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Enzymatic resolution of α-tetralols by CALB-catalyzed acetylation

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Abstract—A series of homochiral α-tetralols, as well as their respective acetates, has been obtained by esterification of racemic tetralols, using *Candida antarctica* lipase (CALB—Novozym® 435) as the biocatalyst. This enzyme is shown to be highly efficient for the kinetic resolution of the substrates studied, affording the (+)-tetralols and the (+)-acetates in excellent enantiomeric excess (up to >99%) and very good yields (>40%).

1. Introduction

Enantiomerically pure α- and β-tetralols constitute versatile homochiral building blocks in organic synthesis.[1–4] In our efforts concerning the asymmetric synthesis of natural products, such as mutisianthol (I),[5,6] and flossonol (II),[7] (Fig. 1), we reasoned that some α-tetralol derivatives could be useful intermediates or even model substrates for these studies.

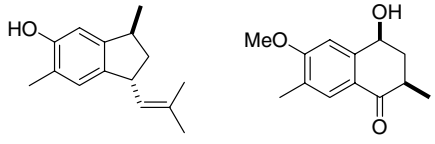


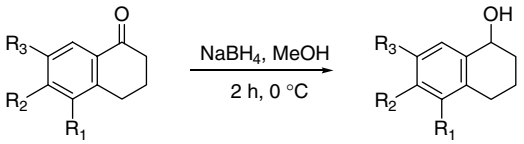
Figure 1. Mutisianthol (I) and flossonol (II).

The kinetic enzymatic resolution of some β-tetralols, by porcine pancreatic lipase-catalyzed acetylation, has been reported by Martinez.[8] The bioreduction of β-tetralones, leading to enantiomerically pure β-tetralols, has been studied by several groups.[9–11] On the other hand, few attention has been addressed to biotransformations involving substituted α-tetralones or α-tetralols. Therefore, we decided to investigate the resolution of a series of substituted racemic α-tetralols, by using an enzymatic acetylation reaction. The lipase B from *Candida antarctica* (CALB—Novozym® 435), chosen as the biocatalyst, has proven to be very efficient for a wide variety of enantioselective reactions, such as transesterification,[12–18] aminolysis,[19] and hydrolysis.[20]

2. Results and discussion

2.1. Preparation of the racemic α-tetralols 1b–7b and acetates 1c–7c

The racemic α-tetralols were prepared by the reduction of the corresponding α-tetralones, using sodium borohydride in methanol. Thus, the commercially available α-tetralones **1a**–**4a** furnished α-tetralols **1b**–**4b** in excellent yields (Scheme 1).



1a: R_1=R_2=R_3=H (±)-**1b** (97%)
2a: R_1=OMe, R_2=R_3=H (±)-**2b** (93%)
3a: R_1=R_2=H, R_3=OMe (±)-**3b** (91%)
4a: R_1=R_3=Me, R_2=H (±)-**4b** (98%)

Scheme 1.

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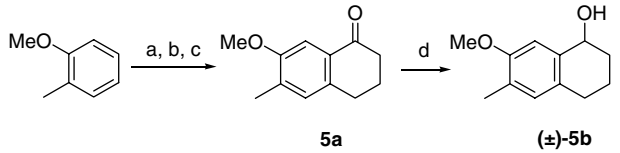
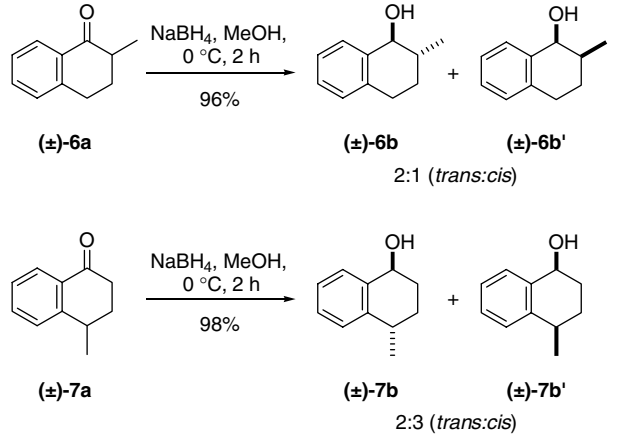
α-Tetralone **5a**, a precursor of α-tetralol (±)-**5b**, was obtained in three steps from 2-methylanisole, through an earlier described procedure (Scheme 2).[6,21]



Scheme 2. Reagents and conditions: (a) succinic anhydride, $C_6H_5NO_2$, 0–5 °C, $AlCl_3$, 24 h (80%); (b) Zn(Hg), H_2O, HCl, toluene, 2 d (83%); (c) TFA, TFAA, 10 min (97%); (d) $NaBH_4$, MeOH, 2 h, 0 °C (95%).

