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Kinetic resolution of (±)-5-bromo-12-oxa-pentacyclo-[6.2.1.1^{6,9}.0^{2,7}.0^{2,10}]dodeca-4-ene-3-*endo*-ol and (±)-5-bromo-13-oxa-pentacyclo[6.2.2.1^{6,9}.0^{2,7}.0^{2,10}]-trideca-4-ene-3-*endo*-ol via *Pseudomonas*-mediated lipase-catalyzed transesterification

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Abstract—The kinetic resolutions of alcohols **1** and **2** were performed using three different types of lipases. From this screening, the high ability of Lipase PS-C 'Amano' I in the resolution of these compounds was observed. The transesterification of the racemic alcohol **1** lead to the acetate (−)-**3** with 42% yield (e.e. >99% by chiral GC) and to the alcohol (+)-**1** with 39% yield after three catalytic cycles (e.e. >99% by chiral GC of the chemically obtained acetate (+)-**3**). The reaction of racemic alcohol **2** lead to the acetate (−)-**4** with 48% yield (e.e. >99% by chiral GC) and to the alcohol (+)-**2** with 32% yield after two catalytic cycles (e.e. >99% by chiral GC). © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Lipases are a class of hydrolases widely distributed among microorganisms, plants and animals. Their natural function is to catalyze the hydrolysis of triacylglycerol ester bonds and/or the synthesis of the same triacylglycerol ester bonds. From an organic chemist's point of view, the primary advantage is that reactions may be carried out in aqueous media, water–organic solvent mixtures or even in anhydrous organic solvents. Depending on the organic medium employed, these enzymes are able to catalyze hydrolysis, esterification, transesterification and interesterification reactions.[1] Among available lipases, those from *Pseudomonas* sp. have been used to enhance kinetic resolutions of ferrocene derivatives,[2] of starting materials for terpenoids and carotenoids synthesis,[3,4] of intermediates for manufacturing Ca^{2+} antagonists and α-blockers[5] and even in the stereoselective synthesis of polyesters[6] and polycarbonates.[7]

Polycyclic compounds are a key research topic with numerous reports in the literature dealing with their theoretical[8,9] and experimental properties.[10,11] Our goal has been to seek new synthetic methodologies for the preparation of these compounds[12–14] and investigate the effects regarding their geometry and steric parameters by NMR spectroscopy.[15–17] On the other hand, we have also focused our attention on the preparation of enantiomerically pure compounds[14] and the development of an adequate analytical method for determining their enantiomeric excess.[18,19] Tetrahydronaphthalene-derived compounds[20,21] and Diels–Alder adducts involving cyclopentadienes and *p*-benzoquinones[22,23] have been used in the synthesis of a series of cyclitols including conduritols, conduramines and derivatives. We have been working on the synthesis of polycyclic analogues of sugar–mimic glycosidase inhibitors and recently, we reported[24] the synthesis and characterization of the nortricyclene derivative 5-bromo-12-oxa-pentacyclo[6.2.1.1^{6,9}.0^{2,7}.0^{2,10}]dodeca-4-ene-3-*endo*-ol **1** and its tridecane analogous **2**.

Motivated by the growing demand for chiral intermediates in the enantiopure form, we here report the lipase-mediated kinetic resolution of model compounds **1** and **2**, using different lipases and vinyl acetate.

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2. Results and discussion

2.1. Kinetic resolution of alcohol (±)-1 and (±)-2

Compounds (±)-**1** and (±)-**2** were obtained in 98 and 80% yield,[24] respectively, from the reduction of the corresponding Diels–Alder adducts.[25,26] In order to obtain kinetic resolution of alcohols **1** and **2**, transesterification reaction between each alcohol and the acyl donor in the presence of different lipases was applied using vinyl acetate as acyl donor and solvent.

Transesterification reactions of alcohol (±)-**1** mediated by *Pseudomonas cepacia* lipase supplied in four different preparations were studied: powder (Lipase PS ‘Amano’), immobilized on ceramic particles (Lipase PS-C ‘Amano’ I), immobilized on ceramic particles chemically modified with methacryl groups (Lipase PS-C ‘Amano’ II) and immobilized on diatomaceous earth (Lipase PS-D ‘Amano’ I). The transesterification reactions mediated by *Pseudomonas fluorescens* lipase (Lipase AK ‘Amano’ 20) and *Candida rugosa* lipase supplied as powder (Lipase AY ‘Amano’ 30) were also investigated. Scheme 1 shows the transesterification reaction of alcohol **1** and Table 1 summarizes the results of these reactions.

