Enzymatic Approach to and Odor Description of the Twelve Enantiomerically Pure Isomers of *Pelargene*®

by **Agnese Abate**, **Maurizio Allievi**, **Elisabetta Brenna***, **Claudio Fuganti**, **Francesco G. Gatti**, and **Stefano Serra**

Dipartimento di Chimica, Materiali ed Ingegneria Chimica, Politecnico di Milano, CNR – Istituto del Riconoscimento Molecolare, Via Mancinelli 7, I-20131 Milano
(phone: ++39-0223993077; fax: ++39-0223993080; e-mail: elisabetta.brenna@polimi.it)

Pelargene® is a commercial fragrance sold as a mixture of three regioisomeric pyran derivatives (**1**–**3**). The enantiomers of each of the two possible diastereoisomers of **1**–**3** were prepared by means of a biocatalyzed approach, and the odor properties of the twelve isolated stereoisomers were evaluated.

Introduction. – In 2004, *Richard Axel* and *Linda Buck* were awarded the *Nobel* Prize in Physiology or Medicine [1] for their discoveries of '*odorant receptors and the organization of the olfactory system*'. In their seminal work published in *Cell* in 1991 [2], they explained how the mammalian olfactory system can recognize and discriminate a large number of different odorant molecules. The detection of chemically distinct odorants presumably results from the association of odorous ligands with specific receptors in the ciliary membrane of olfactory neurons. *Axel* and *Buck* showed that 3% of our genes are used to code for the different odorant receptors on the membrane of the olfactory receptor cells. When an odorant receptor is activated by an odorous substance, an electric signal is triggered in the olfactory receptor cell, and sent to the brain *via* nerve processes. *Axel* and *Buck* showed that the large family of odorant receptors belongs to the G-protein-coupled receptors (GPCR).

Recently, *Hatt* and co-workers [3] cloned, functionally expressed, and characterized some of the human olfactory receptors from chromosome 17. They showed that a receptor protein is capable of recognizing the particular substructure of an odorous molecule and, therefore, is able to respond only to odorants that have a defined molecular structure.

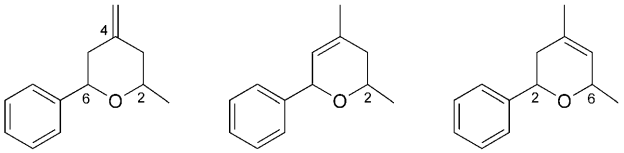
Most odors are due to several odorant molecules, and each odorant molecule, in turn, activates several odorant receptors, which gives rise to a so-called 'odorant pattern' [4]. This pattern is interpreted and leads to the conscious experience of a recognizable odor. Until these findings, very little had been known about the molecular basis of odor detection: the structural features of odorous molecules are fundamental in determining the interaction and the activation of the G-protein.

During the last years, we have been investigating the effects of the absolute configuration of chiral molecules on their odor properties [5]. We expect that the spatial disposition of the substituents around a stereogenic element could influence the way in

which the molecule interacts with the olfactory receptors. Since we are 'chiral being's, we should, in principle, be able to distinguish chiral molecules by their odor.

Herein, we report the preparation and odor description of all twelve possible stereoisomers of *Pelargene*®, which is widely used in perfumery.

Results and Discussion. – *Pelargene* (*Quest International*) is a floral fragrance with a powerful odor reminding of the crushed leaves of the *Pelargonium* plant, which is commonly known as house-geranium. A subtle spicy-floral undertone supports the main character. It combines very well with floral notes; it is extremely fiber substantive, and can be used over quite a wide pH range. Commercial *Pelargene* is a mixture of the three main regioisomers **1**–**3**. According to an in-house GC/MS analysis, the composition of the commercial mixture is as follows: 73.7% *cis*-**1**, 1.7% *cis*-**2**, 17.7% *cis*-**3**, 0.4% *trans*-**2**, 0.8% *trans*-**3**, and 5.7% of unknown constituents.



1 **2** **3**

1. *Synthesis.* We first performed a literature search for the synthesis of this kind of substituted dihydropyrans. *Sequin* and *Schneider* had re-investigated in 1985 [6] the products obtained by *Prins* reaction of 4-methylpent-4-en-2-ol with benzaldehyde[1]). The authors reported that, when the reaction is catalyzed by H_2SO_4, the two tetrahydropyranols *cis*-(2*RS*,4*RS*,6*RS*)-**4** and *cis*-(2*RS*,4*SR*,6*RS*)-**4** are obtained as a 1:2 mixture (*Scheme 1*). The relative configuration was assigned on the basis of ^{1}H- and ^{13}C-NMR spectra[2]).

Dehydration of both the stereoisomers **4** over $KHSO_4$ gave a mixture of olefins, 80% of which consisted of *cis*-**1**, as inferred from the typical resonance of the methylidene group at δ(H) 4.78 in the ^{1}H-NMR spectrum. When the dehydration was carried out by heating the two tetrahydropyranols with 20% H_2SO_4 at 120° for 6 h, mainly *cis*- and *trans*-**3** were obtained[3]). The authors assumed that the dehydration with H_2SO_4 led first to *cis*-**3**, where the relative configuration at C(2) and C(6) was the same of the start-

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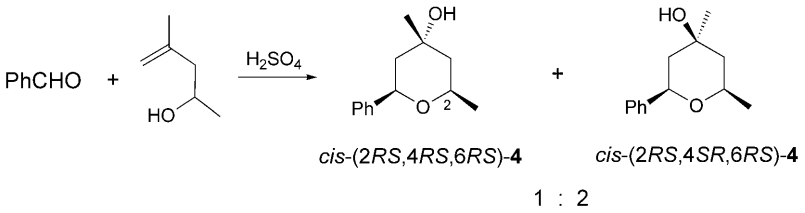
[1]) This reaction had been previously described in several publications [7].

[2]) H–C(2) and H–C(6) showed – besides the coupling of H–C(2) with the neighboring Me group – coupling to CH_2(3) and CH_2(5), resp., with *J* values of *ca.* 11 and 3 Hz, which indicated that the Me and Ph groups were both in equatorial position. The signals of the axial H-atoms at C(2) and C(6) in *cis*-(2*RS*,4*RS*,6*RS*)-**4** were observed at lower field than the corresponding resonances in the other stereoisomer, suggesting that the 4-OH group was also in axial position. This assignment was corroborated by ^{13}C-NMR: the signal of the axial Me group at C(4) in *cis*-(2*RS*,4*SR*,6*RS*)-**4** was shifted upfield by 5.6 ppm as compared to the same resonance in the spectrum of *cis*-(2*RS*,4*RS*,6*RS*)-**4**.

[3]) Both compounds showed a *dd* for H–C(6), and H–C(2) gave rise to a *m*, which could be interpreted as a *q* broadened by the small homoallylic coupling.

Scheme 1



ing pyranols. This compound then epimerized to *trans*-**3** *via* ring opening. They did not observe the formation of any product showing the C=C bond in 4,5-position, *i.e.*, *cis*- and *trans*-**2**.

Both *cis*- and *trans*-**3** could be prepared also by *Diels–Alder* reaction of benzaldehyde with 2-methylpenta-1,3-diene under different conditions, *e.g.*, in the presence of *1*) $AlCl_3$ [8], *2*) cationic Pd complexes [9], *3*) $BF_3 \cdot Et_2O$ [10], or *4*) triflic acid (CF_3SO_3H) [11].

In another approach, *trans*-**3** had been obtained by treatment of 2-phenyl-4-[(4-methylphenyl)sulfonyl]-3,4-dihydro-2*H*-pyran with BuLi and MeI, followed by reaction with Me_3Al [12]. And *cis*-**2** can be prepared by reduction of the corresponding pyrilium salt with triacetoxyborohydride [13]. Finally, *cis*-**1** was obtained by a procedure of a *Lewis* acid promoted allylsilane–acetal cyclization [14].

Our purpose was to prepare all the twelve (3×4) possible stereoisomers of the regioisomers **1**–**3** in enantiomerically pure form. So, we had to find a synthetic approach different from those reported in the literature. We envisaged tetrahydropyranols of type **4** as key intermediates, to be eventually obtained in all the eight possible stereoisomeric forms. As a matter of fact, previous experience on dehydration of irol derivatives [15] had taught us that the outcome of the dehydration of cyclohexanol derivatives is highly influenced by the configuration of the OH group. The synthetic path reported in *Scheme 2* seemed be a good approach to obtain the single stereoisomers of the monoacetates **5** as suitable acyclic precursors of **4**.

