluation of enantiomeric excesses.

rule[12,13] (Figure 1), and therefore the (*S*)-**1** enantiomer was acetylated faster than the (*R*)-**1**. However, the reverse situation was found using CRL (Table 1, entry 2). All of the active lipases showed different degrees of enantioselectivity. Among them, CAL-B gave by far the best enantiomeric excesses and yields (Table 1 entry 4) and therefore the highest *E* values for both (*S*)-**1** and (*R*)-**1** derivatives. This result agrees with the high selectivity observed by this lipase in the discrimination of enantiomers of a variety of unsaturated secondary alcohols.[9,10,14] Similarly to the findings reported by Burgess and Jennings,[13] PCL gave poor enantiomeric resolution for this compound (Table 1, entry 3). Moreover, no reaction was observed with PPL (Table 1, entry 6), although other authors have reported its ability to resolve enantiomeric mixtures of other propargylic 2-alkanols.[15,16]

After resolution the alkyl chain was incorporated by reaction with 1-bromo-9,11-dioxadodecane to give (*S*)-**3** and (*R*)-**3**. No racemization was observed during this reaction as demonstrated by ^{1}H NMR after derivatization with (*R*)-(−)-α-methoxyphenylacetic acid (MPA)[17] and comparison with authentic samples of (*S*)-**8** and (*R*)-**8** (Figure 2). Catalytic hydrogenation was first attempted with $LiAlH_4$, Pd/C, and Wilkinson catalysts. No reduction was observed in the former case using THF as solvent at room temperature. In the latter two cases, 25−30% formation of a saturated ketone and, using Pd/C, an additional 10−15% of aliphatic product were obtained. Fortunately, Rh (5%)/Al_2O_3 in ethanol[18] furnished the saturated secondary alcohols (*S*)-**5** and (*R*)-**5** in 90% isolated yield (90% and 85% ee, respectively) with only 8−10% of the corresponding saturated ketone. The optical purity was also maintained in this step as observed by ^{1}H NMR spectra of the corresponding (*R*)-(−)-AMA derivatives and comparison with authentic samples of (*S*)-**9** and (*R*)-**9** (Figure 2). The authentic samples described in this work were prepared from commercially available (*S*)-**1** and (*R*)-**1** by the same sequence of chemical reactions depicted in Scheme 1.

As indicated above, our next interest was to assess if the racemic mixture of **3** can also be resolved enzymatically. To this end, the lipases were screened as putative biocatalysts for the enantioselective acylation of **3** under similar reaction conditions. The results obtained are summarized in Table 2. Again, in good agreement with the Kazlauskas rule, the acylation of the (*R*)-**3** enantiomer was faster than that of the corresponding (*S*)-**3**. In this case, acylation of **3** with HLL (Table 2, entry 12) gave 90% enantiomeric excess with an *E* value greater than 20, which make this approach suitable for a practical preparation of (*R*)-**3** and (*S*)-**3**[19] alcohols. CAL-B gave poor selectivity ($E = 10$) (Table 2, entry 4), probably because of the relative size of the substituents. It has been reported that CAL-B is more enantioselective when the medium-size substituent (Figure 1) is relatively small.[10] The difference between the enantiomeric excesses of compounds (*S*)-**2** and (*R*)-**4** (Tables 1 and 2, entry 4) is consistent with this observation. Catalytic hydrogenation of the resolved unsaturated alcohols (*R*)-**3** and (*S*)-**3** was carried out as described above.



(a) Lipase adsorbed onto EP-100, vinyl acetate, diisopropyl ether, 25°C

For the sake of comparison, the corresponding racemic saturated alcohol **5** was also tested for resolution by lipases (eq 1). Experiments were performed under identical conditions as used for the resolution of alcohol **3**. Among the lipases screened, CAL-B, RNL, MJL, and HLL gave low activities (10% conversion after 48 h) and negligible enantiomeric excesses (<5% ee). CRL and PCL were the most active lipases for acylation of **5**, affording conversions of 25% (48 h) and 40% (3 h), respectively. Nevertheless, only CRL gave a slight differentiation of both enantiomers (10% ee). In this case, the acylation of the (*S*)-**5** enantiomer was faster than that of the (*R*)-**5**; therefore, it did not follow the Kazlauskas rule. It is likely that this may happen when the sizes of both substituents are very similar.[10] Hence, the introduction of a triple bond functionality, near the stereogenic center of the molecule, improved greatly both the enantiomeric excesses and reactivity compared with the saturated alcohol. These results suggest that electronic and/or steric effects induced by the acetylenic functionality may enhance both the substrate reactivity and the differentiation of the enzymatic acylation rates between both enantiomers.

