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Artigo

BIOREDUCTION OF SUBSTITUTED *a*-TETRALONES PROMOTED BY *Daucus carota* ROOT‡

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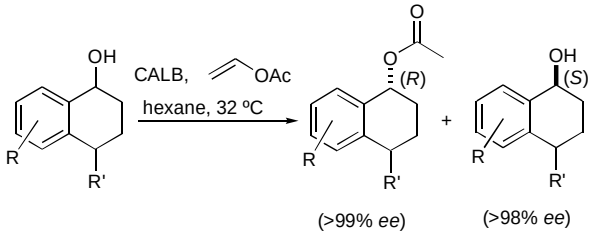
The bioreduction of a series of substituted *a*-tetralones, carried out using *Daucus carota* root (carrot), afforded the corresponding homochiral *a*-tetralols in variable conversions (9 to 90%) and excellent enantiomeric excesses. Two of the assayed *a*-tetralones were resistant to the bioreduction conditions. The absolute configurations of four *a*-tetralols were assigned as being (*S*), by comparison to the (*S*)-enantiomers obtained by kinetic resolution promoted by CALB-catalysed acetylation. Additionally, the new 5-methoxy-6-methyl-1-tetralone was synthesized in seven steps from 3-methylsalicylic acid.

Keywords: bioreduction; *Daucus carota; a*-tetralols.

INTRODUCTION

α-Tetralols are versatile intermediates in organic synthesis, being employed as building blocks and as catalysts ligands.[1-4] Therefore, many efforts have been dedicated to search for reactions that can furnish homochiral α-tetralols. There are several reports dealing with the asymmetric hydrogenation of the α-tetralone itself,[5-11] as well as with its bioreduction, using either isolated enzymes or microorganisms.[12-16] It is of note that substituted homochiral β-tetralols have been obtained by reacting a large variety of enzymes and microorganisms with the corresponding β-tetralones.[11,17-21] To our knowledge, however, there are no previous works dealing with the analogous substituted α-tetralones.

In a recent paper, we reported the enzymatic kinetic resolution of a series of *a*-tetralols, using the lipase B from *Candida antarctica* (CALB).[22] The (*S*)-1-tetralols and their respective (*R*)-acetates were obtained in excellent enantiomeric excesses. The absolute configurations of the products were assigned by comparison of the optical rotation values to those of literature. These results are summarized in Scheme 1.



Scheme 1

The *Daucus carota* root is frequently used to promote the bioreduction of a number of ketones, constituting an efficient way for the preparation of enantiomerically pure secondary alcohols.[12, 23-30] To our knowledge, there is just one paper concerning the *Daucus carota* promoted bioreduction of two α-tetralones, namely the α-tetralone itself and the 6-methoxy-1-tetralone.[12]

Therefore, we decided to investigate the behaviour of a series of substituted α-tetralones towards the bioreduction with *Daucus carota*, aiming higher yields (theoretically 100%) than those earlier obtained using CALB in the kinetic resolution (theoretically 50%).[22] Moreover, the α-tetralol derivatives could be useful model substrates in our studies concerning the synthesis of some natural products, such as the sesquiterpenes mutisianthol (I)[31,32] and jungianol (II),[33-35] and the lignane flossonol (III)[36] (Figure 1).

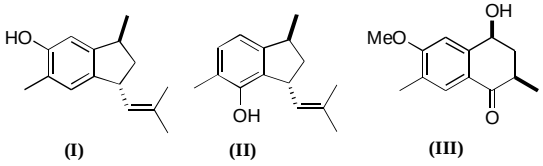
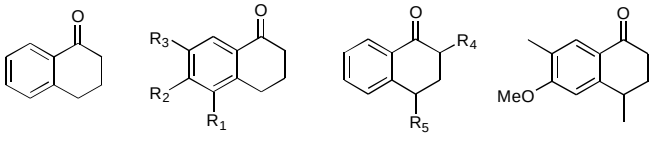


Figure 1. *Mutisianthol (I), jungianol (II) and flossonol (III)*

RESULTS AND DISCUSSION

A series of nine substituted *a*-tetralones, besides the α-tetralone itself (Figure 2) were employed as substrates for the bioreduction studies. The tetralones **1a-7a** are commercially available, while the others (**8a-10a**) were synthesized as described in the next sections.