Lipase PS mediated acetylation of the hydroxy ketone **6** gave, after 48 h, the acetyl derivative (*R*)-**7** in an enantiomeric excess (ee) of 98% (chiral HPLC analysis of the corresponding alcohol). Prolonged enzyme-mediated acetylation of the unreacted alcohol gave, after 15 d, the enantiomer (−)-(*S*)-**6** (ee = 90%). The biocatalyzed kinetic resolution of **6** had been already reported by *Nair* and *Joly* [16][17], together with the assignment of the absolute configuration. They described that, after a 28-h reaction time, *Candida rugosa* lipase afforded (+)-(*R*)-**7** (ee > 96%) and (−)-(*S*)-**6** (ee = 50%).

Next, (*R*)-**7** and (*S*)-**6** were reacted separately with 'β-metallyl magnesium chloride'[4]) in THF. The mixtures were then treated with Ac_2O in pyridine, and submitted to ozonolysis at $-78°$ in CH_2Cl_2/MeOH. After quenching with $NaBH_4$, (1*R*,3*RS*,5*RS*)-**5** and (1*S*,3*RS*,5*RS*)-**5** were obtained, respectively, both as mixtures of diastereoisomers.

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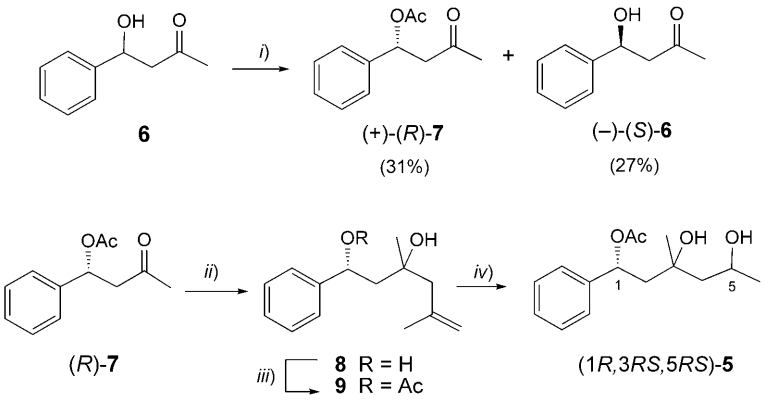
[4]) Systematic name: (chloro)(2-methylprop-2-enyl)magnesium.

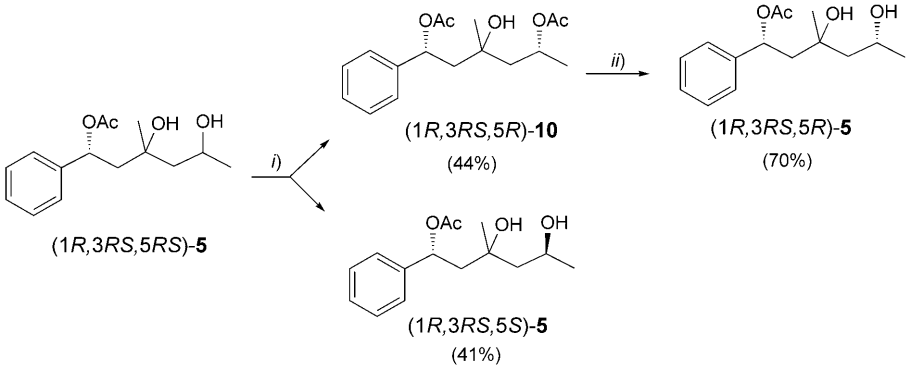
Scheme 2



i) Lipase PS, *t*-BuOMe, vinyl acetate. *ii*) *β*-Metallyl magnesium chloride[4]); 78%. *iii*) Ac_2O, pyridine; 89%. *iv*) 1. O_3, CH_2Cl_2/MeOH 2:1; 2. $NaBH_4$; 76%.

As shown in *Scheme 3*, we found that treatment of (1*R*,3*RS*,5*RS*)-**5** with lipase PS in *t*-BuOMe in the presence of vinyl acetate affords a 1:1 mixture of the two diastereoisomeric diacetates (1*R*,3*RS*,5*S*)-**10**. The absolute configuration at C(5) was first tentatively assigned on the basis of the known preference of lipase PS for the acetylation of stereogenic centers of (*R*)-configuration. This assignment was confirmed by the analysis of the relative configuration of the corresponding tetrahydropyranols. Prolonged lipase PS treatment of the survived alcohol gave a 1:1 mixture of the monoacetates (1*R*,3*RS*,5*S*)-**5**.

Scheme 3



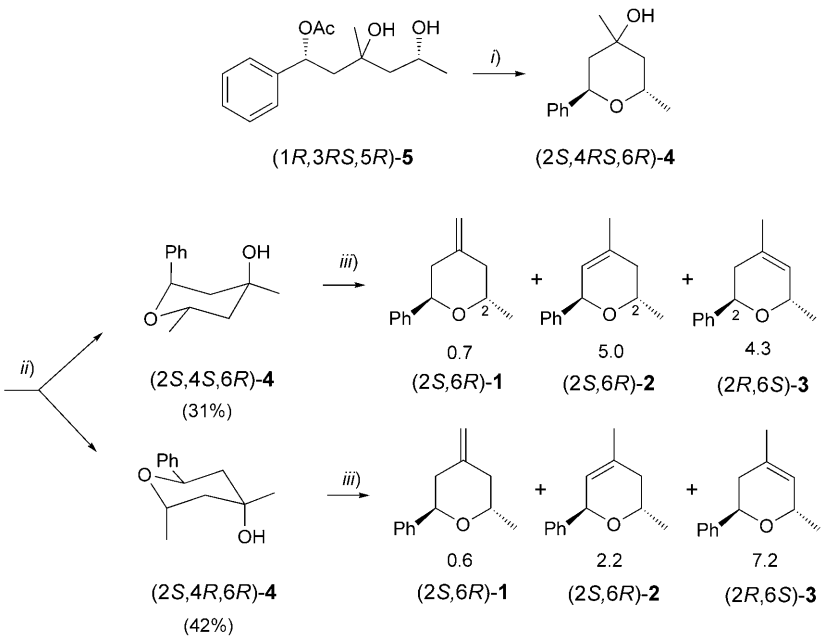
i) Lipase PS, *t*-BuOMe, vinyl acetate; purification by column chromatography. *ii*) Lipase PS, THF/H_2O (pH 7.8).

When the mixture of diacetates **10** was submitted to lipase PS mediated saponification in THF/H_2O (pH 7.8), a 1:1 mixture of the two monoacetates (1*R*,3*R,5R*)- and (1*R*,3*S,5R*)-**5** was obtained. The combination of the two enantioselective lipase-catalyzed acetylations with the regioselective enzyme-mediated hydrolysis, thus, allowed

us to separate the stereoisomers of (1*R*)-**5**, with opposite relative configurations at C(1) and C(5).

Next, the two mixtures of monoacetates were submitted separately to ring closure by treatment with methanesulfonyl chloride (MsCl) in pyridine, followed by exposure to MeONa in MeOH (*Scheme 4*). The 1:1 mixture of (1*R*,3*RS*,5*R*)-**5** gave (2*S*,4*S*,6*R*)- and (2*S*,4*R*,6*R*)-**4**, which could be separated by column chromatography. Both the stereoisomers showed a *trans* arrangement of the substituents at C(2) and C(6). The first eluted diastereoisomer, *i.e.*, (2*S*,4*S*,6*R*)-**4**, was found to have the Ph group in axial and the Me group in equatorial position, respectively (δ(H) 5.05 (*dd*, J = 3.7, 9.6 Hz, H–C(6)); 4.25 (*dquint.*, J = 3.3, 6.4 Hz, H–C(2))). The OH group was assumed to be in axial position in both stereoisomers, on the basis of the outcome of the subsequent dehydration steps.

