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Chiral Precursors of Optically Active Juvenoids

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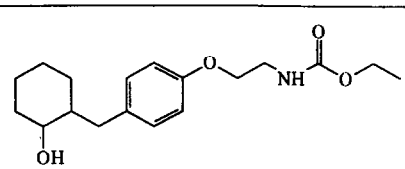
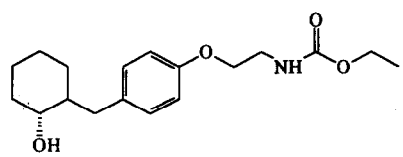
Abstract: For preparation of all four enantiomers of 2-(4-hydroxybenzyl)-1-cyclohexanol (**1a-4a**) by biotransformation reactions, *Saccharomyces cerevisiae* (SC) and pig pancreatic lipase (PPL) were used in aqueous media. The THP-protected substrates (**5b**, **6b** and **7b**) gave products with a good enantiomeric excess comparable with that of the CH_3-protected substrates (**5c**,**6c** and **7c**), whereas the deprotection was much easier in case of the THP-protected compounds.

In our search for new compounds imitating the effect of the natural insect juvenile hormones (juvenoids) a series of compounds derived from 2-(4-hydroxybenzyl)-1-cyclohexanone (**10**) has been prepared[1a]. We have found[1b] that in many cases the biological activity values of juvenoids differ considerably when compared the racemic cis- and trans-isomers of compounds derived from 2-(4-hydroxybenzyl)-1--cyclohexanol (e.g. see Table 1).

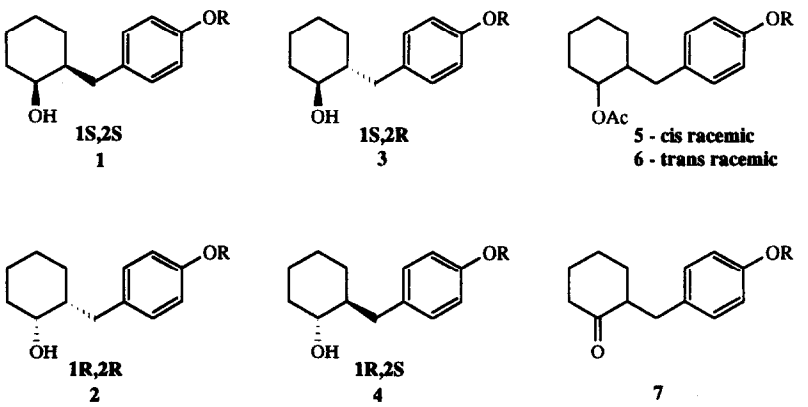
Table 1: Biological activity values of cis- and trans-isomers on *Dysdercus cingulatus*

	ED 50 [μg.g^{-1}]
	0.001
	0.04

In order to extend our knowledge on the influence of spatial arrangement of substituents on carbons C_1 and C_2 of the cyclohexane ring on biological activity, we have prepared all optical isomers of 2-(4-hydroxybenzyl)-1-cyclohexanol (**1a-4a**), that will be used as chiral precursors for preparation of optically active juvenoids by a simple O-alkylation of the phenolic hydroxyl group using $X\text{-}CH_2CH_2NHCOOCH_2CH_3$ (X=Cl or Br)[1c].

The enzymatic hydrolysis of the CH_3-protected substrates **5c** and **6c** using PPL[2] resulted in a preparation of the optically active alcohols **2c** or **4c**, respectively, while the enzymatic reduction of **7c** SC[3] yielded the alcohols **1c** and **3c**. The same pair of separable alcohols was obtained by enzymatic reduction of the phenolic substrate **7a**, however, the optical purity of the products was considerably lower[4] (see Scheme 1 and Table 2).

SCHEME 1



In the formulae **a**: R = H; **b**: R = THP; **c**: R = CH_3

Table 2: Summary of previous results

Substrate	Biocatalyst	Product	Absolute Configuration	e.e. [%]	Refs.
5c	PPL	2c	1R,2R	96.2	2
6c	PPL	4c	1R,2S	99.4	2
7c	SC	1c	1S,2S	95.1	3
		3c	1S,2R	98.2	3
7a	SC	1c	1S,2S	86.9	4
		3c	1S,2R	92.9	4

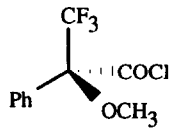
For the subsequent synthesis of the final juvenoids a demethylation of the chiral intermediates (**1c-4c**) was requested. A treatment with HBr in refluxing Ac_2O[5], iodotrimethylsilane in quinoline[6], monochloroborane-

-dimethyl sulfide in refluxing benzene[7] and BBr_3 in refluxing CH_2Cl_2 or $ClCH_2CH_2Cl$[8], respectively, gave either poor yields (under 20%) or no product at all[9]. Therefore we used THP-protected substrates (**5b**, **6b** and **7b**). The removal of the THP group from the resulting chiral intermediates (**1b-4b**) using Dowex 50W in MeOH gave yields about 95%.