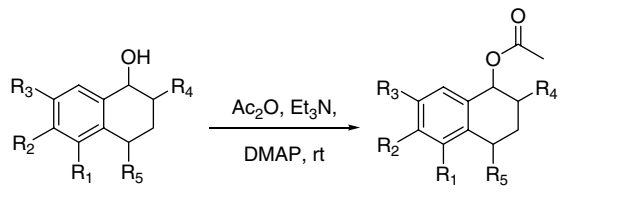
Finally, the diastereomeric tetralols **6b/6b′** and **7b/7b′** were obtained as 2:1 (*trans*:*cis*) and 2:3 (*trans*:*cis*) mixtures, respectively, by reduction of the commercially available tetralones **6a** and **7a** (Scheme 3).



Scheme 3.

The relative configurations of tetralols **6b/6b′**[3,22] and **7b/7b′**[22,23] were established by comparison to the literature data.

Tetralols **1b**–**7b** were then acetylated using classical conditions, to afford the corresponding racemic acetates **1c**–**7c** (Scheme 4). These products were analytically resolved into their enantiomers by chiral gas chromatography, which was shown to be efficient for all the acetates, except for **2c**. A representative chromatogram of the resolution process is shown in Figure 2.



(±)-**1b:** R_1=R_2=R_3=R_4=R_5=H (±)-**1c** (93%)
(±)-**2b:** R_1=OMe, R_2=R_3=R_4=R_5=H (±)-**2c** (92%)
(±)-**3b:** R_3=OMe, R_1=R_2=R_4=R_5=H (±)-**3c** (97%)
(±)-**4b:** R_1=R_3=Me, R_2=R_4=R_5=H (±)-**4c** (98%)
(±)-**5b:** R_1=R_4=R_5=H, R_2=Me, R_3=OMe (±)-**5c** (90%)
(±)-**6b/b':** R_1=R_2=R_3=R_5=H, R_4=Me (±)-**6c/c'** (97%)
(±)-**7b/b':** R_1=R_2=R_3=R_4=H, R_5=Me (±)-**7c/c'** (96%)

Scheme 4.

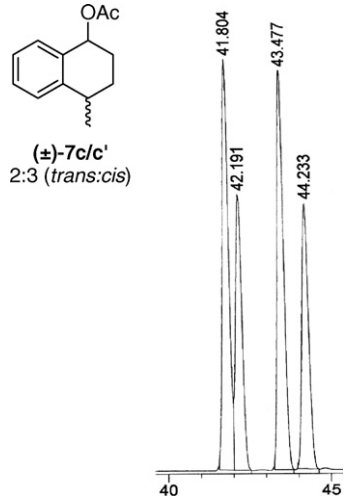


Figure 2. Chromatogram of the racemic acetates **7c/7c′**—signals at 41.80 and 43.48 min: *cis*-enantiomer **7c′**; signals at 42.19 and 44.23 min: *trans*-enantiomer **7c**.

2.2. Enzymatic resolution

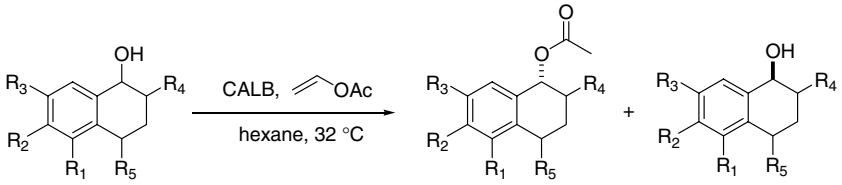
The racemic α-tetralols were submitted to CALB-catalyzed enzymatic acetylation employing vinyl acetate as the acyl donor. This reagent has shown excellent performance in this type of reaction.[24,25] The reactions were performed in hexane at 32 °C, by the times indicated in Table 1. The resulting acetates and the remaining tetralols were separated by flash chromatography, and obtained in high yields and excellent ee.

Doubling the amount of CALB increased the ee to >99% for tetralol (+)-**4b** and acetate (+)-**4c**. α-Tetralols **6b/6b′** were submitted to different experimental conditions (variation in time, temperature, and amount of CALB), but the results were unsuccessful.

The stereochemical preference of CALB was determined by establishing the absolute configuration of the remaining tetralols and of the obtained acetates. By comparison of the specific rotation values to those in the literature, the (*S*)-configuration was given to tetralols (+)-**1b**,[27] (+)-**2b**,[3] (+)-**3b**,[28] and (+)-**4b**,[3] while the acetates were assigned as (*R*). Therefore, the acetylation takes place almost exclusively in the (*R*)-tetralol, in according to Kazlauskas' rule[29] (Fig. 3a and b).