The procedure described in this paper appears to be an advantageous alternative when compared to other chemical methods of production of enantiomerically pure secondary alcohols such as reduction of alkynones by chiral borane reagents.[20] Likewise, we think that the present enzymatic approach could be easily extrapolated to the preparation of chiral homopropargyl[21] alcohols that

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have been used as precursors of chiral fluorinated synthons in mechanistic studies of fatty acid biomodification.[22]

Conclusions

A novel chemoenzymatic methodology was developed for the synthesis of enantiopure secondary alcohols with sterically similar substituents. Two strategies were devised starting with racemic mixtures of propargylic alcohol derivatives. Both strategies differed on the enzymatic resolution step. In the first one, the propargylic alcohol **1** was resolved efficiently using CAL-B as catalyst. In the second one, the resolution was performed after the alkyl chain incorporation using HLL lipase as catalyst. Then, catalytic hydrogenation of the alkynyl functionality using Rh/Al_2O_3 as catalyst furnished the corresponding saturated secondary alcohol with 90% ee for both enantiomers. Work is in progress to synthesize other secondary alcohols with ee ≥90% in other positions in the hydrocarbon aliphatic chain. It should be emphasized that the present methodology has a potential broad scope for the synthesis of novel mechanistic probes, in accordance with the growing interest in understanding the highly selective oxidation chemistry of fatty acid desaturases.[23,24]

Experimental Section

General Methods. Commercial grade reagents and solvents were directly used as supplied with the following exceptions: tetrahydrofuran (THF) and CH_2Cl_2 were distilled over Na/benzophenone and CaH_2, respectively, under argon atmosphere; anhydrous diisopropyl ether was stored under argon atmosphere. Reactions sensitive to moisture and oxygen were carried out under argon or nitrogen atmosphere. Unless otherwise stated, organic solutions obtained from workup of crude reaction mixtures were dried over anhydrous $MgSO_4$, purification procedures were carried out by flash chromatography on silica gel (230−400 mesh), and products were mostly obtained as oils. Visualization of UV-inactive materials was accomplished by soaking the TLC plates in an ethanolic solution of *p*-anisaldehyde and sulfuric acid (v/v/v, 96:2:2) or in an ethanolic solution of phosphomolybdic acid (5%). Polypropylene EP100 (particle size 200−400 μm; mean pore diameter 900 nm; specific surface area BET method 78 $m^2\ g^{-1}$) was used as support for enzyme immobilization.

All ^1H NMR spectra were acquired at 300 MHz, and ^{13}C NMR spectra at 75 MHz, in freshly neutralized $CDCl_3$ solutions, and chemical shifts are given in ppm downfield from $Si(CH_3)_4$ for ^1H and $CDCl_3$ for ^{13}C. GC−MS was performed by chemical ionization (CI), using methane as ionization gas, on a GC coupled to a mass detector. The system was equipped with capillary column HP5-MS 30 m, 0.25 mm internal diameter and 0.25 μm stationary phase thickness. All IR spectra were run in film. Elemental analyses were obtained in the Microanalysis Service of IIQAB-CSIC. Enantiomeric excesses (ee) were calculated by ^1H NMR spectroscopy of the corresponding (*R*)-(−)-MPA diastereomeric esters of the unsaturated alcohols (*S*)-**1**, (*R*)-**1**, (*S*)-**3**, and (*R*)-**3** and (*R*)-(−)-9-AMA diastereomeric esters of the saturated alcohols (*S*)-**5** and (*R*)-**5.** Optical rotations were determined at 25 °C in $CHCl_3$ solution at the specified concentration (g/100 mL). (*R*)-(−)-9-AMA (97% ee) was prepared by the procedure described by Latypov et al.[17,25]