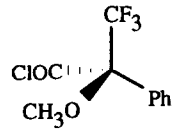
Results and Discussion

The principle of the NMR assignment of absolute configuration requires the preparation of a pair of diastereomeric compounds[10]. For the synthesis of diastereomeric esters of the isomers of the protected alcohols **1b-4b** or **1c-4c**, respectively, we used (S)-(+)- and (R)-(-)-2-methoxy-2-phenyl-3,3,3--trifluoropropanoyl chloride (**8**) and (**9**) (chloride of MTPA)[11-14] (Scheme 2).

SCHEME 2



(S)-(+)-MTPCl
8



(R)-(-)-MTPCl
9

The absolute configuration at C-1 carbon atom can be assigned from the differences of the chemical shifts of the H7 and H7' signals in the pair of the diastereomeric esters with (R) or (S) configuration of MTPA. A detailed comparison of the ^1H NMR spectra of MTPA esters of the cis alcohols **1b** or **1c**, respectively, indicated that the signals of hydrogens H7 and H7' in (R)-MTPA-esters are shifted upfield in comparison with those of the (S)-MTPA-esters (δ 2.46 and 2.24 in comparison with δ 2.52 and 2.33). According to Rinaldi[10], this upfield shift is explicable only for the (S)-configuration at C-1 carbon atom.The absolute configuration at C-1 carbon atom in the alcohols **2b-4b** or **2c-4c**, respectively, was assigned in an analogous manner. From the assigned (S) absolute configuration at C-1 carbon atom of the alcohols **1** and **3**, from the (R) absolute configuration at C-1 carbon atom of the alcohols **2** and **4**, and from the known relative configuration of substituents in positions 1 and 2, the absolute configuration at C-2 carbon atom also follows (cf. Table 3).

The ^{19}F NMR spectra lead to the same conclusion. A downfield shift of the signal of the CF_3 group in the (R)-MTPA-esters of alcohols **1** and **3**, and an analogous difference in the paired MTPA-esters of the alcohols **2** and **4** are in agreement with the expected protruding of the CF_3 group from the eclipsed arrangement with the carbonyl in consequence of a steric interaction of the bulkier groups[10] (in our case phenyl with both respective 4-methoxybenzyl or 4-(2-tetrahydropyranyloxy)benzyl), which is operative in the (R)-MTPA-esters of **1** and **3** and (S)-MTPA-esters of **2** and **4** (cf. Table 3).

Table 3: ^{1}H and ^{19}F NMR data

source acid	(R)-MTPA		(S)-MTPA		(R)-MTPA	(S)-MTPA	A.C.
source alcohol	H7	H7´	H7	H7´	δ (CF_3)		
MTPA esters of 2-(4-methoxybenzyl)-1-cyclohexanol							
2c	2.33	2.52	2.24	2.46	-67.31	-67.12	1R,2R
4c	2.18	2.89	2.08	2.71	-67.56	-67.49	1R,2S
1c	2.24	2.46	2.33	2.51	-67.13	-67.28	1S,2S
3c	2.08	2.71	2.18	2.89	-67.46	-67.54	1S,2R
MTPA esters of 2-[4-(2-tetrahydropyranyloxy)benzyl]-1-cyclohexanol							
2b	2.33	2.51	2.24	2.45	-67.29	-67.15	1R,2R
4b	2.17	2.89	2.07	2.70	-67.54	-67.44	1R,2S
1b	2.24	2.46	2.33	2.52	-67.10	-67.28	1S,2S
3b	2.08	2.71	2.17	2.89	-67.44	-67.55	1S,2R

The optical purity of the alcohols was determined on the basis of the HPLC data of the corresponding MTPA-esters (Table 4).