A possible explanation for the lack of reactivity of tetralols **6b/6b′**, may be the influence of the methyl group at C-2, as depicted in Figure 3c. Since the relative sizes of the two substituents are similar, the enzyme becomes less able to distinguish between them. In a previous study, Naemura et al.[30] reported that this same substrate is inert toward the lipase YS (from *Pseudomonas fluorescens*). Moreover,

Table 1. CALB-catalyzed acetylation of (±)-tetralols **1b**–**7b**



(±)-1b-7b **(+)-1c-7c** **(+)-1b-7b**

Substrate	Time (h)	Product[a]				Remaining substrate[a]				E[d]
			ee_p[b] (%)	Isolated yield (%)	$[\alpha]_D$[c]		ee_s[b] (%)	Isolated yield (%)	$[\alpha]_D$[c]	
1b	2.3	(*R*)-**1c**	>99	48	+109.7	(*S*)-**1b**	>99	46	+33.9	>500
2b	3	(*R*)-**2c**	>99	42	+101.8	(*S*)-**2b**	>99	42	+23.3	>500
3b	2.5	(*R*)-**3c**	>99	46	+88.5	(*S*)-**3b**	>99	47	+41.9	>500
4b	20	(*R*)-**4c**	99	38	+98.1	(*S*)-**4b**	99	44	+38.9	>500
5b	4	(+)-**5c**	>99	47	+106.6	(+)-**5b**	98	48	+36.9	>500
6b+**6b′**	Various times	—	—	—	—	—	—	—	—	—
7b+**7b′**	20	**7c**+**7c′**	*Trans* >99 *Cis* >99 (2:3 *trans*:*cis*)	47	—	**7b**+**7b′**	*Trans* >99 *Cis* >99 (2:3 *trans*:*cis*)	47	—	>500

[a] The conversion rate [$c = ee_s/(ee_s + ee_p)$] was 50% in all reactions.
[b] Determined by chiral GC.
[c] See Section 4 for values of temperature and concentration.
[d] The enantiomeric ratio (E) was calculated using Sih's method.[26]

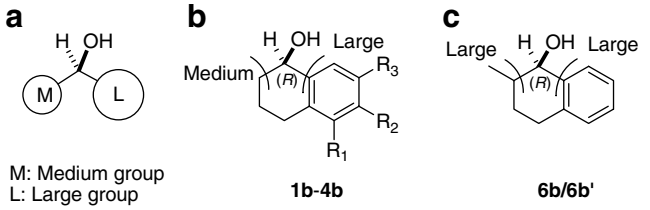


Figure 3. (a) Enantiomer more reactive; (b) reactive substrates; (c) unreactive substrate.

Kasai et al.[31] reported that the hydrolysis of the corresponding acetate **6c** gave the desired alcohol in poor ee (22%) and 42% of conversion, by using the mold *Rhizopus nigricans*.

The stereoselectivity of CALB was studied by Uppenberg et al.[32] through crystallographic and molecular modeling. This study provided a structural explanation for the high stereoselectivity of CALB toward many secondary alcohols, and the authors concluded that the (*R*)-enantiomer of this type of substrate fits better into the active site pocket of the enzyme than the (*S*)-enantiomer. Our results are in agreement with these observations, since the enzyme promotes the preferential acetylation of the (*R*)-enantiomer of all the tetralols studied.

The absolute configuration of acetate (+)-**5c** was not determined, but we strongly believe that it is (*R*), by analogy with the others. Acetates **7c** and **7c′** (*trans*:*cis* mixture) could not be separated either by flash chromatography or by high performance liquid chromatography (HPLC). Figure 4a shows the chromatogram of acetates **7c**/**7c′** obtained from the remaining tetralols **7b**/**7b′**, which did not undergo

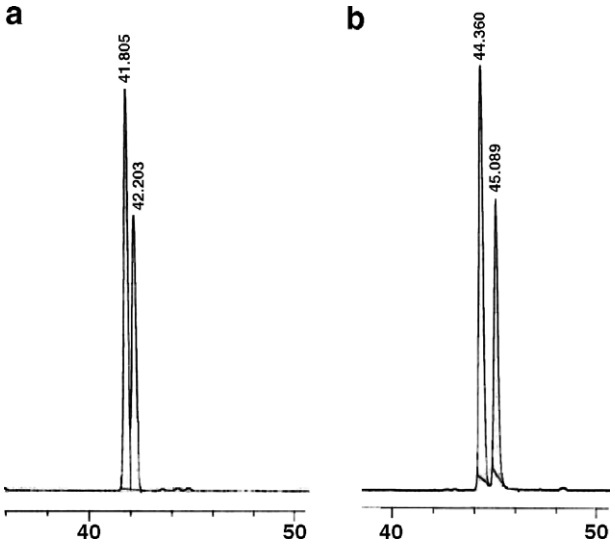
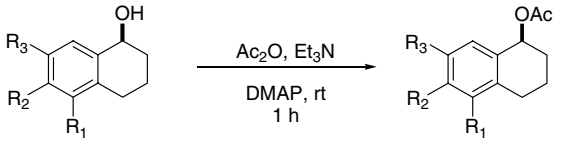


Figure 4. Chromatogram of acetates **7c**/**7c′** (2:3 *trans*:*cis*) (a) produced in the enzymatic acetylation and (b) obtained from the remaining tetralols **7b**/**7b′**. For better comprehension, see Figure 2, which shows the chromatogram of racemic acetates (±)-(**7c**+**7c′**).

good separation by chiral gas chromatography. The chromatogram of the acetates produced in the enzymatic acetylation is shown in Figure 4b. It was possible to observe that only one enantiomer of each pair *cis* and each pair *trans* was formed.