The *a*-tetralones **8a** and **10a** were prepared according to known procedures from 2-methyl-anisole, as depicted in Scheme 2.[32, 37]



1a **2a-5a, 8a-9a** **6a-7a** **10a**

2a. R_2=R_3=H; R_1=OMe
3a. R_1=R_3=H; R_2=OMe
4a. R_1=R_2=H; R_3=OMe
5a. R_2=H; R_1=R_3=Me
8a. R_1=H; R_2=Me; R_3=OMe
9a. R_3=H; R_1=OMe; R_2=Me

6a. R_5=H; R_4=Me
7a. R_5=Me; R_4=H

Figure 2. *Tetralones **1a-10a***

† *in memorian*, 1948-2007.
‡ This article is dedicated to Prof. Helena M. C. Ferraz
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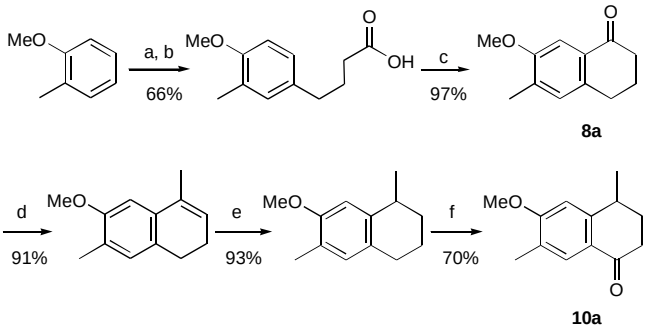
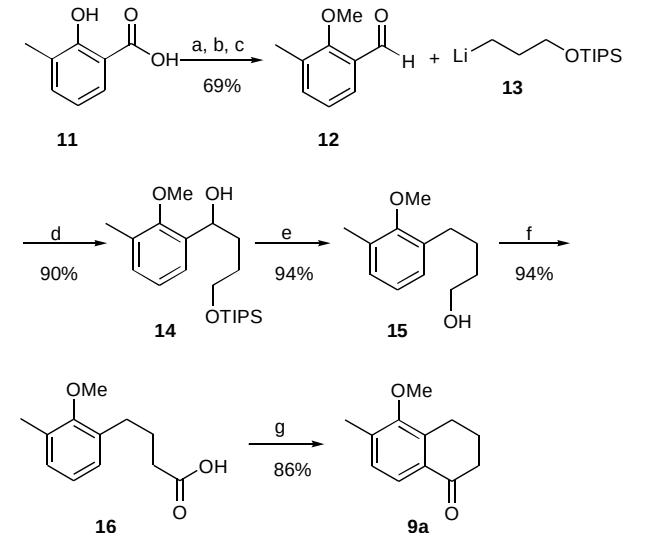


Scheme 2. *Reagents and conditions: a) succinic anhydride, $C_6H_5NO_2$, $AlCl_3$, 0-5 ºC, 24 h; b) Zn(Hg), H_2O, HCl, toluene, rt, 48 h; c) trifluoracetic acid, trifluoracetic anhydride, rt, 10 min; d) i: MeMgI, Et_2O, reflux, 1 h; ii: 10% HCl, rt, 3 h, e) 6 atm $H_{2(g)}$, Pd/C, rt, 16 h; f) CrO_3, H_2O/AcOH, rt, 20 min*

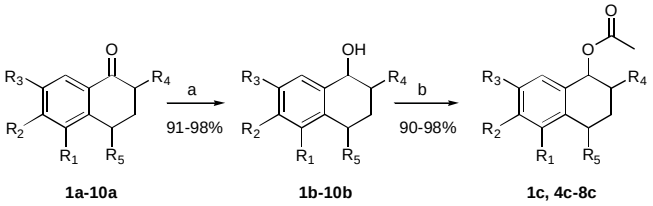
The *a*-tetralone **9a** was synthesized in seven steps from 3-methylsalicylic acid (**11**), as summarized in Scheme 3. Although the 2-methoxy-3-methyl benzaldehyde (**12**) is commercially available, this compound was prepared in 3 steps from the acid **11**, through known reactions.[38] Addition of the alkyllithium **13** to the aldehyde **12** afforded the intermediate **14**, which was then submitted to hydrogenolysis under acidic conditions. These conditions promoted the concomitant deprotection of the silylether, furnishing the primary alcohol **15** in 85% yield from **12**. Oxidation of **15** with Jones reagent, followed by intramolecular cyclization, led to the desired product **9a** in 81% yield for the two steps.



Scheme 3. *Reagents and conditions: a) $LiAlH_4$, THF, $N_{2(g)}$, rt, 16 h; b) MeI, K_2CO_3, acetone, 85 ºC, 16 h; c) PCC, CH_2Cl_2, rt, 3 h; d) THF, 0 °C, 2 h; e) 4 atm $H_{2(g)}$, Pd/C, $HClO_4$, rt, 16 h; f) CrO_3/ H_2SO_4, acetone, 0 ºC, 2 h; g) polyphosphoric acid, 65 ºC, 1 h*

The tetralones were initially submitted to reduction with sodium borohydride, to obtain the racemic patterns of the tetralols. Several of them (**1b**, **4b-8b**) could not be analytically resolved by chiral gas chromatography, and therefore were acetylated using classical conditions. The results are shown in Scheme 4.

