Enzyme-Mediated Preparation of Chiral 1,3-Dioxane Odorants

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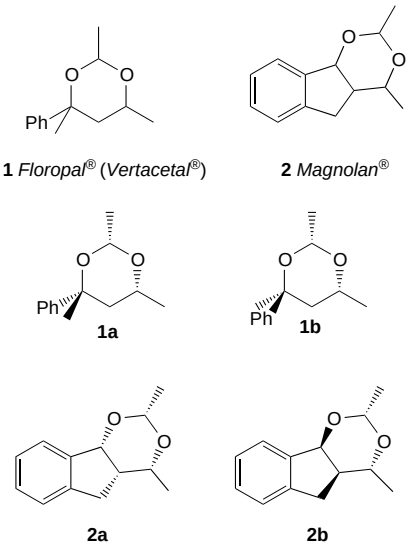
The enantiomerically enriched diastereoisomers of the chiral 1,3-dioxane odorants *Floropal*® (**1**) and *Magnolan*® (**2**) were prepared by an enzyme-mediated approach. Their olfactory properties were evaluated to investigate differences in the odor perception for the stereoisomers.

1. Introduction. – *Floropal*® (or *Vertacetal*®; **1**) and *Magnolan*® (**2**) are two structurally correlated dioxane derivatives showing interesting olfactory properties. *Floropal* is a grapefruit fragrance with 'fruity rhubarb undertones' [1]; *Magnolan* is a 'substantive floral, rosy odorant' employed to convey the 'freshness of rose-flower dew' in perfume compositions [1]. *Floropal* and *Magnolan* are prepared by *Prins* reaction of α-methylstyrene and 1*H*-indene, respectively, with acetaldehyde [2][3], and they are commercialized as racemic mixtures of the two main diastereoisomers **1a**/**1b** and **2a**/**2b**, respectively.



The mixture **1a**/**1b** has been employed for more than twenty years as an aromatic substance and sold under the names *Vertacal* (*Dragoco Gerberding & Co. AG*, Holzminden) and *Floropal/Corps 717* (*Haarmann & Reimer GmbH*, Holzminden). In the corresponding product specification sheets, the aroma of *Vertacetal* is described as

'fresh-herbal, typically the impression of grapefruit', and the aroma of *Floropal/Corps 717* is described as 'herbal-fresh, floral-green, similar to chrysanthemum, cyprus, and grapefruit'. In 2000, *Pickenhagen* and co-workers [4] reported the odor properties of the two diastereoisomers **1a** and **1b**. Ketal **1a** was described as 'strong, herbal-fresh, green, and typical grapefruit'; **1b** was found to be 'very weak, chemical solvent-like', and to have a detracting influence upon the sensory properties of the mixture. They also discovered, by in-house analyses, that the two commercial products differed with respect to the relative content of the two diastereoisomers [4]: *Vertacetal* contained 54.38% of **1a** and 44.33% of **1b**, while *Floropal* contained 63.71% of **1a** and 34.52% of **1b**. They developed a procedure, based either on fractional distillation or on reaction with $BF_3 \cdot Et_2O$, to enrich the mixture with the more valuable derivative **1a**.

In the light of this interesting stereoselectivity in the odor perception of 1,3-dioxane isomeric odorants, we decided to undertake the enzyme-mediated synthesis of the enantiomers of compounds **1** and **2** to investigate the olfactory response of each single isomer. This kind of investigation is part of a research program aimed to apply the procedure of the so-called 'chiral switch', developed for drugs, to the fragrance industry [5]. The use of the olfactory-active isomer of odorants would allow the elicitation of a given odorous effect by adding a minor quantity of the chemical to the products of fine and functional perfumery.

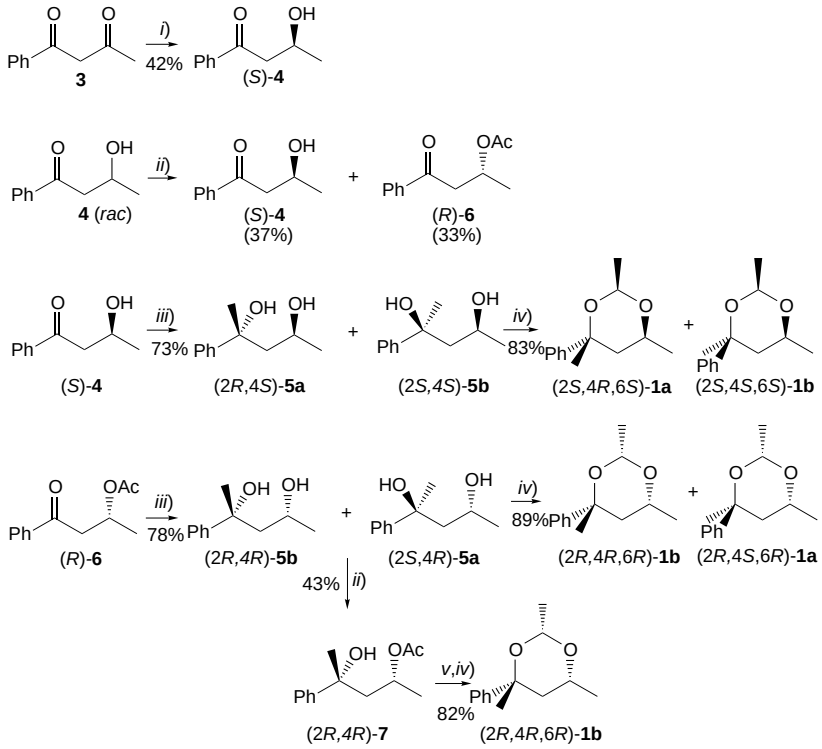
As for the choice of the method of optical activation, the enzyme-mediated approach is particularly advantageous for the preparation of enantiomerically enriched chiral odorants. These latter derivatives are usually scarcely functionalized compounds, such as aldehydes, ketones, cyclic ethers, and lactones, often difficult to treat with the methods of asymmetric catalysis. We had already shown in the past [5] the efficiency of lipase-catalyzed kinetic resolution of suitable alcohol precursors in the synthesis of enantiomerically pure single aromatic diastereoisomers. Herein we report the usefulness of this approach for the preparation of the single isomers of **1** and **2**, and the olfactory properties of these compounds.

2. Results and Discussion. – 2.1. Floropal® *Isomers.* Two different approaches to the enantiomerically enriched isomers of *Floropal* were envisaged (*Scheme 1*). The first was based on the enantiospecific reduction of diketone **3** to hydroxy ketone (*S*)-**4** mediated by baker's yeast (BY), and the second employed lipase-catalyzed kinetic resolution of racemic **4** and of diastereoisomeric diols **5a** and **5b**.

Diketone **3** was submitted to BY fermentation according to the literature [6a], to give (*S*)-**4** showing an ee of 92%. This latter derivative was treated with MeMgI in Et_2O, providing a 1:1.25 mixture of the two diastereoisomeric diols (2*R*,4*S*)-**5a** and (2*S*,4*S*)-**5b**. Treatment of this mixture with acetaldehyde in CH_2Cl_2 solution in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH) afforded a 1:2 mixture of the two *Floropal* isomers (2*S*,4*R*,6*S*)-**1a** and (2*S*,4*S*,6*S*)-**1b**. When racemic hydroxy ketone **4**, prepared by aldol condensation of acetophenone and acetaldehyde [7], was submitted to lipase-mediated esterification in *tert*-butyl methyl ether (^{t}BuOMe) solution, in the presence of vinyl acetate, acetate (*R*)-**6** (ee 97%)[1]) and unreacted alcohol (*S*)-**4** (ee 93%) were recovered. Both (*R*)-**6** and (*S*)-**4** were

[1]) For the description of (±)-**6**, see [6b].

Scheme 1



i) Baker's yeast. *ii*) Lipase PS, ^{t}BuOMe, vinyl acetate. *iii*) 6 equiv. of MeMgI, Et_2O; *iv*) MeCHO, CH_2Cl_2, TsOH. *v*) KOH, MeOH.

submitted to MeMgI treatment, followed by reaction with acetaldehyde, to afford two mixtures, one of enantiomerically pure (2*R*,4*R*,6*R*)-**1b** (66%) and (2*R*,4*S*,6*R*)-**1a** (33%), and the other of enantiomerically pure (2*S*,4*R*,6*S*)-**1a** (33%) and (2*S*,4*S*,6*S*)-**1b** (66%) (*Scheme 1*).

The mixture of diol derivatives (2*S*,4*R*)-**5a** and (2*R*,4*R*)-**5b**, prepared by reaction of MeMgI with (*R*)-**6**, was submitted to enzyme-mediated transesterification under the usual conditions, and a diastereoselective acetylation of (2*R*,4*R*)-**5b** was observed, affording acetate (2*R*,4*R*)-**7**. This latter was hydrolyzed with KOH in MeOH, to provide (2*R*,4*R*)-**5b** (ee > 99%; de 86%, *i.e.*, (2*R*,4*R*)-**5b**/(2*S*,4*R*)-**5a** 93 : 7), which was easily converted to *Floropal* (2*R*,4*R*,6*R*)-**1b** (ee > 99%; de 76%, *i.e.* (2*R*,4*R*,6*R*)-**1b**/(2*R*,4*S*,6*R*)-**1a** 88 : 12).

The two mixtures of enantiomerically pure diastereoisomers **1a** and **1b** were enriched in the most valuable diastereoisomer by treatment with $BF_3 \cdot Et_2O$, according to [4]. The following samples were obtained: *a*) from (2*R*,4*R*,6*R*)-**1b** (ee 97%, de 33%): (2*R*,4*S*,6*R*)-**1a** (ee 80%, de 76%); *b*) from (2*S*,4*S*,6*S*)-**1b** (ee 93%, de 33%): (2*S*,4*R*,6*S*)-**1a** (ee 68%, de 73%).