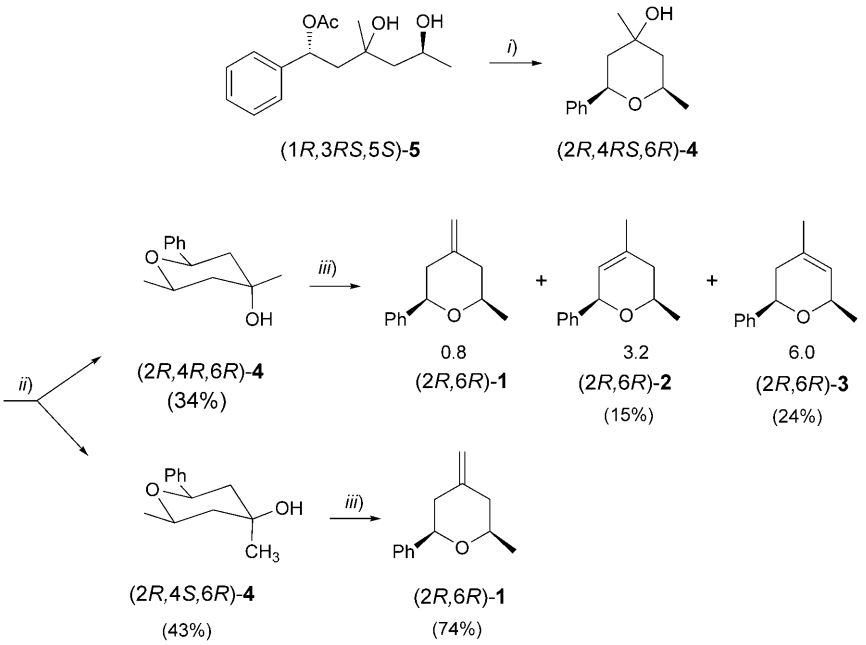
Scheme 4



i) 1. $MeSO_2Cl$, pyridine; 2. MeONa in MeOH. *ii*) Purification by column chromatography. *iii*) $POCl_3$, pyridine.

As shown in *Scheme 5*, the 1:1 mixture of (1*R*,3*RS*,5*S*)-**5** gave (2*R*,4*R*,6*R*)-**4** and (2*R*,4*S*,6*R*)-**4**, which could be separated by column chromatography. Both the stereoisomers showed a *cis*-diequatorial arrangement of the substituents at C(2) and C(6). The ^{1}H-NMR spectrum of the first eluted diastereoisomer showed the following typical resonances: δ(H) 4.76 (*dd*, J = 2.4, 11.5 Hz, H–C(6)) and 4.00 (*ddq*, J = 11.5, 6.2, 2.3 Hz, H–C(2)); the second eluted one gave rise to signals at 4.40 (*dd*, J = 12.0, 2.3 Hz, H–C(6)) and 3.68 (*ddq*, J = 12.0, 6.1, 2.3 Hz, H–C(2)). The OH group was assumed to be in axial position in the first eluted compound, and in equatorial position in the second one, in accord with reference [6].

Scheme 5



i) 1. $MeSO_2Cl$, pyridine; 2. MeONa in MeOH. *ii*) Purification by column chromatography. *iii*) $POCl_3$, pyridine.

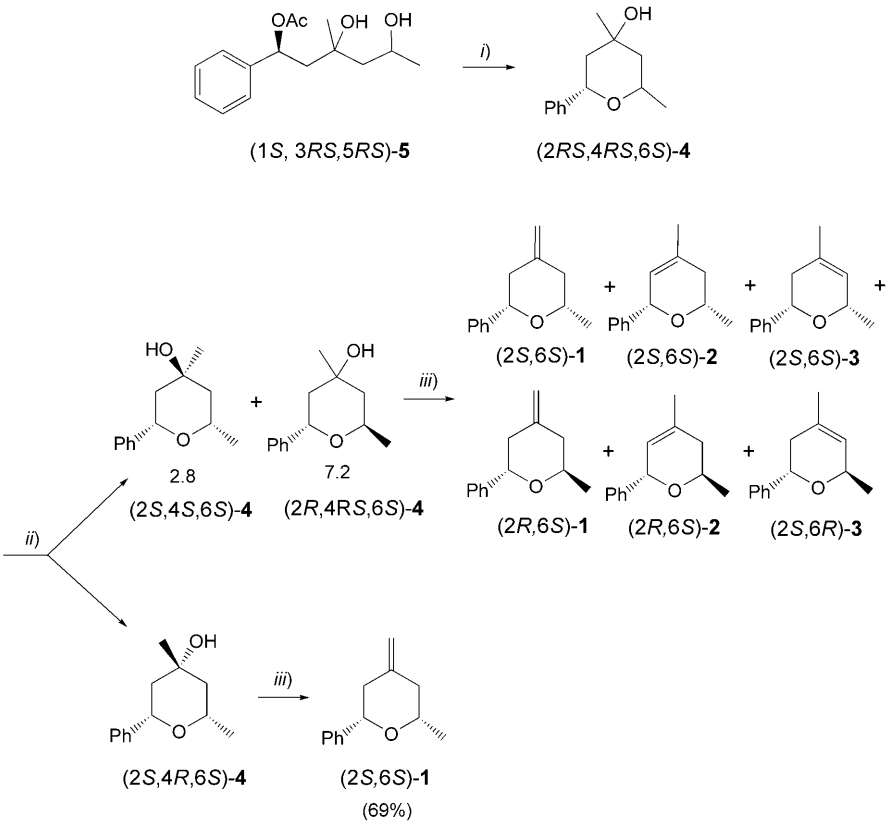
The cyclization of the monoacetates **5** proceeded under inversion of configuration at C(5). The relative configuration at C(2) and C(6) of the resulting tetrahydropyranols **4** was, thus, in accord with that of the starting monoacetates, assigned on the basis of the known preference of lipase PS for (*R*)-configured stereogenic centers.

The dehydration of these four diastereoisomeric tetrahydropyranols was performed by treatment with $POCl_3$ in pyridine. We had already employed this reaction in the chemistry of irol derivatives [15]. We observed that this transformation requires precise stereochemical requisites, typical of an E_2-type elimination, *i.e.*, an antiperiplanar arrangement of the H-atom and the leaving group. In such cyclohexane derivatives, this steric condition is best satisfied when the H-atom and, in this case, the phosphate ester are in a *trans*-diaxial relation. Dehydration of (2*S*,4*S*,6*R*)-, (2*S*,4*R*,6*R*)-, and (2*R*,4*R*,6*R*)-**4**, showing the OH group in axial position, gave mainly the endocyclic olefins. Column-chromatographic (CC) purification of these mixtures allowed us to isolate the following dihydropyran products (*Schemes 4* and *5*): (2*S*,6*R*)-**2** (98% pure, ee 98%); (2*R*,6*S*)-**3** (99% pure, ee 98%); a sample enriched in (2*S*,6*R*)-**1** (39% pure, ee 98%); (2*R*,6*R*)-**2** (94% pure, ee 98%); (2*R*,6*R*)-**3** (97% pure, ee 98%).

The reaction of (2*R*,4*S*,6*R*)-**4** with the equatorial OH group afforded, exclusively, the *exo*-olefinic pyran (2*R*,6*R*)-**1** (99% pure, ee 98%). In this substrate, the H-atom of the Me group may satisfy an antiperiplanar arrangement with respect to the equatorial OH group.

As for the series prepared starting from (*S*)-**6**, the enzymatic acetylation of the mixture of the four stereoisomers (1*S*,3*RS*,5*RS*)-**5** was too slow to allow practical application. Ring closure and CC purification gave a mixture of the three tetrahydropyranols (2*S*,4*S*,6*S*)-**4** and (2*R*,4*RS*,6*S*)-**4** as the first eluted product, while the fourth one, (2*S*,4*R*,6*S*)-**4**, was obtained as a pure crystalline compound (*Scheme 6*).

Scheme 6



i) 1. $MeSO_2Cl$, pyridine; 2. MeONa in MeOH. *ii*) Purification by column chromatography. *iii*) $POCl_3$, pyridine.

The dehydration reaction of the mixture of (2*S*,4*S*,6*S*)-**4** and (2*R*,4*RS*,6*S*)-**4** required a very careful and laborious CC purification, which gave rise to the following compounds: (2*R*,6*S*)-**2** (92% pure, ee 90%); (2*S*,6*R*)-**3** (94% pure, ee 90%); a sample enriched in (2*R*,6*S*)-**1** (33% pure, ee 90%); (2*S*,6*S*)-**2** (93% pure, ee 90%); (2*S*,6*S*)-**3** (94% pure, ee 90%). Finally, treatment of (2*S*,4*R*,6*S*)-**4** with $POCl_3$ and pyridine gave the corresponding *exo* compound (2*S*,6*S*)-**1** (97% pure, ee 90%).