All three lipases recognized the same enantiomer of alcohol **1**, producing the same enantiomer of the acetate **3**. With regard to the immobilized lipase from *P. cepacia*, the support change only affected the reaction time. The enantiomeric excess of the acetate was maintained.

Although the enantiomeric ratio[27] (E) values suggest Lipase PS-D ‘Amano’ I as the best enzymatic catalyst for the resolution of alcohol **1**, we favored Lipase PS-C ‘Amano’ I since it presented good chemical conversion to the enantiopure acetate **3** and shorter reaction time. Thus, after chromatographic separation of the enantiomerically pure acetate **3** from the enantiomerically enriched alcohol **1**, we determined the specific rotation values of the pure acetate **3** at 589 and 365 nm in solution of ethyl acetate, chloroform and methanol. These values are listed in Table 2.

After separation, the enantiomerically enriched alcohol **1** was submitted twice to the reaction with lipase PS-C ‘Amano’ I. ^{1}H NMR with the chiral chemical shift reagent (+)-Eu(hfc)$_3$ for direct determination of enantiomeric excess of alcohol **1** was employed. As a standard, 10 mg of the chiral shift reagent was added to a solution of 20 mg/0.5 mL of the alcohol (±)-**1** in $CDCl_3$. It was possible to distinguish the two olefinic hydrogens H_4 of each enantiomer at 7.91 and 7.80 ppm (Fig. 1a). For the reaction product of the three consecutive reactions between alcohol **1** and lipase PS-C ‘Amano’ I only one signal was observed at 7.89 ppm (Fig. 1b) which, after specific rotation determination, was attributed to the olefinic hydrogen H_4 of (+)-**1** enantiomer $[\alpha]_D^{20}=+34$ (c 0.5, EtOAc) and $[\alpha]_{365}^{20}=+60$ (c 0.5, EtOAc) (Table 2).

Our efforts to find reasonable conditions for the resolution of the racemic alcohol **1** by chiral GC did not succeed and a sample of the (+)-**1** was chemically acylated with acetic anhydride and pyridine. This reaction led to the isolation of the corresponding acetate in its enantiopure form observed by chiral GC (t_R 24.6 min). The specific rotations in ethyl acetate solution of acetate (+)-**3** were $[\alpha]_D^{20}=+67$ (c 0.5, EtOAc) and $[\alpha]_{365}^{20}=+189$ (c 0.5, EtOAc) (Table 2).

The sign reversal of the specific rotation [α] of alcohol **1** is of note. Several examples of change in the magnitude of specific rotation with solvent may be found in the literature[28] and have been ascribed mainly to solvation effects. In many instances, hydrogen bonding is know to be responsible for changes in [α] with concentration and/or solvent.[28] In our case, the sign reversal of [α] with solvent suggests that in ethyl acetate and methanol predominate solute–solvent interactions instead of solute–solute interactions which is the case in chloroform.[28]

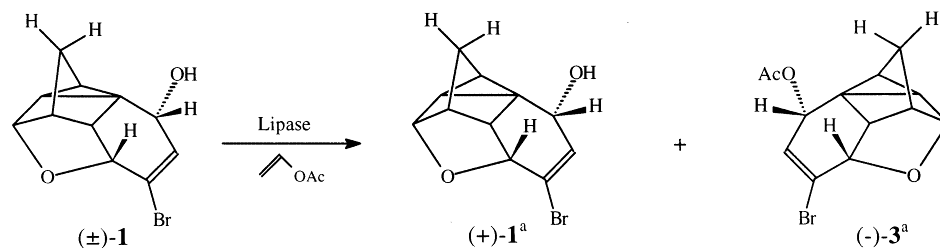
Table 1. Lipase-catalyzed transesterification reactions of alcohol (±)-**1**

Lipase	Reaction time[a] (h)	Chemical conversion to acetate **3** (%) by GC[b,c]
PS ‘Amano’	264	20
PS-C ‘Amano’ I	4	42
PS-C ‘Amano’ II	22	45
PS-D ‘Amano’ I	30	47
AK ‘Amano’ 20	30	21
AY ‘Amano’ 30	72	6.5

[a] Reaction time to achieve the best chemical yield of acetate **3** with the enantiomeric excess >99% (Chiral GC).

