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Chirality and Fragrance Chemistry: Stereoisomers of the Commercial Chiral Odorants Muguesia and Pamplefleur

Agnese Abate, Elisabetta Brenna,* Claudio Fuganti, Francesco G. Gatti, Tommaso Giovenzana, Luciana Malpezzi, and Stefano Serra

Dipartimento di Chimica, Materiali ed Ingegneria Chimica del Politecnico, Istituto CNR per la Chimica del Riconoscimento Molecolare, Via Mancinelli 7, I-20131 Milano, Italy

elisabetta.brenna@polimi.it

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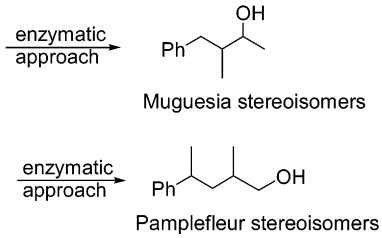


The work describes the enzyme-mediated preparation and the odor evaluation of the single stereoisomers of the commercial odorants Muguesia and Pamplefleur. The synthetic approach to Muguesia stereoisomers helped to clear the assignment of the relative configuration of intermediate diols **5**. The odor response of Pamplefleur isomers was found to be rather unusual. No stereoisomer prevailed, but each one played a definite role in establishing the odor sensation of the final blend.

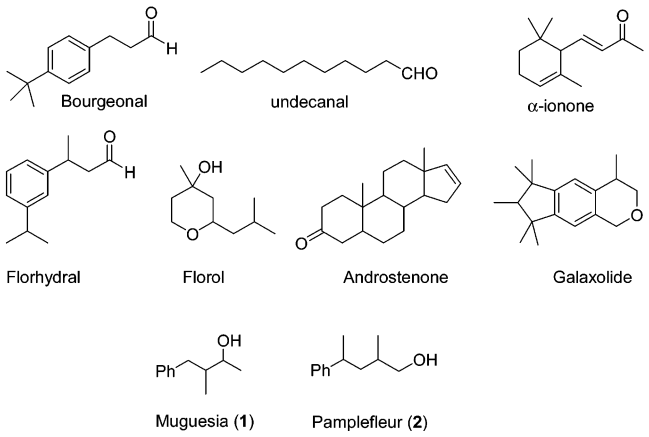
Introduction

A scented breath marks the way for a new Life: this is the outcome of a study recently reported in *Science*.[1] Olfactory receptors are known to reside in spermatozoa. Hatt et al. have shown that the floral odorant bourgeonal is capable of influencing human sperm chemotaxis and of increasing the speed of sperm cells (Chart 1). If bourgeonal and undecanal are simultaneously present, the bourgeonal effect is completely suppressed. Undecanal is a competitive antagonist at the binding site of bourgeonal. Thus, the perception of odor, even at the beginning of Life, is basically a molecular recognition process.

According to a mechanism which is not clear yet, the structural features of a molecule are recognized by our brain as a definite and characteristic odor sensation. The olfactory receptors of human nose are capable of detecting and discriminating thousands of volatile organic compounds with different structure, thus showing a great capacity for molecular recognition.

The spatial distribution of substituents around stereogenic elements, such as stereogenic centers, is expected to be crucial when a process of molecular recognition is involved. Since the recognition is performed by proteins, the enantiomers of chiral molecules can be perceived in different ways by our nose.

CHART 1



So far, the investigation of the odor properties of single stereoisomers has shown different situations.[2] (*R*)- and (*S*)-α-ionone have very similar odor character, "Floral-woody note, with an additional honey aspect", and nearly the same odor threshold (3.2 and 2.7 ng/L, respectively).[3]

* Corresponding author. Phone: ++39 0223993077. Fax: ++39 0223993080.

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(+)- and (−)-florhydral show similar odor tonalities and different odor thresholds (odor threshold = 0.035 and 0.88 ng/L, respectively.[4] (+)-Androstenone is odorless, while the (−)-enantiomer is sweaty, urine, strong, and musky.[5]

When more than one stereogenic carbon atom are present in a molecule, it may happen that the odor vectors are the enantiomers of the same or of different diastereoisomers.

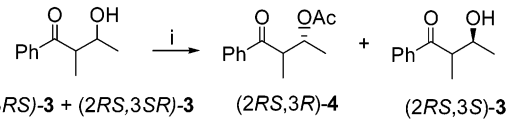
The scent of commercial Florol (two racemic diastereoisomers) is mainly due to the (2*R,*4*R*) and (2*S,*4*S*) stereoisomers (odor threshold 1.21 and 26 ng/L air, respectively), while the (2*R,*4*S*) and (2*S,*4*R*) isomers are nearly odorless (odor threshold 520 and >600 ng/L air, respectively).[6]

When the odor properties of the four stereoisomers of Galaxolide were evaluated the following results were obtained.[7] The two (4*S*) stereoisomers were found to be responsible for the odor of the commercial product. (4*S,*7*R*)-*cis*-Galaxolide was described to be the most powerful (odor threshold = 0.63 ng/L air) of the Galaxolide isomers and to possess *a very pleasant clean musk note*. Slightly less powerful was the *trans*-diastereoisomer (4*S,*7*S*) (odor threshold = 1.0 ng/L air), which showed a *similar musk odor that differed from that of the*(4*S,*7*R*) *diastereoisomer by its dry character*. The (4*R*)-isomers were found to be much weaker and to give no contribute to the odor profile of the commercial product ((4*R,*7*S*)-*cis* isomer odor threshold = 130 ng/L air; (4*R*,7*R*)-*trans* isomer odor threshold = 440 ng/L air)).

Thus, the outcome of the study of enantioselectivity in odor perception is completely unpredictable, but it is now of great relevance. As a matter of fact, in the field of fragrance chemistry, an increasing concern for human health, and also for environmental preservation, has favored the trend to employ single-enantiomer chemicals in those products that are to directly interact with human beings. If only the odor-active isomers are employed in commercial products, the toxicological risks connected with the exposure to chemicals present in perfumed articles can be reduced. The first stereoisomerically enriched fragrances have been put on the market: Kharismal, Hedione HC, and Super Cepionate are methyl dihydrojasmonates with a high content of cis diastereoisomer; Paradisone is optically active (+)-*cis*-methyl dihydrojasmonate; and Sandranol, Dartanol, Sanjinol, and Levosandol are optically active (−)-2-ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol.

We are going to report herein on the preparation and on the odor evaluation of all the stereoisomers of the commercial odorants Muguesia (**1**) and Pamplefleur (**2**). The work is part of a project devoted to the investigation of the odor properties of single stereoisomers of known absolute configuration. The preparation of the single stereoisomers of these two fragrances gave us the chance to investigate the potentiality of enzyme chemistry in the control of the relative and absolute configuration of vicinal stereogenic carbon atoms. Interesting findings in the chemistry of substrates with stereocenters in position 1,2 and 1,3 will be reported.

SCHEME 1[a]



[a] Key: (i) Lipase PS, tert-butylmethyl ether, vinyl acetate.

Results and Discussion

Muguesia (**1**) and Pamplefleur (**2**) are available commercially by IFF as mixtures of two racemic diastereoisomers. In the IFF catalog online, Muguesia is described as floral, muguet, rose, and minty. Its usage is suggested when aldehydic muguet ingredients are not stable. Pamplefleur is described as citrus, grapefruit, floral, vetivert, green, and diffusive. It represents the animal moiety for jasmin types.

We optimized two enzyme-mediated approaches to all the steroisomers of odorants **1** and **2**.

Muguesia. Aldolic condensation of propiophenone with acetaldehyde gave hydroxyketone **3** as a 1:1 mixture of two racemic diastereoisomers, (2*RS,*3*RS*)-**3** and (2*RS,*3*SR*)-**3**.

Lipase PS-mediated acetylation of this mixture in *tert*-butylmethyl ether, in the presence of vinyl acetate, gave after 24 h an acetate fraction which was found to be a 3.1:1 mixture of the two enantiopure (ee = 99%, HPLC) 3*R* diastereoisomers of derivative **4** (Scheme 1).