Enzymes. *Aspergillus niger*, lipase A (ANL) (136 000 U g^{-1} Amano's method), and *Pseudomonas cepacia*, lipase PS (PCL) (32 100 U g^{-1} Amano's method) were a generous gift of Amano Pharmaceuticals Co. Ltd. (Nagoya, Japan). *Candida antarctica* lipase, Novozym 435 (CAL-B) (7000 PLU g^{-1}, PLU: propyl laurate units) and *Rhizomucor miehei* lipase, Lipozyme IM (RML) (5−6 BAUN g^{-1}, BAUN: batch acidolysis units Novo) were a generous gift of Novozymes A/S (Bagsvaerd, Denmark). *Candida rugosa* lipase (CRL) (724 U/mg solid), *Thermomyces lanuginosus* lipase (HLL) (Novozyme 871L) (50,000 U/g), and porcine pancreatic lipase (PPL) Type II, crude (60 U/mg), and lipases from *Rhizopus oryzae* (ROL) (13.4 U/mg), *Rhizomucor miehei* (RML) recombinant from *Aspergillus oryzae* (9.0 U/mg), *Rhizopus niveus* (RNL) (1.7 U/mg), *Rhizopus arrhizus* (RAL) (2.2 U/mg), and *Mucor javanicus* (MJL) (10 U/mg) were obtained commercially.

Enzyme Deposition. Adsorption onto polypropylene support (EP100) was carried out following the methodology described by Gitlesen et al.[11] The lipase (1 g) was dissolved in aqueous phosphate buffer (20 mL, 0.1 M, pH 7.0) and mixed with the solid support EP100 (1 g), containing ethanol/water (3 mL), 24:1 v/v. The mixture was shaken reciprocally (120 rpm) over 24 h at 25 °C. After this period, the enzyme-support preparation was filtered off and dried under vacuum until a constant weight was obtained. *Candida antarctica* (CAL-B) and *Rhizomucor miehei* (RML-IM) lipases were supplied as immobilized preparations on a macroporous acrylic resin and macroporous anion-exchange resin, respectively.

The activity of each immobilized lipase preparation was measured using the acylation of 1-dodecanol in organic media. 1-Dodecanol (18.6 mg, 0.10 mmol) and vinyl acetate (15 μL, 0.16 mmol) were dissolved in anhydrous diisopropyl ether (2 mL). To this solution was added immobilized lipase preparation (1−20 mg depending on the experiment). The reaction was followed by gas chromatography analysis until a substrate conversion around 20%. The activity was calculated from the slope of the linear interval of the time concentration curves. Unit definition: 1 Unit corresponds to the amount of enzyme, which converts 1 μmol of dodecyl acetate from 1-dodecanol and vinyl acetate (0.2 mmol) in anhydrous diisopropyl ether at 25 °C. The specific activities (U mg^{-1} immobilized preparation) of the immobilized preparations were the following: RML, 0.64; CRL, 0.04; PCL, 0.24; CAL-B, 5.05, RML-IM, 0.27, PPL, 0.03, ANL, 0.002; ROL, 0.16; RAL, 0.08; RNL, 0.024; MJL, 0.09 and HLL, 0.30.

8-Bromo-1-octanol and **1-bromo-9,11-dioxadodecane ($Br(CH_2)_8OMOM$)** were prepared according to previously described procedures.[3,26,27]