In the configurational assignment of these derivatives, (*S*) configuration at C(3) of derivative (+)-**4** was established by comparison with literature data [6a]. The configuration of this stereogenic C-atom was not altered in the sequence leading from (*S*)-**4** to *Floropal* stereoisomers **1a** and **1b** (MeMgI treatment and subsequent ketalization). The relative configurations of the stereocenters of compounds **1a** and **1b** was defined by NMR spectroscopy, and confirmed by comparison with [4]. The absolute configuration of the final *Floropal* stereoisomers was unambiguously established[2]).

For derivative **1a**, a clear NOE effect (8.3%) was observed between H–C(2) and H–C(6), and an intensification of the signals of both H–C(5) (1.0%, 2.8%) was obtained when Me–C(4) was irradiated. In the spectrum of derivative **1b**, NOEs were observed between Me–C(4) and H–C(6) (9.4%) and H–C(2) (13.1%).

2.2. Magnolan® *Isomers. Prins* reaction of 1*H*-indene with acetaldehyde in the presence of formic acid and hydroquinone gave a mixture of only two racemic diastereoisomers, whose relative configuration, depicted by structural formulas **2a** [10] and **2b** (*Scheme 2*), was established by means of NMR spectroscopy.

In the NOE experiment with **2a**, an intensification of the signals of H–C(3) (8%), H–C(4a) (1.9%), and H–C(9a) (7.6%) was obtained when H–C(1) was irradiated[3]). NOEs were observed also between H–C(9a) and H–C(4a) (5.4%) and H–C(1) (6.6%). The vicinal coupling constant *J*(4a,9a) of 4.0 Hz was in accordance with an equatorial location of H–C(9a), and an axial location of H–C(4a). For derivative **2b**, NOEs were observed between H–C(3) and H–C(1) (9.4%), and between H–C(4a) and H–C(9a) (5.2%)[3]). The values of the vicinal coupling constants *J*(4a,9a) and *J*(9a,1) (6.4 and 10.5 Hz, resp.) were in accordance with an axial location both of H–C(9a) and H–C(1), and with an equatorial location of H–C(4a).

Hydrolysis of **2a** and **2b** to provide diol derivatives **8a** [11] and **8b** was troublesome and proceeded with low yields. We found that $NaBH_4$ reduction of racemic diketone **9**, prepared according to [12], gave a mixture that mainly contained (80%) the same diols **8a** and **8b** as those obtained by hydrolysis of the two products of the *Prins* reaction

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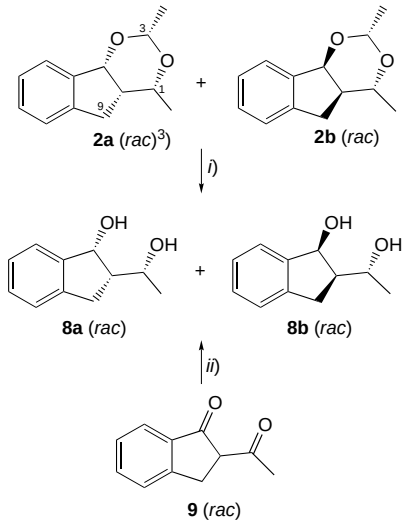
[2]) These data on the configuration of (*S*)-**4** and of the *Floropal* stereoisomers allowed us to determine the absolute configuration of the intermediate diol (2*R*,4*R*)-**5b** (obtained by hydrolysis of acetate (2*R*,4*R*)-**7**). Two contrasting values of specific rotation were reported in the literature for this compound. The enantiomer (2*R*,4*R*) was described to show $[\alpha]_D = +25.4$ ($c = 1.26$, $CHCl_3$) by *Ruano et al.* [8]. For the enantiomer (2*S*,4*S*), the value $[\alpha]_D = +31.2$ ($c = 1.0$, CH_2Cl_2) was given by *Yus et al.* [9]. The ^{1}H-NMR spectra reported for the two enantiomers were different. In the same works, the enantiomers of the *anti*-diol **5a** were described: (2*S*,4*R*) with $[\alpha]_D = -21.5$ ($c = 1.0$, $CHCl_3$) by *Ruano et al.* and (2*R*,4*S*) with $[\alpha]_D = -27.0$ ($c = 1.0$, CH_2Cl_2) by *Yus et al.*

The comparison of the ^{1}H-NMR spectra of all these compounds revealed that the inconsistency in the sign of the specific rotations arose from inversion of the *syn*/*anti* diastereoisomers. The ^{1}H-NMR spectrum of our compound **5b** matched that described for *syn*-diol by *Ruano et al.* and for *anti*-diol by *Yus et al.* The configuration at C(4) in our derivative (+)-**5b** had to be *R*, because this compound was prepared starting from (*R*)-**6**. The relative configuration of our diol could be deduced to be *syn*, since **5b** gave *Floropal* **1b** by ketalization. It is true that ketalization in acid environment can produce epimerization at the benzylic stereocenter *via* the carbocation. We describe in this work the conversion of **1b** into **1a** by $BF_3 \cdot Et_2O$ treatment. The formation of diastereoisomer **1a** is thus favored under acid conditions. As a matter of fact, diol (2*R*,4*R*)-**5b** (de 86%) gave *Floropal* **1b** with lower diastereoisomeric excess (de 76%).

[3]) The numbering of the molecular skeleton of **2a**, **2b**, **13**, and **14** is arbitrary; for systematic names, see *Exper. Part.*

Scheme 2

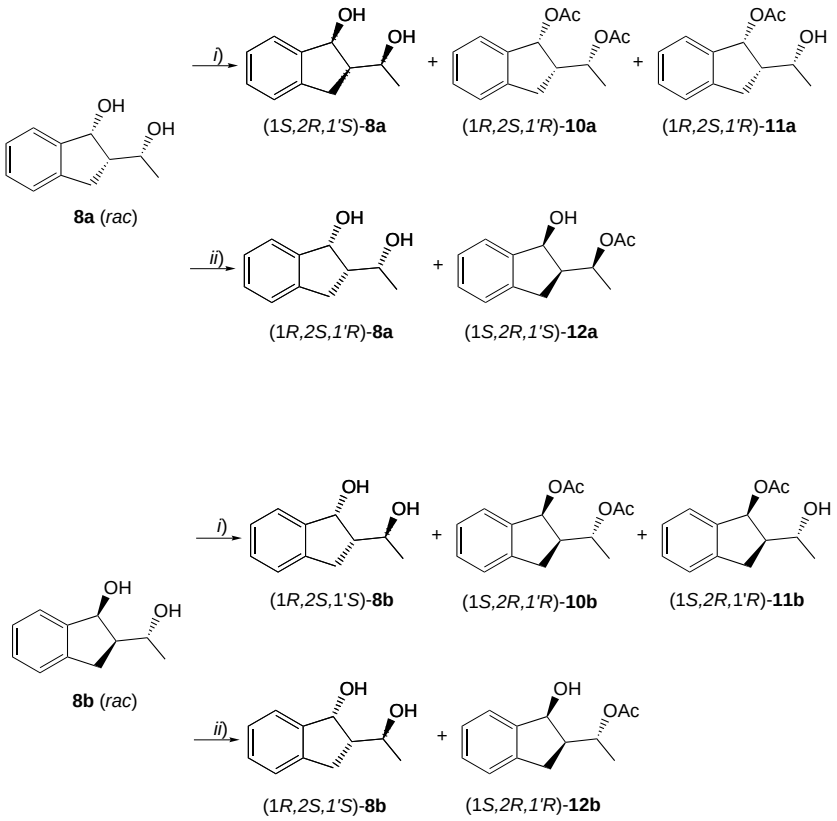


i) HCl,THF (**8a** 12%, **8b** 18%). *ii*) $NaBH_4$, CH_2Cl_2/MeOH (**8a** 44%, **8b** 36%).

(*Scheme 2*). Diols **8a** and **8b** were separated by column chromatography and submitted separately to lipase-mediated acetylation with lipase PS and CCL as catalysts. Interestingly enough, different regiochemistry and enantioselectivity were observed with the two different enzymes (*Scheme 3*). When racemic diol **8a** was treated with CCL, diacetate (1*R*,2*S*,1′*R*)-**10a** (ee >99%), monoacetate (1*R*,2*S*,1′*R*)-**11a** (ee 92%), and diol (1*S*,2*R*,1′*S*)-**8a** (ee 77%) were isolated. Treatment of racemic **8a** with lipase PS promoted the acetylation of the OH group in position 1′ of the opposite enantiomer, affording (1*S*,2*R*,1′*S*)-**12a** (ee 87.5%), and unreacted (1*R*,2*S*,1′*R*)-**8a** (ee 93%). Different behavior was observed when racemic diol **8b** was submitted to enzyme-mediated transesterification. CCL Treatment provided diacetate (1*S*,2*R*,1′*R*)-**10b** (ee >99%), monoacetate (1*S*,2*R*,1′*R*)-**11b** (ee 89%), and diol (1*R*,2*S*,1′*S*)-**8b** (ee 86%). Lipase PS promoted the acetylation of **8b** with the same enantioselectivity and different regiochemistry, to afford monoacetate (1*S*,2*R*,1′*R*)-**12b** (ee 93%) and diol (1*R*,2*S*,1′*S*)-**8b** (ee 93%).