The unreacted alcohol was submitted to prolonged Lipase PS-catalyzed transesterification, by monitoring the steric course of the reaction by chiral HPLC. At the end of the procedure, an alcoholic fraction was recovered which was found to be a 1:1 mixture of the two enantiopure (chiral HPLC) 3*S* diastereoisomers of compound **3**.

The mixture of (2*RS*,3*S*)-**3** was reduced with sodium boron hydride in CH_2Cl_2−MeOH (Scheme 2).

The ^{1}H NMR spectrum of the crude reduction mixture showed that the main products (84%) were the two (3*S*) diastereoisomers of diol **5** showing a *syn* conformation at C_1−C_2. The mixture was chromatographed on a silica gel column to afford diols (1*S*,2*R,*3*S*)-**5** (de = 99%, GC/MS) and (1*R*,2*S,*3*S*)-**5** (de = 99%, GC/MS). This latter was obtained as a crystalline compound. The two diol derivatives were submitted to hydrogenolysis to afford (2*S*,3*S*)-**1** and (2*S*,3*R*)-**1**.

The mixture of (2*RS*,3*R*)-**4** was reduced with lithium aluminum hydride in THF. The ^{1}H NMR spectrum of the crude reduction mixture showed that the main products (77%) were the two (3*R*) diastereoisomers of diol **5** showing an *anti* conformation at C_1−C_2. The mixture was chromatographed on a silica gel column to give diol (1*S*,2*S,*3*R*)-**5** (de = 99%, GC/MS) and (1*R*,2*R,*3*R*)-**5** (de = 99%, GC/MS). This latter was obtained as a crystalline compound. The two diol derivatives were submitted to hydrogenolysis to afford (2*R*,3*R*)-**1** and (2*R*,3*S*)-**1**.

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(5) Prelog, V.; Ruzicka, L.; Wieland, P. *Helv. Chim. Acta* **1944**, *27*, 66; Ohloff, G.; Maurer, B.; Winter, B.; Giersch, W. *Helv. Chim. Acta* **1983**, *66*, 192.
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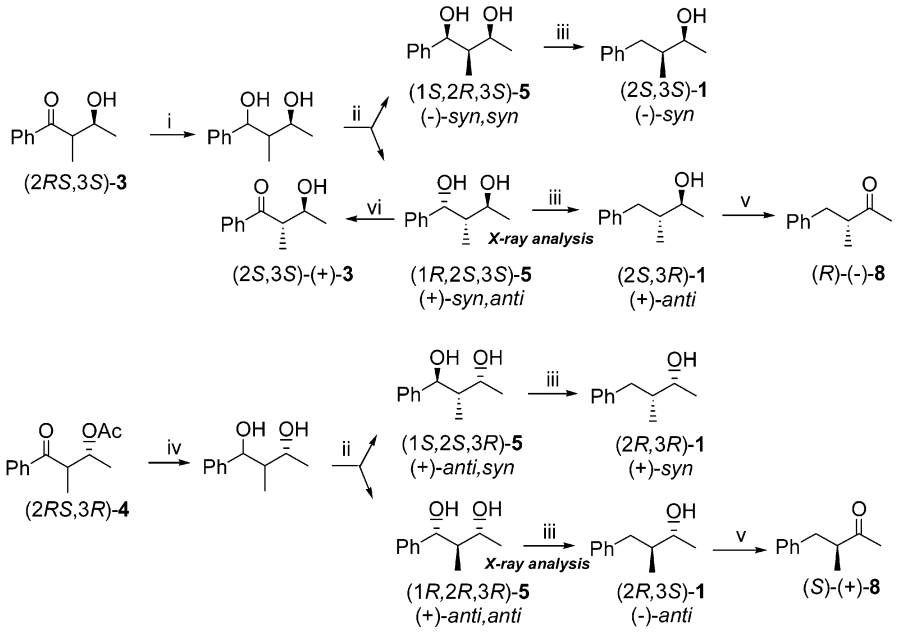
SCHEME 2[a]



[a] Key: (i) $NaBH_4$, CH_2Cl_2, MeOH; (ii) column chromatography; (iii) H_2, Pd/C, $HClO_4$, EtOH; (iv) $LiAlH_4$, THF; (v) Jones' reagent, acetone, 0 °C; (vi) MnO_2, $ChCl_3$, rt.

TABLE 1. ^{1}H NMR Data of *syn*- and *anti*-1

compd	ref	δ H-C(2)
syn-**1**	8	3.85−3.76, multiplet
	our work	3.76, qd, $J_{2,Me} = 6.3$ Hz, $J_{2,3} = 3.7$,
anti-**1**	8	3.78−3.68, multiplet
	9	3.70, quintet, $J_{2,3} = J_{2,Me} = 6$ Hz
	our work	3.70, quintet, $J_{2,3} = J_{2,Me} = 6.4$ Hz

The relative configuration of Muguesia stereoisomers was assigned according to the following considerations. Dinnocenzo et al.[8] prepared (2*RS*,3*RS*)-**1** (*syn*-**1**) and (2*RS*,3*SR*)-**1** (*anti*-**1**) by reaction of benzylmagnesium bromide with *trans*- and *cis*-2,3-epoxybutane. The ^{1}H NMR signals of H-C(2), that is to say of *CH*OH, are reported in Table 1. Kazlauskas et al.[9] prepared racemic (2*RS*,3*SR*)-**1** by the same procedure, and the corresponding NMR data are reported in Table 1. The analysis of the ^{1}H NMR spectra allowed us to establish the relative configuration of our Muguesia samples.

Interestingly enough, the reduction of (2*RS,*3*S*)-**3** and that of (2*RS,*3*R*)-**4** were characterized by different steric courses; i.e., the two reactions afforded two different pairs of diastereoisomers.

The relative configuration of diols **5** was assigned on the basis of these considerations. The relative configuration of the stereogenic carbon atoms C_2 and C_3 of our diol samples was univocally established by the ^{1}H NMR spectra of the hydrogenolysis products. Hence, the relative configuration of C_1 and C_2 had to be assessed. For this purpose, we submitted the two crystalline diol samples to X-ray diffraction analysis. The molecular structure of the one obtained by $NaBH_4$ reduction of hydroxy ketone **3** is shown in Figure 1. The benzylic OH

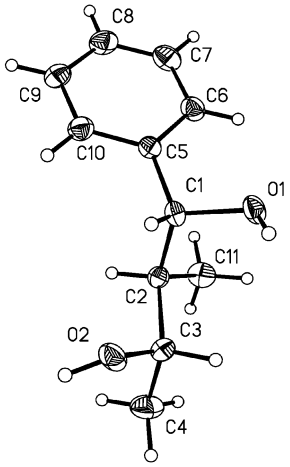


FIGURE 1. View of (1*R*,2*S*,3*S*)-*syn-anti*-**5**; the numbering corresponds to that used in the X-ray analysis. Selected torsion angles (deg): O1−C1−C2−C11, 52.0(5); O1−C1−C2−C3, 73.4(5); C5−C1−C2−C3, 162.8(4); C11−C2−C3−O2, 179.9(4); C1−C2−C3−C4, 179.6(4).

group was found to be in a syn arrangement with respect to the methyl group and in an anti arrangement with respect to the other OH group, as can be deduced from the molecular geometry shown in Figure 1. The relative configurations of the three carbon atoms C1, C2 and C3 are completely described also by the torsion angles reported in the caption of Figure 1. It is interesting to note that the aliphatic chain C_1−C_4 is perfectly transplanar, while the C1−C5 bond is rotated 17.2° out of the chain plane. This feature accounts for the deviation of the O1−C1−C3−C4 and O1−C1−C2−C11 torsion angles from the standard gauche value of 60°.

The other diol, obtained together with this crystalline one in the same reduction reaction, showed the same coupling constant ($J_{1,2}$ = 3 Hz) between H-C(1) and

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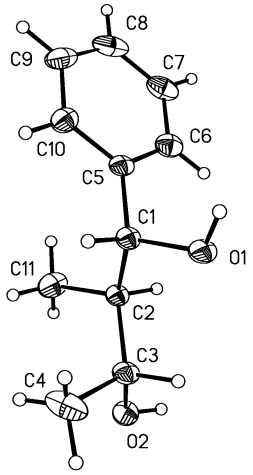

FIGURE 2. View of (1*R*,2*R*,3*R*)-*anti-anti*-**5**; the numbering corresponds to that used in the X-ray analysis. Selected torsion angles (deg): O1−C1−C2−C11, 177.9(3); O1−C1−C2−C3, 55.3(3); C5−C1−C2−C3, 178.3(2); C11−C2−C3−O2, 61.8(3); C1−C2−C3−O2, 171.6(2).

