Synthesis, Olfactory Evaluation, and Determination of the Absolute Configuration of the 3,4-Didehydroionone Stereoisomers

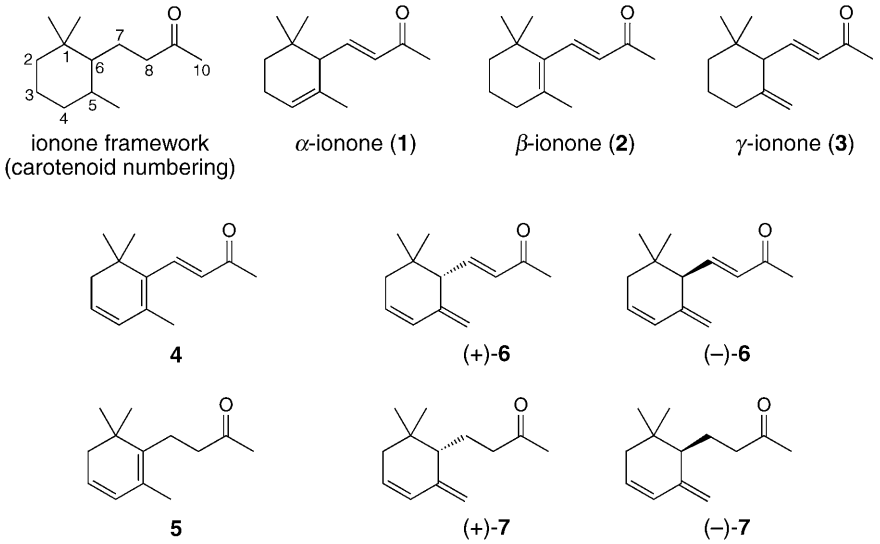
by **Stefano Serra***, **Claudio Fuganti**, and **Elisabetta Brenna**

C.N.R. Istituto di Chimica del Riconoscimento Molecolare, Sezione 'Adolfo Quilico', Dipartimento di Chimica, Materiali ed Ingegneria Chimica 'Giulio Natta', Politecnico di Milano, Via Mancinelli 7, I-20133 Milano
(phone: +39 02 2399 3076; fax: +39 02 2399 3080; e-mail: stefano.serra@polimi.it)

The synthesis of 3,4-didehydroionone isomers **4**, (+)-**6**, and (−)-**6** and of 3,4-didehydro-7,8-dihydroionone isomers **5**, (+)-**7**, and (−)-**7** was accomplished starting from commercially available racemic α-ionone (**1**). Their preparation of the racemic forms **4**–**7** was first achieved by mean of a number of chemo- and regioselective reactions (*Schemes 1* and *2*). The enantio- and diastereoselective lipase-mediated kinetic acetylation of 4-hydroxy-γ-ionone (**10a**/**10b**) provided 4-hydroxy-γ-ionone (+)-**10a**/(±)-**10b** and (+)-4-(acetyloxy)-γ-ionone ((+)**12b**) (*Scheme 3*). The latter compounds were used as starting materials to prepare the 3,4-didehydro-γ-ionones (+)- and (−)-**6** and the 3,4-didehydro-7,8-dihydro-γ-ionones (+)- and (−)-**7** in enantiomer-enriched form. The absolute configuration of (+)-**12b** was determine by chemical correlation with (+)-(6*S*)-γ-ionone ((+)-**3**) and with (−)-(6*S*)-α-ionone ((−)-**1**) therefore allowing to assign the (*S*)-configuration to (+)-**6** and (+)-**7**. Olfactory evaluation of the above described 3,4-didehydroionone isomers shows a significant difference between the enantiomers and regioisomers both in fragrance feature and in detection threshold (*Table*).