Monoacetate derivatives (1*S*,2*R*,1′*S*)-**12a** (ee 87.5%) and (1*S*,2*R*,1′*R*)-**12b** (ee 93%) were hydrolyzed, to afford diols (1*S*,2*R*,1′*S*)-**8a** and (1*S*,2*R*,1′*R*)-**8b**. Both the enantiomers of **8a** and **8b** were converted to dioxane derivatives according to two different procedures. When ketalization was performed with acetaldehyde in CH_2Cl_2 solution, in the presence of TsOH, inversion of the configuration at the benzylic C-atom was observed in both diastereoisomeric diols. The following samples were obtained (*Scheme 4*): *a*) from (+)-**8a** (ee 93%): (−)-**13** (95%, ee 90%) and other *Magnolan* isomers (5%); *b*) from (−)-**8a** (ee 88%): (+)-**13** (87%, ee 88%) and other *Magnolan* isomers (13%); *c*) from (+)-**8b** (ee 93%): (−)-**14** (90%, ee 94%) and other *Magnolan* isomers (10%); *d*) from (−)-**8b** (ee 93%): (+)-**14** (94%, ee 87%) and other

Scheme 3



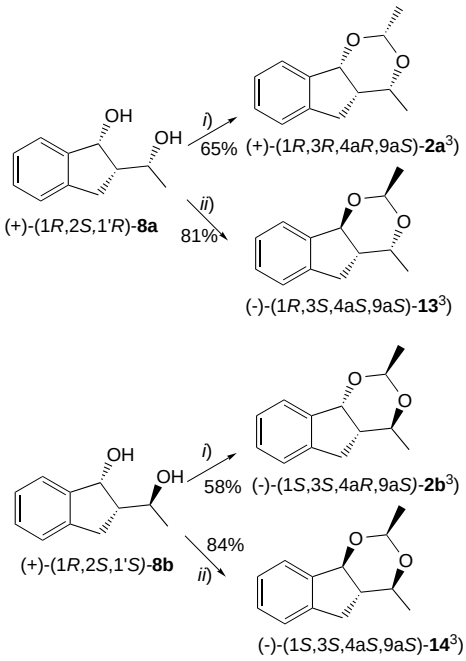
i) CCL, ^{t}BuOMe, vinyl acetate. *ii*) Lipase PS, ^{t}BuOMe, vinyl acetate.

Magnolan isomers (6%). The relative configurations of these new 'Magnolan diastereoisomers' [10] were established by ^{1}H-NMR spectroscopy.

In the NOE experiment with **13**, NOEs were observed between H–C(3) and H–C(4a) (9.8%) and between H–C(1) and H–C(9a) (8.2%). The values of the vicinal coupling constants J(4a,9a) and J(9a,1) (10.8 and 5.0 Hz, resp.) were in accordance with an axial location of both H–C(9a) and H–C(4a), and with an equatorial location of H–C(1). For derivative **14**, intensification of the signals of H–C(4a) (14.3%) and H–C(1) (5%) was obtained when H–C(3) was irradiated. The value of the vicinal coupling constant J(4a,9a) of 10.2 was in accordance with an axial location of both H–C(9a) and H–C(4a).

The use of pyridium *p*-toluenesulfonate as a catalyst allowed us to prepare the desired *Magnolan* isomers from the corresponding enantiomerically enriched diols, with conservation of the configuration at the benzylic C-atom. The following samples were obtained (*Scheme 4*): *a*) from (+)-**8a** (ee 93%): (+)-**2a** (95%) and other *Magnolan* isomers (5%); *b*) from (–)-**8a** (ee 88%): (–)-**2a** (79%) and other *Magnolan*

Scheme 4



i) MeCHO, CH_2Cl_2, pyridium *p*-toluenesulfonate. *ii*) MeCHO, CH_2Cl_2, TsOH.

isomers (21%); *c*) from (+)-**8b** (ee 93%): (−)-**2b** (88%) and other *Magnolan* isomers (12%); *d*) from (−)-**8b** (ee 93%): (+)-**2b** (68%) and other *Magnolan* isomers (32%).

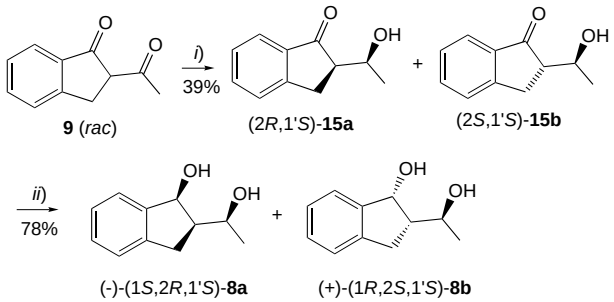
We also investigated a BY-mediated approach to the preparation of diols **8a** and **8b**, which helped us in the assignment of the absolute configurations of the *Magnolan* isomers. Racemic diketone **9** was submitted to BY fermentation. We assumed (*S*) configuration for the stereocenter generated upon BY treatment, in analogy with the stereochemical outcome of BY reduction of diketone **3**[4]). The 1:1 mixture of the two diastereoisomers (2*R*,1′*S*)-**15a** and (2*S*,1′*S*)-**15b** was reduced with $NaBH_4$ to give mainly (1*S*,2*R*,1′*S*)-**8a** (ee 94%) and (1*R*,2*S*,1′*S*)-**8b** (ee 94%) (*Scheme 5*). Chiral GC analysis of the corresponding diacetate derivatives **10a** and **10b** allowed us to transfer this assumption regarding configuration to the enantiomerically enriched diols obtained through enzymic reactions, and to the *Magnolan* isomers prepared from them.

3. Olfactory Evaluation[5]). – 3.1. Floropal *Samples*. The mixture (2*S*,4*R*,6*S*)-**1a**/(2*S*,4*S*,6*S*)-**1b** 1:2 is more powerful than commercial *Floropal*, but it is also reminiscent of 4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane (Corps Pamplemousse), especially in its

[4]) A referee suggested that we tentatively ascertain the absolute configurations of derivatives **15a** and **15b** by chemical correlation starting from known (2*S*,3*R*)-2-benzyl-3-hydroxybutanoic acid derivatives (see [13]).

[5]) Olfactory evaluations of the samples described were performed by *Givaudan* (*A*) and *Dragoco* perfumers (*B*).

Scheme 5



i) Baker's yeast. *ii*) $NaBH_4$, CH_2Cl_2, MeOH.

sulfury aspects (*A*); it is similar to the mixture (2*R*,4*S*,6*R*)-**1a**/(2*R*,4*R*,6*R*)-**1b** 1:2, but not so pungent (*B*).

The mixture (2*R*,4*S*,6*R*)-**1a**/(2*R*,4*R*,6*R*)-**1b** 1:2 exhibits a more sulfury-sweaty character (almost a bit of hydrogen sulfide), more technical in smell than the corresponding mixture of enantiomers, yet still reminiscent of *Floropal* (*A*); it is green, flowery, musty, strong, not very nice, pungent (*B*).

Isomer (+)-(2*R*,4*S*,6*R*)-**1a** is slightly acidic, flowery, gardenia, slightly *Vertacetal* (*B*).

Isomer (−)-(2*S*,4*R*,6*S*)-**1a** is *Vertacetal*, more like styrolyl acetate, with rhubarb note (*B*).

Isomer (+)-(2*R*,4*R*,6*R*)-**1b** has a pronounced floral character, sweet, reminiscent of heliotropin and of the dry character of acetophenone (*A*); it is the weakest of the *Floropal* samples, and it is slightly green (*B*).

Isomer (−)-(2*S*,4*R*,6*S*)-**1a** is the most interesting of the enantiomers of the valuable diastereoisomer **1a**. Its presence confers to the mixture (2*S*,4*R*,6*S*)-**1a**/(2*S*,4*S*,6*S*)-**1b** 1:2 a nice character, in spite of the major component being (2*S*,4*S*,6*S*)-**1b**.

Isomer (+)-(2*R*,4*R*,6*R*)-**1b** with its pronounced floral character is quite different from racemic **1b**.

3.2. Magnolan *Samples*. Racemate (±)-**2a** is richer than commercial *Magnolan*, less plastic, and more floral (*A*).

Racemate (±)-**2b** is the more powerful, much fresher than (±)-**2a**, and with an additional pleasant marine tonality, also more substantive on blotter than (±)-**2a** (*A*).

Enantiomer (−)-**2a** is wet, earthy, greasy, technical (*A*).

Enantiomer (+)-**2a** is reminiscent of caryophyllene, after 24 h very weak, with a touch of woody character (*A*).

Enantiomer (+)-**2b** is weak, acidic, floral, rosy, sweet, warm (*A*).

Enantiomer (−)-**2b** is rosy, floral (geranium, magnolia), citronellyl acetate, citric-fruity, with a slightly green nuance; it is the most interesting enantiomer (*A*).

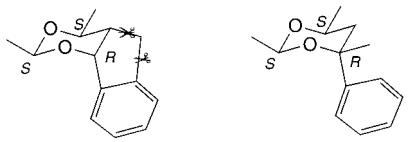
Enantiomer (−)-**13** is odorless (*A*).

Enantiomer (+)-**13** is weak, with a sulfury character (off note) (*A*).

Enantiomer (+)-**14** is less powerful and less rich than all the other *Magnolan* isomers (*A*).

Enantiomer (−)-**14** is chemical and technical in smell, with even some sulfury side notes; it is more powerful than the enantiomer (+)-**14** (*A*).

In the comparison of the two racemic diastereoisomers **2a** and **2b**, constituents of commercial *Magnolan*, a difference in their odor response was found, just as it was reported for the diastereoisomers **1a** and **1b** of *Floropal* [4]. The most appreciated isomer **2b** shows the phenyl moiety linked to C(4a) in an axial arrangement, resembling the axial phenyl group of **1a** (*Fig.*). Enantiomer (−)-**2b** is the most interesting enantiomer of diastereoisomer **2b**. The configuration of the three stereocenters is the same as that observed in (−)-**1a**, the most appreciated of the **1a** enantiomers (*Fig.*). This could be expected based on the hypothesis of the interaction of these structurally related odorants with the same chiral olfactory receptor.