H-C(2). Thus, the same syn arrangement of C_1-C_2 could be attributed to this stereoisomer.

The molecular structure of the crystalline diol, obtained by $LiAlH_4$ reduction of acetate **4**, is shown in Figure 2. The benzylic OH group was found to be in an anti arrangement with respect to the methyl group and in a syn arrangement with respect to the other OH group, as can be deduced from the molecular geometry shown in Figure 2. The relative configurations of the three carbon atoms C1, C2, and C3 is completely described also by the torsion angles reported in the caption of Figure 2. In this molecule, the chain C5−C1−C2−C3−O2 is all transplanar and makes an angle of about 64° with the aromatic ring plane.

The other stereoisomer, obtained together with this crystalline one in the same reduction reaction, showed a coupling constant ($J_{1,2}$ = 8.1 Hz) similar to that ($J_{1,2}$ = 6.2 Hz) of *anti,anti*-**5**. Thus, an anti conformation at C_1-C_2 was assigned to both of them.

The conclusion was that sodium boron hydride reduction of hydroxy ketones (2*RS*,3*S*)-**3** gave mainly the two diol diastereoisomers showing a syn conformation at C_1-C_2; lithium aluminum hydride reduction of acetoxy ketones (2*RS*,3*R*)-**4** gave the two diastereoisomers showing an anti conformation at C_1-C_2. Thus, 1,2-induction dominated over 1,3-induction: the stereogenic center at C_2 controlled the steric course of the reduction of the adjacent carbonyl group.[10] It was reported in the literature that $LiAlH_4$ treatment of *tert*-butyldimethylsilyl ethers of acyclic 2-alkyl-3-hydroxyketones was characterized by high 1,2-anti diastereoselectivity.[11] This result was attributed to the fact that the bulky *tert*-butyldimethylsilyl protecting group prevented intramolecular chelation, so that the reaction proceeded through the open-chain model proposed by Felkin[12] and Anh.[13] The same preferential steric course was observed in $LiAlH_4$ reduction of acetoxy ketones (2*RS*,3*R*)-**4**.

$NaBH_4$ reduction usually gives poor 1,2-syn diastereoselectivity:[10b] it is well established that the use of $ZnBH_4$ provides higher values of 1,2-syn selectivity due to a contribution of zinc chelation.[14] In the case of hydroxy ketone **3** a particularly high value of selectivity was observed.

Our findings on the configuration of diols **5** were found to be in contrast with some results described in the literature. The ^{1}H NMR signals of *CH*PhOH and of *CH*OH of the four isomeric diols **5** described by various authors[15−20] are reported in Table 2, compared to our values. The following conclusions can be drawn, taking into account that in diols **5** the presence of an intramolecular hydrogen bond may induce a certain conformational rigidity.

The vicinal coupling constant J_{1-2} between H-C(1) and H-C(2) is smaller when the conformation at C_1-C_2 is syn rather than anti. Some perplexity is arisen by the data reported for *anti*,*syn*-**5** in ref 19.

The vicinal coupling constant J_{2-3} is similar to the coupling constant between H-C(3) and the methyl group, when the conformation at C_{2-3} is anti. It shows a lower value when the conformation is syn. Some perplexity arises from the data reported for *syn,anti*-**5** in ref 19 and for *syn,syn*-**5** in refs 15−17.

In Table 3, the ^{13}C NMR spectra of diols **5** found in the literature are compared with our data. Once again, some perplexity is caused by the spectrum described for *syn*,*syn*-**5** in refs 15−17 and by those described for *anti,syn*-**5** and *syn,anti*-**5** in ref 19.

It had been already noticed by Bloch in 1988[11] that in 1,3-diol derivatives the chemical shift (^{13}C) of the carbon atom of the methyl group linked to C(2) was sensible to the relative configuration of the three vicinal stereocenters. Typical values were described to be as follows: δ = ∼4 ppm for syn,syn diols, δ = ∼10−11 ppm for syn,anti diols, and δ = ∼13 ppm for anti,anti diols. The upfield shift of the chemical shift of $CH_3-C(2)$ is clearly due to the γ-effect of the OH groups.[21]

(10) To obtain 1,3-induction two strategies have been optimized: (i) the use of a reducing agent capable of binding the hydroxyl function and of promoting intramolecular hydride transfer; (ii) the use of an additive to preorganize the substrate prior to the addition of the reducing agent which gives intermolecular hydride addition. Examples of the first strategy: (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. (b) Anwar, S.; Bradley, G.; Davis, A. P. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1383. Examples of the second strategy: (c) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2238. (d) Evans, D. E.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190. (e) Sarko, C. R.; Collibee, S. E.; Knorr, A. L.; DiMare, M. *J. Org. Chem.* **1996**, *61*, 868. (f) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Chem. Eur. J.* **2000**, *6*, 2590. (g) Bartoli, G.; Bosco, M.; Marcantoni, E.; Massaccesi, M. Rinaldi, S.; Sambri, L. *Eur. J. Org. Chem,* **2001**, 4679;

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TABLE 2. ^{1}H NMR Data of Diols 5

compd	ref	δ H-C(1)	δ H-C(3)
syn,anti-**5**	15−17	5.12, d, $J_{1,2}$ = 1.8 Hz	3.83, quintuplet, $J_{2,3} = J_{3,Me}$ = 6.3 Hz
	20	5.11, d, $J_{1,2}$ = 3 Hz	3.84, m
	19	5.00, d, $J_{1,2}$ = 2.8 Hz	4.23, qd, $J_{3,Me}$ = 6.6 Hz, $J_{2,3}$ = 1.7 Hz,
	our work	5.08, d, $J_{1,2}$ = 3 Hz	3.80, quintuplet, $J_{2,3} = J_{3,Me}$ = 6.2 Hz
syn,syn-**5**	15−17	5.04, d, $J_{1,2}$ = 1.7 Hz	3.83, quintuplet, $J_{2,3} = J_{3,Me}$ = 6.3 Hz
	20	5.05, d, $J_{1,2}$ = 3.3 Hz	4.24, qd, $J_{3,Me}$ = 6.9 Hz, $J_{2,3}$ = 1.8 Hz
	19	5.00, d, $J_{1,2}$ = 2.8 Hz	4.42, qd, $J_{3,Me}$ = 6.4 Hz, $J_{2,3}$ = 1.9 Hz
	our work	5.03, d, $J_{1,2}$ = 2.7 Hz	4.22, qd, $J_{3,Me}$ = 6.2 Hz, $J_{2,3}$ = 1.9 Hz,
anti,anti-**5**	15, 17	4.52, d, $J_{1,2}$ = 7.4 Hz	3.90, m
	Our work	4.54 ppm, d, $J_{1,2}$ = 9 Hz	3.92 ppm, dq, $J_{2,3}$ = 8.1 $J_{3,Me}$ = 6.1 Hz
anti,syn-**5**	18	4.68 ppm, d, $J_{1,2}$ = 7 Hz	4.04 ppm, qd, $J_{3,Me}$ = 6.5 Hz, $J_{2,3}$ = 2.5 Hz
	15, 17	4.71 ppm, d, $J_{1,2}$ = 6.6 Hz	4.04 ppm, m
	20	4.72 ppm, d, $J_{1,2}$ = 7.2 Hz	4.05 ppm, qd, $J_{3,Me}$ = 6.3 Hz, $J_{2,3}$ = 2.4 Hz,
	19	5.01 ppm, d, $J_{1,2}$ = 2.8 Hz	4.21 ppm, qd, $J_{3,Me}$ = 6.4 Hz, $J_{2,3}$ = 1.8 Hz
	Our work	4.70 ppm, d, $J_{1,2}$ = 6.9 Hz	4.05 ppm, qd, $J_{3,Me}$ = 6.5 Hz, $J_{2,3}$ = 1.9 Hz.