[b] The retention time (t_R) of the enantiomers of acetate (±)-**3** were 24.1 and 24.6 min by chiral GC and the t_R of the obtained enantiomer was always 24.1 min.

[c] All E values >100 and they were calculated by Sih's equation.[27]



Scheme 1. (a) Polarimetric measurements using ethyl acetate as solvent.

Table 2. Specific rotation values of enantiomerically pure substrates **1** and **3** in different solvents

Substrate	c (g/100 mL)	Ethyl acetate		Chloroform		Methanol	
		$[\alpha]_D^{20}$	$[\alpha]_{365}^{20}$	$[\alpha]_D^{20}$	$[\alpha]_{365}^{20}$	$[\alpha]_D^{20}$	$[\alpha]_{365}^{20}$
(−)-**1**	0.5	−34	−61	0	+71	−26	−16
(+)-**1**	0.5	+34	+60	0	−70	+26	+15
(−)-**3**	0.5	−68	−190	−56	−164	−58	−168
(+)-**3**	0.5	+67	+189	+57	+164	+58	+167

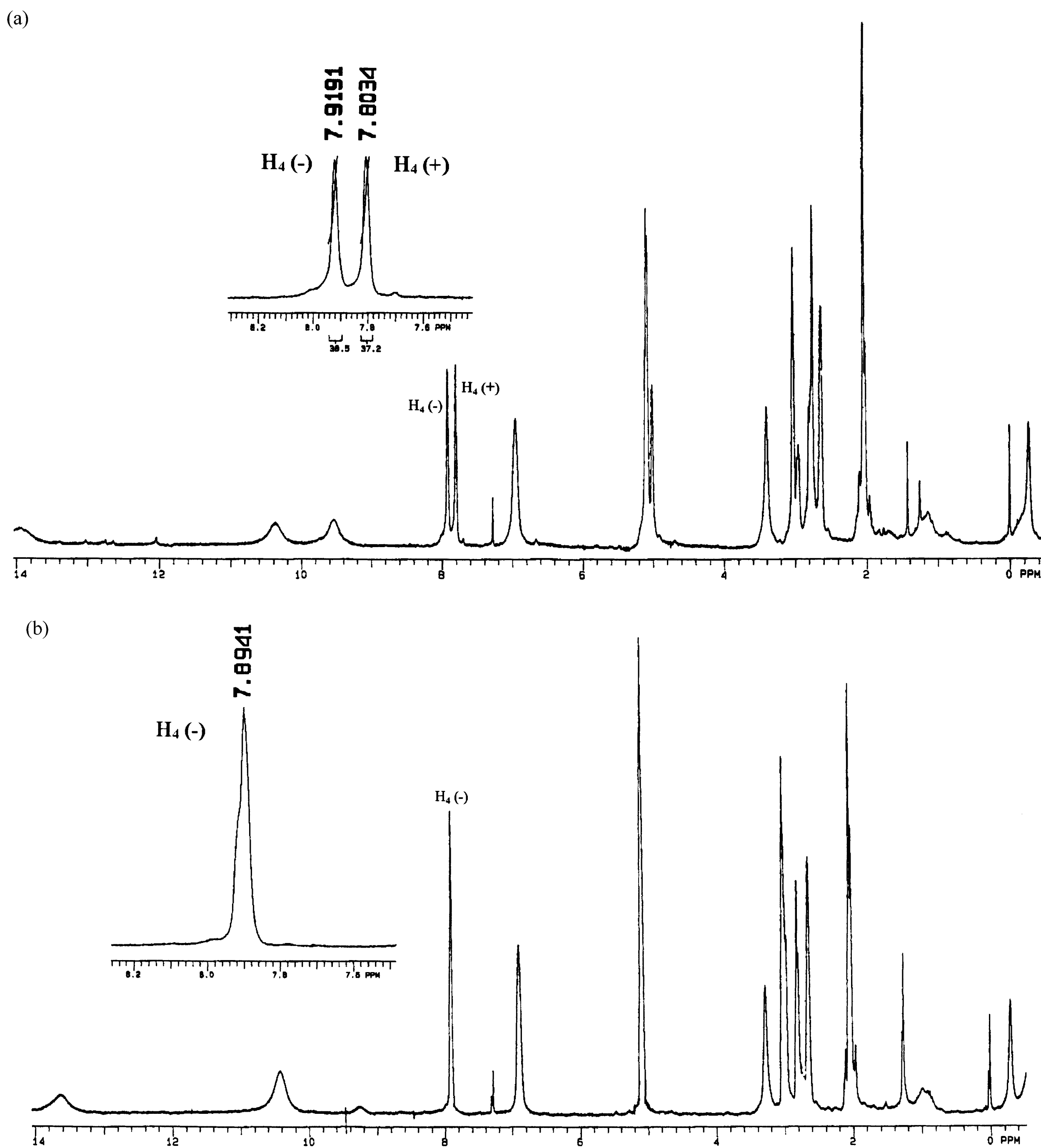


Figure 1.

As a consequence we decided that ethyl acetate should be the standard solvent to measure specific rotation for compounds **1** and **3** at Hg 365 nm line. Under these conditions the specific rotations of enantiomerically pure acetate (−)-**3** were $[\alpha]_D^{20} = -68$ (*c* 0.5, EtOAc) and $[\alpha]_{365}^{20} = -190$ (*c* 0.5, EtOAc). The basic hydrolysis of (−)-**3** yielded the enantiomerically pure alcohol (−)-**1** with the specific rotations $[\alpha]_D^{20} = -34$ (*c* 0.5, EtOAc) and $[\alpha]_{365}^{20} = -61$ (*c* 0.5, EtOAc) (Table 2).

Transesterification reactions of alcohol **2** (Scheme 2) were carried out using lipases from *P. cepacia* (four different preparations), *P. fluorescens* (powder) and *C. rugosa* (powder). For alcohol **2** all enzymes in their different