Table 4: MTPA esters of 2-(4-methoxybenzyl)-1-cyclohexanol, HPLC data

Source alcohol	Absolute configuration	MTPA	HPLC area	Time [min]	e.e. [%]
Saccharomyces cerevisiae					
1c:2c	1S,2S:1R,2R	R	40.868:1.424	26.634:24.072	93.27
3c:4c	1S,2R:1R,2S	R	36.400:2.531	23.397:20.255	87.00
Pig pancreatic lipase*					
1c:2c	1S,2S:1R,2R	S	3.325:42.633	34.651:32.926	85.53
		R	2.285:27.963	32.860:34.284	84.89
3c:4c	1S,2R:1R,2S	S	0.486:12.849	28.450:26.752	92.71
		R	1.382:31.313	27.080:28.606	91.55

*Calculated average e.e. of **1c:2c** 85.2% and of **3c:4c** 92.1%

We were not able to determine directly the enantiomeric excess of the THP-protected products **1b-4b** of the biotransformations. We suppose that the removal of the THP-group occurs under the conditions of the HPLC analysis. First we had to remove the protecting group and then to methylate the phenolic compounds **1a-4a** using diazomethane to prepare the more stable derivatives **1c-4c**. The stereochemical correlation between the THP-ethers **1b-4b** and the corresponding methylethers **1c-4c** showed no changes in the absolute configuration during this chemical course (Table 3).

Optical characteristics (CD spectra and specific rotation) of the target compounds **1a-4a** are summarized in table 5.

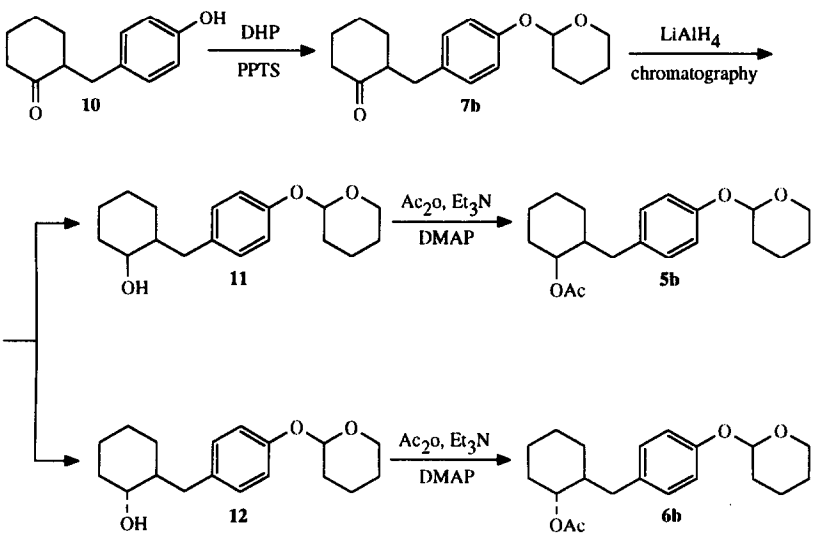
Table 5: CD spectra and specific rotation

Compound	Abs. config.	λ [nm]	Δ ε[1]	$[\alpha]^{24}_D$	c [g.100ml^{-1}][2]
1a	1S,2S	278	-0.06	+25.71	0.59
2a	1R,2R	276	+0.04	-24.44	0.43
3a	1S,2R	283	+0.06	+56.09	0.50
4a	1R,2S	281	-0.08	-57.37	0.45

[1](CH_3OH, 0.1 cm); [2]($CHCl_3$)

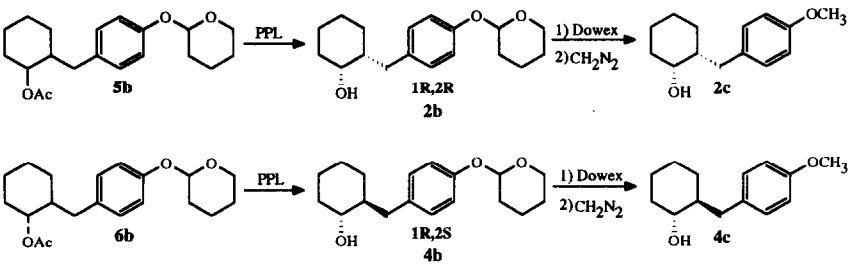
The synthesis of the phenolic key product **10** using cyclohexanone and p-methoxybenzyl chloride via a Stork reaction[15] has already been described[16]. A treatment of **10** with 3,4-dihydro-2H-pyran in the presence of pyridinium p-toluenesulfonate (PPTS) yielded the substrate **7b**. Its reduction by lithium aluminum hydride, subsequent chromatography on silica gel, and acetylation of the isomeric alcohols **11** and **12** in the presence of triethylamine and 4-dimethylaminopyridine (DMAP) yielded the substrates **5b** and **6b** (Scheme 3).