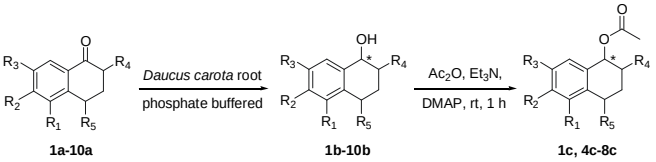
The *a*-tetralones **1a-10a** were then submitted to the reaction with carrot, in a phosphate buffered aqueous medium, employing acetonitrile and ethanol for solubilization of the substrates. The



Scheme 4. *Reagents and conditions: a) 2 eq. $NaBH_4$, MeOH, 0 °C-ta, 1 h; b) 3 eq. Ac_2O, Et_3N, DMAP, ta, 1 h*

erlenmeyers containing the reactional mixture were stirred at 32 °C and 180 rpm during 4 days. In the first set of experiments (conditions A, Table 1), for 20 mg of the tetralones were used 10 g of carrot. In the second set (conditions B, Table 1) the amount of carrot was doubled.

Table 1. Bioreduction of the α-tetralones **1a-10a** mediated by *Daucus carota* root in 4 days



Substrate	*Conditions A*[a] Conversion[c,d] (%)	*ee*[d] of **1b-10b** (%) (*conf.*)	*Conditions B*[b] Conversion[c,d] (%)	*ee*[d] of **1b-10b** (%) (*conf.*)
1a	57	95 (*S*)	88	95 (*S*)
2a	80	>99 (*S*)	13	1
3a	11	60 (nd)	29	30 (nd)
4a	82	>99 (*S*)	90	98 (*S*)
5a	20	>99 (*S*)	53	97 (*S*)
6a	0	—	0	—
7a	37	*cis:* 64; *trans*: 99	79	*cis*:90; *trans*:97
8a	9	>99 (nd)	34	>99 (nd)
9a	75	>99 (nd)	70	85 (nd)
10a	0	—	0	—

[a] 20 mg of **1a-10a** in 40 mL of phosphate buffer and 10 g of *Daucus carota* root. [b] 20 mg of **1a-10a** in 80 mL of phosphate buffer and 20 g of *Daucus carota* root. [c] Conversion of **1a-10a** to the alcohols **1b-10b** after acetylation reaction of **1b**, **4b-8b**. [d] Determined by chiral GC. nd: not determined; conf: configuration.

The conversions of the α-tetralones to the α-tetralols in the conditions A were variable, ranging from 9 to 82%, while the enantiomeric excesses were very good for the majority of the obtained α-tetralols. Doubling the amount of carrot (conditions B) increased the conversion of six tetralones, namely **1a**, **3a**, **4a**, **5a**, **7a** and **8a**, but the enantiomeric excess was better just for the reduction of **7a**. The tetralone **2a** gave a high enatiomeric excess and conversion in the conditions A. However, it was surprising that in the conditions B these good results could not be reproduced. The tetralones **6a** and **10a** were resistant to both the reduction conditions.

A possible explanation for the lack of reactivity of the tetralone **6a** would be the *a*-carbonylic position of the methyl group, which certainly causes a steric hindrance. It is of note that the difficulty of the analogous tetralol **6b** in reacting with isolated enzymes[22,39] and microorganisms[40] was already observed. The tetralone **10a**

showed to be resistant also to chemical reduction, requiring 5 equivalents of sodium borohydride for the preparation of (±)-**10b**.[32]

The chromatograms of the products obtained in the bioreduction of the *a*-tetralones **1a** and **4a** are presented in Figures 3 and 4, respectively.

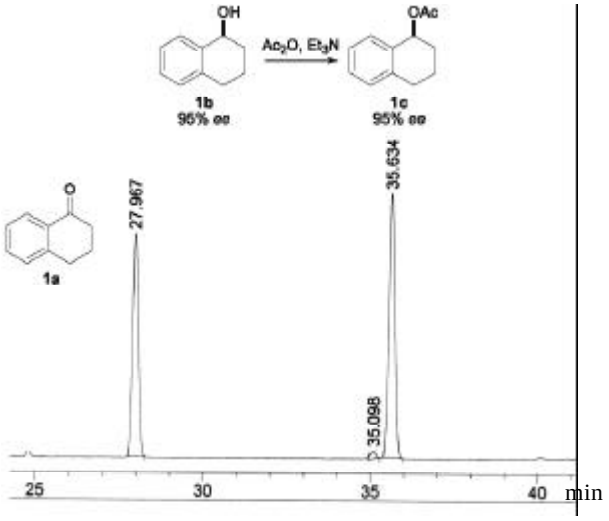


Figure 3. *Chromatogram obtained after bioreduction of tetralone* ***1a*** *in the conditions A*