preparations yielded the acetate **4** and all products with the same t_R value (31.8 min). In the case of *P. cepacia*, the support type of the preparation affected only the reaction rate maintaining the product enantiomeric purity for all reactions, as observed for alcohol **1**. Scheme 2 shows the transesterification reaction of alcohol **2** and Table 3 summarizes the results of these reactions.

The results presented in Table 3 allowed the high ability of Lipase PS-C 'Amano' I in the kinetic resolution of alcohol **2** to be identified. Thus, racemic alcohol **2** was submitted to transesterification reaction followed by chromatographic separation yielding the acetate (−)-**4** (t_R 31.8 min) in enantiomerically pure form, $[\alpha]_D^{20} = -162$ (*c* 0.5, EtOAc) and $[\alpha]_{365}^{20} = -486$ (*c* 0.5, EtOAc), and also an amount of enriched alcohol **2**.

Using the enriched alcohol **2** in a second reaction, enantiomerically pure alcohol (+)-2 was isolated $[\alpha]_D^{20} = +60$ (*c* 0.5, EtOAc) and $[\alpha]_{365}^{20} = +140$ (*c* 0.5, EtOAc) (Table 4). It is worth mentioning that alcohol **2** was analyzed by chiral GC presenting e.e. >99% and that no change in specific rotation was observed. Alcohol (−)-**2**, $[\alpha]_D^{20} = -59$ (*c* 0.5, EtOAc) and $[\alpha]_{365}^{20} = -140$ (*c* 0.5, EtOAc) (Table 4), was obtained by the basic hydrolysis of the acetate (−)-**4**. The acetate (+)-**4** $[\alpha]_D^{20} = +162$ (*c* 0.5, EtOAc) and $[\alpha]_{365}^{20} = +485$ (*c* 0.5, EtOAc) (Table 4), was obtained by reaction of alcohol (+)-**2** with acetic anhydride and pyridine.