SCHEME 3



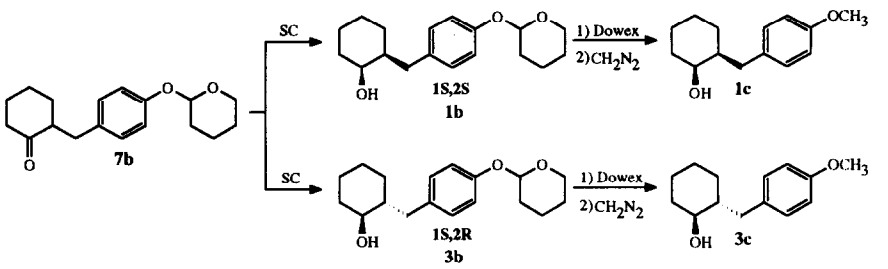
The enzymatic hydrolysis of the THP-protected acetates **5b** and **6b** yielded chiral alcohols **2b** or **4b**, respectively. A deprotection of these alcohols and a consequent methylation by diazomethane yielded the methoxyderivatives **2c** or **4c**, respectively, that were used for the HPLC determination of the optical purity (Scheme 4).

SCHEME 4



An enzymatic reduction of **7b** and consequent chromatography on silica gel yielded the chiral alcohols **1b** and **3b**. After a deprotection of these alcohols and methylation of the intermediate by diazomethane, the methoxyderivatives **1c** or **3c**, respectively, were prepared and used for the HPLC determination of the enantiomeric purity (Scheme 5).

SCHEME 5



The conditions and the chemical yields of the biotransformations are summarized in Tables 6 and 7.

Table 6: Biotransformation conditions

	Saccharomyces cerevisiae	Pig Pancreatic Lipase
Source	strain CCY 21-4-63-e	Sigma chemicals
Cultivation	48h at 27±1°C	-
Cultivation medium	liquid malt	-
Biotransformation	7 days at 27±1°C phosphate buffer; pH=7.0	7 days at 27±1°C phosphate buffer; pH=7.0
Sodium deoxycholate	-	100 mg
Substrate	**7b**, 100mg (0.45mmol) in 100mL of the phosphate buffer	**5b,6b** 1g(3.01mmol) in 100mL of the phosphate buffer
Amount of the biocatalyst	5 g	75 mg

Table 7: Yields of the biotransformation

Substrate	Product	Yield [%][a]	Note
5b	2b	5.2[b]	
6b	4b	6.2[b]	
7b	1b	50.0	The isomers were separated
	3b	24.8	by column chromatography.

[a]the theoretical yield is 50%; [b]the chemical yields did not encrease even after 21 days of the biotransformation

Experimental

The ^{1}H NMR spectra were recorded on a Varian UNITY-200 spectrometer at 200.06 MHz frequency in deuteriochloroform, using tetramethylsilane as internal reference. The ^{13}C NMR were recorded on Varian UNITY-500 spectrometer at 125.7 MHz frequency in deuteriochloroform using central line of the solvent as internal reference (δ = 77.0 ppm). The ^{19}F NMR spectra were recorded on a Varian UNITY-200 spectrometer at 188.15 MHz in deuteriochloroform, with a capillary containing hexafluorobenzene as external reference (δ = -162.9 ppm). The IR spectra were recorded on a Perkin-Elmer 580 instrument in tetrachloromethane. HPLC analyses were carried out on a Hewlett-Packard HP 1090 instrument, coupled with a HP-85B microcomputer. Detection was carried out at 220 nm wavelenght by means of an ultraviolet DAD; integration was carried out at 250 nm using a DPU multichannel integrator. A set of 3 columns connected in series was used for analysis, each 150 x 3 (i.d.) mm, filled with Separon SGX (particle size 5 μm) as stationary phase. Light petroleum with 5% ether was used as mobile phase, flow rate 0.5 mL.min^{-1}. Column chromatographies were carried out on silica gel (Gebr. Herrman, Koeln-Ehrenfeld). Optical rotations were measured on Perkin-Elmer 241 polarimeter. The CD spectra were obtained from Jobin Yvon Mark V instrument in methanol. Microanalyses were performed using a Perkin-Elmer 240 C elemental analyser.