(-)-**2b** (-)-**1a**

Figure. *Structural similarity of* **2b** *and* **1a**

Enantiomers (+)- and (−)-**13**, (+)- and (−)-**14** did not show any value as fragrant substances. Fortunately, their formation is disfavored under the conditions of *Prins* reaction.

4. Conclusions. – This work presents another interesting example of stereoselection in the odor perception of chiral odorants. The enantiomerically enriched isomers of the dioxane odorants *Floropal* and *Magnolan* elicited different olfactory sensations.

Racemic **1a** and **2b** were found to show olfactory properties more pleasant than those of the corresponding diastereoisomers **1b** and **2a**. The preparation of all the enantiomerically pure isomers of (±)-**1a**, (±)-**1b**, (±)-**2a**, and (±)-**2b** by enzymic methods allowed us also to establish that the enantiomers of these compounds are differently recognized by the corresponding odor receptors. Interestingly, the best *Floropal* and *Magnolan* enantiomers are characterized by the same absolute configuration.

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Experimental Part

General. Hydroxy ketone **4** and diketone **9** were prepared according to [7][12]. Lipase PS *Pseudomonas cepacia* (*Amano Pharmaceuticals Co.*, Japan) and *Candida rugosa* lipase (*Sigma*) were employed in this work. Chiral GC analyses: 25 m × 0.25 mm *Chirasil-DEX-CB* (*Chrompack*) column, *DANI-HT-86.10* gas chromatograph); t_R in min; *a*) chiral GC of acetate **6**: temp. program 40° (1 min) − 5°/min − 150° (2 min) 10°/min − 180° (5 min), t_R ((*S*)-**6**) 20.64, t_R ((*R*)-**6**) 20.77; *b*) chiral GC of diacetates **10a** and **10b**: temp. program 90° (1 min) − 3.5°/min − 120° − 0.5°/min − 135° (1 min) − 8°/min − 180° (5 min), t_R ((1*R*,2*S*,1′*R*)-**10a**) 26.22, t_R ((1*S*,2*R*,1′*S*)-**10a**) 26.54, t_R ((1*R*,2*S*,1′*S*)-**10b**) 26.75, t_R ((1*S*,2*S*,1′*R*)-**10b**) 27.99; *c*) chiral GC of *Floropal* samples **1a**,**b** and

Magnolan samples **2a**,**b**, **13**, and **14**: temp. program 50° (1 min) −1°/min −120° −10°/min −180° (5 min), t_R ((2*R*,4*S*,6*R*)-**1a**) 30.02, t_R ((2*S*,4*R*,6*S*)-**1a**) 31.17, t_R (**1b**) 39.02, t_R ((1*R*,3*R*,4a*R*,9a*S*)-**2a**) 56.95, t_R ((1*S*,3*S*,4a*S*,9a*R*)-**2a**) 56.37, t_R ((1*R*,3*R*,4a*S*,9a*R*)-**2b**) 51.32, t_R ((1*S*,3*S*,4a*R*,9a*S*)-**2b**) 51.72, t_R ((1*R*,3*R*,4a*R*,9a*R*)-**14**) 52.22, t_R ((1*S*,3*S*,4a*S*,9a*S*)-**14**) 55.42, t_R ((1*R*,3*S*,4a*S*,9a*S*)-**13**) 60.71, t_R ((1*S*,3*R*,4a*R*,9a*R*)-**13**) 55.32. GC/MS: *HP-6890* gas chromatograph equipped with a *5973* mass detector and a *HP-5MS* column (30 m × 0.25 mm × 0.25 μm); temp. program: 60° (1 min) −6°/min −150° (1 min) −12°/min −280° (5 min). TLC: *Merck* silica gel *60* F_{254} plates. Column chromatography (CC): silica gel. $[\alpha]_D$: Dr. *Kernchen Propol* digital automatic polarimeter. ^{1}H-NMR Spectra; $CDCl_3$ solns. at r.t. unless otherwise stated; *Bruker AC-250* spectrometer (250 MHz ^{1}H); δ in ppm rel. to internal $SiMe_4$; *J* values in Hz. Microanalyses: Analyzer *1106 Carlo Erba*.

1,4a,9,9a-Tetrahydro-1,3-dimethyl-2,4-dioxafluorene (=*4,4a,5,9b-Tetrahydro-2,4-dimethylindeno[1,2-*d*]-1,3-dioxin*; **2a** and **2b**) [3]. A mixture of 90% formic acid (400 ml), acetaldehyde (280 ml), hexane (650 ml), 1*H*-indene (232 ml, 1.96 mol), and hydroquinone (0.75 g) was stirred at r.t. for 3 days. The mixture was poured into H_2O, the org. phase washed with H_2O, sat. $NaHCO_3$ soln. and H_2O, dried (Na_2SO_4), and evaporated, and the residue submitted to CC (hexane/AcOEt): **2a** (156 g, 39%) followed by **2b** (140 g, 35%).

*Data of (1*RS,*3*RS,*4a*RS,*9a*SR*)-***2a**: chemical purity 86% by GC/MS (t_R 18.25), with 7.9% of **2b** and 6.1% of an unidentified stereoisomer (*m*/*z* 204). ^{1}H-NMR[3]): 7.50–7.10 (*m*, 4 arom. H); 4.92 (*d*, *J* = 4, H−C(4a)); 4.84 (*q*, *J* = 5.0, H−C(3)); 4.15 (*dq*, *J* = 3.5, 6.4, H−C(1)); 3.17 (*dd*, *J* = 10.4, 15.0, 1 H−C(9)); 2.75 (*dd*, *J* = 6.9, 15.0, 1 H−C(9)); 2.08 (*m*, H−C(9a)); 1.33 (*m*, Me−C(3), Me−C(1)). GC/MS: 204 (5, M^+), 189 (14), 160 (16), 143 (95), 116 (100).

*Data of (1*RS,*3*RS,*4a*SR,*9a*RS*)-***2b**: chemical purity 98% by GC/MS (t_R 17.70), with 2% of **2a**. ^{1}H-NMR[3]): 7.56–7.00 (*m*, 4 arom. H); 5.47 (*d*, *J* = 6.4, H−C(4a)); 4.74 (*q*, *J* = 4.9, H−C(3)); 3.32 (*dq*, *J* = 10.5, 6.0, H−C(1)); 2.91 (*dd*, *J* = 6.4, 16.2, 1 H−C(9)); 2.48 (*d*, *J* = 16.2, 1 H−C(9)); 2.40 (*dt*, *J* = 10.5, 6.4, H−C(9a)); 1.35 (*d*, *J* = 4.9, Me−C(3)); 1.26 (*d*, *J* = 6.0, Me−C(1)). GC/MS: 204 (7, M^+), 189 (3), 143 (62), 116 (100).

*(1*RS,*2*SR,*1′*RS*)- and (1*RS,*2*SR,*1′*SR*)-2-(1-Hydroxyethyl)indan-1-ol* (=*(α*RS,*1*RS,*2*SR*)- and (α*RS,*1*SR,*2*RS*)-2,3-Dihydro-1-hydroxy-α-methyl-1*H*-indene-2-methanol*; **8a** and **8b**, resp.). Diketone **9** (100 g, 0.574 mol) was treated with $NaBH_4$ (26.2 g, 0.690 mol) in CH_2Cl_2/MeOH 2:1 (400 ml). After the usual workup, the residue was submitted to CC (hexane/AcOEt 5:5): **8b** (36.8 g, 36%), followed by **8a** (44.9 g, 44%).

Data of **8b**: M.p. 57°. Chemical purity 98% by GC/MS (t_R 19.37). ^{1}H-NMR: 7.33 (*m*, 4 arom. H); 5.10 (*d*, *J* = 7.5, H−C(1)); 4.13 (*m*, MeC*H*OH); 3.01 (*dd*, *J* = 8.6, 15.7, 1 H−C(3)); 2.75 (*dd*, *J* = 9.4, 15.7, 1 H−C(3)); 2.128 (*m*, H−C(2)); 1.32 (*d*, *J* = 6.4, Me). GC/MS: 178 (5, M^+), 160 (56), 145 (100), 131 (37). Anal. calc. for $C_{11}H_{14}O_2$: C 74.13, H 7.92; found: C 74.31, H 7.68.

Data of **8a**: M.p. 88°. Chemical purity 97% by GC/MS (t_R 19.53). ^{1}H-NMR: 7.18 (*m*, 4 arom. H); 5.01 (*d*, *J* = 7.1, H−C(1)); 4.00 (*m*, MeC*H*OH); 2.85 (*dd*, *J* = 8.6, 15.7, 1 H−C(3)); 2.63 (*dd*, *J* = 9.0, 15.7, 1 H−C(3)); 2.16 (*m*, H−C(2)); 1.17 (*d*, *J* = 6.4, Me). GC/MS: 178 (4, M^+), 160 (57), 145 (100), 131 (35). Anal. calc. for $C_{11}H_{14}O_2$: C 74.13, H 7.92; found: C 73.98, H 8.10.

1. *Baker's Yeast Reduction*. 1.1. *General Procedure 1* (*GP1*). A suspension of baker's yeast (2.5 kg) and D-glucose (2.0 kg) in tap water (7.5 l) was stirred for 30 min at 32°. A soln. of the suitable substrate (0.30 mol) in EtOH (20 ml) was then added. After 48 h at r.t., *Celite* (1 kg) was added, the mixture filtered, and the *Celite* pad washed with AcOEt. The filtrate was adjusted to pH 4 with 2N HCl, and extracted with AcOEt. The org. layer was dried (Na_2SO_4) and evaporated and the residue purified by CC (silica gel).