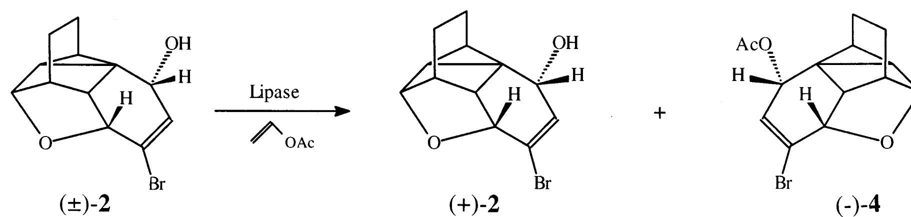
A rule for stereochemical preferences of *P. cepacia* lipase, *C. rugosa* lipase and cholesterol esterase toward linear and cyclic alcohols was formulated by Kazlauskas et al.[29,30] It has been suggested that alcohols having a small and a large substituent at the stereocenter should have the efficiency of their enzymatic resolutions improved. Considering the structure of alcohols **1** and **2**, they present a stereocenter at carbon C_3 (α-hydroxyl) carrying a large substituent (the nortricyclenic moiety) attached at one side and a small substituent (olefinic moiety) attached at the other side. As it can be observed in Tables 1 and 3, the *P. cepacia* lipase in different preparations and the *P. fluorescens* lipase was able to resolve both alcohols **1** and **2** with high enantiomeric ratio (*E*). Furthermore, the enantiomeric ratio (*E*) values were higher for the resolution of alcohol **2**, which presents an ethylenic bridge, when compared to those for alcohol **1** which has a methylenic bridge. Therefore, the behavior of the enzymes while working with these two compounds is in accordance to the postulated rule.

Table 3. Lipase-catalyzed transesterification reactions of alcohol (±)-**2**

Lipase	Reaction time[a] (h)	Chemical conversion to acetate **4** (%) by GC[b,c]
PS 'Amano'	336	32
PS-C 'Amano' I	6	48
PS-C 'Amano' II	9	38
PS-D 'Amano' I	10	40
AK 'Amano' 20	15	46
AY 'Amano' 30	336	3

[a] Reaction time to achieve the best chemical yield of acetate **4** with the enantiomeric excess >99% (Chiral GC).
[b] The retention time (t_R) of the enantiomers of acetate (±)-**4** were 31.8 and 32.4 min by chiral GC and the t_R of the obtained enantiomer was always 31.8 min.
[c] All *E* values >100 and they were calculated by Sih's equation.[27]

As reported in the literature, the enzyme in lyophilized powder form usually presents lower activity than when immobilized on a solid support.[31–35] Thus, as expected, the lipase PS 'Amano' (powder) reacts slower than the immobilized preparations of the same lipase. However the preparations PS-C 'Amano' II and PS-D 'Amano' I presented higher reaction rates and similar chemical conversion when carrying out the enantiomeric resolutions of racemic alcohol **2**, the preparation PS-C 'Amano' I was chosen as the best catalyst considering the reaction rate for conversion of alcohols **1** and **2** into enantiomerically pure acetate. On the other hand, lipase AK 'Amano' 20, which is a simple lyophilized powder of *P. fluorescens*, showed greater ability to resolve the racemic alcohol **2** ($E = 535$) than alcohol **1** ($E = 257$).



Scheme 2.

Table 4. Specific rotation values of enantiomerically pure substrates **2** and **4** in different solvents

Substrate	c (g/100 mL)	Ethyl acetate		Chloroform		Methanol	
		$[\alpha]_D^{20}$	$[\alpha]_{365}^{20}$	$[\alpha]_D^{20}$	$[\alpha]_{365}^{20}$	$[\alpha]_D^{20}$	$[\alpha]_{365}^{20}$
(+)-**2**	0.5	+60	+140	+4	+8	+56	+28
(−)-**2**	0.5	−59	−140	−5	−8	−56	−28
(−)-**4**	0.5	−162	−486	−218	−662	−22	−462
(+)-**4**	0.5	+162	+485	+217	+662	+23	+462

3. Conclusions

5-Bromo-12-oxa-pentacyclo[6.2.1.$1^{6,9}$.$0^{2,7}$.$0^{2,10}$]dodeca-4-ene-3-*endo*-ol **1** and its analogue **2** have been resolved using lipases from *P. cepacia* and *P. fluorescens*. The best reaction times and *E* values were achieved particularly in the transesterification of both alcohols **1** and **2** using lipase PS-C 'Amano' I in vinyl acetate as acyl donor. Furthermore, the *P. fluorescens* lipase showed greater ability to accomplish enantiomeric resolution of alcohol **2** than alcohol **1**. These lipases yielded, for both alcohols, the acetates with the same specific rotation value in enantiopure form (chiral GC). The *C. rugosa* lipase was found to be ineffective in performing the enantiomeric resolution of both alcohols. These results reveal good perspectives for preparation of enantiopure polycyclic sugar–mimic glycosidase inhibitors in the near future.