TABLE 3. ^{13}C NMR Data of Diols 5

compd	ref	δ ^{13}C NMR
syn,anti-**5**	15−17	142.6, 128.0, 127.0, 126.1, 75.0, 70.9, 45.5, 21.9, 11.5
	19	143.3, 127.7, 126.3, 125.2, 78.6, 71.5, 44.9, 21.6, *3.6*
	our work	142.7, 128.0, 127.0, 126.1, 74.7, 70.9, 45.7, 21.9, 11.3
syn,syn-**5**	15−17	142.6, 128.0, 127.0, 126.1, 75.0, 70.9, 45.5, 21.9, *11.5*
	19	143.0, 127.8, 126.7, 125.3, 78.2, 71.8, 44.8, 21.4, 3.6
	our work	143.3, 128.1, 127.0, 125.6, 78.5, 72.0, 45.0, 21.5, 4.1
anti,anti-**5**	15, 17	143.3, 128.5, 128.0, 127.1, 81.2, 73.3, 46.4, 21.8, 13.5
	our work	143.3, 128.3, 127.8, 127.1, 81.0, 73.3, 46.1, 21.7, 13.3
anti,syn-**5**	15, 17	143.7, 128.4, 127.6, 126.4, 78.1, 69.2, 44.5, 19.4, 12.1
	19	143.5,127.9, 126.8, 125.3, 78.2, 71.8, 44.8, 21.3, *3.7*
	our work	143.7, 128.2, 127.6, 126.4, 77.7, 68.9, 44.4, 18.9, 12.0

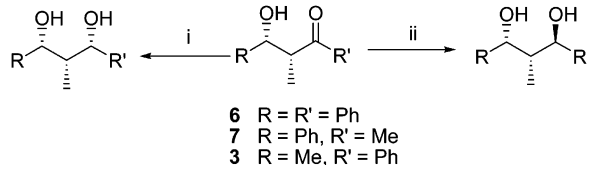
These observations are in agreement with the ^{13}C NMR spectra of our samples.

In ref 15, 1,3-diols of structure **5** were prepared from silirane by benzaldehyde insertion and oxidation. The authors had assigned the relative configuration of the four possible stereoisomers of diol **5** by NMR analysis of the corresponding acetonides and by X-ray structural determination of crystalline derivatives. In the Supporting Information of ref 15 and in the Experimental Section of refs 16 and 17 the ^{13}C NMR spectra of *syn,syn*-**5** and of *syn,anti*-**5** are described to be perfectly identical, and the ^{1}H NMR spectra of these two stereoisomers are the same, starting from the quintet at 3.83 ppm to the doublet at 0.82 ppm. Our idea is that a mistake in the transcription of these data had been done at the beginning in ref 15 and then reiterated by the same authors in the following papers.

In ref 19, the authors described an "easy and cheap methodology to access to 1,3-dioxygenated chiral nonracemic building blocks". They employed (*S*,*S*)-(+)-pseudoephedrine to perform stereoselective aldol reactions. The chiral nonracemic aldol products were used as starting materials for the conversion into useful chiral building blocks, such as α-hydroxy acids, esters, and ketones and into 1,3-syn and 1,3-anti diols. The key step for the preparation of 1,3 -diols was described to be the reduction of hydroxy ketones with $BH_3(Me_2S)$ to give diols 1,3-syn and with $LiBH_4$ to afford diols 1,3-anti (Scheme 3).

Hydroxy ketone **6** was employed as a model compound, and the conclusions drawn on this substrate were then extended to the reduction of other hydroxy ketones, among which (2*R*,3*S*)-**3**. The following sybilline sentence was used to explain the assignment of configuration:

SCHEME 3[a]



[a] Key: (i). $BH_3(Me_2S)$; (ii) $LiBH_4$.

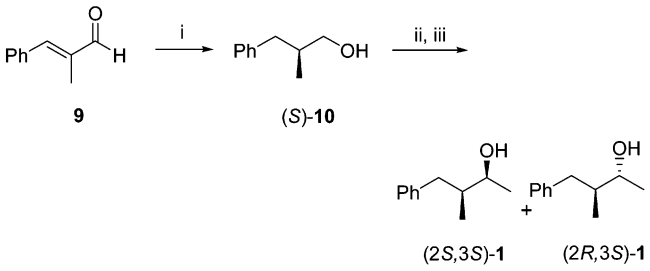
"The 1,3-syn/1,3-anti product distribution and the absolute configuration of the newly created chiral center were assigned by ^{1}H NMR spectroscopy by comparison of the coupling constants ($J_{1,2}$ = 2.8 Hz for the syn isomer and $J_{1,2}$ = 6.8 Hz and $J_{2,3}$ = 2.4 Hz for the anti isomers, see Experimental Section) and also from the fact that in this particular case (the reduction product of **6**) the 1,3-syn diol is a meso compound in which both carbon atoms C1 and C3 are equivalent". Syn and anti are referred by these authors to the relative arrangement of the OH groups. However, neither the ^{1}H NMR spectra of diols **5**, obtained by reduction of hydroxy ketones **3** and **7**, nor those of the diols obtained by reduction of **6** seem to support these statements. According to the ^{1}H and ^{13}C NMR spectra reported for substrates **5** in this work, it seems that both BH_3 and $LiBH_4$ reduction of hydroxy ketones **3** and **7** gave *syn*,*syn*-**5**.

The absolute configuration of Muguesia samples was established as follows. The two Muguesia samples (+)- and (−)-anti-**1** (Scheme 2) were oxidized with Jones' reagent at 0 °C to give (*R*)-(−)- and (*S*)-(+)-**8**, respectively. The absolute configuration of 3-methyl-4-phenyl-2-butanone had been established by correlation with 2-meth-

TABLE 4. $[\alpha]_D$ Values of Diols 5

compd	reference	
(1*R*,2*S*,3*R*)-*syn,syn*-**5**	19	$[\alpha]_D = -12.3$ (c 0.2, CH_2Cl_2)
	26	$[\alpha]_D = +35.5$ (c 0.46, $CHCl_3$
(1*S*,2*R*,3*S*)-*syn,syn*-**5**	19	$[\alpha]_D = +12.4$ (c 0.1, CH_2Cl_2)
	our value	$[\alpha]_D = -27.7$ (c 0.7, $CHCl_3$)
(1*R*,2*S*,3*S*)-*syn,anti*-**5**	19	$[\alpha]_D = +15.6$ (c 0.1, CH_2Cl_2) wrong NMR
	our value	$[\alpha]_D = +52.3$ (c 1.12, CH_2Cl_2)
(1*R*,2*R*,3*S*)-*anti,syn*-**5**	19	$[\alpha]_D = +15.8$ (c 0.1, CH_2Cl_2) wrong NMR
(1*S*,2*S*,3*R*)-*anti,syn*-**5**	26	$[\alpha]_D = -44.6$ (c 0.40, $CHCl_3$)
	our value	$[\alpha]_D = +25.2$ (c 1.1, $CHCl_3$)
(1*R*,2*R*,3*R*)-*anti,anti*-**5**	our value	$[\alpha]_D = +27.8$ (c 1.0, $CHCl_3$)

SCHEME 4[a]



[a] Key: (i) Baker's yeast, water, glucose; (ii) DMSO, $(COCl)_2$; (iii) MeMgCl, Et_3O.

yl-4-phenylpropionic acid.[22−24] A further confirmation was given by the fact that (+)-*syn,anti*-**5** was oxidized with MnO_2 in CH_2Cl_2, to give (2*S*,3*S*)-(+)-**3**.[25]

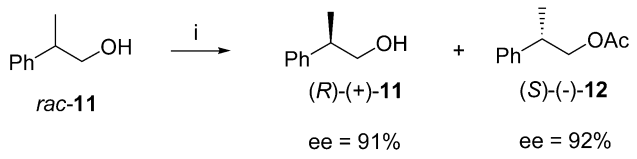
The specific optical rotations of some stereoisomers of diol **5** were reported in the literature and are collected in Table 4: we could not find total correspondence between our values of $[\alpha]_D$ and the known data.[26] The $[\alpha]_D$ value we obtained for (1*S*,2*R*,3*S*)-*syn,syn*-**5** was in accordance with that described in ref 26 for the enantiomer (1*R*,2*S*,3*R*)-*syn,syn*-**5**. This latter was used by Hatakeyama et al. as a precursor for the preparation of (+)-conagenin. On the contrary, the $[\alpha]_D$ value described by the same authors for (1*S*,2*S*,3*R*)-*anti,syn*-**5** is contrast with the value we obtained for the same enantiomer. No NMR spectra are reported in ref 26, and the absolute configurations are determined by the MTPA ester technique. (1*S*,2*S*,3*R*)-*anti,syn*-**5** is described as a byproduct in the preparation of (1*R*,2*S*,3*R*)-*syn,syn*-**5**, and it is not correlated to any natural compound.