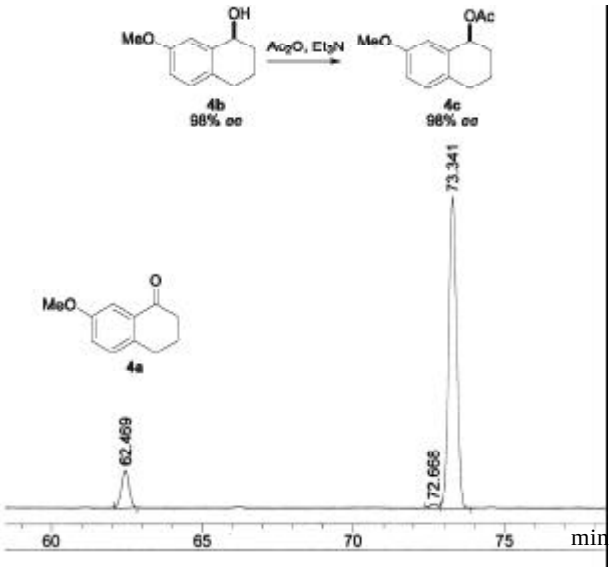


Figure 4. *Chromatogram obtained after bioreduction of tetralone* ***4a*** *in the conditions B*

We have assigned the (*S*)-configuration to the tetralols **1b**, **2b**, **4b** and **5b**, by comparison of the retention time in the GC analysis with those obtained previously for these tetralols.[22] The (*S*) configuration agrees to Prelog's rule,[41] which predict that hydrogen transfer to the prochiral ketone occurs to the face where the large group is in the right side (Figure 5a), in this case the *Re*-face (Figure 5b). Additionally, Yadav *et al.*[12] attributed the (*S*)-configuration to the *a*-tetralol (**1b**) and to the 6-methoxy-1-tetralol (**3b**) obtained by bioreduction mediated by carrot of the corresponding α-tetralones.

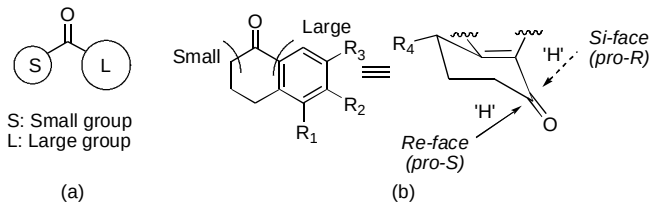


Figure 5. (a) *Ketone more reactive (b) Prelog's rule applied to the* α*-tetralones*

Finally, the bioreduction of the tetralone (±)-**7a** led to either the enantiomer of the *cis* isomer (90% *ee*) and of the *trans* isomer (97% *ee*). This result showed that the keto-reductase from carrot (probably *pro-S* enantioselective) was not sensitive to substituents at the 4-position, since a mixture of 1:1 (*cis:trans*) was obtained (Figure 6). It is noteworthy that Bégué *et al.* observed a similar behaviour when (±)-**7a** was submitted to bioreduction mediated by *Rhodotorula rubra*.[42]

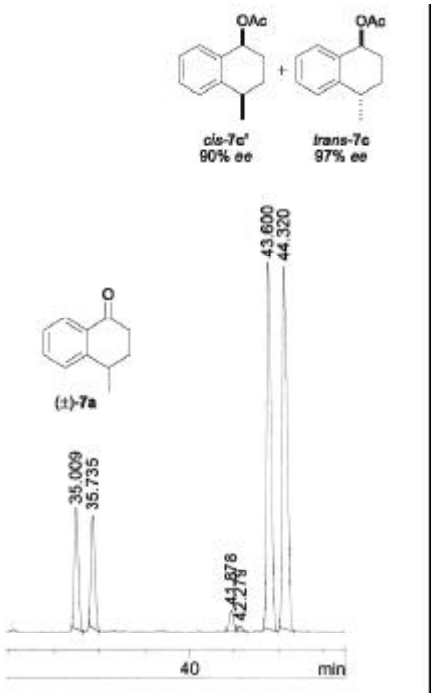


Figure 6. *Chromatogram obtained after bioreduction of tetralone (±)-****7a*** *in the conditions B – signals at 41.88 and 43.60 min: cis-enantiomer* ***7c'****; signals at 42.28 and 44.32 min: trans-enantiomer* ***7c***

CONCLUSION

The *Daucus carota*-promoted bioreduction of eight substituted *a*-tetralones afforded the corresponding homochiral alcohols in conversions ranging from 9 to 90% and in very good enantiomeric excesses. Four of the *a*-tetralols thus obtained have the absolute configuration assigned as (*S*). This biotransformation may be an useful tool for the asymmetric synthesis of natural products with biological properties such as flossonol.[36]