4. Experimental

4.1. General

Melting points were determined on an Electrothermal IA9000 apparatus and are presented without corrections. Infrared spectra were recorded using a FTIR–Mattson 3020 spectrometer. Mass spectra were acquired on an HP 5988A spectrometer. NMR spectra were recorded on a Varian VXR-200 spectrometer at a magnetic field of 4.7 T at 22°C. Chemical shifts are expressed as δ (ppm) relative to TMS as internal standard and the J values are given in Hz. Elemental analyses were recorded on a Perkin–Elmer 2400 CHN elemental analyzer. The products were analyzed by GC on a Shimadzu GC-17A Gas Chromatograph equipped with a FID detector. Optical rotations were recorded on a Perkin–Elmer 341 polarimeter using sodium D line or mercury 365 nm line with a 0.1 dm cell at a temperature of 20°C. Lipase PS 'Amano' (Lot. LPSAX10508), PS-C 'Amano' I (Lot. IPSAX08531K), PS-C 'Amano' II (Lot. ILPSAX01520K), PS-D 'Amano' I (Lot. ILPSAX02520K), AK 'Amano' 20 (Lot. LAKX09510) from *Pseudomonas* and lipase AY 'Amano' 30 (Lot. LAYY0450102S), were kindly provided by Amano Enzyme USA Co. Vinyl acetate was distilled from hydroquinone just before use. All enzymatic resolutions were carried out at 20°C under anhydrous conditions on a Mistral Multi-Mixer apparatus. GC parameters for achiral analysis: injector 250°C; detector 300°C; oven 100°C for 5 min then 10°C/min until 300°C; column pressure 15 kPa; column flow 9.5 mL/min; linear velocity 84.7 cm/s; total flow 200 mL; split ratio 1:20; column DB1 15 m×0.53 mm (internal diameter). GC parameters for chiral analysis: injector 250°C; detector 300°C; oven 150°C for 10 min then 5°C/min until 200°C; column pressure 138 kPa; column flow 2.7 mL/min; linear velocity 75.5 cm/s; total flow 35 mL; split ratio 1:10; column β-cyclodextrin 30 m×0.25 mm (internal diameter).

4.2. Procedure for alcohol 1 NMR analysis with the chiral shift reagent

The chiral NMR analysis was conducted with a 20 mg sample of alcohol **1** in 0.5 mL of $CDCl_3$. The ^1H spectrum of the pure racemic sample was recorded. Then, spectra were recorded after adding 5 mg portions of the shift reagent (+)-Eu(hfc)$_3$. The procedure was performed until complete signal separation of hydrogen at position H_4 (br s, 1H, olefinic) of each enantiomer was achieved, which required 10 mg of the shift reagent. After separation, the signal corresponding to the enantiomers of alcohol **1** was observed at δ ppm 7.91 and δ ppm 7.80.

4.3. 5-Bromo-12-oxa-pentacyclo[6.2.1.$1^{6,9}$.$0^{2,7}$.$0^{2,10}$]dodeca-4-ene-3-*endo*-ol (±)-1

The *endo*-2,5-dibromotricyclo[6.2.1.$0^{2,7}$]undeca-4,9-dien-3,6-dione[25] (350 mg, 1.05 mmol) was added to a stirred solution of $CeCl_3\cdot 6H_2O$ (1.5 g, 4 mmol) in methanol (6 mL). The resulting mixture was cooled in an ethanol/dry ice bath at −68°C and sodium borohydride (151 mg, 4 mmol) was added. After 30 min the reaction was quenched with 10 mL of water and extracted with ether (5×20 mL). After chromatographic purification (25% EtOAc–hexane), a colorless solid corresponding to alcohol (±)-**1** was isolated (247 mg, 92%). Mp 160–162°C; anal. calcd for $C_{11}H_{11}BrO_2$: C, 51.56; H, 4.29. Found: C, 51.48; H, 4.22; IR (KBr) 3385, 1622, 823; EIMS m/z (relative intensity) 256 (M^++2, 3.2), 254 (M^+, 3.2), 239 (3.5), 237 (3.2), 175 (100.0), 157 (3.3), 115 (28.3); ^1H NMR (200 MHz, $CDCl_3$) δ 6.38 (1H, d, J=1.91 Hz), 4.63 (1H, br s), 4.43 (2H, m), 2.42 (1H, t, J=2.76 Hz), 2.25 (1H, br s), 1.95 (1H, br s), 1.82 (1H, d, J=4.9 Hz), 1.74 (2H, m), 1.31 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.8 (CH), 127.8 (C), 83.0 (CH), 79.6 (CH), 65.8 (CH), 49.1 (CH), 43.1 (CH), 30.1 (CH_2), 29.0 (C), 18.3 (CH) and 17.5 (CH).