The remaining tetralols (+)-**1b**, (+)-**3b**, (+)-**4b**, and (+)-**5b** were acetylated, in order to measure the $[\alpha]_D$ values of the acetates obtained and thus verify their absolute configurations (Table 2). The specific rotation values are in

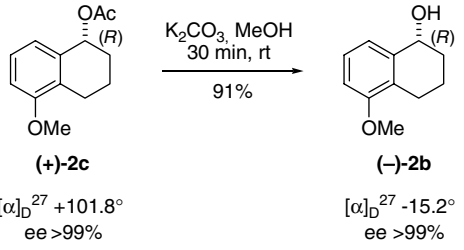
Table 2. Acetylation of (+)-tetralols **1b** and **3b**–**5b**



Entry		Substrate	ee[a] (%)	$[\alpha]_D$[b]	Product	ee[a] (%)	$[\alpha]_D$[b]
1	(+)-(*S*)-**1b**	$R_1 = R_2 = R_3 = H$	>99	+33.9	(−)-(*S*)-**1c**	>99	−89.1
2	(+)-(*S*)-**3b**	$R_1 = R_2 = H$, $R_3 = OMe$	>99	+41.9	(−)-(*S*)-**3c**	>99	−85.5
3	(+)-(*S*)-**4b**	$R_1 = R_3 = Me$, $R_2 = H$	99	+38.9	(−)-(*S*)-**4c**	99	−90.4
4	(+)-**5b**	$R_1 = H$, $R_2 = Me$, $R_3 = OMe$	98	+36.9	(−)-**5c**	98	−96.9

[a] Determined by chiral GC.
[b] See Section 4 for values of temperature and concentration.

agreement with the expected ones, since all the obtained (*S*)-acetates are levorotatory, while those produced by enzymatic resolution are dextrorotatory. In the same fashion, acetate (+)-**2c** was hydrolyzed to tetralol (−)-**2b** (Scheme 5), since the analytical resolution of acetate (±)-**2c** was not achieved.



Scheme 5.

3. Conclusion

It was possible to prepare a series of optically active α-tetralols, as well as their respective acetates, in excellent enantiomeric excess and high conversion rate. CALB was shown to be highly efficient for the resolution of the racemic α-tetralols studied, allowing their enantiomeric resolution in very good yields. These results certainly contribute to corroborate the enantioselectivity of the enzyme CALB toward secondary alcohols. α-Tetralols **7b**/**7b**′ should be employed in model studies directed toward the asymmetric synthesis of mutisianthol. Moreover, the homochiral α-tetralol (+)-**5b** seems to be a useful intermediate for the synthesis of flossonol, as indicated by some preliminary experiments performed in our laboratory.

4. Experimental

4.1. General

All solvents and chemicals used were previously purified according to the usual methods. Column chromatography was performed using silica gel Acros 200–400 Mesh. TLC analyses were performed with silica gel plates Merck, using UV-254 nm and *p*-anisaldehyde solutions for visualization. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ with Me_4Si as the internal standards and recorded on Bruker and Varian spectrometers. IR spectra were measured on a Perkin–Elmer 1750-FT, absorbances are reported in cm^{-1}. Gas chromatography analyses were performed in a HP-6890 series II. Conversions and enantiomeric excesses of the enzyme-catalyzed reactions were determined using a HP-6890 series II gas chromatograph equipped with a chiral capillary column AG100-2000 (packed β-cyclodextrin (30 m × 0.32 mm × 0.25 μm)—Agilent-HP). The carrier gas was hydrogen. GC–MS analyses were performed using Finnigan-MAT INCOS 50B and GC Varian 2400. Elemental analyses were performed using Perkin–Elmer 2400 apparatus. High-resolution mass spectra were performed on a Bruker Daltonics Microtof Eletrospray instrument. Optical rotation values were measured in a JASCO DIP-378 polarimeter and the reported data refer to the Na-line value using a 1 dm cuvette. CALB was a gift from Novo Nordisk (Paraná-Brazil).

4.2. General procedure for reduction of the tetralones

4.2.1. Preparation of 1,2,3,4-tetrahydronaphthalen-1-ol 1b.[3] To a solution of 1,2,3,4-tetrahydronaphthalen-1-one **1a** (0.45 g, 3.1 mmol) in anhydrous MeOH (9 mL) at 0 °C under N_2, $NaBH_4$ (0.34 g, 8.9 mmol) was added portionwise. The mixture was allowed to reach room temperature and then stirred for 2 h. The reaction mixture was quenched with water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica flash chromatography (hexanes–AcOEt, 7:3 as eluent), to give **1b** as a viscous oil (97%; 0.44 g, 3.0 mmol).

4.2.2. 1,2,3,4-Tetrahydro-5-methoxynaphthalen-1-ol 2b.[3] Using the general procedure described for **1b**, 1,2,3,4-tetrahydro-5-methoxynaphthalen-1-one **2a** (0.53 g, 3.0 mmol) was converted into **2b** (93%; 0.50 g, 2.8 mmol); white solid mp: 102.0–103.0 °C.