Preparation of 17,19-Dioxa-7-eicosyn-6-ol (3). To a mixture of 1-octyn-3-ol (253 mg, 2 mmol), 3 mL of dry HMPA, and 3 mL of THF was added dropwise a solution of butyllithium (1.6 M) in hexanes (2.6 mL, 4.2 mmol) at −10 °C. After 10 min a solution of $Br(CH_2)_8OMOM$ (252 mg, 1 mmol) in 1 mL of THF was added dropwise. Stirring was continued overnight at 0 °C. The reaction mixture was then poured into saturated $NaHCO_3$ (5 mL) and extracted with hexane (3 × 4 mL). Solvent was evaporated, and the residue was purified by flash chromatography on silica gel using a gradient hexane/MTBE (0−30%) to afford 208 mg of the expected alcohol **3** in 70% yield: IR 3445, 2930, 2855, 1460, 1130, 1110, 1050, 920 cm^{-1}; ^1H NMR δ 4.62 (s, 2H), 4.35 (m, 1H), 3.52 (t, J = 6.5 Hz, 2H), 3.36 (s, 3H), 2.20 (dt, J_1 = 7 Hz, J_2 = 2 Hz, 2H), 1.81 (bs, 1H), 1.72−1.20 (24H), 0.90 (t, J = 7 Hz, 3H); ^{13}C NMR δ

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96.3, 85.4, 81.4, 67.8, 62.7, 55.1, 38.2, 31.5, 29.7, 29.2, 29.0, 28.7, 28.6, 26.1, 24.9, 22.6, 18.6, 14.0; MS *m*/*z* (CI) 281 ($M^{+\bullet}$ + 1 − H_2O, 5), 267 (10), 249 (40), 237 (20), 149 (25), 135 (25), 123 (30), 109 (30), 95 (50), 83 (100), 81 (50), 71 (40), 67 (35), 45 (55). Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found: C, 72.45; H, 11.68.

Preparation of 17,19-Dioxaeicosan-6-ol. (5). A mixture of compounds **3** (30 mg, 0.1 mmol) and 4 mg of Rh/Al_2O_3 (5%) in MeOH was stirred under hydrogen atmosphere (1 atm) for 6 h and then filtered through Celite. The filtrate was concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel using a solvent gradient of MTBE in hexane (0−30%) to afford 27 mg of the saturated alcohol **5** (90%): IR 3445, 2930, 2855, 1460, 1130, 1110, 1050, 920 cm $^{-1}$; ^{1}H NMR δ 4.62 (s, 2H), 4.35 (m, 1H), 3.52 (t, J = 6.5 Hz, 2H), 3.36 (s, 3H), 2.20 (dt, J_1 = 7 Hz, J_2 = 2 Hz, 2H), 1.81 (bs, 1H), 1.72−1.20 (24H), 0.90 (t, J = 7 Hz, 3H); ^{13}C NMR δ 96.3, 85.4, 81.4, 67.8, 62.7, 55.1, 38.2, 31.5, 29.7, 29.2, 29.0, 28.7, 28.6, 26.1, 24.9, 22.6, 18.6, 14.0; MS (CI) *m*/*z* 285 ($M^{+\bullet}$ + 1 − H_2O, 5), 253 (45), 241 (25), 239 (25), 199 (30), 169 (15), 151 (25), 139 (20), 137 (25), 123 (40), 111 (55), 109 (45), 97 (75), 83 (100), 69 (62), 45 (70). Anal. Calcd for $C_{18}H_{38}O_3$: C, 71.47; H, 12.66. Found: C, 71.33; H, 12.89.

Kinetic Resolution of Alcohols. Reactions were performed in 4-mL screw-capped flat bottom vials. To a mixture of the racemic alcohol (0.05 mmol) and inmobilized lipase (50−150 mg) in 1 mL of diisopropyl ether was added vinyl acetate (14 μL, 0.15 mmol). The resulting mixture was shaken reciprocally (125 rpm) at 25 °C. Reaction evolution was followed by GC. At the desired conversion, the reaction mixture was filtered off, the solid was washed with Et_2O, and the solvent was evaporated under vacuum to give a residue that was purified by column chromatography on silica gel. A gradient of MTBE in hexane (0−30%) allowed the separation of the acetate from alcohol. Experiments were repeated twice.