No correspondence was found between our data of specific rotation and those described in ref 19 for compounds of correct relative configuration.

The evaluation of Muguesia samples by professional perfumers (see Olfactory evaluation) showed that the two 3*S* stereoisomers had the most interesting odor properties. We, then, optimized a baker's yeast approach to the mixture of the two (3*S*) isomers of Muguesia (Scheme 4).

Baker's yeast reduction of unsaturated aldehyde **9**[27] gave enantiomerically pure (*S*)-**10**. This latter was oxidized according to the Swern procedure and treated with methylmagnesium chloride in diethyl ether. A 1:1 a mixture of the two enantiopure (3*S*)-**1** stereoisomers was thus obtained.

SCHEME 5[a]



[a] Key: (i) PPL, *tert*-butylmethyl ether, vinyl acetate.

Pamplefleur. (*R*)- and (*S*)-2-phenyl-1-propanol (**11**) are commercial products. The need for a large quantity of enantiopure (*R*)- and (*S*)-**11**, to be used as starting materials for the preparation of the four isomers of Pamplefleur, induced us to investigate the lipase-mediated kinetic resolution of racemic primary alcohol **11**. Only a few examples of the lipase-mediated kinetic resolution of racemic **11** were reported in the literature. PPL-catalyzed acetylation in water-saturated hexane, in the presence of vinyl acetate, gave after 12 h at 30 °C an acetate derivative and an unreacted alcohol with poor enantiomeric excess (ee = 65% and 69%, respectively). A mistake in the assignment of the CIP descriptors did not allow us to verify the real stereochemistry of the acetate and of the unreacted alcohol.[28] Naemura et al. reported that when racemic **11** was treated with Lipase YS at 30 °C in diisopropyl ether solution, with isopropenyl acetate as an acyl donor, after 7 h a (−)-acetate derivative and a (+)-unreacted alcohol were obtained, with very low optical purity ($[\alpha]_D = -0.08$ and $[\alpha]_D = +0.60$, respectively).[29] Better results were described for Lipase PS-mediated transesterification of racemic **11** with vinyl 3-(para-substituted phenyl)propanoates in cyclohexane: (*S*)-**12** (ee = 97−98%) and (*R*)-**11** (ee = 34−56%) were obtained.[30] Enantiomeric ratios not higher than 2.7 were described when sol−gel encapsulated lipases were employed.[31]

Short reaction times and the use of PPL allowed us to recover acetate **12** with ee = 92% (chiral GC of the corresponding alcohol) (Scheme 5).

The unreacted alcohol was enriched with the (*R*)-isomer (ee = 91%, chiral GC) by prolonged PPL-mediated

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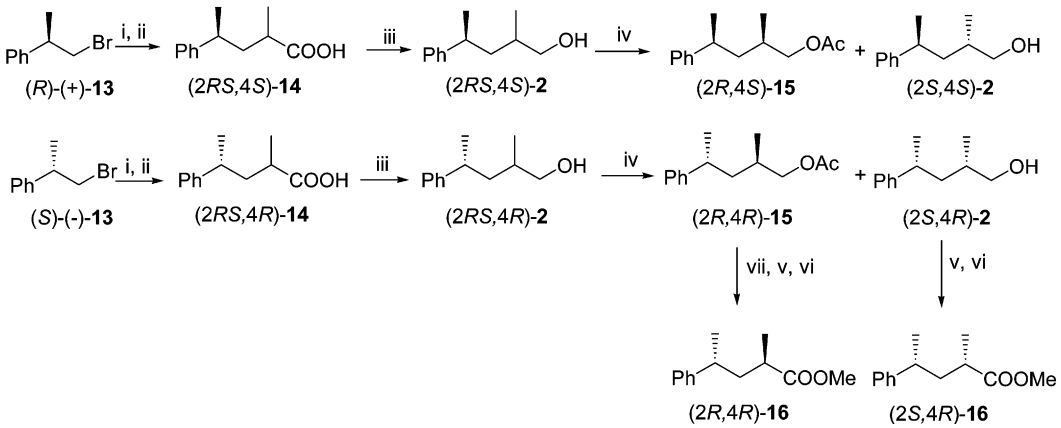
SCHEME 6[a]



[a] Key: (i) methylmalonic acid, diethyl ester, NaH, DMF; (ii) KOH, H_2O, EtOH, reflux; (iii) $LiAlH_4$, THF; (iv) PPL, *tert*-butylmethylether, vinyl acetate; (v) Jones' reagent, acetone; (vi) CH_2N_2 in Et_2O; (vii) KOH, MeOH.

transesterification, and the steric course of the reaction was monitored by chiral GC. (*R*)- and (*S*)-**11** were converted into the corresponding bromo derivatives (*R*)- and (*S*)-**13** (Scheme 6), which were then submitted to malonic reaction with methylmalonic acid diethyl ester. Saponification and decarboxylation of the reaction mixture allowed us to obtain (2*RS,*4*S*)-**14** and (2*RS*,4*R*)-**14**. The two mixtures of enantiomerically enriched acid diastereoisomers were then reduced to alcohols (2*RS,*4*S*)-**2** and (2*RS*,4*R*)-**2**, respectively. (2*RS,*4*S*)-**2** was treated with PPL in *tert*-butylmethyl ether in the presence of vinyl acetate. Short reaction times allowed us to recover (2*R*,4*S*)-**15** with de = 84% (^{1}H NMR δ CH_3COO). The unreacted alcohol was enriched with the (2*S*,4*S*) diastereoisomer by prolonged PPL treatment to reach de = 52%.

When the same procedure was applied to (2*RS,*4*R*)-**2**, (2*R*,4*R*)-**15** (de = 85%, ^{1}H NMR δ CH_3COO) and (2*S*,4*R*)-**2** (de = 87%) were obtained. We took advantage of the PPL-catalyzed enantioselective acetylation of the primary function of alcohol **2** to separate the two enantiopure diastereoisomers.

As for the configuration assignment, the absolute configuration of 2-phenyl-1-propanol was known. The relative configuration of the two stereogenic carbon atoms was established as follows. The alcohol recovered unreacted by the PPL-mediated transesterification of (2*RS*,4*R*)-**2** was oxidized by Jones' reagent and esterified with diazomethane to give the corresponding methyl esters **16**. The same procedure was applied to the alcohol obtained by hydrolysis of the acetate produced by PPL-catalyzed transesterification of (2*RS*,4*R*)-**2.** The ^{1}H NMR spectra of the two methyl esters **16** were recorded and compared with those described by Fleming for the two racemic diastereoisomers. The relative configuration of the corresponding Pamplefleur isomers was thus assigned.[32] The ^{1}H and ^{13}C NMR spectra of the two enantiomers of *anti*-**2** were found to be in agreement with those described by Heathcock et al. for the racemic substrate.[33]

Olfactory Evaluation. (2*R,*3*S*)-**1**: top note: floral, rosy, buttery, rich, slightly green; dry down: floral, sweet, lily of the valley and linalool-like.

(2*S*,3*S*)-**1**: top note: floral, balsamic, sweet, floral, slightly fruity; dry down: floral, cinnamic, balsamic, sweet.

(2*S*,3*R*)-**1**: top note: weak, floral-hesperidic, tea-like; dry down: empty.