4.2.3. 1,2,3,4-Tetrahydro-7-methoxynaphthalen-1-ol 3b.[28] Using the general procedure described for **1b**, 1,2,3,4-tetrahydro-7-methoxynaphthalen-1-one **3a** (1.9 g, 11 mmol) was converted into **3b** (91%; 1.8 g, 10 mmol); white solid mp: 38.0–39.0 °C.

4.2.4. 1,2,3,4-Tetrahydro-5,7-dimethylnaphthalen-1-ol 4b.[3] Using the general procedure described for **1b**, 1,2,3,4-tetrahydro-5,7-dimethylnaphthalen-1-one **4a** (0.71 g, 4.1 mmol) was converted into **4b** (98%; 0.70 g, 4.0 mmol); white solid mp: 79.0–80.0 °C.

4.2.5. 1,2,3,4-Tetrahydro-6-methyl-7-methoxynaphthalen-1-ol 5b.[33] Using the general procedure described for **1b**, 1,2,3,4-tetrahydro-6-methyl-7-methoxynaphthalen-1-one **5a** (0.38 g, 2.0 mmol) was converted into **5b** (95%; 0.36 g, 1.9 mmol); white solid mp: 67.5–68.5 °C.

4.2.6. 1,2,3,4-Tetrahydro-2-methylnaphthalen-1-ol 6b/6b′.[22] Using the general procedure described for **1b**, 1,2,3,4-tetrahydro-2-methylnaphthalen-1-one **6a** (0.82 g, 5.1 mmol) was converted into a *trans*:*cis* (2:1) mixture of **6b/6b′** (96%; 0.79 g, 4.9 mmol) as a viscous oil.

4.2.7. 1,2,3,4-Tetrahydro-4-methylnaphthalen-1-ol 7b/7b′.[22] Using the general procedure described for **1b**, 1,2,3,4-tetrahydro-4-methylnaphthalen-1-one **7a** (0.82 g, 5.1 mmol) was converted into a *trans*:*cis* (2:3) mixture of **7b/7b′** (98%; 0.81 g, 5.0 mmol) as a viscous oil.

4.3. General procedure for acetylation of the tetralols

4.3.1. Preparation of 1,2,3,4-tetrahydronaphthalen-1-yl acetate 1c. To a solution of 1,2,3,4-tetrahydronaphthalen-1-ol **1b** (0.41 g, 2.8 mmol) in Et_3N (5 mL), Ac_2O (0.85 mL, 8.5 mmol) was added, followed by DMAP (cat.) at room temperature. After stirring for 1 h, the reaction mixture was diluted with MeOH and concentrated under reduced pressure. The residue was quenched with water, extracted with AcOEt, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was chromatographed on silica flash (hexanes–AcOEt, 8:2 as eluent), to give **1c** (93%; 0.49 g, 2.6 mmol) as a colorless oil.

4.3.2. 1,2,3,4-Tetrahydro-5-methoxynaphthalen-1-yl acetate 2c.[34] In the same manner as described in the general procedure, **2b** (0.091 g, 0.51 mmol) was converted into **2c** (92%; 0.10 g, 0.47 mmol); white solid mp: 36.0–37.0 °C.

4.3.3. 1,2,3,4-Tetrahydro-7-methoxynaphthalen-1-yl acetate 3c.[28] In the same manner as described in the general procedure, **3b** (0.18 g, 1.0 mmol) was converted into **3c** (97%; 0.21 g, 0.97 mmol); white solid mp: 67.5–68.5 °C.

4.3.4. 1,2,3,4-Tetrahydro-5,7-dimethylnaphthalen-yl acetate 4c.[35] In the same manner as described in the general procedure, **4b** (0.18 g, 1.0 mmol) was converted into **4c** (98%; 0.21 g, 0.98 mmol); white solid mp: 40.0–41.0 °C.

4.3.5. 1,2,3,4-Tetrahydro-6-methyl-7-methoxynaphthalen-1-yl acetate 5c. In the same manner as described in the general procedure, **5b** (0.92 g, 4.8 mmol) was converted into **5c** (90%; 1.0 g, 4.3 mmol) as a colorless oil. ^{1}H NMR (300 MHz) δ: 1.73–2.04 (m, 4H), 2.08 (s, 3H), 2.18 (s, 3H), 2.58–2.80 (m, 2H), 3.79 (s, 3H), 5.95–5.97 (m, 1H), 6.72 (s, 1H), 6.89 (s, 1H); ^{13}C NMR (125 MHz) δ: 16.0, 18.9, 21.6, 28.1, 29.2, 55.4, 70.2, 110.5, 127.3, 129.6, 131.1, 132.4, 156.1, 171.0; IR (film) ν_{max}: 3425, 2960, 2840, 1719, 1619, 1510 cm^{-1}; LRMS (EI) m/z (%): 234 ($M^{+\cdot}$, 6), 191 (4), 174 (100), 159 (56), 91 (22).