1.2. *(+)-(3*S*)-3-Hydroxy-1-phenylbutan-1-one* ((*S*)-**4**). According to *GP1*, derivative **3** (48.6 g, 0.30 mol) was submitted to yeast reduction. CC (hexane/AcOEt 7:3) gave (*S*)-**4** (20.7 g, 42%). Chemical purity 92% by GC/MS (t_R 15.54); ee 92% (chiral GC of the corresponding acetate). $[\alpha]_D^{20} = +67.4$ (*c* = 0.94, $CHCl_3$) ([6a]: $[\alpha]_D^{20} = +68.4$ (*c* = 3.6, $CHCl_3$)). ^{1}H-NMR: 7.96 (*m*, 2 arom. H); 7.65–7.40 (*m*, 3 arom. H); 4.41 (*m*, H−C(3)); 3.18 (*dd*, *J* = 3, 17.8, H−C(2)); 3.04 (*dd*, *J* = 8.4, 17.8, H−C(2)); 1.30 (*d*, *J* = 6.4, Me). GC/MS: 164 (4), 146 (16), 120 (20), 105 (100).

1.3. *(2*R*)- and (2*S*)-2,3-Dihydro-2-[(1*S*)-1-hydroxyethyl]-1*H*-inden-1-one* ((2*R*,1′*S*)-**15a** and (2*S*,1′*S*)-**15b**, resp.). According to *GP1*, from **9** (10.0 g, 0.057 mol). CC (hexane/AcOEt 7:3) gave (2*R*,1′*S*)-**15a**/(2*S*,1′*S*)-**15b** 1:1 (3.91 g, 39%). ^{1}H-NMR (deduced from the mixture): 7.80–7.30 (*m*, 8 arom. H); 4.49 (*m*, MeC*H*OH); 3.99 (*m*, MeC*H*OH); 3.38–3.08 (*m*, 2 H); 2.90–2.60 (*m*, 2 H); 1.30 (*m*, 2 Me). GC/MS: 1st diastereoisomer (t_R 18.78): 176 (1), 158 (21), 132 (100), 2nd diastereoisomer (t_R 18.98): 176 (1), 158 (22), 132 (100). Anal. calc. for $C_{11}H_{12}O_2$: C 74.98, H 6.84; found: C 75.23, H 6.69.

2. *Addition of Methylmagnesium Iodide to Ketone Derivatives*. 2.1. *General Procedure 2* (*GP2*). The suitable ketone derivative (0.061 mol) was added dropwise to a MeMgI soln. (from 0.366 mol of MeI and 0.335 mol of Mg) in Et_2O (400 ml) at 10°. The mixture was refluxed for 1 h, poured into ice, quenched with sat.

NH_4Cl soln., and extracted with Et_2O. The org. phase was dried (Na_2SO_4) and evaporated and the residue submitted to CC (hexane/AcOEt 7:3).

2.2. *(2*R*,4*S*)- and (2*S*,4*S*)-2-Phenylpentane-2,4-diol* ((2*R*,4*S*)-**5a** and (2*S*,4*S*)-**5b**, resp.). According to *GP2*, from (*S*)-**4** (10.0 g, 0.061 mol): (2*R*,4*S*)-**5a**/(2*S*,4*S*)-**5b** 1:1.25 (8.01 g, 73%). ^{1}H-NMR: 7.60–7.08 (*m*, arom. H); 4.29 (*m*, 1 H–C(3) of **5b**); 3.57 (*m*, 1 H–C(3) of **5a**); 2.05–1.71 (*m*, 2 H, H–C(3) of **5a**/**5b**); 1.64 (*m*, Me(1) of **5b**); 1.50 (*s*, Me(1) of **5a**); 1.17 (*d*, $J = 6.4$, Me(5) of **5b**); 1.07 (*d*, $J = 6.4$, Me(5) of **5a**). GC/MS: **5a** (t_R 16.19): 180 (1), 162 (18), 121 (100), 105 (84); **5b** (t_R 17.10): 180 (1), 165 (18), 121 (100), 105 (84).

2.3. *(2*R*,4*R*)- and (2*S*,4*R*)-2-Phenylpentane-2,4-diol* ((2*R*,4*R*)-**5b** and (2*S*,4*R*)-**5a**, resp.). According to *GP2*, from (*R*)-**6** (4.00 g, 0.019 mol): (2*R*,4*R*)-**5b**/(2*S*,4*R*)-**5a** 1:1 (2.72 g, 78%). GC/MS and ^{1}H-NMR: in accordance with those described for (2*R*,4*S*)-**5a**/(2*S*,4*S*)-**5b** 1:1.25.

3. *Lipase-Mediated Acetylation*. 3.1. *General Procedure 3* (*GP 3*). A mixture of the suitable substrate (10 g), lipase (7 g), and vinyl acetate (10 ml) in ^{t}BuOMe (80 ml) was stirred at r.t. for 24 h. The residue obtained upon evaporation of the filtered mixture was chromatographed.

3.2. *(3*R*)-3-Hydroxy-1-phenylbutan-1-one Acetate* ((*R*)-**6**) *and (3*S*)-3-Hydroxy-1-phenylbutan-1-one* ((*S*)-**4**). According to *GP3* (lipase PS), from racemic **4** (10.0 g, 0.061 mol). CC (hexane/AcOEt 7:3) gave (*R*)-**6** (4.15 g, 33%) and (*S*)-**4** (3.70 g, 37%).

*Data of (*R*)-**6***: Chemical purity 98% by GC/MS (t_R 18.89); ee 97% (chiral GC). $[\alpha]_D^{20} = +24.1$ ($c = 1.205$, $CHCl_3$). ^{1}H-NMR: 7.96 (*m*, 2 arom. H); 7.63–7.42 (*m*, 3 arom. H); 5.46 (*sext.*, $J = 6.4$, H–C(3)); 3.44 (*dd*, $J =$ 6.4, 16.5, 1 H–C(2)); 3.04 (*dd*, $J = 6.4$, 16.5, 1 H–C(2)); 2.0 (*s*, MeCOO); 1.36 (*d*, $J = 6.4$, Me(4)). GC/MS: 163 (11, $[M-43]^+$), 146 (7), 105 (100).

*Data of (*S*)-**4***: Chemical purity 93% by GC/MS (t_R 15.54); ee 93% (chiral GC of the corresponding acetate). $[\alpha]_D^{20} = +68.7$ ($c = 1.01$, $CHCl_3$) ([6a]: $[\alpha]_D^{20} = +68.4$ ($c = 3.6$, $CHCl_3$)). ^{1}H-NMR and GC/MS: in accordance with those described in *1.2*.

3.3. *(2*R*,4*R*)-2-Phenylpentane-2,4-diol 4-Acetate* ((2*R*,4*R*)-**7**). According to *GP3* (lipase PS), from (2*R*,4*R*)-**5b**/(2*S*,4*R*)-**5a** 1:1 (2.00 g, 0.011 mol). CC (hexane/AcOEt 7:3) gave (2*R*,4*R*)-**7** (1.05 g, 43%). Chemical purity 93% by GC/MS (t_R 18.36); ee >99% (chiral GC). $[\alpha]_D^{20} = -5.45$ ($c = 0.11$, $CHCl_3$); de 84% (^{1}H-NMR). ^{1}H-NMR: 7.48–7.15 (*m*, 5 arom. H); 5.19 (*m*, C*H*OAc); 2.36 (*dd*, $J = 9.9$, 15.0, H–C(2)); 1.95 (*dd*, $J = 3.1$, 15.0, H–C(2)); 1.50 (*s*, Me); 1.47 (*s*, Me); 1.23 (*d*, $J = 6.3$, Me(5)). ^{13}C-NMR: 171.1; 147.4; 127.9; 126.2; 124.7; 72.8; 67.4; 49.0; 31.9; 21.4. GC/MS: 222 (1), 162 (28), 121 (100), 105 (89). Anal. calc. for $C_{13}H_{18}O_3$: C 70.24, H 8.10; found: C 70.41, H 7.95.

3.4. *Enzyme-Mediated Acetylation of (1*RS*,2*SR*,1′*RS*)-Diol* **8a**. According to *GP3*, CCl-mediated acetylation of diol **8a** (22.0 g, 0.124 mol) gave the following products in order of elution (hexane/AcOEt 7:3): diacetate (1*R*,2*S*,1′*R*)-**10a** (4.04 g, 12%), monoacetate (1*R*,2*S*,1′*R*)-**11a** (4.38 g, 16%), and diol (1*S*,2*R*,1′*S*)-**8a** (2.65 g, 12%).

*Data of (1*R*,2*S*,1′*R*)-Acetic Acid 2-(1-Acetoxyethyl)indan-1-yl Ester* (=(α*R*,1*R*,2*S*)-1-(*Acetyloxy*)-2,3-*dihydro*-α-*methyl*-1H-*indene*-2-*methanol Acetate*; (1*R*,2*S*,1′*R*)-**10a**): Chemical purity 98% by GC/MS (t_R 21.95); ee >99% (chiral GC). $[\alpha]_D^{20} = +87.6$ ($c = 1.57$, $CHCl_3$). ^{1}H-NMR: 7.25 (*m*, 4 arom. H); 6.19 (*d*, $J = 5.7$, H–C(1)); 5.13 (*quint.*, $J = 6.4$, C*H*OAc); 3.16 (*dd*, $J = 8.6$, 15.9, 1 H–C(3)); 2.83 (*dd*, $J = 6.9$, 15.9, 1 H–C(3)); 2.66 (*m*, H–C(2)); 2.10 (*s*, AcO); 1.98 (*s*, AcO); 1.38 (*d*, $J = 6.4$, *Me*CH). ^{13}C-NMR: 170.9; 170.5; 142.1; 140.7; 128.9; 126.9; 125.0; 124.7; 78.9; 70.5; 50.5; 31.2; 21.2; 18.0. GC/MS: 202 (8, $[M-60]^+$), 160 (82), 142 (100). Anal. calc. for $C_{15}H_{18}O_4$: C 68.68, H 6.92; found: C 68.56, H 6.79.