1. Introduction. – The ionone isomers **1**–**3** are natural[1]) C_{13} norterpenoid ketones [1]. The α- and β-ionones are widely used as flavor ingredients [2] and as starting materials in several industrial processes, whereas regioisomerically- and enantiomerically pure α- and γ-ionones [3] are suitable building blocks in the synthesis of different natural products. As part of a programme of synthesis of enantiomer-enriched norterpenoid odorants, we have previously reported the preparation and the olfactory evaluation of ionones **1**–**3** [3][4]. Our studies showed that regioisomer and enantiomer composition greatly affected the fragrance properties either in terms of features or as odor thresholds. For example, (*S*)-γ-ionone was recognized [5] as the most pleasant ionone isomer with an odor threshold 150 times lower than that of the (*R*)-enantiomer and 50 times lower than that of the α-isomer. These notable results prompted us to investigate the preparation of further C_{13} norterpenoid compounds with a ionone skeleton. In this context, we focalized our attention on the 3,4-didehydroionone isomers **4**–**7**. The 3,4-didehydro-β-ionone (**4**), the corresponding 7,8-dihydro derivative **5**, and 3,4-didehydro-γ-ionone (**6**) have been found[2]), usually as trace components, in several natural sources [6]. Compounds **4** and **5** are used in a flavor formulation [7] and have been previously prepared by different methods [7–9]. The acid-catalyzed elimination of 4-hy-

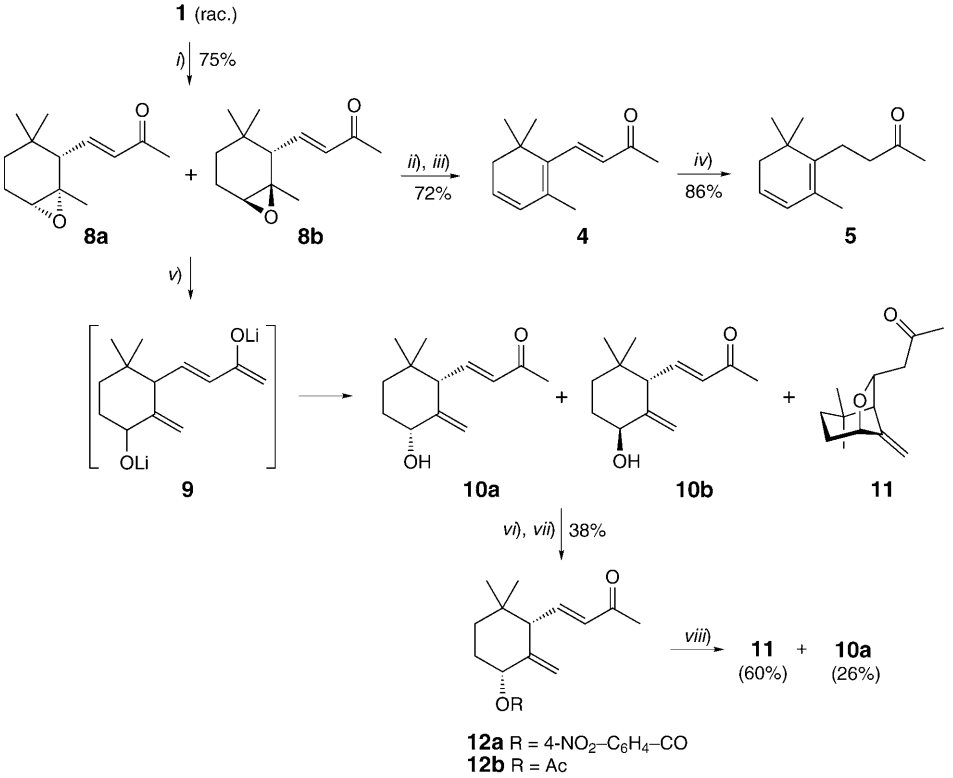
[1]) For the distribution of α- and β-ionone in nature, see [1a,b]; for γ-ionone see [1c,d].
[2]) For the distribution of **4**, **5**, and **6** in nature, see [6a,b], [6c], and [6d,e], respectively.



droxy-β-ionone [8c] and the selective reduction of **4** [9] are the most regioselective paths to **4** and **5**, respectively. Moreover, the bromination followed by debromination of α-ionone (**1**) [8a] and of dihydro-α-ionone [7], respectively affords the above-mentioned compounds contaminated with other regioisomers. For example, 3,4-didehydro-7,8-dihydro-γ-ionone (**7**) is also produced in the latter process as a by-product. Otherwise, to the best of our knowledge, no specific preparation of **6** and **7** have been reported until now. Therefore, the selective preparation of the enantiomeric forms of **6** and **7**, as well as the comprehensive olfactory evaluation of all the isomers of compounds **4**–**7**, are still lacking. Based on these observations, it seemed desirable to develop a new synthetic method to the enantiomerically pure forms of **6** and **7** by means of a procedure not necessarily involving troublesome isomer separations or the use of expensive enantiomerically pure starting materials.