MTPA esters of alcohols, 1b-4b and 1c-4c

A general procedure used for the preparation of the MTPA esters in a milligram scale starting from the chloride of MTPA has already been described in detail[6]. The characterization of the MTPA esters by spectral data is summarized in Table 3.

2-[4-(2-Tetrahydropyranyloxy)benzyl]-1-cyclohexanone 7b

To a mixture of 3.8442g (18.8 mmol) of 2-(4-hydroxybenzyl)-1-cyclohexanone **7a** and 0.2g (0.8 mmol) of pyridinium p-toluenesulfonate in 40 mL of dry methylene chloride, 6.0mL (65.8 mmol) of freshly distilled 3,4-dihydro-2H-pyran was added in portions under stirring and a room temperature. The stirring continued for 45 minutes, then the mixture was diluted with diethylether (50 mL) and washed with brine (3 x 250 mL). The organic layer was dried over potassium carbonate. The solvents were evaporated and the crude product (5.646g) was purified by column chromatography on silica gel (500g). The chromatography afforded 5.4191g of the pure **7b** (99.72%). IR : 3061, 3032, 1714, 1612, 1583, 1511, 1441, 1233, 1202, 1183, 1176, 1110, 1139, 1021, 971, 922, 873 cm^{-1}; ^{1}H NMR :δ (m, 2H), 6.95 (m, 2H), 5.37 (t, J=3.2, 1H), 3.93

(m, 1H), 3.59 (m, 1H), 3.16 (dd, J=13.5, 4.1, 1H), 2.35 (dd, J=13.5, 8.8, 1H), 2.35 (m, 1H), 1.29-2.10 (m, 1H); ^{13}C NMR : δ 212.66 (C-1), 52.60 (C-2), 33.29 (C-3), 28.01 (C-4), 25.20 (C-5), 42.10 (C-6), 34.56 (C-7), 133.27 (C-8), 129.92 (C-9, C-13), 116.28 (C-10, C-12), 155.32 (C-11), 96.44 (C-14), 30.38 (C-15), 18.83 (C-16), 24.98 (C-17), 62.03 (C-18); Mass: m/z 288 (M^+, 3), 204 (66), 175 (6), 133 (6), 107 (100), 94 (18), 85 (52), 57 (10), 41 (15), 29 (10); Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.91; H, 8.41.

cis- and trans-2-[4-(2-Tetrahydropyranyloxy)benzyl]-1-cyclohexanol, 11 and 12

To a cooled (O°C) and stirred suspension of lithium aluminum hydride (0.4790g, 12.6mmol) in 100mL of dry diethylether, 1.0507g (3.6mmol) of the ketone **7b** in 100mL of dry diethylether was added. After 7h of stirring 35mL of 25% potassium sodium tartrate tetrahydrate solution was added. The mixture was extracted by diethylether (4 x 50mL). The organic extracts were collected, dried over potassium carbonate and the solvent was evaporated (1.09g of the crude mixture). The mixture was purified by column chromatography on silica gel (50g) affording 0.0895g (8.4% yield) of **11**; IR : 3613, 3360, 1614, 1596, 1515, 1441, 1021, 1000, 1230, 1116, 832, 1201, 1036, 972 cm^{-1}; ^{1}H NMR : δ 7.10 (m, 2H), 6.96 (m, 2H), 5.38 (t, J=3.2, 1H), 3.94 (m, 1H), 3.79 (dt, J=4.5, 3.0, 1H), 3.60 (m, 1H), 2.65 (dd,J=13.4, 7.6, 1H), 2.48 (dd, J=13.4, 7.4, 1H), 1.05-2.10 (m, 15H); ^{13}C NMR: δ 68.21 (C-1), 43.46 (C-2), 26.13 (C-3), 25.05(C-4),20.23 (C-5), 33.03 (C-6), 37.49 (C-7), 133.94 (C-8), 129.71 (C-9,C-13), 116.07 (C-10, C-12), 154.98 (C-11), 96.31 (C-14), 30.24 (C-15),18.67 (C-16), 25.05 (C-17), 61.79 (C-18); Mass: m/z 290 (M^+, 3), 206(14), 188 (21), 107 (43), 85 (100); Anal. Calcd. for $C_{18}H_{26}O_3$: C,74.44; H, 9.03. Found: C, 74.43; H, 9.07; and 0.7378g (69.6% yield) of **12**; IR : 3613, 3361, 3064, 3025, 3013, 1614, 1596, 1514, 1442,1231, 834, 1118, 1025, 1034, 1201, 1111, 978 cm^{-1}; ^{1}H NMR: δ 7.08 (m, 2H), 6.96 (m, 2H), 5.37 (t, J=3.2 1H), 3.93 (m, 1H), 3.60 (m, 1H), 3.27 (td, J=9.5, 4.6, 1H), 3.08 (dd, J=13.4, 3.9, 1H),2.30 (dd, J=13.4, 3.9, 1H), 0.82-2.10 (m, 15H); ^{13}C NMR: δ 3.85 (C-1), 46.70 (C-2), 29.63 (C-3), 25.18 (C-4), 24.69 (C-5), 35.49 (C-6), 37.75 (C-7), 133.55 (C-8), 129.93 (C-9, C-13), 115.91 (C-10, C-12), 154.89 (C-11), 96.27 (C-14), 30.17 (C-15), 18.62 (C-16), 25.00 (C-17), 61.74 (C-18); Mass: m/z 290 (M^+, 3), 206 (17), 188 (30), 107 (46), 84 (100); Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C,74.46; H, 9.08.