3-Acetoxy-1-octyne (2). IR 3295, 2955, 2935, 2865, 1745 (CO), 1450, 1375, 1235, 1025 cm $^{-1}$; ^{1}H NMR δ 5.34 (dt, J_1 = 7 Hz, J_2 = 2 Hz, 1H), 2.45 (d, J = 2 Hz, 1H), 2.09 (s, 3H), 1.82−1.71 (2H), 1.52−1.38 (2H), 1.38−1.22 (2H), 0.90 (t, J = 7 Hz, 3H); ^{13}C NMR δ 169.9, 81.3, 73.3, 63.8, 39.7, 34.5, 31.2, 24.5, 22.4, 20.9, 17.7, 13.9; MS *m*/*z* 169 (M^+ + 1, 5), 155 (6), 127 (50), 109 (100), 89 (30).

6-Acetoxy-17,19-dioxa-7-eicosyne (4). IR 3445, 2930, 2855, 1460, 1130, 1110, 1050, 920 cm $^{-1}$; ^{1}H NMR δ 5.35 (tt, J_1 = 7 Hz, J_2 = 2 Hz, 2H), 3.52 (t, J = 6.5 Hz, 2H), 3.36 (s, 3H), 2.20 (dt, J_1 = 7 Hz, J_2 = 2 Hz, 2H), 2.07 (s, 3H), 1.76−1.64 (2H), 1.64−1.20 (18H), 0.89 (t, J = 7 Hz, 3H); ^{13}C NMR δ 170.1, 96.3, 86.1, 77.7, 67.8, 64.6, 55.0, 35.0, 31.2, 29.7, 29.3, 29.0, 28.7, 28.4, 26.1, 24.7, 22.5, 21.1, 18.6, 14.0; MS *m*/*z* 340 ($M^{+\bullet}$, 2), 339 ($M^{+\bullet}$ − 1, 4), 308 (5), 281 (15), 267 (15), 249 (85), 231 (15), 149 (20), 135 (25), 123 (30), 109 (25), 95 (35), 81 (28), 71 (25), 61 (100), 45 (55).

6-Acetoxy-17,19-dioxaeicosane (6). IR 2930, 2860, 1735, 1465, 1370, 1240, 1150, 1110, 1045, 920 cm $^{-1}$; ^{1}H NMR δ 4.86 (quint, J = 6 Hz, 1H), 4.62 (s, 2H), 3.52 (t, J = 6.5 Hz, 2H), 3.36 (s, 3H), 2.04 (s, 3H), 1.59 (m, 2H), 1.50 (m, 2H) 1.44−1.18 (22H), 0.88 (t, J = 7 Hz, 3H); ^{13}C NMR δ 171.0, 96.4, 74.4, 67.9, 62.7, 55.1, 34.1, 34.1, 31.7, 29.7, 29.5, 29.4, 26.2, 25.3, 25.0, 22.5, 21.3, 14.0; MS (CI) *m*/*z* 344 ($M^{+\bullet}$, 4), 253 (65), 239 (15), 222 (10), 181 (15), 151 (25), 137 (30), 123 (30), 111 (50), 97 (55), 83 (85), 71 (55), 61 (80), 45 (100).

Acetate Saponification. Alcohols (0.02 mmol) were regenerated by treatment of the corresponding acetoxy derivative with a mixture of K_2CO_3 (50 mg) in MeOH (2 mL) for 16 h. After neutralization with HCl (1 N), the usual workup and purification by flash chromatography on silica afforded the pure alcohols in quantitative yields.

Aryl Acetic Esters Preparation. Method A. Oxalyl chloride (30 μL, 0.35 mmol) was added to a mixture of (*R*)-(−)-arylacetic acid (0.03 mmol MPA or 9-AMA) and DMF (4 μL, 0.06 mmol) in dry hexane (10 mL) under argon atmosphere at room temperature. After 24 h, the solvent was evaporated to dryness at reduced pressure. The residue was dissolved in dry CH_2Cl_2 (350 μL) and added to a mixture of the alcohol (0.02 mmol), dry Et_3N (10 μL, 0.14 mmol), and DMAP (2 mg, 0.02 mmol). After 2 h of stirring at room temperature, the solvent was removed under vacuum. **Method B.** Carbodiimide (0.14 mmol) was added to a mixture of alcohol (0.01 mmol), DMAP (0.014 mmol), and (*R*)-(−)-arylacetic acid (0.016 mmol; MPA, 9-AMA) in dry CH_2Cl_2 (4 mL). The mixture was stirred for 2 h at room temperature, washed with $NaHCO_3$ solution, and concentrated to reduced pressure. In both cases, the residue was purified by flash chromatography on silica gel using a gradient of 0−20% MTBE (methyl *tert*-butyl ether) in hexane (75−90% isolated yields).