2. *Odor Evaluation*. All the stereoisomers of compounds **1**–**3** were submitted to odor evaluation by skillful perfumers (*Givaudan Schweiz AG*). The following odor-descriptions resulted:

- (2*S*,6*R*)-*trans*-**1** (39.5%): *Green, Rose Oxide like, fruity, orange-type, and somewhat dusty odor. Dry down weak, green, fruity.*
- (2*R*,6*S*)-*trans*-**1** (24.7%): *Harsh, green, technical, pyrazine-type, vegetal odor, with acetic, Rose Oxide type, floral-rosy facets. Dry down green, fruity, and rosy.*
- (2*R*,6*R*)-*cis*-**1**: *Weak, green, agrestic, and herbaceous odor, with a slightly fruity side. Dry down very weak green, fruity.*
- (2*S*,6*S*)-*cis*-**1**: *Weak, fruity-floral, mushroom-like odor. Dry down very weak, fruity-floral, somewhat technical.*
- (2*S*,6*R*)-*trans*-**2**: *Green, petit-grain and orange flower-type pleasant odor, with aspects of neroli oil. Dry down linear, but more herbal, buccoxime-like.*
- (2*R*,6*S*)-*trans*-**2**: *Green, floral odor, with slightly wine- and food-like nuances, and somewhat oily, technical aspects. Dry down linear, weak, green, vegetal.*
- (2*R*,6*S*)-*trans*-**3**: *Green, metallic, Rose Oxide note, stronger than (2*S,*6*R*)-trans-**2** *and (2*R,*6*R*)*-cis-**2**. *Dry down green, fruity, buccoxime-like.* This compound is the most substantive of the series of enantiomers obtained from (*R*)-**7**.
- (2*S*,6*R*)-*trans*-**3**: *Strong, green-fruity, fresh, but also somewhat harsh-technical odor. Dry down fruity, Rose Oxide like, with a sweet rosy touch.* This compound is the strongest of the series of enantiomers prepared from (*S*)-**6**.
- (2*R*,6*R*)-*cis*-**2**: *Green, metallic, Rose Oxide like odor, with fruity, slightly earthy, and potato-like aspects. Dry down weak, green, fruity.* This compound is weaker and less-substantive than (2*R*,6*S*)-*trans*-**3**.
- (2*S*,6*S*)-*cis*-**2**: *Rather weak, sharp, green, Rose Oxide like, stem odor, with a slightly fruity and acetic tonality. Dry down very weak, slightly green.*
- (2*R*,6*R*)-*cis*-**3**: *Fruity, green, metallic odor. Dry down green fruity.*
- (2*S*,6*S*)-*cis*-**3**: *Strong, floral-green Rose Oxide odor, with a metallic inflection and a typical rose tonality. Dry down linear, Rose Oxide like, floral, rosy.*

Conclusions. – This careful work concerning the synthesis and odor evaluation of all the possible stereoisomers of *Pelargene* highlights the importance of stereochemistry. *Cis*-**1** is the main component of the commercial *Pelargene* mixture. Both enantiomers of **1** were found to have weak, not interesting odor profiles. Similarly, the enantiomers of *trans*-**1**, which are not present in the commercial mixture, and which were obtained as by-products in our dehydration reaction, are of no value from an odor point of view.

Trans-**2** and *trans*-**3** are present only in traces in commercial *Pelargene*. (2*S*,6*R*)-*trans*-**2** shows a very nice petit-grain and neroli odor not found in its enantiomer. Both the enantiomers of *trans*-**3** are very substantive. (2*R*,6*S*)-*trans*-**3** has been assessed to be much more interesting than its enantiomer.

Cis-**2** and *cis*-**3** are present in commercial *Pelargene* in 1.7 and 17%, respectively. Both the enantiomers of *cis*-**2** are rather weak, with no interesting odor. The (2*S*,6*S*)-enantiomer of *cis*-**3** is of great value for its rosy odor, while (2*R*,6*R*)-*cis*-**3** has a fruity and metallic odor.

(2*S*,6*R*)-*trans*-**2**, (2*R*,6*S*)-*trans*-**3**, and (2*S*,6*S*)-*cis*-**3** are the most-valuable components of *Pelargene*, although they represent just a very small percentage of the whole commercial mixture.

From a synthetic point of view, our work shows the great versatility of lipase PS in the enantioselective acetylation of hydroxy ketones such as **6**. Stereoselective acetyla-

tion of the monoacetate (1*R*,3*RS*,5*RS*)-**5** allowed us to separate the two (1*R*,5*S*)-diastereoisomers from the (1*R*,5*R*)-isomers. Chemoselective saponification in 5-position of the acetate gave us the chance to recover the monoacetate, which can be used for the desired ring closure. Biocatalysis, thus, has proven, once again, to be an efficient tool for the selective synthesis of stereoisomers.

We would like to thank Dr. *Philip Kraft* and Mr. *Jean Jacques Rouge* (*Givaudan Schweiz AG*, Fragrance Research, Switzerland) for the odor descriptions. *COFIN–Murst* is acknowledged for financial support.

Experimental Part

1. *General.* Lipase PS *Burkholderia cepacia* (*Amano Pharmaceuticals Co.*, Japan) was employed in this work. 4-Hydroxy-4-phenylbutan-2-one (**6**) was prepared according to [18]. TLC: *Merck Kieselgel 60 F_{254}* plates. All the column-chromatographic (CC) separations were carried out on *Merck* silica gel. Chiral HPLC: *Chiralcel OD* column (*Daicel*, Japan), *Merck-Hitachi L-6200* apparatus, with UV detector (254 nm), elution with hexane/i-PrOH 95 : 5 at 0.6 ml/min (t_R 26.1 and 28.2 min for (*S*)- and (*R*)-**6**, resp.). Optical rotations: *Dr. Kernchen Propol* digital automatic polarimeter. ^{1}H- and ^{13}C-NMR Spectra: *Bruker AC-250* spectrometer; in $CDCl_3$ soln. at r.t., unless otherwise stated; chemical shifts δ in ppm rel. to internal Me_4Si, *J* in Hz. 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)/60 → 150° at 6°/min, 150° (1 min), 150 → 280° at 12°/min, 280° (5 min). Elemental analyses: *Carlo Erba 1106* analyzer.

2. *(*R*)-3-Oxo-1-phenylbutyl Acetate* ((*R*)-**7**) *and (*S*)-4-Hydroxy-4-phenylbutan-2-one* ((*S*)-**6**). A soln. of *rac*-**6** (70.0 g, 0.43 mol) in *t*-BuOMe (600 ml) was treated with Lipase PS (35 g) in the presence of vinyl acetate (80 ml). After 48 h, the mixture was filtered, and purified by CC (SiO_2; hexane/AcOEt 9 : 1) to afford (*R*)-**7** (27.5 g, 31%). Prolonged enzyme-mediated acetylation of the unreacted alcohol gave, after 15 d, (*S*)-**6** (19.0 g, 27%).

*Data of (*R*)-***7**. Chemical purity: 98% (by GC/MS; t_R 16.99); 98% ee (chiral HPLC of the corresponding alcohol). M.p. 43–44°. $[\alpha]_D = +64.7$ ($c = 1.05$, $CHCl_3$) (lit. $[\alpha]_D = +64.6$ ($c = 0.71$, $CHCl_3$) [17]). ^{1}H-NMR [17]: 7.40–7.20 (*m*, Ph); 6.16 (*dd*, *J* = 8.6, 4.8, H–C(1)); 3.09 (*dd*, *J* = 16.6, 8.6, H–C(2)); 2.78 (*dd*, *J* = 16.6, 4.8, H–C(2)); 2.11 (*s*, Me(4)); 2.00 (*s*, Ac). ^{13}C-NMR [17]: 204.6; 169.6; 139.7; 128.4; 128.0; 126.1; 71.4; 49.5; 30.1; 20.8. GC/MS: 163 (91, $[M-43]^+$), 145 (45), 131 (54), 105 (100), 43 (86).