4.4. 5-Bromo-13-oxa-pentacyclo[6.2.2.1^{6,9}.0^{2,7}.0^{2,10}]trideca-4-ene-3-*endo*-ol (±)-2

Alcohol (±)-**2** was synthesized following the same protocol used in the synthesis of alcohol (±)-**1**. It was isolated as a colorless microcrystalline solid (164 mg, 60%). Mp 156–157°C; anal. calcd for $C_{12}H_{13}BrO_2$: C, 53.53; H, 4.83. Found: C, 53.74; H, 4.77; IR (KBr) 3450, 1630, 823; EIMS m/z (relative intensity) 270 (M^++2, 1.3), 268 (M^+, 1.5), 241 (1.4), 239 (1.7), 189 (78), 171 (18.8), 161 (26.3), 143 (36), 115 (59.1), 77 (100); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.31 (1H, d, J=2.2 Hz), 4.51 (1H, br s), 4.32 (1H, br s), 4.14 (1H, d, J=2.93 Hz), 2.74 (1H, br s), 2.52 (1H, d, J=1.71 Hz), 1.89 (1H, br s), 1.71–1.36 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 136.1 (CH), 125.7 (C), 79.0 (CH), 78.6 (CH), 65.7 (CH), 44.8 (CH), 40.3 (CH), 25.2 (C), 20.8 (CH_2), 17.9 (CH_2), 14.4 (CH), 13.9 (CH).

4.5. Lipase-catalyzed acetylation of alcohols (±)-1 and (±)-2

4.5.1. Procedure of lipase screening for the transesterification reactions. A 20 mg sample of the racemic alcohol was shaken in 2 mL of vinyl acetate until complete dissolution, then 10 mg of the lipase was added. The system was shaken at 20°C and followed by achiral and chiral GC.

4.5.2. Typical procedure for the preparative transesterification reactions. This protocol concerns to reaction applying to the optimized enzymatic system. Thus, Lipase PS-C 'Amano' I (500 mg) was added to a solution of alcohol (±)-**1** or (±)-**2** (1 g) in 10 mL of recently distilled hydroquinone vinyl acetate. The reaction vessel was shaken for the time described in Tables 1 and 3, at room temperature. At the end of the reaction, the enzyme was filtered off, washed three times with chloroform and stored in chloroform at 0°C. The enzyme should be vacuum dried just before using. The vinyl acetate was removed under reduced pressure and the residue was dissolved in $CHCl_3$, washed with 5% aqueous $NaHCO_3$, water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The reaction products were purified by silica gel column chromatography (eluted with cyclohexane: AcOEt 4:1) to give the enriched alcohol and enantiomerically pure acetate. It is worth mentioning that the reaction vessel must be shaken and not magnetically or mechanically stirred.

4.6. 5-Bromo-12-oxa-pentacyclo[6.2.1.1^{6,9}.0^{2,7}.0^{2,10}]dodeca-4-ene-3-*endo*-ol (+)-1

After executing the typical procedure three times, alcohol (+)-**1** was obtained in its optically pure form as a colorless crystalline solid (392 mg, 39%, >99% e.e.). The values of specific rotation are listed in Table 2. It is important to note that sign reversal of specific rotation was observed when chloroform was used as solvent.