4.3.6. 1,2,3,4-Tetrahydro-2-methylnaphthalen-1-yl acetate 6c/6c′.[22] In the same manner as described in the general procedure, **6b/6b′** (0.047 g, 0.29 mmol) was converted into **6c/6c′** (97%; 0.057 g, 0.28 mmol) as a viscous colorless oil.

4.3.7. 1,2,3,4-Tetrahydro-4-methylnaphthalen-1-yl acetate 7c/7c′.[22] In the same manner as described in the general procedure, **7b/7b′** (0.083 g, 0.51 mmol) was converted into **7c/7c′** (96%; 0.10 g, 0.49 mmol) as a colorless oil.

4.4. Control of the enzymatic resolution of the (±)-α-tetralols

Tetralols and the corresponding acetates were compared with the racemic mixtures previously analyzed. GC conditions: injector: 250 °C, detector: 350 °C, oven: 120–180 °C (120 min), rate: 0.5 °C/min, flow: 1.4 mL/min; pressure of $H_{2(g)}$: 10 psi, constant pressure, split ratio 1:50. t_R = retention time (min).

4.4.1. General procedure for the enzymatic resolution of the (±)-α-tetralols. To a magnetically stirred solution of the tetralol in hexane (32 mL/mmol), CALB (1.2 g/g tetralol) was added, followed by vinyl acetate (4 equiv). This mixture was stirred at 32 °C, for the time indicated in Table 1. The enzyme was filtered off and washed with AcOEt. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (hexanes–AcOEt, 7:3 as eluent).

4.4.2. (*S*)-1,2,3,4-Tetrahydronaphthalen-1-ol 1b, (*S*)- and (*R*)-1,2,3,4-tetrahydronaphthalen-1-yl acetate 1c. Reaction time: 2 h 20 min; (±)-**1b** (0.16 g, 1.1 mmol) was converted into (+)-(*S*)-**1b** (46%; 0.075 g, 0.51 mmol) and (+)-(*R*)-**1c** (48%; 0.10 g, 0.53 mmol).

(+)-(*S*)-**1b** $[\alpha]_D^{27} = +33.9$ (*c* 1.13, $CHCl_3$), ee >99%; {lit.[27] (*S*)-**1b** $[\alpha]_D^{27} = +32.2$ (*c* 2.51, $CHCl_3$), ee = 99%}.

(+)-(*R*)-**1c** $[\alpha]_D^{27} = +109.7$ (*c* 1.21, $CHCl_3$), ee >99%; t_R = 35.53 min (100%); {lit.[30] (*R*)-**1c** $[\alpha]_D^{24} = +106.1$ (*c* 0.15, $CHCl_3$), ee = 93%}. (+)-(*S*)-**1b** was converted into (−)-(*S*)-**1c** by chemical acetylation, as described in the general procedure. (−)-(*S*)-**1c** $[\alpha]_D^{27} = -89.1$ (*c* 1.85, $CHCl_3$), ee >99%; t_R = 36.14 min (100%).

4.4.3. (*S*)- and (*R*)-1,2,3,4-Tetrahydro-5-methoxynaphthalen-1-ol 2b and (*R*)-1,2,3,4-tetrahydro-5-methoxynaphthalen-1-yl acetate 2c. Reaction time: 3 h; (±)-**2b** (0.18 g, 1.0 mmol) was converted into (+)-(*S*)-**2b** (42%; 0.075 g, 0.42 mmol) and (+)-(*R*)-**2c** (42%; 0.092 g, 0.42 mmol).

(+)-(*S*)-**2b** $[\alpha]_D^{27} = +23.3$ (*c* 1.04, $CHCl_3$), ee >99%; t_R = 75.10 min (99.84%); {lit.[3] (*R*)-**2b** $[\alpha]_D^{20} = -15.3$ (*c* 0.99, $CHCl_3$), ee = 100%}; white solid mp: 97.0–98.0 °C; ^{1}H NMR (500 MHz) δ: 1.71 (br s, 1H), 1.77–2.07 (m, 4H), 2.54–2.60 (m, 1H), 2.76–2.81 (m, 1H), 3.85 (s, 3H), 4.79–4.80 (m, 1H), 6.79 (dd, *J* 8 Hz and *J* 0.8 Hz, 1H), 7.09 (d, *J* 5.0 Hz, 1H), 7.22 (t, *J* 8 Hz, 1H); ^{13}C NMR

(75 MHz) δ: 18.1, 22.9, 31.7, 55.4, 68.1, 108.7, 120.5, 126.1, 126.5, 140.1, 157.1; IR (film) ν_{max}: 3333, 2936, 2836, 1583, 1467, 1314 cm^{-1}; LRMS (EI) *m/z* (%) 178 ($M^{+\cdot}$, 75), 160 (100), 147 (40), 121 (41), 91 (79). HRMS [ESI(+)]: *m/z* calcd for $[C_{11}H_{14}O_2Na]^+$ 201.0891, found 201.0883.