*Data of (*S*)-***6**. Chemical purity: 97% (by GC/MS; t_R 14.26); 90% ee (chiral HPLC). $[\alpha]_D = -64.8$ ($c = 1.1$, $CHCl_3$) (lit. $[\alpha]_D$ for (*R*)-**6**: $= -36.1$ (50% ee; $c = 1.7$, $CHCl_3$) [17]; +60.0 (83% ee; $c = 0.67$, $CHCl_3$) [19]). ^{1}H-NMR [17][19]: 7.40–7.20 (*m*, Ph); 5.18 (*m*, H–C(4)); 2.86 (*dd*, *J* = 17.0, 8.6, H–C(3)); 2.75 (*dd*, *J* = 17.0, 3.3, H–C(3)); 2.11 (*s*, MeCO). GC/MS: 164 (13, M^+), 146 (27), 106 (100), 77 (100).

3. *(1*R*,3*RS*)-3,5-Dimethyl-1-phenylhex-5-ene-1,3-diol* ((1*R*,3*RS*)-**8**). β-Metallyl chloride (= 3-chloro-2-methylprop-1-ene; 29.2 g, 0.325 mol) and (*R*)-**7** (27.0 g, 0.13 mol) were added simultaneously under N_2 to a suspension of Mg (9.60 g, 0.400 mol) in THF (500 ml), where the *Grignard* formation had already been started by addition of a few drops of β-metallyl chloride. The mixture was poured into a soln. of sat. aq. NH_4Cl at 0°, and extracted with Et_2O. The org. phase was dried (Na_2SO_4) and evaporated to afford, after purification by CC (SiO_2; hexane/AcOEt 9 : 1), a 1 : 1 mixture of the two diastereoisomers (1*R*,3*RS*)-**8** (22.3 g, 78%). Chemical purity: 96% (by GC/MS; t_R 21.58). ^{1}H-NMR (diastereoisomer mixture): 7.50–7.10 (*m*, Ph); 5.12 (*dd*, *J* = 7.4, 2.1, H–C(1) of one isomer); 5.08 (*dd*, *J* = 7.6, 1.9, H–C(1) of one isomer); 4.98, 4.96 (2*m*, H–C(6)); 4.82, 4.73 (2 br. *s*, H–C(6)); 2.59, 2.33 (2*d*, *J* = 13.3 each, H–C(4)); 2.1–1.6 (*m*, 3 H of each isomer); 1.87, 1.84 (2*s*, Me(6)); 1.42, 1.23 (2*s*, Me–C(3)). GC/MS: 202 (3, $[M-18]^+$), 187 (6), 165 (10), 147 (88), 107 (100). Anal. calc. for $C_{14}H_{20}O_2$ (220.31): C 76.33, H 9.15; found: C 76.47, H 9.07.

4. *(1*S*,3*RS*)-***8**. β-Metallyl chloride (25.8 g, 0.287 mol) and (*S*)-**6** (18.8 g, 0.114 mol) were added simultaneously under N_2 to a suspension of Mg (8.16 g, 0.310 mol) in THF, where the *Grignard* formation had already been started by addition of a few drops of β-metallyl chloride. The mixture was worked up and

purified as above to afford a 1:1 mixture of the two diastereoisomers (18.8 g, 75%). Chemical purity: 95% (by GC/MS; t_R = 21.58). The NMR and GC/MS data were in accord with those of the enantiomers. Anal. calc. for $C_{14}H_{20}O_2$ (220.31): C 76.33, H 9.15; found: C 76.26, H 9.24.

5. *(1*R,*3*RS*)-3-Hydroxy-3,5-dimethyl-1-phenylhex-5-enyl Acetate* ((1*R*,3*RS*)-**9**). The 1:1 mixture of (1*R*,3*RS*)-**8** (22.0 g, 0.10 mol) was treated with Ac_2O (50 ml) in pyridine (50 ml). After usual workup, a 1:1 diastereoisomer mixture of (1*R*,3*RS*)-**9** was obtained (23.3 g, 89%). Chemical purity: 98% (by GC/MS; t_R 22.01 and 22.07). ^{1}H-NMR (diastereoisomer mixture): 7.50–7.10 (*m*, Ph); 6.07 (*dd*, *J* = 7.1, 3.6, H–C(1) of one isomer); 6.05 (*dd*, *J* = 7.3, 3.6, H–C(1) of one isomer); 4.93 (*m*, H–C(6) of one isomer); 4.77 (br. *s*, H–C(6) of one isomer); 2.35–2.17 (*m*, 3 H of each isomer); 2.07, 2.05 (2*s*, AcO); 1.99–1.86 (*m*, 1 H of each isomer); 1.85, 1.84 (2*s*, Me(6)); 1.26, 1.25 (2*s*, Me–C(3)). GC/MS (isomer 1; t_R 22.01): 219 (1, $[M-43]^+$), 147 (100), 107 (15). GC/MS (isomer 2; t_R 22.07): 219 (0.5, $[M-43]^+$), 147 (100), 107 (20). Anal. calc. for $C_{16}H_{22}O_3$ (262.35): C 73.25, H 8.45; found: C 73.16, H 8.51.

6. *(1*S,*3*RS*)*-**9**. The 1:1 mixture of (1*S*,3*RS*)-**8** (18.5 g, 0.084 mol) was treated with Ac_2O (30 ml) in pyridine (30 ml). After usual workup, a 1:1 diastereoisomer mixture of (1*S*,3*RS*)-**9** was obtained (20.0 g, 91%). Chemical purity: 94% (by GC/MS; t_R = 22.01 and 22.07). The NMR and GC/MS data were in accord with those of the enantiomers. Anal. calc. for $C_{16}H_{22}O_3$ (262.35): C 73.25, H 8.45; found: C 73.32, H 8.53.

7. *(1*R*)-3,5-Dihydroxy-3-methyl-1-phenylhexyl Acetate* ((1*R*,3*RS*,5*RS*)-**5**). A soln. of (1*R*,3*RS*)-**9** (23.1 g, 0.088 mol) in CH_2Cl_2/MeOH 2:1 (500 ml) was treated with O_3 at −78°. The mixture was quenched with $NaBH_4$ (10.0 g, 0.264 mol), poured into H_2O, and extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated to give a mixture of the four possible diastereoisomers of (1*R*)-**5** (17.8 g, 76%). Chemical purity: 96% (by GC/MS; t_R 23.33). ^{1}H-NMR (isomer mixture): 7.50–7.20 (*m*, Ph); 6.10–5.80 (*m*, H–C(1)); 4.35–4.15 (*m*, H–C(5)); 2.50–2.10 (*m*); 2.10–2.00 (*s*, AcO); 1.99–1.35 (*m*); 1.35–1.10 (*s*, Me–C(3) and Me(6)). GC/MS: 248 (1, $[M-18]^+$), 188 (22), 147 (205), 104 (100). Anal. calc. for $C_{15}H_{22}O_4$ (266.34): C 67.65, H 8.33; found: C 67.71, H 8.26.

8. *(1*S,*3*RS,*5*RS*)*-**5**. A soln. of (1*S*,3*RS*)-**9** (18.3 g, 0.070 mol) in CH_2Cl_2/MeOH 2:1 (500 ml) was treated with O_3 at −78°. The mixture was quenched with $NaBH_4$ (7.96 g, 0.21 mol), poured into H_2O, and extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated to give a mixture of the four possible diastereoisomers of (1*S*)-**5** (13.9 g, 75%). Chemical purity: 93% (by GC/MS; t_R 23.33). The NMR and GC/MS spectra were in accord with those of the enantiomers. Anal. calc. for $C_{15}H_{22}O_4$ (266.34): C 67.65, H 8.33; found: C 67.59, H 8.27.

9. *(1*R,*3*RS,*5*R*)-3-Hydroxy-3-methyl-1-phenylhexane-1,5-diyl Diacetate* ((1*R*,3*RS*,5*R*)-**10**). A soln. of the mixture of the four diastereoisomers of (1*R*)-**5** (17.5 g, 0.066 mol) in *t*-BuOMe (150 ml) was treated with Lipase PS (10.0 g) in the presence of vinyl acetate (20 ml). After 10 d, the mixture was filtered, and the products were separated by CC (SiO_2; hexane/AcOEt 9:1) to afford (1*R*,3*RS*,5*R*)-**10** (8.94 g, 44%) and (1*R*,3*RS*,5*S*)-**5** (7.19 g, 41%), both as 1:1 mixtures of two diastereoisomers.