2. Results and Discussion. – Accordingly, we prepared compounds **4**–**7** in racemic and enantiomer-enriched form starting from commercially available racemic α-ionone (**1**). The regioselective base-mediated isomerization of 4,5-epoxy-4,5-dihydro-α-ionone (**8a**/**8b**) followed by elimination of the obtained allylic alcohols were the key steps of our divergent syntheses. Isomerization of **8a**/**8b** catalyzed by a nucleophilic base [10] gave access to **4** and **5** (*Scheme 1*), and the reaction of **8a**/**8b** with a stoichiometric amount of a strong, non-nucleophilic base furnished 4-hydroxy-γ-ionone (**10a**/**10b**) as a key intermediate for the synthesis of **6** and **7** and of their enantiomers (*Schemes 2* and *3*). The latter were obtained by the lipase-mediated resolution of **10a**/**10b** yielding enantiomerically and diastereoisomerically pure (+)-4-(acetyloxy)-γ-ionone ((+)-**12b**) and enantiomer-enriched (+)-**10a**. The configuration of the stereoisomers of **6** and **7** was assigned unambiguously, by chemical correlation of (+)-**12b** with (+)-γ-ionone ((+)-**3**) and (−)-α-ionone ((−**1**), both of known absolute configuration [5][11] (*Scheme 3*).

Scheme 1



i) MCPBA, CH_2Cl_2; **8a**/**8b** 5:1. *ii*) NaOMe (cat.), MeOH. *iii*) TsOH (cat.), toluene, reflux. *iv*) Bu_3-SnH, $[PdCl_2(PPh_3)_2]$ (cat.), NH_4Cl, H_2O, THF. *v*) LDA, THF, reflux; 80% of **10a**/**10b** 4:1, 6% of **11**. *vi*) 4-*N*-nitrobenzoyl chloride, pyridine *vii*) Two crystallizations from MeOH. *viii*) KOH, MeOH.

2.1. *3,4-Didehydro-β-ionone Isomers* **4** *and* **5**. The β-ionone derivatives **4** and **5** were obtained from α-ionone (**1**) by a slight modification of a previously reported synthesis. The bromination/debromination method proved to be efficient but gave regioisomerically impure products. Thus a two-step process was considered. Epoxidation of **1** with 3-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 [12] gave an unseparable 5:1 mixture of the two diastereoisomers **8a** and **8b** in 75% yield (*Scheme 1*). Treatment of **8a**/**8b** with a catalytic amount of NaOMe in MeOH [10a,b] yielded crude 4-hydroxy-β-ionone which was heated in toluene in the presence of a catalytic amount of TsOH [8c] to afford, after chromatographic separation, pure **4**. The regiospecific reduction of the conjugated C(7)=C(8) bond of **4** was achieved by Pd-catalyzed hydride addition [5] [9a] in $THF/H_2O/NH_4Cl$ on treatment with an excess of tributylstannane in the presence of cat. $[PdCl_2(PPh_3)_2]$ (5 mol-%), furnishing isomer-free **5** in 86% yield.

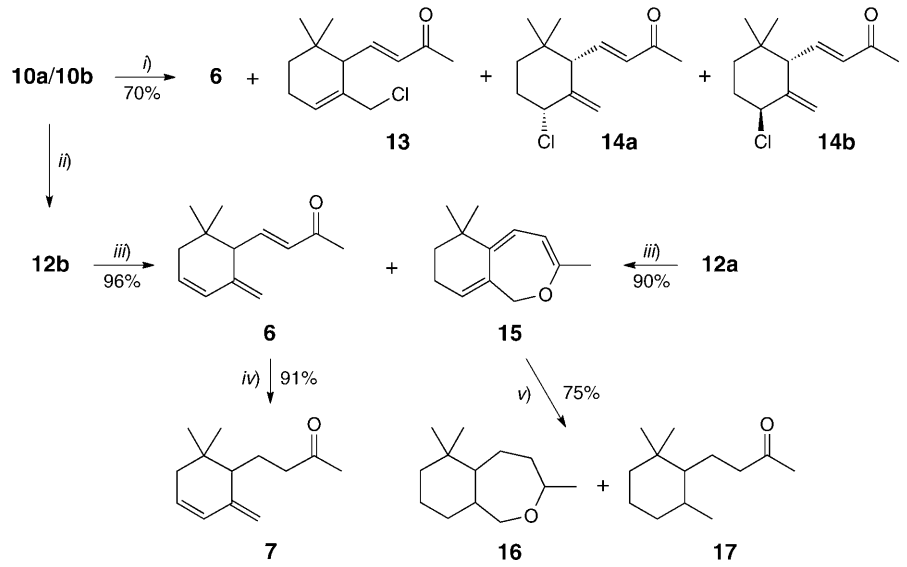
2.2. *3,4-Didehydro-γ-ionone Isomers* **6** *and* **7**. Although the base-mediated isomerization of epoxides has been extensively used in organic synthesis [13], its application to the isomerization of **8a**/**8b** is an intriguing synthetic step. Indeed, the necessary use of harsh condition and the presence of the unsaturated ketone functionality could give rise