cis- and trans-2-[4-(2-Tetrahydropyranyloxy)benzyl]-1-acetoxycyclohexane, 5b and 6b

To a stirred mixture of 6.2063g (21.4mmol) of the cis-alcohol **11** in 100mL of dry triethylamine and 10mg (0.08mmol) of 4-dimethylaminopyridine, 2.1mL (22.3mmol) of acetic anhydride was added through a septum in portions, and under a room temperature. After 5h of stirring the reaction mixture was poured into a cooled potassium bicarbonate solution. The mixture was extracted by light petroleum (3x 20mL), the collected organic extracts were dried over potassium carbonate and a mixture of the solvents was evaporated under reduced pressure. A crude residue (6.003g) was purified by column chromatography on silica gel (50g) affording 5.7581g (81.04% yield) of the acetate **5b**. IR : 3061, 3032, 3010, 1736, 1611, 1583, 1511, 1441, 1237, 1021, 1202, 1126, 1110, 1039, 972, 833 cm^{-1}; ^{1}H NMR: δ 6.98 (m, 4H), 5.36 (t, J=3.2, 1H), 4.91 (m, 1H), 3.93 (m, 1H), 3.60, (m, 1H), 2.57 (dd, J=13.7, 6.8, 1H), 2.39 (dd, J=13.7, 7.8, 1H), 2.10 (s, 3H), 1.20-2.10 (m, 14H); ^{13}C NMR: δ 75.25 (C-1), 42.41 (C-2), 29.84 (C-3), 25.38 (C-4), 24.97 (C-5), 30.63(C-6), 37.64 (C-7), 131.98 (C-8), 129.94 (C-9, C-13), 115.13 (C-10,C-12), 154.19 (C-11), 96.43 (C-14), 30.41 (C-15), 18.83 (C-16), 25.20(C-17), 62.06 (C-18), 171.20 and 21.29 (OAc); Mass: m/z 332 (M^+, 3),248 (35), 188 (100), 107 (63), 85 (45); Anal. Calcd. for $C_{20}H_{28}O_4$: C,72.26; H, 8.49. Found: C, 72.24; H, 8.48. The same procedure was used for the preparation of trans-acetate **6b** starting from the

corresponding trans-alcohol **12** (12.28g, 42.3mmol).11.1529g of **6b** presents 79.32% of the theory. IR : 3060, 3030,3019, 1734, 1612, 1583, 1510, 1442, 1241, 1022, 1002, 1126, 1111, 1039,972, 834 cm^{-1}; ^1H NMR: δ 7.02 (m, 2H), 6.96 (m,2H), 5.38 (t, J=3.4, 1H), 4.55 (td, J=10.0, 4.5, 1H), 3.92 (m, 1H),3.59 (m, 1H), 2.83 (dd, J=13.7, 3.9, 1H), 2.21 (dd, J=13.7, 9.0, 1H),2.02 (s, 3H), 0.92-1.86 (m, 14H); ^{13}C NMR :δ 76.76 (C-1), 43.69(C-2), 29.93 (C-3), 24.98 (C-4), 24.42 (C-5), 31.76 (C-6), 38.00 (C-7), 133.13 (C-8), 129.82 (C-9, C-13), 116.16 (C-10, C-12), 155.17 (C-11),96.42 (C-14), 30.34 (C-15), 18.78 (C-16), 25.14 (C-17), 61.90 (C-18), 170.64 and 21.15 (OAc); Mass: m/z 332 (M^+, 3), 248 (35), 188 (100) ,107 (63), 85 (45); Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found:C, 72.23; H, 8.45.