(2*R*,3*R*)-**1**: top note: very weak, slightly acidic and agrestic, dry down: empty

(2*R,*4*S*)-**2**: natural fruity odor in the direction of grapefuit and rhubarb, close to gardenol (methyl phenyl carbinyl acetate) and 2,5-dimethyloct-2-en-6-one, slightly metallic.

(2*S*,4*S*)-**2**: floral-fruity odor in the direction of grapefruit and linalool with earthy, woody, and bitter nuances, also reminiscent of 2,5-dimethyloct-2-en-6-one and of some aspects of vetiver oil.

(2*S*,4*R*)-**2**: fruity-citric odor, with some harsh, animalic, and slightly woody nuances, also is a bit rubbery.

(2*R*,4*R*)-**2**: floral-fruity odor in the direction of rhubarb with a touch of grapefruit, reminiscent of gardenol (methylphenyl carbinyl acetate).

The Pamplefleur isomers have a high tenacity on blotter (>24 h), so they are all quite substantive. In the IFF catalog Pamplefleur is described as "Citrus, Grapefruit, Floral, Vetivert": the odor descriptions show that each isomer contributes to a particular facet of the final odorant, to produce an unique blend. All the isomers share a hesperidic grapefruit tonality. With respect to this grapefruit note (2*R*,4*S*)-**2** is the most typical, but Pamplefleur is a complex blend in which all compounds play a definite role.

On the contrary, the configuration at the carbon atom in position 3 seems to be important in establishing the odor properties of Muguesia: the (3*R*) stereoisomers are weak and completely devoid of odor in the dry down note. The (3*S*) stereoisomers are the effective odor vectors of commercial Muguesia.

Conclusions

The preparation of the single isomers of Muguesia and Pamplefleur is part of an extensive investigation of the

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phenomenon of stereoselectivity in the process of odor perception. It is impossible to predict the results of this kind of study. Single stereoisomers have to be prepared and evaluated separately.

The odor response of Pamplefleur isomers is rather unusual in the realm of chiral fragrances. It represents a yet undiscovered case, in which no stereoisomer prevails, but each one plays a definite role in establishing the odor sensation of the final blend. Stereoselectivity is shown not in the preference of our olfaction for a certain stereoisomer, as it happens with Muguesia, but in the fact that we perceive distinctly each stereoisomer in the whole fragrant mixture.

Once again, we have the opportunity to discover how much data is encoded in the absolute configuration of a chiral odorant.

The enantioselective approach to the four stereoisomers of **1** and **2** was rather challenging, because of the presence of two stereocenters in position 1−2 and 1−3, respectively. The work shows how efficiently biocatalyzed routes can provide samples of single stereoisomers for the evaluation of odor properties.

According to our experience, the lipase-mediated transesterification of hydroxy ketones is a highly enantioselective process. We took advantage of it in the case of Muguesia, but also in recent works devoted to the preparation of all the stereoisomers of the chiral odorants Floropal,[34] Florol, and Clarycet[6]. Simple and accurate chemistry allowed us to control the relative stereochemistry of the two vicinal stereogenic centers of final compound **1**. The additional stereocenter, introduced rather unexpectedly in a diastereoselective way by conventional reductions of substrates **3** and **4**, was fundamental to assist the separation of the precursors of Muguesia stereoisomers.

We tried also to bring clarity in the assignment of the relative configuration of diols **5**. A certain confusion was present in the literature as for the ^{1}H and ^{13}C NMR data of the four diastereoisomers. 1,3-Diols of this type are described to be important synthons of modern organic chemistry. Thus, the univocal determination of their configuration by spectroscopic data is of great relevance.

As for Pamplefleur, we optimized the lipase-mediated acetylation of a racemic primary alcohol. We also exploited the preference of the enzyme for the acetylation of OH groups of a certain absolute configuration, to separate the two mixtures of enantiomerically enriched diastereoisomers (2*RS*,4*R*)-**2** and (2*RS*,4*S*)-**2**.

Experimental Section

Acetate of 3-Hydroxy-2-methyl-1-phenylbutan-1-one (2*RS*,3*R*)-4 and 3-Hydroxy-2-methyl-1-phenylbutan-1-one (2*RS*,3*S*)-3. The 1:1 mixture of (2*RS,*3*RS*)-**3** and (2*RS,*3*SR*)-**3** (26.0 g, 0.l46 mol) was treated with Lipase PS (20 g) in *tert*-butylmethyl ether solution (200 mL), in the presence of vinyl acetate (50 mL). After 24 h, an acetate fraction (7.38 g, 23%) was recovered which was found to be a 3.1:1 mixture of (2*R,*3*R*)-**4** (ee = 99%, HPLC) and (2*S*,3*R*)-**4** (ee = 99%, HPLC)): ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 8.07 (m, H_{ortho} of (2*R,*3*R*)-**4**), 7.90 (m, $H_{ortho}$of (2*S,*3*R*)-**4**), 7.54 (m, aromatic hydrogens of both diastereoisomers), 5.26 (m, C*H*-OAc of both diastereoisomers), 3.81 (quintet, J = 6.9 Hz, C*H*-CH_3 of (2*R,*3*R*)-**4**), 3.73 (quintet, J = 6.9 Hz, C*H*-CH_3 of (2*S,*3*R*)-**4**), 1.98 (s, OCOC*H*$_3$ of (2*S,*3*R*)-**4**), 1.94 (s, OCOC*H*$_3$ of (2*R,*3*R*)-**4**), 1.15−1.30 (four overlapping d, CHC*H*$_3$ of both diast); GC/MS (2*R,*3*R*)-**4** t_R = 19.32 min, *m/z* 177 (M^+ − 43, 2), 165 (10), 134 (18), 105 (100), 77 (25), (2*S,*3*R*)-**4** t_R = 19.39 *m/z* 177 (M^+ − 43, 2), 165 (10), 134 (10), 105 (100), 77 (22). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.67; H, 7.58.

The alcohol fraction (10.4 g, 40%) was submitted to prolonged Lipase-PS transesterification in the same conditions. The reaction was monitored by chiral HPLC until a 1:1 of the (2*RS,*3*S*)-**3** (ee = 99%, ee = 99%) was obtained (6.71 g, 65%). ^{1}H NMR and MS spectra were in accordance with those of the mixture of racemic diastereoisomers.

(1*S*,2*R*,3*S*)-1-Phenyl-2-methyl-1,3-butanediol ((1*S*,2*R*,3*S*)-*syn,syn*-5) and (1*R*,2*S*,3*S*)-1-Phenyl-2-methyl-1,3-butanediol ((1*R*,2*S*,3*S*)-*syn,anti*-5). The 1:1 mixture of (2*RS*,3*S*)-**3** (6.60 g, 0.037 mol) was treated with $NaBH_4$ (1.41 g, 0.037 mol) in CH_2Cl_2−MeOH 2:1 (100 mL). After the usual workup, the crude product was chromatographed on a silica gel column (hexane/ethyl acetate 7:3) to afford, in order of elution, first (1*S*,2*R*,3*S*)-*syn,syn*-**5** (2.53 g, 38%) and then (1*R*,2*S*,3*S*)-*syn,anti*-**5** (2.32 g, 35%).

(1*S*,2*R*,3*S*)-*syn,syn*-**5**: $[\alpha]_D$ = −27.7 (*c* 0.7, $CHCl_3$); de = 99% (GC/MS); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.40−7.20 (m, 5H, aromatic hydrogens), 5.03 (d, 1H, J = 2.7 Hz, Ph*CH*OH), 4.22 (qd, 1H, J = 6.2, 1.9 Hz, CH_3*CH*OH), 1.70 (m, 1H, *CH*C(2)), 1.22 (d, 3H, J = 6.2 Hz, *CH*$_3$CHOH), 0.82 (d, 3H, J = 6.9 Hz, *CH*$_3$C(2)); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ (ppm) 143.3, 128.1, 127.0, 125.6, 78.5, 72.0, 45.0, 21.5, 4.1; GC/MS t_R = 18.37 min, *m/z* 162 (M^+ − 18, 10), 117 (13), 107 (100). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.09; H, 8.79.