Physical data of authentic samples (*S*)-**7**, (*R*)-**7**, (*S*)-**8**, (*R*)-**8**, (*S*)-**9** and (*R*)-**9** are described below. Delta (δ) values in bold face were used to quantify the diastereomeric excess of the derivatives and therefore to calculate the enantiomeric excesses of the corresponding alcohols.

(*S*)-(−)-3-Oct-1-inyl-(*R*)-(−)-α-*O*-methyl-α-phenyl Acetate (*S*)-7. IR 3290, 2930, 2865, 1755 (CO), 1455, 1170, 1110, 1000 cm $^{-1}$; ^{1}H NMR δ 7.50−7.41 (2H), 7.40−7.30 (3H), 5.40 (dt, J_1 = 6.5 Hz, J_2 = 2 Hz, 1H), 4.80 (s, 1H), **3.43** (s, 3H), 3.38 (s, 3H), **2.46** (d, J = 2 Hz, 1H), 1.67 (m, 2H), 1.25−1.10 (6H), 0.80 (t, J = 6.5 Hz, 3H); ^{13}C NMR δ 169.6, 136.0, 128.8, 128.6, 127.2, 82.2, 80.7, 73.8, 64.3, 57.4, 34.3, 30.9, 24.0, 22.3, 13.8; $[\alpha]_D$ = −99.0 (*c* 1, 98% de).

(*R*)-(+)-3-Oct-1-inyl-(*R*)-(−)-α-*O*-methyl-α-phenyl Acetate (*R*)-7. IR 3290, 2930, 2865, 1755 (CO), 1455, 1170, 1110, 1000 cm $^{-1}$; ^{1}H NMR 7.50−7.42 (2H), 7.42−7.30 (3H), 5.39 (dt, J_1 = 6.5 Hz, J_2 = 2 Hz, 1H), 4.80 (s, 1H), **3.44** (s, 3H), **2.37** (d, J = 2 Hz, 1H), 1.77 (m, 2H), 1.45−1.18 (6H), 0.87 (t, J = 6.5 Hz, 3H); ^{13}C NMR δ 169.8, 135.7, 128.7, 128.6, 127.1, 82.6, 80.4, 73.9, 64.6, 57.4, 34.4, 31.1, 24.4, 22.4, 13.9; $[\alpha]_D$ = −10.8 (*c* 0.5, 98% de).

(*S*)-(−)-17,19-Dioxa-6-eico-7-inyl-(*R*)-(−)-α-*O*-methyl-α-phenyl Acetate (*S*)-8. IR 2930, 2860, 1755 (CO), 1455, 1245, 1200, 1110, 1050 cm $^{-1}$; ^{1}H NMR δ 7.48−7.43 (2H), 7.42−7.28 (3H), 5.40 (tt, J_1 = 6.5 Hz, J_2 = 2 Hz, 1H), 4.78 (s, 1H), 4.62 (s, 2H), 3.52 (t, J = 6.5 Hz, 2H), **3.42** (s, 3H), 3.36 (s, 3H), **2.18** (dt, J_1 = 7 Hz, J_2 = 2 Hz, 2H), 1.68−1.42 (6H), 1.42−1.22 (8H), 1.22−1.12 (6H), 0.80 (t, J = 7 Hz, 3H); ^{13}C NMR δ 169.7, 136.2, 128.7, 128.5, 127.3, 96.4, 86.6, 82.4, 77.3, 67.8, 65.2, 57.3, 55.1, 34.9, 31.0, 29.7, 29.3, 29.0, 28.7, 28.4, 26.2, 24.3, 22.3, 18.6, 13.8; $[\alpha]_D$ = −44.4 (*c* 1, 92% de).