*Data of (1*R*,2*S*,1′*R*)-Acetic Acid 2-(1-Hydroxyethyl)indan-1-yl Ester* (=(α*R*,1*R*,2*S*)-1-(*Acetyloxy*)-2,3-*dihydro*-α-*methyl*-1H-*indene*-2-*methanol*; (1*R*,2*S*,1′*R*)-**11a**): Chemical purity 92% by GC/MS (t_R 20.79); ee 92% (chiral GC of the corresponding diacetate). $[\alpha]_D^{20} = +98.6$ ($c = 0.56$, $CHCl_3$). ^{1}H-NMR: 7.26 (*m*, 4 arom. H); 6.23 (*d*, $J = 5.7$, H–C(1)); 4.06 (*dq*, $J = 4.9$, 6.4, MeC*H*OH); 3.13 (*dd*, $J = 8.7$, 16.4, 1 H–C(3)); 2.87 (*dd*, $J = 7.2$, 16.4, 1 H–C(3)); 2.52 (*m*, H–C(2)); 2.15 (*s*, AcO); 1.22 (*d*, $J = 6.4$, Me). ^{13}C-NMR: 171.8; 142.4; 140.5; 128.8; 126.8; 124.8; 124.7; 79.2; 67.5; 53.7; 31.2; 21.3; 20.8. GC/MS: 220 (1, M^+), 202 (1), 160 (36), 145 (50), 116 (100). Anal. calc. for $C_{13}H_{16}O_3$: C 70.89, H 7.32; found: C 70.77, H 7.51.

*Data of (1*S*,2*R*,1′*S*)-2-(1-Hydroxyethyl)indan-1-ol* (=(α*S*,1*S*,2*R*)-2,3-*Dihydro*-1-*hydroxy*-α-*methyl*-1H-*indene*-2-*methanol*; 1*S*,2*R*,1′*S*)-**8a**): Chemical purity 92% by GC/MS (t_R 19.53); ee 77% (chiral GC of the corresponding diacetate). $[\alpha]_D^{20} = -16.6$ ($c = 0.91$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the racemate **8a** (see above).

According to *GP3*, Lipase PS-mediated acetylation of diol **8a** (22.0 g, 0.124 mol) gave the following products in order of elution: monoacetate (1*S*,2*R*,1′*S*)-**12a** (6.01 g, 24%) and diol (1*R*,2*S*,1′*R*)-**8a** (6.84 g, 31%).

*Data of (1*S*,2*R*,1′*S*)-2-(1-Acetoxyethyl)indan-1-ol* (=(α*S*,1*S*,2*R*)-2,3-*Dihydro*-1-*hydroxy*-α-*methyl*-1H-*indene*-2-*methanol* α-*Acetate*; (1*S*,2*R*,1′*S*)-**12a**): Chemical purity 89% by GC/MS (t_R 21.00); ee 87.5% (chiral GC

of the corresponding diacetate). $[\alpha]_D^{20} = -4$ ($c = 0.485$, $CHCl_3$). ^{1}H-NMR: 7.37 (*m*, arom. H); 7.26 (*m*, 3 arom. H); 5.29 (*quint.*, $J = 6.2$, MeC*H*OAc); 4.97 (*d*, $J = 7.3$, H–C(1)); 3.13 (*dd*, $J = 8.4$, 15.8, 1 H–C(3)); 2.77 (*dd*, $J = 9.6$, 15.8, 1 H–C(3)); 2.38 (*m*, H–C(2)); 2.04 (*s*, AcO); 1.37 (*d*, $J = 6.2$, Me). ^{13}C-NMR: 171.4; 145.0; 141.2; 128.4; 127.2; 125.1; 124.5; 77.5; 67.9; 55.3; 31.7; 21.6; 19.3. GC/MS: 202 (1, M^+), 160 (56), 145 (100), 131 (38). Anal. calc. for $C_{13}H_{16}O_3$: C 70.89, H 7.32; found: C 70.74, H 7.23.

*Data of (1*R*,2*S*,1′*R*)-***8a***: Chemical purity by GC/MS (t_R 19.53); ee 93.1% (chiral GC of the corresponding diacetate). $[\alpha]_D^{20} = +20.4$ ($c = 0.69$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the racemate.

3.5. *Enzyme-Mediated Acetylation of Diol (1*RS*,2*SR*,1′*SR*)-***8b***.* According to *GP3*, CCL treatment of diol **8b** (18.0 g, 0.101 mol) gave the following products in order of elution: diacetate (1*S*,2*R*,1′*R*)-**10b** (2.91 g, 11%), monoacetate (1*S*,2*R*,1′*R*)-**11b** (3.33 g, 15%), and diol (1*R*,2*S*,1′*S*)-**8b** (3.23 g, 18%).

*Data of (1*S*,2*R*,1′*R*)-Acetic Acid 2-(1-Acetoxyethyl)indan-1-yl Ester (=(α*R*,1*S*,2*R*)-1-(Acetyloxy)-2,3-dihydro-α-methyl-1*H*-indene-2-methanol Acetate*; (1*S*,2*R*,1′*R*)-**10b**): Chemical purity 86% by GC/MS (t_R 21.9); ee >99% (chiral GC). $[\alpha]_D^{20} = +95.7$ ($c = 0.68$, $CHCl_3$). ^{1}H-NMR: 7.30–7.15 (*m*, 4 arom. H); 6.31 (*d*, $J = 5.1$, H–C(1)); 5.08 (*quint.*, $J = 6.4$, C*H*OAc); 3.17 (*m*, 1 H–C(3)); 2.71 (*m*, 1 H–C(3), H–C(2)); 2.11 (*s*, AcO); 1.97 (*s*, AcO); 1.29 (*d*, $J = 6.4$, Me). ^{13}C-NMR: 170.7; 170.5; 141.9; 140.8; 128.9; 127.1; 125.1; 124.6; 79.0; 71.7; 50.5; 33.1; 21.2; 21.3; 18.3. GC/MS: 202 (5, $[M-60]^+$), 160 (45), 142 (100). Anal. calc. for $C_{15}H_{18}O_4$: C 68.68, H 6.92; found: C 68.47, H 6.88.

*Data of (1*S*,2*R*,1′*R*)-Acetic Acid 2-(1-Hydroxyethyl)indan-1-yl Ester (=(α*R*,1*S*,2*R*)-1-(Acetyloxy)-2,3-dihydro-α-methyl-1*H*-indene-2-methanol*; (1*S*,2*R*,1′*R*)-**11b**): Chemical purity 89% by GC/MS (t_R 20.81); ee 89% (chiral GC of the corresponding diacetate). $[\alpha]_D^{20} = +51.3$ ($c = 0.635$, $CHCl_3$). ^{1}H-NMR: 7.26 (*m*, arom. H); 6.29 (*d*, $J = 5.0$, H–C(1)); 3.87 (*dq*, $J = 8.5$, 6.2, MeC*H*OH); 3.20 (*dd*, $J = 8.5$, 16.2, 1 H–C(3)); 2.68 (*dd*, $J = 6.9$, 16.2, 1 H–C(3)); 2.48 (*m*, H–C(2)); 2.14 (*s*, AcO); 1.26 (*d*, $J = 6.2$, Me). ^{13}C-NMR: 172.0; 142.4; 140.2; 128.9; 126.9; 125.1; 123.9; 80.4; 69.5; 53.6; 33.5; 21.4. GC/MS: 220 (1), 202 (1), 177 (13), 160 (28), 145 (49), 116 (100). Anal. calc. for $C_{13}H_{16}O_3$: C 70.89, H 7.32; found: C 70.75, H 7.48.

*Data of (1*R*,2*S*,1′*S*)-2-(1-Hydroxyethyl)indan-1-ol (=(α*S*,1*R*,2*S*)-2,3-Dihydro-1-hydroxy-α-methyl-1*H*-indene-2-methanol*; (1*R*,2*S*,1′*S*)-**8b**): Chemical purity 87% by GC/MS (t_R 19.37); ee 86% (chiral GC of the corresponding diacetate). $[\alpha]_D^{20} = +7.98$ ($c = 0.601$, $CHCl_3$). ^{1}H-NMR and GC/MS spectra: in accordance with those of the racemate.

According to *GP3*, lipase-PS-mediated acetylation of diol **8b** (18.0 g, 0.101 mol) gave the following products in order of elution: monoacetate (1*S*,2*R*,1′*R*)-**12b** (7.95 g, 39%) and diol (1*R*,2*S*,1′*S*)-**8b** (5.75 g, 32%).

*Data of (1*S*,2*R*,1′*R*)-2-(1-Acetoxyethyl)indan-1-ol (=(α*R*,1*S*,2*R*)-2,3-Dihydro-1-hydroxy-α-methyl-1*H*-indene-2-methanol α-Acetate*; (1*S*,2*R*,1′*R*)-**12b**): Chemical purity 92% by GC/MS (t_R 20.91); ee 93% (chiral GC of the corresponding diacetate). $[\alpha]_D^{20} = -7.24$ ($c = 0.525$, $CHCl_3$). ^{1}H-NMR: 7.37 (*m*, arom. H); 7.23 (*m*, 3 arom. H); 5.15 (*m*, MeC*H*OAc, H–C(1)); 3.06 (*dd*, $J = 8.7$, 15.8, 1 H–C(3)); 2.62 (*dd*, $J = 9.0$, 15.8, 1 H–C(3)); 2.45 (*m*, H–C(2)); 2.08 (*s*, AcO); 1.36 (*d*, $J = 6.4$, Me). ^{13}C-NMR: 170.6; 144.2; 140.2; 127.7; 126.5; 124.1; 123.8; 77.5; 72.3; 53.9; 32.3; 20.9; 18.3. GC/MS: 202 (2, M^+), 160 (54), 145 (100), 131 (35). Anal. calc. for $C_{13}H_{16}O_3$: C 70.89, H 7.32; found: C 71.02, H 7.48.