(−)-(*R*)-**2b** $[\alpha]_D^{27} = -15.2$ (*c* 0.65, $CHCl_3$), ee >99%; t_R = 74.29 min (100%).

(+)-(*R*)-**2c** $[\alpha]_D^{27} = +101.8$ (*c* 1.30, $CHCl_3$), ee >99%; white solid mp: 36.0–37.0 °C; ^1H NMR (500 MHz) δ: 1.79–2.0 (m, 4H), 2.08 (s, 3H), 2.50–2.56 (m, 1H), 2.80–2.85 (m, 1H), 3.82 (s, 3H), 5.98–5.99 (m, 1H), 6.78 (dd, *J* 8.0 Hz and *J* 0.7 Hz, 1H), 6.90 (d, *J* 8 Hz, 1H), 7.17 (t, *J* 8 Hz, 1H); ^{13}C NMR (125 MHz) δ: 18.0, 21.5, 22.7, 28.6, 55.4, 70.0, 109.2, 121.4, 126.4, 127.1, 135.7, 157.1, 170.8; IR (film) ν_{max}: 3441, 2932, 2867, 1728, 1588, 1472 cm^{-1}; LRMS (EI) *m/z* (%): 220 ($M^{+\cdot}$, 2), 160 (100), 145 (24), 129 (22), 91 (18). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.77; H, 7.35.

4.4.4. (*S*)-1,2,3,4-Tetrahydro-7-methoxynaphthalen-1-ol 3b, (*S*)- and (*R*)-1,2,3,4-tetrahydro-7-methoxynaphthalen-1-yl acetate 3c.

Reaction time: 2 h 30 min. (±)-**3b** (0.19 g, 1.1 mmol) was converted into (+)-(*S*)-**3b** (47%; 0.093 g, 0.52 mmol) and (+)-(*R*)-**3c** (46%; 0.11 g, 0.51 mmol).

(+)-(*S*)-**3b**: $[\alpha]_D^{24} = +41.9$ (*c* 1.05, $CHCl_3$), ee >99%; {lit.[28] (*S*)-**3b**: $[\alpha]_D^{25} = +45.8$ (*c* 3.63, $CHCl_3$), ee = 100%}; mp: 45.0–46.0 °C; ^1H NMR (300 MHz) δ: 1.65–1.97 (m, 4H), 2.29 (s, 1H), 2.56–2.76 (m, 2H), 3.75 (s, 3H), 4.65–4.68 (m, 1H), 6.95–6.99 (m, 2H), 6.74 (dd, *J* 8 Hz and *J* 3 Hz, 1H), 2.29 (br s, 1H); ^{13}C NMR (75 MHz) δ: 19.1, 28.3, 32.3, 55.1, 68.2, 112.6, 114.1, 129.0, 129.7, 139.8, 157.8; IR (film) ν_{max}: 3434, 3367, 2847, 1611, 1502 cm^{-1}; LRMS (EI) *m/z* (%): 178 ($M^{+\cdot}$, 85), 160 (100), 121 (73), 91 (36). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.08; H, 8.19.

(+)-(*R*)-**3c**: $[\alpha]_D^{24} = +88.5$ (*c* 1.14, $CHCl_3$), ee >99%; t_R = 73.92 min (100%); white solid mp: 92.0–93.0 °C; ^1H NMR (500 MHz) δ: 1.77–1.98 (m, 4H), 2.09 (s, 3H), 2.65–2.81 (m, 2H), 2.76–2.81 (m, 1H), 3.77 (s, 3H), 5.95–5.96 (m, 1H), 6.80–6.82 (m, 2H), 7.04 (d, *J* 9 Hz, 1H); ^{13}C NMR (125 MHz) δ: 19.0, 21.5, 28.2, 29.1, 55.4, 70.2, 113.7, 114.8, 130.0, 130.0, 135.5, 157.8, 170.8; IR (film) ν_{max}: 3432, 3025, 2939, 2839, 1731, 1503 cm^{-1}; LRMS (EI) *m/z* (%): 220 ($M^{+\cdot}$, 4), 160 (100), 145 (23), 129 (19), 115 (16), 91 (15). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.59; H, 7.56.

(−)-(*S*)-**3c**: $[\alpha]_D^{24} = -85.5$ (*c* 1.27, $CHCl_3$), ee >99%; t_R = 74.49 min (100%).

4.4.5. (*S*)-1,2,3,4-Tetrahydro-5,7-dimethylnaphthalen-1-ol 4b, (*S*)- and (*R*)-1,2,3,4-tetrahydro-5,7-dimethyl naphthalen-1-yl acetate 4c.

Reaction time: 20 h. (±)-**4b** (0.089 g, 0.50 mmol) was converted into (+)-(*S*)-**4b** (44%; 0.039 g, 0.22 mmol) and (+)-(*R*)-**4c** (38%; 0.041 g, 0.19 mmol).