EXPERIMENTAL

General

All solvents and chemicals used were previously purified according to the usual methods. Column chromatography was performed using silica gel 200-400 mesh. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with TMS as the internal standards and recorded on Bruker and Varian spectrometers. IR spectra were measured on a Perkin-Elmer 1750-FT. Gas chromatography analyses were performed in a HP-6890 series II. Conversions and enantiomeric excesses were determined using a HP-6890 series II

gas chromatograph equipped with a chiral capillary column AG100-2000 (packed with β-cyclodextrin (30 m x 0.32 mm x 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. The carrot was bought in a local market. The racemic tetralols **1b**, **2b**, **4b**-**8b** and acetates **1c**, **4c**-**8c** were prepared according to known procedures.[22] The spectroscopic data of these compounds were identical to those earlier reported.[22]

Preparation of the tetralone 9a

4-(triisopropylsililoxy)-1-(2-methoxy-3-methylphenyl)butane-1-ol (**14**)

To a two-necked flask, under nitrogen, was added metallic lithium (0.88 g, 0.13 mol) in small pieces that was washed with dry hexanes. After a few minutes under nitrogen, (3-bromopropoxy)triisopropylsilane (8.8 g, 30 mmol) was added in dry THF (100 mL). This solution was irradiated by ultrasound for 2 h. The grey solution of **13** was transferred by cannula to another two-necked flask equipped with a magnetic stirrer, ice bath and under nitrogen containing a solution of aldehyde **12** (3.0 g, 20 mmol) in dry Et_2O (100 mL). This mixture was stirred for 2 h at 0 °C. The reaction was quenched with water and then extracted with EtOAc. The combined organic layers were washed with water, brine and then dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography [silica gel 200-400 mesh, eluent with a mixture of 7:3 hexanes: EtOAc] to afford **14** (6.6 g, 18 mmol, 90%) as a colorless oil. ^{1}H NMR (300 MHz) δ: 1.04-1.15 (m, 21H), 1.60-1.97 (m, 4H), 2.29 (s, 3H), 3.75-3.79 (m, 5H), 5.02 (dd, *J* 7.7 and 4.8 Hz, 1H), 7.00-7.05 (m, 1H), 7.06-7.10 (m, 1H), 7.27-7.30 (m, 1H); ^{13}C NMR (75 MHz) δ: 12.0, 16.1, 18.0, 29.8, 35.7, 60.8, 63.6, 69.0, 124.2, 124.6, 130.2, 130.7, 137.7, 155.7; IR (film) $n_{máx}$/cm^{-1}: 3418; LRMS (EI) *m/z* (%):175 ($M^{+\cdot}$, 100). Anal. calcd for $C_{21}H_{38}O_3Si$: C, 68.89; H, 10.45. Found: C, 68.76; H, 10.35.

4-(2-methoxy-3-methylphenyl)butan-1-ol (**15**)

To an autoclave system equipped with a magnetic stirrer were added **14** (7.2 g, 21 mmol), dry methanol (50 mL) and $HClO_4$ (1 mL). This mixture was stirred until completed homogenization and then 10% Pd/C (0.20 g) was added. The autoclave was purged three times with hydrogen gas and then pressurized at the 4 atm. After 16 h at the room temperature, the excess of hydrogen gas was released. The reactional mixture was filtered through silica gel column chromatography using CH_2Cl_2. The organic phase was washed with water, brine and then dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography [silica gel 200-400 mesh, eluent with a mixture of 1:1 hexanes: EtOAc] to afford **15** (3.9 g, 20 mmol, 94%) as a yellow oil. ^{1}H NMR (300 MHz) δ: 1.58-1.74 (m, 1H), 2.29 (s, 3H), 3.63-3.68 (m, 2H), 3.65-3.70 (m, 2H), 3.73 (s, 3H), 6.92-6.97 (m, 1H), 7.01-7.03 (m, 2H); ^{13}C NMR (75 MHz) δ: 16.2, 26.9, 29.4, 32.5, 60.3, 62.8, 123.9, 127.8, 129.0, 130.9, 135.1, 156.7. IR (film) $\nu_{máx}$/cm^{-1}: 3363; LRMS (EI) *m/z* (%): 194 ($M^{+\cdot}$, 46), 135 (85), 105 (100). HRMS [ESI (+)]: *m/z* calcd for $[C_{12}H_{18}O_2+Na]^+$ 217.1204, found 217.1203.

4-(2-methoxy-3-methylphenyl)butanoic acid (**16**)