*Data of (1*R,*3*RS,*5*R*)*-**10**. Chemical purity: 98% (by GC/MS; t_R 23.37 and 23.40). ^{1}H-NMR (isomer mixture): 7.40–7.25 (*m*, Ph); 6.01 (*dd*, *J* = 5.9, 3.2, H–C(1) of one isomer); 5.99 (*dd*, *J* = 5.8, 3.2, H–C(1) of one isomer); 5.22–5.13 (*m*, H–C(5)); 2.35–2.15 (*m*, 1 H of each isomer); 2.05, 2.04 (2*s*, AcO); 1.98, 1.97 (2*s*, AcO); 2.00–1.50 (*m*, 3 H of each isomer); 1.26 (*d*, *J* = 6.4, Me(6) of one isomer); 1.25 (*d*, *J* = 6.1, Me(6) of one isomer); 1.24, 1.23 (2*s*, Me–C(3)). GC/MS (isomer 1; t_R 23.30): 290 (1, $[M-18]^+$), 265 (1), 230 (1), 188 (10), 147 (20), 104 (100), 85 (50). GC/MS (isomer 2; t_R 23.40): 290 (1, $[M-18]^+$), 265 (1), 230 (1), 188 (9), 147 (23), 104 (100), 85 (55). Anal. calc. for $C_{17}H_{24}O_5$ (308.38): C 66.21, H 7.84; found: C 66.36, H 7.78.

*Data of (1*R,*3*RS,*5*S*)*-**5**. Chemical purity: 97% (by GC/MS; t_R 23.33). ^{1}H-NMR (isomer mixture): 7.40–7.25 (*m*, Ph); 6.02, 5.94 (2*dd*, *J* = 9.0 and 3.9 each, H–C(1)); 4.35–4.20 (*m*, H–C(5)); 2.45, 2.21 (2*dd*, *J* = 14.6 and 9.0 each, 1 H); 2.08, 2.07 (2*s*, AcO); 1.95, 1.93 (2*dd*, *J* = 14.6 and 3.9 each, 1 H); 1.73–1.61 (*m*, 1 H of each isomer); 1.52, 1.47 (2*dd*, *J* = 14.6, 2.0, 1 H of each isomer); 1.33, 1.31 (2*s*, Me–C(3)); 1.19, 1.12 (2*d*, *J* = 6.1 each, Me(6)). Anal. calc. for $C_{15}H_{22}O_4$ (266.34): C 67.65, H 8.33; found: C 67.56, H 8.25.

10. *(1*R,*3*RS,*5*R*)*-**5**. To a suspension of Lipase PS (5.0 g) in H_2O (50 ml), a soln. of the diacetate (1*R,* 3*RS,*5*R*)-**10** (8.70 g, 0.028 mol) in THF (5 ml) was added. The pH was kept at 7.8 by means of a pH-stat. After 12 h, the mixture was extracted with AcOEt, the org. phase was dried (Na_2SO_4), and concentrated

under reduced pressure to give (1*R*,3*RS*,5*R*)-**5** (5.21 g, 70%) as a 1:1 mixture of two diastereoisomers. Chemical purity: 99% (by GC/MS; t_R 23.33). ^{1}H-NMR (isomer mixture): 7.40–7.25 (*m*, Ph); 6.03, 5.98 (2*dd*, *J* = 9.0, 3.8, H–C(1)); 4.40–4.20 (*m*, H–C(5)); 2.27, 2.24 (2*dd*, *J* = 14.6 and 9.0 each, 1 H of each isomer); 2.11, 1.90 (2*dd*, *J* = 14.6 and 3.8 each, 1 H of each isomer); 2.06, 2.04 (2*s*, AcO); 1.73–1.61 (*m*, 3 H); 1.49 (*dd*, *J* = 14.6, 2.0, 1 H); 1.35, 1.27 (2*s*, Me–C(3)); 1.20, 1.19 (2*d*, *J* = 6.1, Me(6)). Anal. calc. for $C_{15}H_{22}O_4$ (266.34): C 67.65, H 8.33; found: C 67.55, H 8.41.

11. *Cyclization of the Monoacetates* **5**. 11.1. *General Procedure* (*GP 1*). To a soln. of the appropriate monoacetate **5** (5.0 g, 0.019 mol) in pyridine (20 ml) was added mesyl chloride (3.20 g, 0.028 mol) at 0°. The mixture was stirred at r.t. for 1 h, poured onto ice, extracted with AcOEt, dried (Na_2SO_4), and concentrated. The residue was dissolved in MeOH (20 ml), and a 4M soln. of MeONa in MeOH (6 ml) was added. The mixture was stirred at r.t. for 1 h. After usual workup, the residue was purified by CC (SiO_2; hexane/AcOEt 95:5).

11.2. *(2S,4S,6R)- and (2S,4R,6R)-3,4,5,6-Tetrahydro-2,4-dimethyl-6-phenyl-2H-pyran-4-ol* ((2*S*,4*S*,6*R*)- *and* (2*S*,4*R*,6*R*)-**4**). Prepared according to *GP 1* from (1*R*,3*RS*,5*R*)-**5** (2 diastereoisomers; 5.0 g, 0.019 mol).

*Data of (2S,4S,6R)-***4**. Yield: 1.21 g (31%). Chemical purity: 61% (by GC/MS; t_R 18.07). $[\alpha]_D^{20} = +1.1$ (*c* = 0.90, $CHCl_3$). ^{1}H-NMR: 7.50–7.20 (*m*, Ph); 5.10 (*dd*, *J* = 5.7, 3.0, H–C(6)); 4.04 (*ddq*, *J* = 10.2, 6.4, 3.0, H–C(2)); 2.36 (*ddd*, *J* = 14.0, 3.0, 1.9, H_{eq}–C(5) or H_{eq}–C(3)); 2.04 (*dd*, *J* = 14.0, 6.4, H_{ax}–C(5)); 1.60 (*ddd*, *J* = 14.0, 3.0, 1.9, H_{eq}–C(3) or H_{eq}–C(5)); 1.46 (*dd*, *J* = 10.2, 14.0, H_{ax}–C(3)); 1.29 (*s*, Me–C(4)); 1.25 (*d*, *J* = 6.4, Me–C(2)). ^{13}C-NMR: 141.3; 128.4; 126.8; 125.7; 71.7; 68.6; 63.5; 45.4; 39.9; 30.8; 21.0. GC/MS: 188 (51, $[M-18]^+$), 173 (83), 104 (80), 58 (100).

*Data of (2S,4R,6R)-***4**. Yield: 1.64 g (42%). Chemical purity: 90% (by GC/MS; t_R 18.77). $[\alpha]_D^{20} = +6.64$ (*c* = 1.2, $CHCl_3$). ^{1}H-NMR: 7.50–7.20 (*m*, Ph); 5.05 (*dd*, *J* = 9.6, 3.7, H–C(6)); 4.25 (*dquint.*, *J* = 6.4, 3.3, H–C(2)); 1.95–1.80 (*m*, 2 H); 1.76 (*dd*, *J* = 13.9, 9.6, H_{ax}–C(5)); 1.58 (*ddd*, *J* = 13.9, 3.3, 1.9, H_{eq}–C(5) or H_{eq}–C(3)); 1.49 (*d*, *J* = 6.4, Me–C(2)); 1.23 (*s*, Me–C(4)). ^{13}C-NMR: 142.7; 128.2; 127.0; 125.9; 68.9; 68.4; 68.2; 45.2; 42.2; 31.7; 19.8. GC/MS: 188 (60, $[M-18]^+$), 173 (95), 105 (100), 58 (90). Anal. calc. for $C_{13}H_{18}O_2$ (206.29): C 75.69, H 8.80; found: C 75.57, H 8.71.

11.3. *(2S,4S,6R)- and (2S,4R,6R)-***4**. Prepared according to *GP 1* from (1*R*,3*RS*,5*S*)-**5** (diastereoisomer mixture; 6.90 g, 0.026 mol).