*Data of Diol (1*R*,2*S*,1′*S*)-***8b***: Chemical purity 85% by GC/MS (t_R 19.37); ee 93.0% (chiral GC of the corresponding diacetate). $[\alpha]_D^{20} = +8.74$ ($c = 0.595$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the racemate.

4. *Acetals from Enantiomerically Enriched Diols, Catalyzed by* p-*Toluenesulfonic Acid*. 4.1. *General Procedure 4* (*GP4*). A mixture of the suitable diol (0.014 mol), acetaldehyde (1 ml), and TsOH (100 mg) in CH_2Cl_2 was stirred at r.t. overnight. The mixture was poured into H_2O, the org. phase dried (Na_2SO_4) and evaporated, and the residue chromatographed (hexane/AcOEt 95:5).

4.2. *(2*S*,4*R*,6*S*)- and (2*S*,4*S*,6*S*)-2,4,6-Trimethyl-4-phenyl-1,3-dioxane* ((2*S*,4*R*,6*S*)-**1a** and (2*S*,4*S*,6*S*)-**1b**, resp.). According to *GP4*, (2*R*,4*S*)-**5a**/(2*S*,4*S*)-**5b** 1:1 (7.90 g, 0.044 mol) gave (2*S*,4*R*,6*S*)-**1a**/(2*S*,4*S*,6*S*)-**1b** 1:2 (7.32 g, 81%); ee 93% (chiral GC). $[\alpha]_D^{20} = -49.5$ ($c = 1.21$, $CHCl_3$). ^{1}H-NMR: 7.56–7.16 (*m*, arom. H); 5.19 (*q*, $J = 5.0$, H–C(2) (**1b**)); 4.70 (*q*, $J = 5.2$, H–C(2) (**1a**)); 4.02 (*m*, H–C(6) (**1b**)); 3.67 (*m*, H–C(6(**1a**)); 2.35 (*dd*, $J = 1.8$, 13.8, 1 H–C(5) (**1a**)); 1.81 (*dd*, $J = 2.5$, 13.1, 1 H–C(5) (**1b**)); 1.70 (*dd*, $J = 11.6$, 13.8, 1 H–C(5) (**1a**)); 1.67–1.55 (*m*, 1 H–C(5) and Me–C(4) (**1b**)); 1.42 (*s* + *d*, $J = 5.0$, Me–C(4) (**1a**), Me–C(2) (**1b**)); 1.35 (*d*, $J = 5.2$, Me–C(2) (**1a**)); 1.24 (*d*, $J = 6.4$, Me–C(6) (**1b**)); 1.23 (*d*, $J = 6.4$, Me–C(6) (**1a**)). GC/MS: **1a** (t_R 14.66): 206 (0.5, M^+), 191 (9), 146 (64), 131 (68), 105 (100); **1b** (t_R 16.17): 206 (1, M^+), 191 (39), 162 (26), 145 (30), 105 (100).

4.3. *(2*R*,4*R*,6*R*)- and (2*R*,4*S*,6*R*)-2,4,6-Trimethyl-4-phenyl-1,3-dioxane* ((2*R*,4*R*,6*R*)-**1b** and (2*R*,4*S*,6*R*)-**1a**, resp.). *According to GP4*, (2*R*,4*R*)-**5b**/(2*S*,4*R*)-**5a** 1:1.25 (2.60 g, 0.014 mol) gave (2*R*,4*R*,6*R*)-**1b**/(2*R*,4*S*,6*R*)-**1a**

2:1 (2.57 g, 89%); ee 97% (chiral GC). $[\alpha]_D^{20} = +55.4$ ($c = 1.3$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those described in *4.2*.

4.4. *(2*R,*4*R,*6*R*)-2,4,6-Trimethyl-4-phenyl-1,3-dioxane* ((2*R*,4*R*,6*R*)-**1b**). According to *GP4*, (2*R*,4*R*)-**5b** (0.700 g, 3.88 mmol) gave (2*R*,4*R*,6*R*)-**1b** (0.680 g, 85%); ee >99% (chiral GC); de 76% (GC/MS). $[\alpha]_D^{20} = +44.5$ ($c = 1.29$, $CHCl_3$). ^{1}H-NMR: 7.48–7.20 (*m*, 4 arom. H); 5.19 (*q*, *J* = 5.0, H–C(2)); 4.02 (*m*, H–C(6)); 1.81 (*dd*, *J* = 2.5, 13.1, H–C(5)); 1.67–1.55 (*m*, H–C(5), Me–C(4)); 1.42 (*d*, *J* = 5.0, Me–C(2)); 1.24 (*d*, *J* = 6.4, Me–C(6)). GC/MS: in accordance with that described in *4.2*.

4.5. *(1*R,*3*S,*4a*S,*9a*S*)-1,4a,9,9a-Tetrahydro-1,3-dimethyl-2,4-dioxafluorene* (= *(2*S,*4*R,*4a*S,*9b*S*)-4,4a,5,9b-Tetrahydro-2,4-dimethylindeno[1,2-*d*]-1,3-dioxin*; (1*R*,3*S*,4a*S*,9a*S*)-**13**). According to *GP4*, (1*R*,2*S*,1′*R*)-**8a** (3.35 g, 0.019 mol) gave (1*R*,3*S*,4a*S*,9a*S*)-**13** (3.10 g, 81%). M.p. 40°. Chemical purity 95% by GC/MS (t_R 19.25); ee 90% (chiral GC). $[\alpha]_D^{20} = -10.97$ ($c = 0.93$, $CHCl_3$). ^{1}H-NMR[3]): 7.41–7.13 (*m*, 4 arom. H); 5.25 (*q*, *J* = 5.4, H–C(3)); 4.93 (*d*, *J* = 10.8, H–C(4a)); 4.51 (*dq*, *J* = 5.0, 7.0, H–C(1)); 2.76 (*dd*, *J* = 6.4, 14.3, 1 H–C(9)); 2.64 (*m*, H–C(9a)); 2.40 (*t*, *J* = 14.3, 1 H–C(9)); 1.44 (*d*, *J* = 7.0, Me–C(1)); 1.42 (*d*, *J* = 5.4, Me–C(3)). GC/MS: 204 (15), 203 (2), 160 (35), 143 (30), 132 (70), 117 (100). Anal. calc. for $C_{13}H_{16}O_2$: C 76.44, H 7.90; found: C 76.32, H 7.77.

4.6. *(1*S,*3*R,*4a*R,*9a*R*)-1,4a,9,9a-Tetrahydro-1,3-dimethyl-2,4-dioxafluorene* (= *(2*R,*4*S,*4a*R,*9b*R*)-4,4a,5,9b-Tetrahydro-2,4-dimethylindeno[1,2-*d*]-1,3-dioxin*; (1*S*,3*R*,4a*R*,9a*R*)-**13**). According to *GP4*, (1*S*,2*R*,1′*S*)-**8a** (2.35 g, 0.013 mol) gave (1*S*,3*R*,4a*R*,9a*R*)-**13** (2.31 g, 85%). Chemical purity 87% by GC/MS (t_R 19.25); ee 88% (chiral GC). $[\alpha]_D^{20} = +8.26$ ($c = 0.775$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of its enantiomer. Anal. calc. for $C_{13}H_{16}O_2$: C 76.44, H 7.90; found: C 76.53, H 8.03.

4.7. *(1*R,*3*R,*4a*R,*9a*R*)-1,4a,9,9a-Tetrahydro-1,3-dimethyl-2,4-dioxafluorene* (= *(2*R,*4*R,*4a*R,*9b*R*)-4,4a,5,9b-Tetrahydro-2,4-dimethylindeno[1,2-*d*]-1,3-dioxin*; 1*R*,3*R*,4a*R*,9a*R*)-**14**). According to *GP4*, (1*S*,2*R*,1′*R*)-**8b** (3.80 g, 0.021 mol) gave (1*R*,3*R*,4a*R*,9a*R*)-**14** (3.47 g, 79%). Chemical purity 94% by GC/MS (t_R 18.00); ee 87% (chiral GC). $[\alpha]_D^{20} = +16.35$ ($c = 0.685$, $CHCl_3$). ^{1}H-NMR[3]): 7.42–7.14 (*m*, 4 arom. H); 5.03 (*q*, *J* = 5.3, H–C(3)); 4.58 (*d*, *J* = 10.2, H–C(4a)); 3.98 (*m*, H–C(1)); 2.81 (*dd*, *J* = 6.6, 14.6, 1 H–C(9)); 2.40 (*t*, *J* = 14.6, 1 H–C(9)); 1.96 (*m*, H–C(9a)); 1.48 (*d*, *J* = 5.03, Me–C(3)); 1.24 (*d*, *J* = 6.2, Me–C(1)). GC/MS: 204 (6), 203 (5), 160 (10), 143 (15), 131 (31), 115 (100). Anal. calc. for $C_{13}H_{16}O_2$: C 76.44, H 7.90; found: C 76.60, H 7.75.

4.8. *(1*S,*3*S,*4a*S,*9a*S*)-1,4a,9,9a-Tetrahydro-1,3-dimethyl-2,4-dioxafluorene* (= *(2*S,*4*S,*4a*S,*9b*S*)-4,4a,5,9b-Tetrahydro-2,4-dimethylindeno[1,2-*d*]-1,3-dioxin*; (1*S*,3*S*,4a*S*,9a*S*)-**14**). According to *GP4*, (1*R*,2*S*,1′*S*)-**8b** (1.55 g, 8.7 mmol) gave (1*S*,3*S*,4a*S*,9a*S*)-**14** (1.51 g, 84%). Chemical purity 90% by GC/MS (t_R 18.00); ee 94% (chiral GC). $[\alpha]_D^{20} = -13.3$ ($c = 0.685$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of its enantiomer. Anal. calc. for $C_{13}H_{16}O_2$: C 76.44, H 7.90; found: C 76.33, H 7.68.