to different regioisomers and/or by-products. However, we found that under carefully controlled conditions, an efficient isomerization occurs. Thus, the addition of **8a**/**8b** to a cooled (−78°) solution of lithium diisopropylamide (LDA; 2.2 equiv.) in THF selectively converted the ketone function to the corresponding lithium enolate without affecting the epoxide group (*Scheme 1*). To achieve isomerization, the enolate solution was heated under reflux whereupon the scarcely soluble salt **9** precipitated with concomitant disappearance of **8a**/**8b**. After completion of the reaction, the heterogeneous mixture was added to a cooled diluted HCl solution and rapidly extracted, yielding 80% of the diasteroisomeric 4-hydroxy-γ-ionones **10a**/**10b** as an unseparable 4:1 mixture, besides a small amount of the bicyclic ether **11**, the latter conceivably deriving from **10a** by 1,4-addition of the OH group on the conjugated double bond. Different modifications of the experimental conditions gave inferior results. For example, direct addition of **8a**/**8b** to a heated LDA solution or basic workup conditions increased the amount of polymerized by-products or the formation of ether **11**, respectively. The structure of **11** was confirmed by comparison of its NMR data with those reported by *Kaiser* and *Lamparsky* [14] for an identical by-products obtained on $Al(^iPrO)_3$ treatment of **8a**/**8b**. Similarly, the diastereoisomers **10a**/**10b** corresponded to the 4-hydroxy-γ-ionone diastereoisomers previously prepared by *Griesbeck et al.* [15] by photooxygenation of α-ionone (**1**). Moreover, the transformation of **10a**/**10b** to the corresponding 4-nitrobenzoates followed by crystallization from MeOH afforded diastereoisomerically pure **12a**. All attempts to hydrolyze the ester function of **12a** under basic conditions gave mainly ether **11** and only a minor amount of **10a**, demonstrating that 4-hydroxy-γ-ionone is labile on basic treatment; strongly acidic conditions catalyzed both nonregiospecific elimination and ring closure to **11**.

Aimed at finding a selective path to 3,4-didehydro-γ-ionone (**6**) we investigated the elimination reaction of compound **10a**/**10b** and of its derivatives (*Scheme 2*). $POCl_3$-Mediated dehydration of **10a**/**10b** was highly regioselective the didehydroionones obtained consisting of up to 99% of **6**, although not efficient, the yield being only 25–30%, *i.e*, treatment of **10a**/**10b** in pyridine at 0° with an excess of $POCl_3$ afforded pure **6** (27% yield) besides a mixture of unseparable chloro derivatives **13**, **14a**, and **14b** (43% yield). Compound **13** was the main product, most likely formed by S_N2' addition of the Cl^- ion to the intermediate allyl phosphate, and the diastereoisomers **14a** and **14b** [16] arose from the same phosphate by substitution and, under the mild experimental conditions described above, did not undergo elimination.