*Data of (2R,4R,6R)-***4**. Yield: 1.82 g (34%). Chemical purity: 83% (by GC/MS; t_R 18.15). $[\alpha]_D^{20} = +18.5$ (*c* = 1.02, $CHCl_3$). ^{1}H-NMR [6]: 7.50–7.20 (*m*, Ph); 4.76 (*dd*, *J* = 11.5, 2.4, H–C(6)); 4.00 (*ddq*, *J* = 11.5, 6.2, 2.3, H–C(2)); 1.75 (*dt*, *J* = 13.6, 2.3, H_{eq}–C(3) or H_{eq}–C(5)); 1.61 (*dt*, *J* = 13.6, 2.3, H_{eq}–C(5) or H_{eq}–C(3)); 1.55 (*dd*, *J* = 13.6, 11.5, H_{ax}–C(3) or H_{ax}–C(5)); 1.37 (*dd*, *J* = 13.6, 11.5, H_{ax}–C(5) or H_{ax}–C(3)); 1.26 (*s*, Me–C(4)); 1.25 (*d*, *J* = 6.0, Me–C(2)). ^{13}C-NMR [6]: 142.8; 128.2; 127.1; 125.9; 74.9; 69.2; 68.7; 46.0; 45.7; 31.4; 21.6. GC/MS: 188 (84, $[M-18]^+$), 173 (100), 107 (53), 105 (69), 58 (31).

*Data of (2R,4S,6R)-***4**. Yield: 2.30 g (43%). Chemical purity: 97% (by GC/MS; t_R 18.42). M.p.: 107–109°. $[\alpha]_D^{20} = +36.8$ (*c* = 0.87, $CHCl_3$). ^{1}H-NMR [6]: 7.50–7.20 (*m*, Ph); 4.40 (*dd*, *J* = 12.0, 2.3, H–C(6)); 3.68 (*ddq*, *J* = 6.1, 2.3, 12.0, H–C(2)); 1.87 (*dt*, *J* = 12.0, 2.3, H_{eq}–C(3) or H_{eq}–C(5)); 1.74 (*dt*, *J* = 12.0, 2.3, H_{eq}–C(5) or H_{eq}–C(3)); 1.65 (*t*, *J* = 12.0, H_{ax}–C(3) or H_{ax}–C(5)); 1.40 (*t*, *J* = 12.0, H_{ax}–C(5) or H_{ax}–C(3)); 1.43 (*s*, Me–C(4)); 1.29 (*d*, *J* = 6.0, Me–C(2)). ^{13}C-NMR [6]: 142.1; 128.2; 127.3; 125.9; 77.0; 71.3; 69.3; 47.8; 47.6; 25.8; 21.9. GC/MS: 188 (50, $[M-18]^+$), 173 (78), 107 (91), 58 (100).

11.4. *(2S,4S,6S)-, (2R,4RS,6S)-, and (2S,4R,6S)-***4**. Prepared according to *GP 1* from (1*S*,3*RS*,5*RS*)-**5** (four diastereoisomers; 13.7 g, 0.051 mol). A mixture of (2*S*,4*S*,6*S*)-**4** (28%, GC/MS) and (2*R*,4*RS*,6*S*)-**4** (72%, GC/MS) was eluted first (6.72 g, 64%), followed by (2*S*,4*R*,6*S*)-**4** (single stereoisomer; 1.58 g, 15%).

*Data of (2S,4R,6S)-***4**. Chemical purity: 97% (by GC/MS; t_R 18.42). $[\alpha]_D^{20} = -34.1$ (*c* = 1.01, $CHCl_3$). M.p. 109°. The MS and NMR spectra were in accordance with those of the enantiomer.

12. *Dehydration of Compounds* **4**. 12.1. *General Procedure* (*GP 2*). To a soln. of the pertinent starting material **4** (1.60 g, 7.76 mmol) in pyridine (10 ml) was added $POCl_3$ (1.54 g, 0.01 mol) at 0°. The mixture was stirred at r.t. for 1 h, then poured onto ice, extracted with AcOEt, dried (Na_2SO_4), and evaporated. The residue was purified by CC (SiO_2; hexane).

12.2. *(2S,6R)-3,4,5,6-Tetrahydro-2-methyl-4-methylidene-6-phenyl-2H-pyran* ((2*S*,6*R*)-**1**), *(2S,6R)-3,6-Dihydro-2,4-dimethyl-6-phenyl-2H-pyran* ((2*S*,6*R*)-**2**), *and (2R,6S)-3,6-Dihydro-4,6-dimethyl-2-phenyl-2H-pyran* ((2*R*,6*S*)-**3**). Prepared according to *GP 2* from (2*S*,4*S*,6*R*)-**4** (1.10 g) to afford (2*S*,6*R*)-**1** (7%, GC/MS), (2*S*,6*R*)-**2** (50%, GC/MS), and (2*R*,6*S*)-**3** (43%, GC/MS). When prepared from (2*S*,4*R*,6*R*)-**4** (1.50 g) according to *GP 2*, (2*S*,6*R*)-**1** (6%, GC), (2*S*,6*R*)-**2** (22%, GC), and (2*R*,6*S*)-**3** (72%, GC) were obtained. The following anal. data refer to samples purified by CC (SiO_2, hexane) and bulb-to-bulb distillation.

Data of (2S,6R)-**1**. Sample: 0.105 g. Purity: 39% (by GC/MS; t_R 15.42). ^{1}H-NMR (main signals): 4.89 (br. *s*, 1 H of H_2C=C); 4.81 (*m*, H–C(6), 1 H of H_2C=C); 4.11 (*m*, H–C(2)); 1.24 (*d*, *J* = 6.1, Me–C(2)). GC/MS: 188 (5, M^+), 144 (65), 129 (100), 67 (92).

Data of (2S,6R)-**2**. Sample: 0.220 g. Purity: 98% (by GC/MS; t_R 15.46). $[\alpha]_D^{20} = +157.3$ (*c* = 0.75, $CHCl_3$). ^{1}H-NMR: 7.45–7.20 (*m*, Ph); 5.70 (*m*, H–C(5)); 5.23 (*m*, H–C(6)); 3.70 (*m*, H–C(2)); 1.90 (*m*, CH_2(3)); 1.80 (*s*, Me–C(4)); 1.19 (*d*, *J* = 6.3, Me–C(2)). ^{13}C-NMR: 142.6; 133.8; 128.8; 128.4; 127.9; 121.7; 74.6; 64.6; 37.9; 23.7; 21.7. GC/MS: 188 (31, M^+), 173 (74), 129 (70), 105 (100), 77 (52). Anal. calc. for $C_{13}H_{16}O$ (188.27): C 82.94, H 8.57; found: C 82.85, H 8.50.

Data of (2R,6S)-**3**. Sample: 0.310 g. Purity: 99% (by GC/MS; t_R 15.86). $[\alpha]_D^{20} = +157.8$ (*c* = 0.85, $CHCl_3$). ^{1}H-NMR [6]: 7.55–7.20 (*m*, Ph); 5.47 (*m*, H–C(5)); 4.75 (*dd*, *J* = 9.0, 4.0, H–C(2)); 4.44 (br. *s*, H–C(6)); 2.27 (*m*, H–C(3)); 2.11 (*m*, H–C(3)); 1.77 (*s*, Me–C(4)); 1.30 (*d*, *J* = 6.3, Me–C(6)). ^{13}C-NMR: 142.5; 131.2; 128.3; 127.3; 126.3; 124.7; 69.7; 69.2; 36.6; 22.9; 20.2. GC/MS: 188 (8, M^+), 173 (16), 145 (33), 91 (67), 82 (83), 67 (100).

12.3. *(2R,6R)*-**1**, *(2R,6R)*-**2**, *and (2R,6R)*-**3**. Prepared according to *GP 2* from (2*R*,4*R*,6*R*)-**4** (1.70 g, 8.25 mmol) to afford (2*R*,6*R*)-**1** (6%, GC/MS), (2*R*,6*R*)-**2** (26%, GC/MS), (2*R*,6*R*)-**3** (48%, GC/MS), *trans* isomers (2%, GC/MS). When (2*R*,4*S*,6*R*)-**4** (2.20 g, 0.197 mol) was used as starting material, (2*R*,6*R*)-**1** was obtained. The following anal. data refer to samples purified by CC (SiO_2, hexane) and bulb-to-bulb distillation.

Data of (2R,6R)-**1**. Sample: 1.48 g (74%). Purity: 99% (by GC/MS; t_R 14.77). $[\alpha]_D^{20} = -11.5$ (*c* = 1.10, $CHCl_3$). ^{1}H-NMR [6][14]: 7.50–7.20 (*m*, Ph); 4.80 (*m*, CH_2=C); 4.34 (*dd*, *J* = 11.3, 2.5, H–C(6)); 3.60 (*ddq*, *J* = 11.1, 6.3, 2.3, H–C(6)); 2.44 (*m*, 1 H); 2.37–2.17 (*m*, 2 H); 2.05 (*m*, 1 H); 1.32 (*d*, *J* = 6.1, Me–C(2)). ^{13}C-NMR [6][14]: 144.8; 142.5; 128.3; 127.4; 125.9; 108.5; 80.4; 74.9; 42.6; 42.3; 21.9. GC/MS: 188 (14, M^+), 144 (86), 129 (93), 107 (78), 67 (100).