To a two-necked flask equipped with a drying tube, magnetic stirrer and ice bath, acetone (50 mL) and **15** (1.4 g, 7.3 mmol) were added. The mixture was stirred until completed solubilization. The Jones reagent was slowly added until the brown color persists. After 2 h the reaction was quenched by addition of isopropylic alcohol and then extracted with EtOAc. The combined organic layers were washed with water, brine and then dried with anhydrous $MgSO_4$. After the solvent removal under reduced pressure, the desired product was purified by flash chromatography [silica gel 200-400 mesh, eluent with a mixture of 1:1 hexanes: EtOAc] to afford **16** (1.1 g, 6.9 mmol, 94%) as a yellow solid: mp: 54.9- 56.0 ºC; ^{1}H NMR (300 MHz) δ: 1.91-2.01 (m, 2H), 2.29 (s, 3H), 2.40 (t, *J* 7.4 Hz, 2H); 2.69 (t, *J* 7.4 Hz, 2H), 3.72 (s, 3H), 6.92-6.97 (m, 1H), 7.01-7.05 (m, 2H); ^{13}C NMR (75 MHz) δ: 16.2, 25.6, 29.1, 33.6, 60.3, 124.0, 127.8, 129.4, 131.1, 156.8, 179.6; IR (film) $\nu_{máx}$/cm^{-1}: 1706; LRMS (EI) *m/z* (%): 208 ($M^{+\cdot}$,42), 148 (50), 133 (70). Anal. calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.76; H, 7.67.

3,4-dihydro-5-methoxy-6-methylnaphthalen-1(2H)-one (**9a**)

To a two-necked flask equipped with magnetic stirrer, oil bath, condenser and drying tube were added **16** (2.7 g, 13 mmol) and polyphosphoric acid (40 mL). The mixture was stirred at 65-75 ºC for 1 h. After that, the warm red solution was slowly poured into ice (16 g) and then was stirred for 20 min. The aqueous phase was extracted with Et_2O. The combined organic layers were washed with water, brine and then dried with anhydrous $MgSO_4$. After the solvent removal under reduced pressure, the desired product was purified by Kugelrohr distillation (horizontal distillation) (0.7 mmHg, 175 ºC) to afford the tetralone **9a** (2.1 g, 11 mmol, 86%) as a yellow solid: mp: 57.9-58.5 ºC; ^{1}H NMR (300 MHz) δ: 2.06-2.15 (m, 2H), 2.34 (s, 3H), 2.62 (t, *J* 6.1 Hz, 2H), 2.97 (t, *J* 6.1 Hz, 2H), 3.77 (s, 3H), 7.14 (dd, *J* 8.0 and 0.5 Hz, 1H), 7.75 (d, *J* 8.0 Hz, 1H); ^{13}C NMR (75 MHz) δ: 16.5, 22.9, 23.4, 38.8, 59.9, 122.8, 129.1, 132.3, 137.1, 137.5, 155.8, 198.0. IV (film) $\nu_{máx}$/cm^{-1}: 1682; LRMS (EI) *m/z* (%): 190 ($M^{+\cdot}$,100), 175 (33), 134 (39); Anal. calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.46. Found: C, 75.60; H, 7.20.

General procedure for reduction of the tetralones 1a-10a

Preparation of 1,2,3,4-tetrahydro-6-methoxynaphthalen-1-ol (**3b**)[43]

To a solution of 1,2,3,4-tetrahydro-6-methoxynaphthalen-1-one (**3a**) (0.36 g, 2.0 mmol) in anhydrous MeOH (6 mL) at 0 ºC and under N_2, $NaBH_4$ (0.15 g, 4.0 mmol, 2 eq.) was portionwise added. The mixture was allowed to reach room temperature and then was 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 **3b** as a colorless oil (0.32 g, 1.8 mmol, 90%); ^{1}H NMR (300 MHz) δ: 1.68-2.03 (m, 5H), 2.63-2.84 (m, 2H), 3.78 (s, 3H), 4.72-4.74 (m, 1H), 6.61-6.62 (d, *J* 3 Hz, 1H), 6.76 (dd, *J* 9 Hz and *J* 3 Hz, 1H), 7.32 (d, *J* 9 Hz, 1H). The alcohol **3b** is unstable and decomposed before fully characterization.

1,2,3,4-tetrahydro-5-methoxy-6-methylnaphthalen-1-ol (**9b**)

Using the general procedure described for **3b**, the 1,2,3,4-tetrahydro-5-methoxy-6-methylnaphthalen-1-one (**9a**) (0.36g, 1.9 mmol) was converted into **9b** (0.34 g, 1.8 mmol, 95%); ^{1}H NMR (300 MHz) δ: 1.71-2.06 (m, 4H), 2.26 (s, 3H), 2.58-2.68 (m, 1H), 2.80-2.90 (m, 1H), 3.70 (s, 3H), 4.72-4.75 (m, 1H), 7.03 (dd, *J* 7.8 and 0.6 Hz, 1H), 7.11 (d, *J* 7.8 Hz, 1H); ^{13}C NMR (75 MHz) δ: 16.0, 18.3, 23.4, 31.9, 59.4, 68,0, 124.3, 128.8, 129.9, 130.5, 138.2, 156.0. IR (film) $\nu_{máx}$/cm^{-1}: 3237; LRMS (EI) *m/z* (%): 192 ($M^{+\cdot}$,

100), 177 (74), 91 (75). Anal. calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.68; H, 7.91.