(*R*)-(+)-17,19-Dioxa-6-eico-7-inyl-(*R*)-(−)-α-*O*-methyl-α-phenyl Acetate (*R*)-8. IR 2930, 2860, 1755 (CO), 1455, 1245, 1200, 1110, 1050 cm $^{-1}$; ^{1}H NMR δ 7.49−7.42 (2H), 7.42−7.28 (3H), 5.38 (tt, J_1 = 6.5 Hz, J_2 = 2 Hz, 1H), 4.78 (s, 1H), 4.63 (s, 2H), 3.52 (t, J = 6.5 Hz, 2H), **3.43** (s, 3H), 3.36 (s, 3H), **2.10** (dt, J_1 = 7 Hz, J_2 = 2 Hz, 2H), 1.80−1.65 (2H), 1.65−1.50 (2H), 1.46−1.16 (16H), 0.87 (t, J = 7 Hz, 3H); ^{13}C NMR δ 169.9, 135.9, 128.6, 128.5, 127.1, 96.3, 86.5, 82.6, 76.9, 67.8, 65.5, 57.3, 55.0, 34.8, 31.1, 29.7, 29.3, 29.0, 28.6, 28.3, 26.2, 24.6, 22.4, 18.5, 13.9; $[\alpha]_D$ = +11.4 (*c* 1, 96% de).

(*S*)-17,19-Dioxa-6-eicosyl-(*R*)-(−)-α-methoxy-α-(9-anthryl)-acetate (*S*)-9. IR 2930, 2860, 1745 (CO), 1465, 1115, 1045 cm $^{-1}$; ^{1}H NMR δ 8.58 (d, J = 9 Hz, 2H), 8.47 (s, 1H), 8.01 (d, J = 9 Hz, 2H), 7.60−7.40 (4H), 6.26 (s, 1H), 4.86 (m, 1H), **4.63** (s, 2H), 3.52 (t, J = 6.5 Hz, 2H), 3.42 (s, 3H), **3.37** (s, 3H), 1.60 (2H), 1.50−1.10 (18H), 1.04 (2H), 0.78−0.50 (2H), 0.53 (t, J = 6.5 Hz, 3H), 0.29 (2H); ^{13}C NMR δ 171.1, 131.4, 130.5, 129.0, 129.0, 127.6, 126.3, 124.9, 124.5, 96.3, 77.2, 75.5, 67.8, 57.4, 55.1, 33.8, 33.4, 31.1, 29.7, 29.5, 29.4, 29.4, 26.2, 25.3, 23.7, 22.0, 13.7; $[\alpha]_D$ = −84.0 (*c* 1, 94% de).

(*R*)-17,19-Dioxa-6-eicosyl-(*R*)-(−)-α-methoxy-α-(9-anthryl)-acetate (*R*)-9. IR 2930, 2855, 1745 (CO), 1465, 1450, 1115, 1045 cm $^{-1}$; ^{1}H NMR δ 8.57 (d, J = 9 Hz, 2H), 8.47 (s, 1H), 8.01 (d, J = 9 Hz, 2H), 7.58−7.42 (4H), 6.26 (s, 1H), 4.86 (m, 1H), **4.64** (s, 2H), 3.54 (t, J = 6.5 Hz, 2H), 3.42 (s, 3H), **3.38** (s, 3H), 1.60 (2H), 1.50−0.96 (18H), 0.86 (t, J = 6.5 Hz, 3H), 0.59 (4H), 0.29 (2H); ^{13}C NMR δ 171.1, 131.4, 130.5, 129.0, 129.0, 127.6, 126.3, 124.9, 124.5, 96.4, 77.2, 75.4, 67.9, 57.4,

55.1, 33.8, 33.4, 31.6, 29.8, 29.5, 29.4, 29.2, 29.0, 28.9, 26.2, 25.0, 24.1, 22.5, 14.0; $[\alpha]_D = -94.2$ (*c* 1, 92% de).

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Supporting Information Available: ^{1}H and ^{13}C and DEPT spectra for compounds **2**−**6**, (*S*)-**7**, (*R*)-**7**, (*S*)-**8**, (*R*)-**8**, (*S*)-**9**, and (*R*)-**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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