Data of (2R,6R)-**2**. Sample: 0.240 g (15%). Purity: 94% (by GC/MS; t_R 15.29). $[\alpha]_D^{20} = +68.2$ (*c* = 0.90, $CHCl_3$). ^{1}H-NMR: 7.50–7.20 (*m*, Ph); 5.44 (br. *s*, H–C(5); 5.12 (br. *s*, H–C(6)); 3.87 (*m*, H–C(2)); 2.35–1.80 (*m*, 2 H); 1.74 (*s*, Me–C(4)); 1.32 (*d*, *J* = 6.2, Me–C(2)). ^{13}C-NMR: 142.9; 132.8; 128.6; 127.7; 126.5; 124.3; 71.1; 64.5; 38.2; 23.5; 22.3. GC/MS: 188 (25, M^+), 173 (60), 145 (12), 129 (61), 105 (100), 77 (65). Anal. calc. for $C_{13}H_{16}O$ (188.27): C 82.94, H 8.57; found: C 82.86, H 8.65.

Data of (2R,6R)-**3**. Sample: 0.379 g (24%). Purity: 97% (by GC/MS; t_R 15.42). $[\alpha]_D^{20} = +90.65$ (*c* = 0.74, $CHCl_3$). ^{1}H-NMR [6]: 7.50–7.20 (*m*, Ph); 5.39 (*m*, H–C(5)); 4.57 (*dd*, *J* = 3.6, 10.6, H–C(2)); 4.36 (*m*, H–C(6)); 2.35–1.90 (*m*, 2 H); 1.73 (br. *s*, Me–C(4)); 1.29 (*d*, *J* = 6.6, Me–C(6)). ^{13}C-NMR [6]: 142.8; 131.9; 128.3; 127.3; 125.9; 125.2; 76.0; 71.6; 37.7; 22.8; 21.6. GC/MS: 188 (5, M^+), 173 (11), 145 (22), 82 (94), 67 (100).

12.4. *(2S,6S)*-**2**, *(2S,6S)*-**3**, *(2R,6S)*-**1**, *(2R,6S)*-**2**, *and (2S,6R)*-**3**. Prepared according to *GP 2* from a mixture (6.50 g, 0.031 mol) of the three isomers (2*S*,4*S*,6*S*)-**4** (28%, GC/MS) and (2*R*,4*RS*,6*S*)-**4** (72%, GC/MS). Yields (by GC/MS): (2*S*,6*S*)-**1** (2%), (2*S*,6*S*)-**2** (10.1%), (2*S*,6*S*)-**3** and (2*R*,6*S*)-**1** (22.0%), (2*R*,6*S*)-**2** (35.4%), (2*S*,6*R*)-**3** (30.5%). The following anal. data refer to samples purified by CC (SiO_2; hexane) and bulb-to-bulb distillation.

Data of (2S,6S)-**2**. Sample: 0.280 g (4.8%). Purity: 93% (by GC/MS; t_R 15.29). $[\alpha]_D^{20} = -60.4$ (*c* = 1.05, $CHCl_3$). The MS and NMR data were in agreement with those of the enantiomer. Anal. calc. for $C_{13}H_{16}O$ (188.27): C 82.94, H 8.57; found: C 82.84, H 8.49.

Data of (2S,6S)-**3**. Sample: 0.210 g (3.6%). Purity: 94% (by GC/MS; t_R 15.42). $[\alpha]_D^{20} = -79.8$ (*c* = 0.80, $CHCl_3$). The MS and NMR data were in agreement with those of the enantiomer.

Data of (2R,6S)-**1**. Sample: 0.170 g (2.9%). Purity: 33% (by GC/MS; t_R 15.42).

*Data of (2*R*,6*S*)-***2***.* Sample: 0.305 g (5.2%). Purity: 92% (by GC/MS; t_R 15.46). $[\alpha]_D^{20} = -138.8$ ($c = 0.90$, $CHCl_3$). The MS and NMR data were in agreement with those of the enantiomer. Anal. calc. for $C_{13}H_{16}O$ (188.27): C 82.94, H 8.57; found: C 83.06, H 8.63.

*Data of (2*S*,6*R*)-***3***.* Sample: 0.310 g (5.3%). Purity: 94% (by GC/MS; t_R 15.86). $[\alpha]_D^{20} = -136.1$ ($c = 0.70$, $CHCl_3$). The MS and NMR data were in agreement with those of the enantiomer.

12.5. *(2*S*,6*S*)-***1***.* Prepared according to *GP 2* from (2*S*,4*R*,6*S*)-**4** (1.40 g, 6.79 mmol). Yield: 0.881 g (69%). Purity: 97% (by GC/MS; t_R 14.77). $[\alpha]_D^{20} = +9.9$ ($c = 1.00$, $CHCl_3$).

REFERENCES

[1] R. Axel, *Angew. Chem., Int. Ed.* **2005**, *44*, 6110; L. Buck, *Angew. Chem., Int. Ed.* **2005**, *44*, 6128.
[2] L. Buck, R. Axel, *Cell* **1991**, *65*, 175.
[3] M. Spehr, G. Gisselmann, A. Poplawski, J. A. Riffel, C. H. Wetzel, R. K. Zimmer, H. Hatt, *Science* **2003**, *299*, 859; H. Hatt, *Chem. Biodiv.* **2004**, *1*, 1857.
[4] G. M. Shepherd, *PLoS Biology* **2004**, *2,* 572.
[5] E. Brenna, *Curr. Org. Chem.* **2003**, *7*, 1347; A. Abate, E. Brenna, C. Fuganti, F. G. Gatti, S. Serra, *J. Mol. Catal., B* **2004**, *32*, 33; E. Brenna, C. Fuganti, S. Serra, *Tetrahedron: Asymm.* **2003**, *14*, 1.
[6] A. Schneider, U. Sequin, *Tetrahedron* **1985**, *41*, 949.
[7] A. Ballard, R. T. Holm, P. H. Williams, *J. Am. Chem. Soc.* **1950**, *72*, 5734; P. H. Williams, G. G. Ecke, S. A. Ballard, *J. Am. Chem. Soc.* **1950**, *72*, 5738; B. J. F. Hudson, G. Schmerlaib, *Tetrahedron* **1957**, *1*, 284; J. H. P. Tyman, B. J. Willis, *Tetrahedron Lett.* **1970**, 4507.
[8] N. L. J. M. Broekhof, J. J. Hofman, to Naarden International N.V., EP 325000, 1988 (*Chem. Abstr.* **1990**, *112*, 55603).
[9] S. Oi, K. Kashiwagi, E. Terada, K. Ohuchi, Y. Inoue, *Tetrahedron Lett.* **1996**, *35*, 6351.
[10] T. Nishioka, S. Tanaka, J. Koshino, O. Yamashita, T. Ozawa, M. Kohama, to Kao Corporation, EP 0834509, 1997 (*Chem. Abstr.* **1998**, *128*, 257332).
[11] V. K. Aggarwal, G. P. Vennall, P. N. Davey, C. Newman, *Tetrahedron Lett.* **1997**, *38*, 2569.
[12] J. M. Bailey, D. Craig, P. T. Gallagher, *Synlett* **1999**, 132.
[13] T.-S. Balaban, A. T. Balaban, *Tetrahedron Lett.* **1987**, *28*, 1341.
[14] T. M. Sung, W. Y. Kwak, K.-T. Kang, *Bull. Korean Chem. Soc.* **1998**, *19*, 862.
[15] E. Brenna, M. Delmonte, C. Fuganti, S. Serra, *Helv. Chim. Acta* **2001**, *84*, 69.
[16] M. S. Nair, S. Joly, *Tetrahedron: Asymm.* **2000**, *11*, 2049.
[17] S. Joly, M. S. Nair, *J. Mol. Catal., B* **2003**, *22*, 151.
[18] D. S. Noyce, W. L. Reed, *J. Am. Chem. Soc.* **1958**, *80,* 5539.
[19] Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262.

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