Subsequently, the stereospecific Pd-mediated elimination of allylic acetate was tested with the esters of **10a** and **10b**. According to the *Hauser* [17] procedure, the acetate **12b** or the diastereoisomerically pure 4-nitrobenzoate **12a** was heated under reflux in dioxane in the presence of an excess of $CaCO_3$ and of a catalytic amount of $Pd(OAc)_2$ and PPh_3 (*Scheme 2*). Both substrates gave the same product distribution: 3,4-didehydro-γ-ionone (**6**) was isolated in good yield (78 or 71%, resp.) and was formed regioselectively, the didehydroionones obtained consisting of up to 98% of **6**, whereas enol-ether **15** was the only by-product (18 and 19%, resp.). The latter compound was probably formed by Pd-catalyzed S_N2' addition of the ketone enolate on the allylic acetate. This hypothesis was supported by a further experiment in which pure **6** was left unaffected after heating in the presence of $CaCO_3$, $Pd(OAc)_2$, and PPh_3. The structure of **15** was corroborated by its spectroscopic data and by chemical derivatization. Indeed,

Scheme 2



i) $POCl_3$, pyridine, CH_2Cl_2. *ii*) Ac_2O, pyridine. *iii*) $CaCO_3$, $Pd(OAc)_2$, PPh_3, dioxane. *iv*) Bu_3SnH, $[PdCl_2(PPh_3)_2]$ (cat.), NH_4Cl, H_2O, THF. *v*) H_2, $Pd/BaCO_3$ (cat.), AcOEt.

hydrogenation of **15** with $Pd/BaCO_3$ as catalyst afforded saturated ether **16** as a mixture of four stereoisomers and a small amount of the known tetrahydroionone **17**, perhaps formed from **15** by opening of the seven-membered ring. Finally, the reduction of the conjugated C(7)=C(8) bond of **6** was accomplished by the same method as that used for the preparation of **5** from **4**, yielding 3,4-didehydro-7,8-dihydro-γ-ionone (**7**) from **6** in 91% yield.

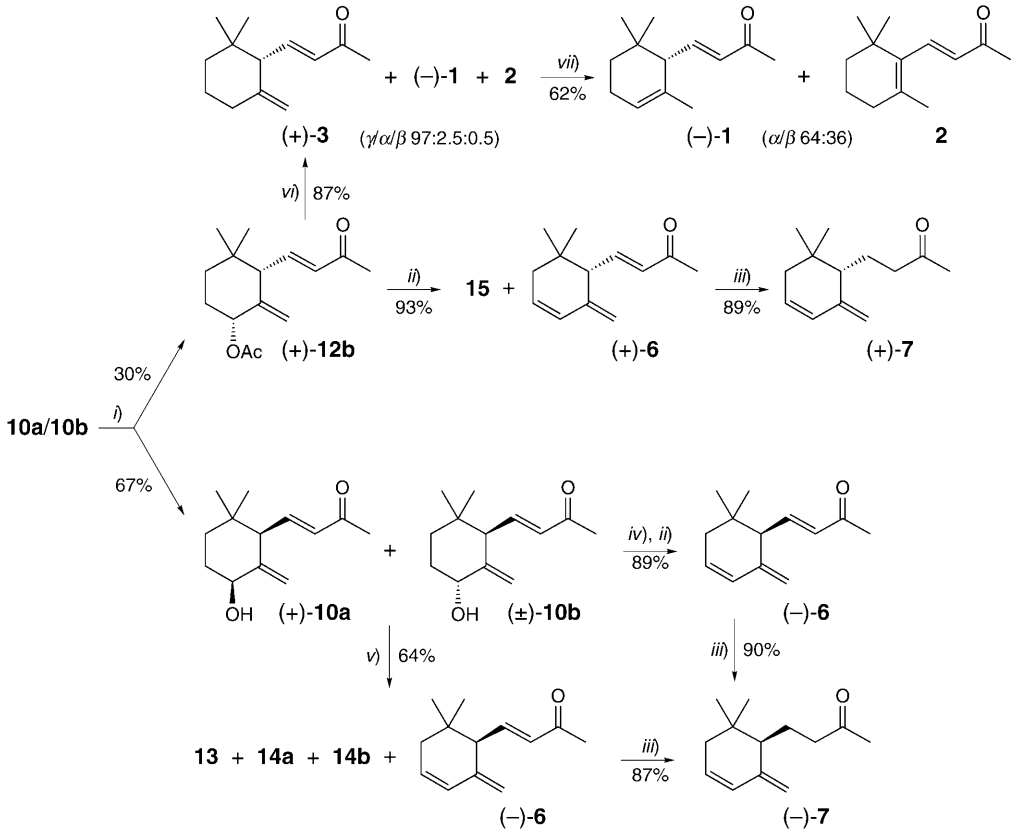
2.3. *Enantiomer-Enriched 3,4-Didehydro-γ-ionone Isomers (+)- and (−)-***6** *and (+)- and (−)-***7**. Taking advantage of the above-described study, we devised a method for the preparation of all the enantiomeric forms of 3,4-didehydro-γ-ionones **6** and **7**. Recently, we prepared the enantiomers of ionone [3] and irone [18] isomers through the enantioselective lipase-mediated resolution of the related ionols and irols. We now extended this enzymic procedure to the resolution of 4-hydroxy-γ-ionone (**10a**/**10b**). A preliminary experiment showed that acetylation of racemic **10a**/**10b** was efficiently catalyzed by lipase PS (*Pseudomonas cepacia*) with very high diastereoselectivity and good enantioselectivity. These results are noteworthy since the same enzyme catalyzes the acetylation of ionol and irol isomers with complete enantioselectivity and very low (or none) diastereoselectivity. Therefore, we treated racemic **10a**/**10b** with vinyl acetate in ^{t}BuOMe solution in presence of lipase PS and obtained diastereomerically and enantiomerically pure (99% ee and de) acetate (+)-**12b** and a mixture of enantiomer-enriched (+)-**10a** and racemic (±)-**10b** (*Scheme 3*). The acetylation was interrupted after *ca.* 30% of conversion since a longer reaction time and conversion near to 50% gave (+)-**12b** with lower ee although with very high de. The recovered mixture (+)-**10a**/(±)-**10b** was submitted again to enzymic acetylation to afford (+)-**12b** with lower ee and a mixture of alcohols which contained a higher amount of (±)-**10b** and (+)-**10a** with