1,2,3,4-tetrahydro-4,7-dimethyl-6-methoxynaphthalen-1-ol (**10b**)

Using the general procedure described for **3b**, except for the amount of $NaBH_4$ (5 eq., 0.10 g, 2.7 mmol), 1,2,3,4-tetrahydro-4,7-dimethyl-6-methoxynaphthalen-1-one (**10a**) (0.11 g, 0.54 mmol) was converted into **10b** (0.10 g, 0.51 mmol, 95%) as a colorless oil. The alcohol **10b** is unstable and decomposed before fully characterization.

Control of the bioreduction of *a*-tetralones

Tetralones **1a-10a** and the corresponding tetralols **1b-10b** obtained from bioreduction were compared with the racemic mixtures previously analyzed. GC conditions: Injector: 250 ºC, Detector: 350 ºC, Oven: 120-180 º C (120 min), Rate: 0.5 ºC/min, flow: 1.4 mL/min; Pressure of $H_{2(g)}$: 10 psi, Constant pressure, Split ratio 1:50. t_R=retention time (min).

General procedures for biorreduction of the tetralones 1a-10a with *Daucus carota* root

Conditions A: Tetralones **1a-10a** (20 mg) were dissolved in a mixture of acetonitrile (0,5 mL) and ethanol (0,5 mL) and the solutions obtained were added to a suspension of freshly cut carrot root (10 g, thickness of 0,5 cm, previously sterilized by washing in 2% NaOCl) in 40 mL of phosphate buffer (0,1 M). The reaction mixtures were incubated in an orbital shaker (180 rpm) at 32 °C for 4 days. A collected aliquot of the reactional mixture was centrifuged and the aqueous medium was extracted with EtOAc. The solvent was removed and the residual product was directly analyzed by GC. The results are summarized in Table 1.

Conditions B: identical, except for carrot (20 g) and buffer (80 mL).

Quiral-GC data

1a: t_R= 27.9 min; (*R*)-**1c**: t_R=35.09 min (minor); (*S*)-**1c**: t_R=35.63 min (major).
2a: t_R=65.2 min; (*S*)-**2b**: t_R=75.20 min (minor); (*R*)-**2b**: t_R=76.32 min (major).
3a: t_R=77.0 min; **3b**: t_R=79.45 min (minor) and t_R=80.48 min (major)
4a: t_R=62.5 min; (*R*)-**4c**: t_R=72.67 min (minor); (*S*)-**4c**: t_R=73.34 min (major);
5a: t_R=59.9 min; (*R*)-**5c**: t_R=66.50 min (minor); (*S*)-**5c**: t_R=67.52 min (major);
(±)-**7a**: 35.0 and 35.7 min; *cis*-**7c**': t_R= 41.88 min (minor) and 43.60 (major); *trans*-**7c**: 42.28 min (minor) and 44.32 min (major)
8a: t_R=74.9 min; **8c**: t_R= 80.00 min (minor) and 81.03 min (major).
9a: t_R=73.0 min; **9b**: t_R=81.36 min (minor) and 82.35 min (major).