(1*R*,2*S*,3*S*)-*syn,anti*-**5**: mp 83−85 °C; $[\alpha]_D$ = +52.3 (*c* 1.12, $CHCl_3$); de = 99% (GC/MS). ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.42−7.22 (m, 5H, aromatic hydrogens), 5.08 (d, 1H, J = 3.0 Hz, Ph*CH*OH), 3.80 (quintet, 1H, J = 6.2 Hz, CH_3*CH*OH), 1.82 (m, 1H, *CH*C(2)), 1.28 (d, 3H, J = 6.2 Hz, *CH*$_3$CHOH), 0.79 (d, 3H, J = 7.2 Hz, *CH*$_3$C(2)); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 142.7, 128.0, 127.0, 126.1, 74.7, 70.9, 45.7, 21.9, 11.3; GC/MS t_R = 18.55 min, *m/z* 162 (M^+ − 18, 12), 117 (15), 107 (100). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.46; H, 8.67.

(1*S*,2*S*,3*R*)-1-Phenyl-2-methyl-1,3-butanediol ((1*S*,2*S*,3*R*)-*anti,syn*-5) and (1*R*,2*R*,3*R*)-1-Phenyl-2-methyl-1,3-butanediol ((1*R*,2*R*,3*R*)-*anti,anti*-5). The 3.1:1 mixture of (2*RS*,3*R*)-**4** (7.20 g, 0.032mol) was treated with $LiAlH_4$ (5.58 g, 0.040mol) in THF (150 mL). After the usual workup, the crude product was chromatographed on a silica gel column (hexane/ethyl acetate 7:3) to afford, in order of elution, first (1*S*,2*S*,3*R*)-*anti,syn*-**5** (1.04 g, 18%) and then (1*R*,2*R*,3*R*)-*anti,anti*-**5** (3.34 g, 58%).

(1*S*,2*S*,3*R*)-*anti,syn*-**5**: $[\alpha]_D$ = +25.2 (*c* 1.1, $CHCl_3$); de = 99% (GC/MS); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.40−7.20 (m, 5H, aromatic hydrogens), 4.70 (d, 1H, J = 6.9 Hz, Ph*CH*OH), 4.05 (qd, 1H, J = 6.5, 1.9 Hz, CH_3*CH*OH), 1.95 (m, 1H, *CH*C(2)), 1.21 (d, 3H, J = 6.5 Hz, *CH*$_3$CHOH)), 0.82 (d, 3H, J = 6.9 Hz, *CH*$_3$C(2)); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ (ppm) 143.7, 128.2, 127.6, 126.4, 77.7, 68.9, 44.4, 18.9, 12.0; GC/MS t_R = 18.32 min, *m/z* 162 (M^+ − 18, 2), 117 (15), 107 (100). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.44; H, 9.09.

(1*R*,2*R*,3*R*)-*anti,anti*-**5**: mp 85−87 °C; $[\alpha]_D$ = +27.8 (*c* 1.0, $CHCl_3$); de = 99% (GC/MS); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H, aromatic hydrogens), 4.54 (d, 1H, J = 9.0 Hz, Ph*CH*OH), 3.92 (dq, 1H, J = 8.1, 6.1 Hz, CH_3*CH*OH), 1.85 (m, 1H, *CH*C(2)), 1.26 (d, 3H, J = 6.1 Hz, *CH*$_3$CHOH), 0.79 (d, 3H, J = 6.9 Hz, *CH*$_3$C(2)); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ (ppm) 143.3, 128.3, 127.8, 127.1, 81.0, 73.3, 46.1, 21.7, 13.3; GC/MS t_R = 18.48 min, *m/z* 162 (M^+ − 18, 10), 117 (30), 107 (100). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.11; H, 9.18.

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(2*S*,3*S*)-3-Methyl-4-phenyl-2-butanol ((2*S*,3*S*)-*syn*-1). (1*S*,2*R*,3*S*)-*syn,syn*-**5** (2.40 g, 0.013 mol) was treated with H_2 at athmospheric pressure and room temperature, in ethanol (50 mL) in the presence of $HClO_4$ (1 mL), using Pd/C 5% (0.240 g) as a catalyst. After the usual workup, the crude product was purified by column chromatography on a silica gel column (hexane/AcOEt 9:1) and bulb-to-bulb distilled (1.51 g, 71%): de = 99% (GC/MS); ee = 99% (chiral GC of the corresponding acetate derivative); $[\alpha]_D = -8.2$ (*c* 0.98, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.39−7.14 (m, 5H, aromatic hydrogens), 3.76 (qd, 1H, J = 6.2, 3.7 Hz, CH_3CHOH), 2.82 (dd, 1H, J = 13.5, 5.9 Hz, *H*-C(4)), 2.40 (dd, 1H, J = 13.5, 8.9 Hz, *H*-C(4)), 1.78 (m, 1H, *CH*C(3)), 1.20 (d, 3H, J = 6.2 Hz, CH_3CHOH), 0.86 (d, 3H, J = 6.7 Hz, CH_3C(3)); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ (ppm) 140.9, 129.1, 128.1, 125.6, 70.4, 41.8, 39.3, 20.6, 13.4; GC/MS t_R = 13.86 min, *m/z* 164 (M^+, 5), 146 (37), 131 (45), 91 (100). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.13; H, 9.68.

(3*S*)-(+)-3-Methyl-4-phenyl-2-butanone ((*S*)-8). (−)-*anti*-**1** (0.050 g, 0.304 mmol) was treated with Jones' reagent at 0 °C. The reaction mixture was filtered on a silica gel column (AcOEt) to afford (*S*)-(+)-**8** (0.033 g, 68%): $[\alpha]_D = +31.8$ (*c* 1.0, $CHCl_3$); $[\alpha]_D = +40.8$ (*c* 0.95, EtOH) [lit.[24] $[\alpha]_D = +45.5$ (*c* 2, EtOH, ee = 99%)]; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.45−7.00 (m, 5H, aromatic hydrogens), 3.00 (dd, 1H, J = 13.7, 6.4 Hz, *H*-C(4)), 2.82 (m, 1H, *H*-C(3)), 2.56 (dd, 1H, J = 13.7, 6.9 Hz, *H*-C(4)), 2.08 (s, 3H, CH_3CO), 1.09 (d, 3H, J = 6.4 Hz, CH_3-C(3)); GC/MS t_R = 12.80 min, *m/z* 162 (M^+, 44), 147 (40), 91 (100). Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.65; H, 8.48.

(2*S*,3*S*)-3-Hydroxy-2-methyl-1-phenylbutan-1-one ((2*S*,3*S*)-3). (+)-*syn,anti*-**5** (0.050 g, 0.304 mmol) was treated with manganese(IV) oxide (0.025 g) in methylene chloride (10 mL) at room temperature. After 24 h, the reaction mixture was filtered and concentrated under reduced pressure to give (2*S*,3*S*)-(+)-**3** (0.043 g, 88%): $[\alpha]_D = +61.2$ (*c* 1.1, $CHCl_3$) [lit.[25] $[\alpha]_D = +62.3$ ($CHCl_3$)]; ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.94 (m, 2H, aromatic hydrogens,), 7.56 (m, 1H, aromatic hydrogen), 7.46 (m, 2H, aromatic hydrogens), 4.11 (quintet, 1H, J = 6.4 Hz, C*H*-OH), 3.48 (quintet, 1H, J = 6.9 Hz, *CH*-CH_3), 1.26 (d, 3H, J = 6.4 Hz, CH_3CHOH), 1.20 (d, 3H, J = 6.9 Hz, CH_3CHCO). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.38; H, 7.78.