increased optical purity. Hence, with the methods previously described, we used the latter set of enantiomerically enriched derivatives to prepare the enantiomers of **6** and **7**. Effectively, Pd-mediated elimination of the acetate group of enantiomerically pure (+)-**12b** gave the suitable (+)-**6**, which by C(7)=C(8) bond reduction, afforded (+)-**7**. In the same way, (+)-**10a**/(±)-**10b** was acetylated by Ac_2O and pyridine and then submitted to the above described reaction sequence. Since the elimination step proceeded without diastereoselectivity, (−)-**6** and (−)-**7** were obtained in low enantiomeric purity as the result of the relative ratio of racemic (±)-**10b** and of the optical purity of (+)-**10a**. On the other hand, the $POCl_3$-mediated elimination reaction showed a considerably diastereoselectivity. Noteworthy, samples of (+)-**10a**/(±)-**10b** with increasing ee and decreasing de gave samples of (−)-**6** with increasing ee. In that order, we also observed a change in the relative ratio of the chloro derivative by-products with improving of compound **13** and **14a**. This behavior was probably due to the relative stability of the allyl phosphate of (±)-**10b**. It is reasonable that the latter intermediate will rearrange to **13** and **14a** more easily than the phosphate of (+)-**10a**, hence rising the optical purity of (−)-**6**. Consequently, we used a sample of (+)-**10a**/(±)-**10b** with good ee and very low de in the latter elimination reaction to afford (−)-**6** and (−)-**7** in reasonable ee.

2.4. *Olfactory Evaluation of 3,4-Didehydroionone Isomers.* All the isomers synthesized as described above were submitted to olfactory evaluation (*Givaudan Schweiz AG, Fragrance Research*). The results are described in the *Table* and allow some remarkable considerations: *a*) all the isomeric forms show distinct olfactory features although between enantiomers, the differences are less evident. *b*) 3,4-didehydro-γ-ionone isomers are more powerful than 3,4-didehydro-7,8-dihydro-γ-ionone isomers. The (+)-**6**(*S*) is more than thousand times more powerful than (+)-**7**(*S*), whilst (−)-**6**(*R*) is about four hundred times more powerful than (−)-**7**(*R*). *c*) The 3,4-didehydro-7,8-dihydro-γ-ionone enantiomers show the same odor threshold, whereas 3,4-didehydro-γ-ionone enantiomers are of different intensity. (+)-**6**(*S*) is more than three time more powerful than (−)-**6**(*R*). Since (−)-**6**(*R*) was obtained with a moderate ee (70%), this difference may be more pronounced.