4.7. 3-*endo*-Acetoxy-5-bromo-12-oxa-pentacyclo-[6.2.1.1^{6,9}.0^{2,7}.0^{2,10}]dodeca-4-ene (−)-3

The acetate (−)-**3** was obtained in its enantiomerically pure form (489 mg, 42%, >99% e.e.) as a colorless crystalline solid after executing the typical procedure once. The values of specific rotation are listed in Table 2. Mp 88°C; IR (KBr) 1746, 1625; EIMS m/s (relative intensity) 298 (M^++2, 0.05), 296 (M^+, 0.04), 256 (28.7), 254 (28.4), 175 (41.6), 157 (13.3), 147 (13.0), 128 (100); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.3 (1H, d, J=1.94 Hz), 5.68 (1H, s), 4.4 (2H, m), 2.48 (1H, t, J=2.61 Hz), 2.24 (1H, br s), 2.0 (3H, s), 1.72–1.65 (3H, m), 1.35–1.32 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.1 (C), 133.6 (CH), 129.0 (C), 82.9 (CH), 79.4 (CH), 67.3 (CH), 49.0 (CH), 42.9 (CH), 29.9 (CH_2), 24.1 (C), 20.8 (CH_3), 18.7 (CH), 18.3 (CH).

4.8. 5-Bromo-13-oxa-pentacyclo[6.2.2.1^{6,9}.0^{2,7}.0^{2,10}]trideca-4-ene-3-*endo*-ol (+)-2

Executing the typical procedure twice, alcohol (+)-**2** was obtained in its optically pure form as a colorless crystalline solid (321 mg, 32%, >99% e.e.). The values of specific rotation are listed in Table 4.

4.9. 3-*endo*-Acetoxy-5-bromo-13-oxa-pentacyclo-[6.2.2.1^{6,9}.0^{2,7}.0^{2,10}]trideca-4-ene (−)-4

The acetate (−)-**4** was obtained in its enantiomerically pure form (553 mg, 48%, >99% e.e.) as a colorless crystalline solid after executing the typical procedure once. The values of specific rotation are listed in the Table 4. Mp 66–67°C; IR (KBr) 1747, 1644; EIMS m/z (relative intensity) 270 (M^++2–C_2H_2O, 35.2), 268 (M^+–C_2H_2O, 33.8), 252 (9.5), 250 (11.6), 224 (35.7), 222 (30.5), 208 (27.6), 189 (43.6), 171 (26.2), 161 (21.2), 142 (48.8), 128 (100), 115 (97.1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.16 (1H, d, J=1.28 Hz), 5.58 (1H, d, J=1.82 Hz), 4.26 (1H, br s), 4.10 (1H, d, J=2.69 Hz), 2.52 (1H, br s), 1.94 (3H, s), 1.81 (1H, br s), 1.63–1.57 (4H, m), 1.37 (1H, d, J=7.63 Hz), 1.02 (1H, d, J=7.57 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.1 (C), 131.8 (CH), 127.4 (C), 78.9 (CH), 78.3 (CH), 67.5 (CH), 44.8 (CH), 40.1 (CH), 22.4 (C), 21.8 (CH), 20,7 (CH), 17.8 (CH_2), 14.5 (CH), 14.3 (CH_2).

4.10. Procedure for the acetylation of (+)-1 to (+)-3 and of (+)-2 to (+)-4

Ac_2O (2.25 mL) and a catalytic amount of DMAP were added to a solution of alcohol (+)-**1** or (+)-**2** (1 mmol) in pyridine (2.25 mL). The resulting mixture was stirred overnight before adding 20 mL of water. The mother liquor was extracted with EtOAc (5×5 mL) and the combined organic layers were washed with 5% aqueous H_2SO_4, water and brine, then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (cyclohexane:EtOAc 4:1) to give acetates (+)-**3** and (+)-**4** (80–90% yield) as a colorless crystalline solid. The specific rotations are listed in Tables 2 and 4, respectively.

4.11. Procedure for the hydrolysis of (−)-3 to (−)-1 and of (−)-4 to (−)-2

A pellet of NaOH was added to a solution of acetate (−)-**3** or (−)-**4** (1 mmol) in methanol (20 mL). The resulting mixture was stirred for 1 h, quenched with 20 mL of water and extracted with ether (5×10 mL). The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (cyclohexane:EtOAc 4:1) to give alcohols (−)-**1** and (−)-**2** (up to 99% yield) as a colorless crystalline solid. The specific rotations are listed in Tables 2 and 4, respectively.

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