(*R*)-2-Phenylpropanol ((*R*)-11) and (*S*)-Acetic Acid 2-Phenylpropyl Ester ((*S*)-12). Racemic **11** (50.0 g, 0.368 mol) was treated with PPL (20 g) in *tert*-butylmethyl ether solution (200 mL), in the presence of vinyl acetate (50 mL). After 30 min, the reaction mixture was filtered and separated by column chromatography on silica gel (hexane/ethyl acetate 9/1) to give (*R*)-**12** (9.81 g, 15%): ee = 92% (chiral GC of the corresponding alcohol); $[\alpha]_D = -3.37$ (*c* 1.18, $CHCl_3$) [lit.[36] $[\alpha]_D = -2.8$ (*c* 10.09, $CHCl_3$) for (*S*)-**12**]; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.13−7.38 (m, 5H, aromatic hydrogens), 4.20 (dd, 1H, J = 10.8, 6.9 Hz, *H*-CHOAc), 4.20 (dd, 1H, J = 10.8, 7.2 Hz, *H*-CHOAc), 3.09 (m, 1H, *CH*CH_3), 2.01 (s, 3H, OAc), 1.30 (d, 3H, J = 6.9 Hz, CH*CH*$_3$); GC/MS t_R = 13.48 min *m/z* 135 (M^+ − 43, 1), 118 (100), 105 (92).

The unreacted alcohol was enriched in the (*R*)-enantiomer by prolonged PPL-mediated acetylation. The reaction was monitored by chiral GC: (*R*)-**11** (12.3 g, 25%), ee = 91% (chiral GC); $[\alpha]_D = +13.1$ (*c* 1.09, $CHCl_3$) [lit.[37] $[\alpha]_D = +16.53$ (*c* 1.471, $CHCl_3$)]. The ^{1}HNMR spectrum was in accordance with that reported in the literature.[37]

(2*RS*,4*S*)-2-Methyl-4-phenylpentanoic Acid ((2*RS*,4*S*)-14). Diethyl methylmalonate (23.0 g, 0.132 mmol) was added dropwise at 0 °C into a suspension of NaH (55% dispersion in mineral oil, 3.40 g, 0.078 mol) in DMF (150 mL). After 1 h at room temperature, (*R*)-**11** (13.0 g, 0.065 mol) was added, and the mixture was stirred for 24 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), and the residue was dissolved in a mixture of NaOH 20% (50 mL) and ethanol (100 mL). The mixture was refluxed for 12 h and poured into water. The aqueous phase was acidified (HCl 10%) and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give (2*RS*,4*S*)-**14** (7.61 g, 61%): ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.35−7.05 (m, 5H, aromatic hydrogens), 2.79 (m, 1H, *H*-C(4) of both diastereoisomers), 2.33 (m, 1H, *H*-C(2) of both diastereoisomers), 2.05 (m, 1H, *H*-C(3) of both diastereoisomers), 1.60 (m, 1H, *H*-C(3) of both diastereoisomers), 1.20−1.28 (2d, 3H, J = 7.0 Hz, CH_3-C(4) of both diastereoisomers), 1.05−1.20 (2d, 3H, J = 6.5 Hz, CH_3-C(2) of both diastereoisomers); GC/MS: I diastereoisomer t_R = 17.80 min, *m/z* 192 (M^+, 4), 119 (100), 105 (77); II diastereoisomer t_R = 18.18 min, *m/z* 192 (M^+, 6), 119 (100), 105 (77). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.64; H, 8.49.

(2*S*,4*S*)-2-Methyl-4-phenylpentanol ((2*S*,4*S*)-2) and (2*R*,4*S*)-Acetic Acid 2-Methyl-4-phenylpent-1-yl Ester ((2*R*,4*S*)-15). (2*RS*,4*S*)-**2** (5.50 g, 0.031 mol) was treated with PPL (5 g) in *tert*-butylmethyl ether solution (50 mL) in the presence of vinyl acetate (10 mL) for 1 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was chromatographed on a silica gel column to give (2*R*,4*S*)-**15** (0.750 g, 11%): $[\alpha]_D = -3.9$ (*c* 0.96, $CHCl_3$), ee = 91% (from (*R*)-**11**), de = 84% (^{1}H NMR δ CH_3COO); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.30−7.05 (m, 5H, aromatic hydrogens), 3.84 (m, 2H, CH_2−OAc), 2.80 (m, 1H, *CH*Ph), 2.02 (s, 3H, CH_3COO), 1.80−1.30 (m, 3H, *H*-C(2) + 2*H*-C(3)), 1.25 (d, 3H, J = 6.1 Hz, CH_3-C(4)), 0.92 (d, 3H, J = 6.9 Hz, CH_3-C(2)). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.58; H, 9.49.

The unreacted alcohol was submitted to prolonged PPL treatment to give (2*S*,4*S*)-**2** (0.772 g, 14%): $[\alpha]_D = +2.2$ (*c* 0.90, $CHCl_3$), ee = 91% (from (*R*)-**11**), de = 52% (^{1}H NMR of the corresponding acetate, δ CH_3COO); ^{1}H NMR (250 MHz, $CDCl_3$)[33] δ (ppm) 7.40−7.20 (m, 5H, aromatic hydrogens), 3.52 (dd, 1H, J = 10.8, 5.2 Hz, C*H*-OH), 3.43 (dd, 1H, J = 10.8, 6.1 Hz, C*H*-OH), 2.81 (m, 1H, *CH*Ph), 1.62 (m, 2H), 1.40 (2H, m), 1.23 (d, 3H, J = 6.5 Hz, CH_3−C(4)), 0.90 (d, 3H, J = 6.5 Hz, CH_3-C(2)); ^{13}C NMR[33] (62.90 MHz, $CDCl_3$) δ (ppm) 147.8, 128.4, 126.9, 125.6, 68.1, 41.9, 37.0, 33.5, 22.2, 16.8. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H 10.18. Found: C, 80.61; H, 10.32.

(2*R*,4*S*)-2-Methyl-4-phenylpentanol ((2*R*,4*S*)-2). Saponification of (2*R*,4*S*)-**15** (0.700 g, 3.18 mmol) with KOH (0.213 g, 3.82 mmol) in methanol (10 mL) gave after the usual workup (2*R*,4*S*)-**2** (0.470 g, 83%): $[\alpha]_D = -27.4$ (*c* 0.95, $CHCl_3$), ee = 91% (from (*R*)-**11**), de = 84% (^{1}H NMR δ CH_3COO of the corresponding acetate). NMR data were in agreement with those of the enantiomer. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H 10.18. Found: C, 81.05; H, 10.01.

(2*S*,4*R*)-2-Methyl-4-phenylpentanoic Acid Methyl Ester ((2*S*,4*R*)-*syn*-16). A sample of the alcohol recovered unreacted from the PPL transesterification of (2*RS*,4*R*)-**2** was treated with Jones' reagent and then with diazomethane in diethyl ether. The methyl ester obtained resulted to be (2*S*,4*R*)-**16** by comparison of its ^{1}H NMR spectrum with the one described for the racemic syn diastereoisomer in the literature:[32] ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 7.35−7.05 (m, 5H, aromatic hydrogens), 3.58 (s, 3H, COO*Me*), 2.73 (m, 1H, *H*-C(4)), 2.33 (m, 1H, *H*-C(2)), 2.05 (ddd, 1H, J = 13.7, 8.8, 6.5 Hz, *H*-C(3)), 1.61 (m, 1H, *H*-C(3)), 1.26 (d, 3H, J = 7.0 Hz, CH_3-C(4)), 1.14 (d, 3H, J = 6.1 Hz, CH_3-C(2)); GC/MS t_R = 16.50 min *m/z* 206 (M^+, 4), 175 (14), 119 (91), 105 (82), 88 (100).

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Supporting Information Available: General experimental methods and X-ray crystallographic crystallographic data. CIF files of (1*R*,2*S*,3*S*)-*syn-anti*-**5** and (1*R*,2*R*,3*R*)-*anti-anti*-**5**. Preparation and spectral data of (2*RS,*3*RS*)- and (2*RS,*3*SR*)-**3**, (2*R*,3*R*)-*syn*-**1**, (2*S*,3*R*)-*anti*-**1**, (2*R*,3*S*)-*anti*-**1**, (*R*)-**8,** (*S*)-**11**, (*R*)- and (*S*)-**13**, (2*RS*,4*R*)-**14**, (2*RS*,4*S*)-**2**, (2*RS*,4*R*)-**2**, (2*S*,4*R*)-**2**, (2*R*,4*R*)-**15**, (2*R*,4*R*)-**2**), and (2*R*,4*R*)-*anti*-**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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