2.5. *Determination of the Absolute Configuration of the 3,4-Didehydro-γ-ionone Isomers.* As mentioned, the absolute configuration of the enantiomeric forms of **6** and **7** are not known. Therefore, we decided to assign these configurations by chemical correlation. Since we were able to determine accurately the ee of compound (+)-**12b**, we converted it to the γ-ionone **3** of known absolute configuration [5][11c]. The reductive removal of the acetyloxy function in the presence of the unsaturated ketone group was a challenging synthetic steps. We found that the Pd-catalyzed reduction of allylic acetate [19] by mean of triethylammonium formate as reducing agent was the procedure of choice for this transformation. Accordingly, treatment of enantiomerically pure (+)-**12b** with a catalytic quantity of $[PdCl_2(PPh_3)_2]$, and an excess of an equimolar amount of Et_3N and HCOOH under reflux in THF gave enantiomerically pure (+)-**3** (99% ee) in good yield (87%). GC and chiral GC analysis confirmed that the γ-isomer was formed regioselectively ($\gamma/\alpha/\beta$ isomer ratio 97 : 2.5 : 0.5) without detectable racemization. Judging from the measured optical rotation $[\alpha]_D^{20} = +25.2$ ($c = 2$, $CHCl_3$) (*vs.* $[\alpha]_D^{20} = +36.2$ ($c = 1$, $CHCl_3$) [5] for pure (*S*)-isomer (+)-**3**), the impurity, *i.e.*, the α-isomer should be optically active ($[\alpha]_D^{20} = -418$ ($c = 1$, $CHCl_3$) [11a] for pure (*S*)-α-ionone ((−)-**1**)). To confirm this assumption, we treated a sample of the γ,α,β mixture

Scheme 3



i) Vinyl acetate, *t*-BuOMe, lipase PS. *ii*) $CaCO_3$, $Pd(OAc)_2$, PPh_3, dioxane. *iii*) Bu_3SnH, $[PdCl_2(PPh_3)_2]$ (cat.), NH_4Cl, H_2O, THF. *iv*) Ac_2O, pyridine. *v*) $POCl_3$, pyridine, CH_2Cl_2. *vi*) HCO_2H, Et_3N, PPh_3, $[PdCl_2(PPh_3)_2]$ (cat.), THF, reflux. *vii*) 85% H_3PO_4.

(97:2.5:0.5) with H_3PO_4. By this means we achieved complete isomerization of the γ-isomer (+)-**3** to α- and β-ionone. The latter mixture, (–)-**1**/**2** (α/β isomer ratio 64:36) showed an optical rotation ($[\alpha]_D^{20} = -251.2$ ($c = 2$, $CHCl_3$), in good accord to that of enantiomerically pure α-ionone ((–)-**1**). In conclusion, the absolute configurations of (+)-**6** and (+)-**7**, and of (–)-**6** and (–)-**7** were assign unambiguously as (*S*) and (*R*), respectively.

3. Conclusions. – A new stereospecific approach to the isomeric forms of 3,4-didehydroionone isomers is described. The 3,4-didehydro-β-ionone isomers **4** and **5** and the 3,4-didehydro-γ-ionone isomers **6** and **7** were prepared starting from commercially available α-ionone (**1**) in a few regioselective steps. Enantiomer-enriched (+)-**6** and (+)-**7**, and (–)-**6**, and (–)-**7** were prepared by means of diastereoselective and enantioselective lipase-mediated acetylation of the racemic intermediate 4-hydroxy-γ-ionone **10a**/**10b** followed by a number of chemoselective and regioselective reactions. The

Table. *Olfactory Evaluation of 3,4-Didehydro-β- and γ-ionone Isomers*

Ionone isomer	Olfactory evaluation	Odor threshold [ng/l of air]
3,4-Didehydro-β-ionone (**4**)	ionone-damascone and saffron-like note, with fruity and slightly leathery aspects	
(*S*)-3,4-Didehydro-γ-ionone ((+)-**6**)	stronger than (−)-(*R*)-isomer on blotter, floral-woody, cetonal-like, slightly fruity, damasconic, sweet	0.080
(*R*)-3,4-Didehydro-γ-ionone ((−)-**6**)	weaker than (+)-(*S*)-isomer, fruity-floral, slightly woody	0.25
3,4-Didehydro-7,8-dihydro-β-ionone (**5**)	β-ionone-like, leathery, woody-floral	
(*S*)-3,4-Didehydro-7,8-dihydro-γ-ionone ((+)-**7**)	stronger on blotter than (−)-(*R*)-isomer, woody-powdery, ionone, slightly fruity-floral, more pronounced ionone character than (−)-(*R*)-isomer.	92
(*R*)-3,4-Didehydro-7,8-dihydro-γ-ionone ((−)-**7**)	weaker on blotter than (+)-(*S*)-isomer, fruity, agrestic, floral, ionone- and damascone-like, slightly woody, and saffron-like	99.4