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REFERENCES

1. Ghatak, A.; Dorsey, J. M.; Garner, C. M.; Pinney, K. G.; *Tetrahedron Lett.* **2003**, *44*, 4145.
2. Yun, J.; Buchwald, S. L.; *J. Org. Chem.* **2000**, *65*, 767.
3. Armstrong, D. W.; Gahm, K. H.; Chang, L. W.; *Microchem. J.* **1997**, *57*, 149.
4. Cassady, J. M.; *J. Nat. Prod.* **1990**, *53*, 23.
5. Zhang, X.; Taketomi, T.; Yoshizumi, T.; Kumobayashi, H.; Akutagawa, S.; Mashima, K.; Takaya, H.; *J. Am. Chem. Soc.* **1993**, *115*, 3318.
6. Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K.; *Organometallics* **1991**, *10*, 500.
7. Faller, J. W.; Lavoie, A. R.; *Organometallics* **2001**, *20*, 5245.
8. Corey, E. J.; Helal, C. J.; *Tetrahedron Lett.* **1995**, *36*, 9153.
9. Jiang, Q.; Xiao, D.; Zhang, Z.; Cao, P.; Zhang, X.; *Angew. Chem., Int. Ed.* **1999**, *38*, 516.
10. Ohkuma, T.; Hattori, T.; Ooka, H.; Inoue, T.; Noyori, R.; *Org. Lett.* **2004**, *6*, 2681.
11. Verzijl, G. K. M.; Vries, J. G.; Broxterman, Q. B.; *Tetrahedron: Asymmetry* **2005**, *16*, 1603.
12. Yadav, J. S.; Nanda, S.; Thirupathi, R.; Rao, A. B.; *J. Org. Chem.* **2002**, *67*, 3900.
13. Jarosz, B.; Siewinski, A.; *J. Basic Microbiol.* **1996**, *36*, 245.
14. Carballeira, J. D.; Álvarez, E.; Campillo, M.; Pardo, L.; Sinisterra, J. V.; *Tetrahedron: Asymmetry* **2004**, *15*, 951.
15. Stampfer, W.; Kosjek, B.; Faber, K.; Kroutil, W.; *J. Org. Chem.* **2003**, *68*, 402.
16. Kabuto, K.; Imuta, M.; Kempner, E. S.; Ziffer, H.; *J. Org. Chem.* **1978**, *43*, 2357.
17. Abalain, C.; Buisson, D.; Azerad, R.; *Tetrahedron: Asymmetry* **1996**, *7*, 2983.
18. Martinez, G. R.; *Tetrahedron: Asymmetry* **1995**, *6*, 1491.
19. Manito, P.; Speranza, G.; Monti, D.; Fontana, G.; Panosetti, E.; *Tetrahedron* **1995**, *51*, 11531.
20. Aina, G.; Nasini, G.; Pava, O. V.; *J. Mol. Catal. B: Enzym.* **2001**, *11*, 367.
21. Yadav, J. S.; Reddy, G. S. K. K.; Sabitha, G.; Krishna, A. D.; Prasad, A. R.; Rahaman, H. U. R.; Rao, K. V.; Rao, A. B.; *Tetrahedron: Asymmetry* **2007**, *18*, 717.
22. Ferraz, H. M. C.; Bianco, G. G.; Teixeira, C. C.; Andrade, L. H.; Porto, A. L. M.; *Tetrahedron: Asymmetry* **2007**, *18*, 1070.
23. Blanchard, N.; van de Weghe, P.; *Org. Biomol. Chem.* **2006**, *4*, 2348.
24. Baskar, B.; Ganesh, S.; Lokeswari, T. S.; Chadha, A.; *J. Mol. Catal. B: Enzym.* **2004**, *27*, 13.
25. Maczka, W.; Mironowicz, A.; *Tetrahedron: Asymmetry* **2002**, *13*, 2299.
26. Yadav, J. S.; Reddy, P. T.; Nanda, S.; Rao, A. B.; *Tetrahedron: Asymmetry* **2001**, *12*, 3381.
27. Chadha, A.; Manohar, M.; Soundararajan, T.; Lokeswari, T. S.; *Tetrahedron: Asymmetry* **1996**, *7*, 1571.
28. Cordell, G. A.; Lemos, T. L. G.; Monte, F. J. Q.; Mattos, M. C.; *J. Nat. Prod.* **2007**, *70*, 478.
29. Bruni, R.; Fantin, G.; Maietti, S.; Medici, A.; Pedrini, P.; Sacchetti, G.; *Tetrahedron: Asymmetry* **2006**, *17*, 2287.
30. Comasseto, J. V.; Omori, A. T.; Porto, A. L. M.; Andrade, L. H.; *Tetrahedron Lett.* **2004**, *45*, 473.
31. Bohlmann, F.; Zdero, C.; Le Van, N.; *Phytochemistry* **1979**, *18*, 99.
32. Ferraz, H. M. C.; Aguilar, A. M.; Silva, L. F., Jr.; *Tetrahedron* **2003**, *59*, 5817.
33. Bohlmann, F.; Zdero, C.; *Phytochemistry* **1977**, *16*, 239.
34. Ho, T.-L.; Lee, K.-Y.; Chen, C.-K.; *J. Org. Chem.* **1997**, *62*, 3365.
35. Hashmi, A. S.; Ding, L.; Bats, J. W.; Fischer, P.; Frey, W.; *Chem. Eur. J.* **2003**, *9*, 4339.
36. Sun, N.; Chang, C.; Cassady, J. M.; *Phytochemistry* **1987**, *26*, 3051.
37. Zubaidha, P. K.; Chavan, S. P.; Racherle, U. S.; Ayyangar, N. R.; *Tetrahedron* **1991**, *47*, 5759.
38. Cannon, J. G.; Koble, D. L.; *J. Med. Chem.* **1980**, *23*, 750.
39. Naemura, K.; Fukuda, R.; Murata, M.; Konishi, M.; Hirose, K.; Tobe, Y.; *Tetrahedron: Asymmetry* **1995**, *6*, 2385.
40. Kasai, M.; Kawai, K.; Imuta, M.; Ziffer, H.; *J. Org. Chem.* **1984**, *49*, 675.
41. Prelog, V.; *Pure Appl. Chem.* **1964**, *9*, 119.
42. Bégué, J.; Cerceau, C.; Dogbeavou, A.; Mathé, L.; Sicsic, S.; *J. Chem. Soc., Perkin Trans 1* **1992**, 3141.
43. Bagal, S. K.; Adlington, R. M.; Baldwin, J. E.; Marquez, R.; Cowley, A.; *Org. Lett.* **2003**, *5*, 3049.