A general procedure for the preparation of 2-(4-hydroxybenzyl)-1-cyclohexanol, 1a-4a (the chiral precursors)

A mixture of cca 100mg of the THP-protected biotransformation product (**1b-4b**) and 0.5g of Dowex 50W (H^+) in 2mL of methanol was stirred for 8h in a microampule . The ion exchanger was filtered off, washed with methanol (2 x 1mL) and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (10g) affording pure compounds **1a-4a**, respectively, in yields varying in a range of 93-96% of the theory. The ^1H,^{13}C NMR, IR, mass spectra and the elemental analysis of the corresponding enantiomers were found to be identical. Summary of the results obtained is, therefore, presented for the paired enantiomers (i.e. **1a** and **2a**, and **3a** and **4a**). The only difference, of course, was found when their CD spectra and optical rotations values were recorded (cf. Table 5).

cis-(1S,2S)- and cis-(1R,2R)-2-(4-hydroxybenzyl)-1-cyclohexanol (1a and 2a): IR : 3445, 3270, 1620, 1520, 1066, 1059, 1042 cm^{-1}; ^1H NMR: δ 7.00 (m, J=8.6, 2H), 6.76 (m, J=8.6, 2H), 3.78(m, w=7.5, 1H), 2.63 (dd, J=7.2, 13.5, 1H), 2.43 (dd, J=7.5, 13.5, 1H), 1.05-1.83 (m, 9H); ^{13}C NMR: δ 68.6 (C-1), 43.6 (C-2), 26.2 (C-3), 25.1 (C-4), 20.3 (C-5), 33.0 (C-6), 37.5 (C-7), 132.2 (C-8),130.0 (C-9, C-13), 115.0 (C-10, C-12), 154.3 (C-11); Mass: m/z 206 (M^+,20), 188 (34), 120 (24), 107 (100); Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. For **1a** found: C, 75.71; H, 8.70. For **2a** found: C,75.83; H, 8.62.

trans-(1S,2R)- and trans-(1R,2S)-2-(4-hydroxybenzyl)-1-cyclohexanol,(3a and 4a): IR : 3440, 1071, 1041, 1014 cm^{-1}; ^1H NMR :δ 6.99 (m, J=8.6, 2H), 6.75 (m, J=8.6, 2H), 3.25 (m,J=4x4.6, 1H), 3.07 (dd, J=4.0, 13.6, 1H), 2.25 (dd, J=9.2, 13.6, 1H), 1.67-0.80 (m, 9H); ^{13}C NMR: δ 74.0 (C-1), 46.7 (C-2), 29.7 (C-3), 25.2 (C-4), 24.7 (C-5), 35.2 (C-6), 37.7 (C-7), 131.6 (C-8), 130.1 (C-9, C-13), 114.7 (C-10, C-12), 154.4 (C-11); Mass: m/z 206 (M^+,20), 188 (31), 120 (31), 107 (100); Anal. Calcd. for $C_{13}H_{18}O_2$: C,75.69; H, 8.79. For **3a** found: C, 75.73; H, 8.81. For **4a** found: C, 75.51; H, 8.67.

A general procedure for the preparation of 2-(4-methoxybenzyl)-1-cyclohexanol, 1c-4c (used for the HPLC analysis)

The pure compounds **1a-4a**, respectively, were dissolved in 10mL of diethylether and 50mL of a saturated solution of diazomethane in diethylether was added. The mixture was stirred for an additional 16h, the solvents were evaporated, and the crude residue was purified by a column chromatography on silica gel (10g). The yields of **1c-4c**, respectively, varied between 71-99% of the theory. The characterization of these alcohols by ^1H NMR, IR and MS spectra has already been published[3,17,18], and our results have been in accordance with the data given therein.

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