5. *Acetals from Enantiomerically Enriched Diols, Catalyzed by Pyridinium* p-*Toluenesulfonate*. 5.1. *General Procedure 5* (*GP5*). A mixture of the suitable diol (0.013 mol), acetaldehyde (1 ml), and pyridinium *p*-toluenesulfonate (100 mg) in CH_2Cl_2 was stirred at r.t. overnight. The mixture was poured into H_2O, the org. phase dried (Na_2SO_4) and evaporated, and the residue chromatographed (hexane/AcOEt 95:5).

5.2. *(1*S,*3*S,*4a*S,*9a*R*)-1,4a,9,9a-Tetrahydro-1,3-dimethyl-2,4-dioxafluorene* (= *(2*S,*4*S,*4a*R,*9b*S*)-4,4a,5,9b-Tetrahydro-2,4-dimethylindeno[1,2-*d*]-1,3-dioxin*; (1*S*,3*S*,4a*S*,9a*R*)-**2a**). According to *GP5*, (1*S*,2*R*,1′*S*)-**8a** (2.35, 0.013 mol) gave (1*S*,3*S*,4a*S*,9a*R*)-**2a** (1.85 g, 68%). Chemical purity 79% by GC/MS (t_R 18.25); ee 82% (chiral GC). $[\alpha]_D^{20} = -57.4$ ($c = 0.575$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the racemate.

5.3. *(1*R,*3*R,*4a*R,*9a*S*)-1,4a,9,9a-Tetrahydro-1,3-dimethyl-2,4-dioxafluorene* (= *(2*R,*4*R,*4a*S,*9b*R*)-4,4a,5,9b-Tetrahydro-2,4-dimethylindeno[1,2-*d*]-1,3-dioxin*; (1*R*,3*R*,4a*R*,9a*S*)-**2a**). According to *GP5*, (1*R*,2*S*,1′*R*)-**8a** (3.35 g, 0.019 mol) gave (1*R*,3*R*,4a*R*,9a*S*)-**2a** (2.52 g, 65%). Chemical purity 95% by GC/MS (t_R 18.25); ee 92% (chiral GC). $[\alpha]_D^{20} = +74.6$ ($c = 0.845$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the racemate.

5.4. *(1*R,*3*R,*4a*S,*9a*R*)-1,4a,4b,8a,9,9a-Tetrahydro-1,3-dimethyl-2,4-dioxafluorene* (= *(2*R,*4*R,*4a*R,*9b*S*)-4,4a,5,9b-Tetrahydro-2,4-dimethylindeno[1,2-*d*]-1,3-dioxin*; (1*R*,3*R*,4a*S*,9a*R*)-**2b**). According to *GP5*, (1*S*,2*R*,1′*R*)-**8b** (3.80 g, 0.021 mol) gave (1*R*,3*R*,4a*S*,9a*R*)-**2b** (2.77 g, 63%). Chemical purity 68% by GC/MS (t_R 17.70); ee 89% (chiral GC). $[\alpha]_D^{20} = +68.9$ ($c = 0.47$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the racemate.

5.5. *(1*S,*3*S,*4a*R,*9a*S*)-1,4a,4b,8a,9,9a-Tetrahydro-1,3-dimethyl-2,4-dioxafluorene* (= *(2*S,*4*S,*4a*S,*9b*R*)-4,4a,5,9b-Tetrahydro-2,4-dimethylindeno[1,2-*d*]-1,3-dioxin*; (1*S*,3*S*,4a*R*,9a*S*)-**2b**). According to *GP5*, (1*R*,2*S*,1′*S*)-**8b** (1.55 g, 8.7 mmol) gave (1*S*,3*S*,4a*R*,9a*S*)-**2b** (1.04 g, 58%). Chemical purity 88% by GC/MS (t_R 17.70); ee = 89% (chiral GC). $[\alpha]_D^{20} = -80.3$ ($c = 0.65$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the racemate.

6. *Inversion of* Floropal *Samples with $BF_3 \cdot Et_2O$*. 6.1. *General Procedure 6* (*GP6*). A soln. of the suitable *Floropal* sample (25 g) in CH_2Cl_2 (25 ml) was treated at 20° under N_2 with $BF_3 \cdot Et_2O$ (0.5 g). The mixture was stirred at r.t. for 7 h, washed to neutrality with 5% (*w*/*w*) NaOH soln., dried (Na_2SO_4), and evaporated. The residue was chromatographed (hexane).

6.2. *(2*R*,4*S*,6*R*)-2,4,6-Trimethyl-4-phenyl-1,3-dioxane* ((2*R*,4*S*,6*R*)-**1a**). According to *GP6*, (2*R*,4*S*,6*R*)-**1a**/(2*R*,4*R*,6*R*)-**1b** 1:2 (2.0 g, 9.7 mmol) gave (2*R*,4*S*,6*R*)-**1a** (1.06 g, 53%); ee 80% (chiral GC); de 76%. $[\alpha]_D^{20} = +59$ ($c = 1.37$, $CHCl_3$). ^{1}H-NMR: 7.48–7.20 (*m*, 4 arom. H); 4.70 (*q*, *J* = 5.2, H–C(2)); 3.67 (*m*, H–C(6)); 2.35 (*dd*, *J* = 1.8, 13.8, 1 H–C(5)); 1.70 (*dd*, *J* = 11.6, 13.8, 1 H–C(5)); 1.42 (*s*, Me–C(4)); 1.35 (*d*, *J* = 5.2, Me–C(2)); 1.23 (*d*, *J* = 6.4, Me–C(6)). GC/MS (t_R 14.66): 206 (0.5, M^+), 191 (9), 146 (64), 131 (68), 105 (100).

6.3. *(2*S*,4*R*,6*S*)-2,4,6-Trimethyl-4-phenyl-1,3-dioxane* ((2*S*,4*R*,6*S*)-**1a**). According to *GP6*, (2*S*,4*R*,6*S*)-**1a**/(2*S*,4*S*,6*S*)-**1b** 1:2 (2.0 g, 9.7 mmol) gave (2*S*,4*R*,6*S*)-**1a**. (1.36 g, 68%); ee 68% (chiral GC); de 73%. $[\alpha]_D^{20} = -50.2$ ($c = 1.29$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the enantiomer.

7. *Hydrolyses*. 7.1. *(2*R*,4*R*)-2-Phenylpentane-2,4-diol* ((2*R*,4*R*)-**5b**). Acetate (2*R*,4*R*)-**7** (0.95 g, 4.27 mmol) was hydrolyzed with KOH (0.359 g, 6.42 mmol) in MeOH (20 ml): (2*R*,4*R*)-**5b** (0.745 g, 97%). Chemical purity 94% by GC/MS (t_R 17.10); ee > 99% (chiral GC of the corresponding diacetate). $[\alpha]_D^{20} = +15.84$ ($c = 0.265$, $CHCl_3$); de 86% (GC/MS). ^{1}H-NMR: 7.60–7.08 (*m*, arom. H); 4.29 (*m*, H–C(3)); 1.81 (*m*, CH_2); 1.64 (*s*, Me(1)); 1.17 (*d*, *J* = 6.4, Me(5)). GC/MS: 180 (1), 165 (18), 121 (100), 105 (84).

7.2. *(1*S*,2*R*,1′*S*)-2-(1-Hydroxyethyl)indan-1-ol* (=*(α*S*,1*S*,2*R*)-2,3-Dihydro-1-hydroxy-α-methyl-1*H*-indene-2-methanol*; (1*S*,2*R*,1′*S*)-**8a**). Acetate (1*S*,2*R*,1′*S*)-**12a** (5.80 g, 0.029 mol) was hydrolyzed with KOH (2.44 g, 0.043 mol) in MeOH (40 ml): (1*S*,2*R*,1′*S*)-**8a** (5.00 g, 98%); ee 93% (GC of the corresponding diacetate). $[\alpha]_D^{20} = -18.8$ ($c = 0.891$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the racemate.

7.3. *(1*S*,2*R*,1′*R*)-2-(1-Hydroxyethyl)indan-1-ol* (=*(α*R*,1*S*,2*R*)-2,3-Dihydro-1-hydroxy-α-methyl-1*H*-indene-2-methanol*; (1*S*,2*R*,1′*R*)-**8b**). Acetate (1*S*,2*R*,1′*R*)-**12b** (7.80 g, 0.039 mol) was hydrolyzed with KOH (3.28 g, 0.058 mol) in MeOH (40 ml): (1*S*,2*R*,1′*R*)-**8b** (6.67 g, 97%); ee > 99% (chiral GC of the corresponding diacetate). $[\alpha]_D^{20} = -8.80$ ($c = 0.661$, $CHCl_3$). ^{1}H-NMR and GC/MS: in accordance with those of the racemate.

8. *(1*S*,2*R*,1′*S*)- and (1*R*,2*S*,1′*S*)-2-(1-Hydroxyethyl)indan-1-ol* ((1*S*,2*R*,1′*S*)-**8a** and (1*R*,2*S*,1′*S*)-**8b**, resp.). The mixture (2*R*,1′*S*)-**15a**/(2*S*,1′*S*)-**15b** 1:1 (3.80 g, 0.022 mol) was submitted to $NaBH_4$ reduction: mixture (3.05, 78%) containing (1*S*,2*R*,1′*S*)-**8a** (ee 94%, chiral GC of the corresponding diacetate) and (1*R*,2*S*,1′*S*)-**8b** (ee 94% of the corresponding diacetate) in 1:1 ratio.

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