(+)-(*S*)-**4b**: $[\alpha]_D^{27} = +38.9$ (*c* 1.20, $CHCl_3$), ee = 99%; {lit.[3] (*R*)-**4b** $[\alpha]_D^{22} = -31.6$ (*c* 1.05, $CHCl_3$), ee = 95%}; white solid mp: 85.0–86.0 °C; ^1H NMR (300 MHz) δ: 1.76–2.05 (m, 5H), 2.19 (s, 3H), 2.29 (s, 3H), 2.44–2.70 (m, 2H), 4.71–4.74 (m, 1H), 6.92 (s, 1H), 7.11 (s, 1H); ^{13}C NMR (75 MHz) δ: 18.5, 19.4, 20.9, 26.2, 31.8, 68.5, 126.9, 130.1, 132.4, 135.2, 136.4, 138.7; IR (film) ν_{max}: 3304, 2922, 2860, 1480, 1072 cm^{-1}; LRMS (EI) *m/z* (%): 176 ($M^{+\cdot}$, 76), 158 (93), 143 (100), 133 (52). HRMS [ESI(+)]: *m/z* calcd for $[C_{12}H_{16}ONa]^+$ 199.1099, found 199.1094.

(+)-(*R*)-**4c**: $[\alpha]_D^{22} = +98.1$ (*c* 1.22, $CHCl_3$), ee = 99%; t_R = 66.51 min (99.50%); white solid mp: 45.5–46.5 °C; ^1H NMR (500 MHz) δ: 1.79–1.99 (m, 4H), 2.07 (s, 3H), 2.20 (s, 3H), 2.27 (s, 3H), 2.47–2.53 (m, 1H), 2.68–2.73 (m, 1H), 5.95–5.97 (m, 1H), 6.95 (br s, 2H); ^{13}C NMR (125 MHz) δ: 18.5, 19.4, 20.8, 21.6, 26.0, 28.6, 70.5, 127.7, 130.7, 133.3, 134.2, 135.2, 136.5, 170.8; IR (film) ν_{max}: 2950, 2861, 1731, 1480, 1237 cm^{-1}; LRMS (EI) *m/z* (%): 218 ($M^{+\cdot}$, 1), 176 (15), 158 (100), 143 (89). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.83; H, 8.53.

(−)-(*S*)-**4c**: $[\alpha]_D^{22} = -90.4$ (*c* 1.35, $CHCl_3$), ee = 99%; t_R = 67.54 min (99.40%).

4.4.6. (*S*)-1,2,3,4-Tetrahydro-6-methyl-7-methoxynaphthalen-1-ol 5b, (*S*)- and (*R*)-1,2,3,4-tetrahydro-6-methyl-7-methoxynaphthalen-1-yl acetate 5c.

Reaction time: 4 h. (±)-**5b** (0.16 g, 0.83 mmol) was converted into (+)-**5b** (48%; 0.77 g, 0.40 mmol) and (+)-**5c** (47%; 0.91 g, 0.39 mmol).

(+)-**5b**: $[\alpha]_D^{27} = +36.9$ (*c* 0.99, $CHCl_3$), ee = 98%; white solid mp: 82.0–83.0 °C; ^1H NMR (500 MHz) δ: 1.70–2.00 (m, 5H), 2.17 (s, 3H), 2.57–2.72 (m, 2H), 3.81 (s, 3H), 4.70–4.72 (m, 1H), 6.85 (s, 1H), 6.88 (s, 1H); ^{13}C NMR (125 MHz) δ: 15.9, 19.2, 28.3, 32.6, 55.4, 68.4, 109.6, 126.3, 128.5, 131.0, 137.0, 156.2; IR (film) ν_{max}: 3391, 3011, 2935, 2861, 2836, 1589, 1253, 1028 cm^{-1}; LRMS (EI) *m/z* (%) 192 (M^+, 100), 177 (76), 159 (50), 149 (38); Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.64; H, 8.55.

(+)-**5c**: $[\alpha]_D^{27} = +106.6$ (*c* 1.22, $CHCl_3$), ee >99%; t_R = 80.09 min (100%); white solid mp: 52.5–53.5 °C; for spectral data, see Section 4.3.5; Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.85; H, 7.58.

(−)-**5c**: $[\alpha]_D^{27} = -96.9$ (*c* 1.15, $CHCl_3$), ee = 98%; t_R = 81.65 min (98.90%).

4.4.7. 1,2,3,4-Tetrahydro-4-methylnaphthalen-1-ol 7b/7b′ and 1,2,3,4-tetrahydro-4-methylnaphthalen-1-yl acetate 7c/7c′.

Reaction time: 20 h. (±)-**7b/7b′** (*trans*:*cis*, 2:3) (0.32 g, 2.0 mmol) was converted into a mixture 2:3 *trans*:*cis* of **7b/7b′** (47%; 0.15 g, 0.93 mmol) and a mixture 2:3 *trans*:*cis* of **7c/7c′** (47%; 0.19 g, 0.94 mmol).

t_R = 41.80 min—**7c′** *cis* (100%); t_R = 42.20 min—**7c** *trans* (100%).

t_R = 44.36 min—**7c′** *cis* (100%); t_R = 45.09 min—**7c** *trans* (100%).

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