reduction of acetate (+)-**12b** to (+)-(*S*)-γ-ionone ((+)-**3**) and the following isomerization to (−)-(*S*)-α-ionone ((−)-**1**) allowing to assign (*S*)-configuration to (+)-**6** and (+)-**7**. The latter process can also be seen as a new enantioselective path to enantiomerically pure (+)-(*S*)-γ-ionone ((+)-**3**. Moreover, the resolution step confirms the utility of the enzymatic approach to the preparation of enantiomer-enriched norterpenoid odorants. Olfactory evaluation of the above described 3,4-didehydroionone isomers shows a significant difference between the enantiomers and regioisomers both in fragrance feature and in detection threshold.

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Experimental Part

1. *General*. All moisture-sensitive reactions were carried out under a static atmosphere of N_2. All reagents were of commercial quality. Lipase PS from *Pseudomonas cepacia* (*Amano Pharmaceuticals Co.*, Japan; 30 U mg^{-1}) was employed in this work. TLC: *Merk* silica gel *60 F_{254}* plates. Column chromatography (CC): silica gel. Gas chromatography (GC): *HP-6890* gas chromatograph; *HP-5* column (30 m × 0.32 mm; *Hewlett Packard*) with the following temp. program; 60° (1 min) – 6°/min – 150° (1 min) – 12°/min – 280° (5 min); t_R in min. Chiral GC: *DANI-HT-86.10* gas chromatograph; enantiomer excesses determined on a *Chirasil-DEX-CB* column with the following temp. program; 60° (3 min) – 3°/min – 180° (5 min); t_R in min. M.p.: *Reichert* apparatus, equipped with a *Reichert* microscope; uncorrected. Optical rotations: *Jasco-DIP-181* digital polarimeter. IR Spectra: *Perkin-Elmer-2000-FT-IR* spectrometer; films; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: $CDCl_3$ solns. at r.t.; *Bruker-AC-400* spectrometer at 400 MHz; chemical shifts δ in ppm rel. to internal $SiMe_4$ (= 0 ppm), *J* values in Hz. Mass spectra: *Finnigan-Mat-TSQ-70* spectrometer; *m*/*z* (rel.%). Microanalyses were determined on an analyzer *1106* from *Carlo Erba*.

2. *3,4-Didehydro-β-ionone Isomers.* 2.1. *3,4-Didehydro-β-ionone* (**4**; *=(3*E*)-4-(2,6,6-Trimethylcyclohexa-1,3-dien-1-yl)but-3-en-2-one*). Epoxidation of racemic α-ionone (**1**) with *3*-chloroperbenzoic acid [12a] afforded *4,5-epoxy-4,5-dihydro-α-ionone* (**8a**/**8b** 5:1; 75%) (NMR analysis). According to [10a], **8a**/**8b** was treated with NaOMe in dry MeOH. The obtained crude 4-hydroxy-β-ionone was then treated with TsOH [8c] to afford pure **4** (72%; 96% pure by GC, t_R 16.7). IR, ^{1}H-NMR, MS: in accordance with those reported [9b].

2.2. *3,4-Didehydro-7,8-dihydro-β-ionone* (*=4-(2,6,6-Trimethylcyclohexa-1,3-dien-1-yl)butan-2-one*; **5**). Bu_3SnH (2.44 g, 8.4 mmol) was added dropwise to a stirred soln. of **4** (790 mg, 4.2 mmol), $[PdCl_2(PPh_3)_2]$ (140 mg, 0.2 mmol), NH_4Cl (500 mg, 9.4 mmol), and H_2O (0.2 ml, 11.2 mmol) in THF (50 ml) under N_2. After 3 h, Et_2O (150 ml) was added and the soln. was washed with brine (50 ml) and evaporated. The residue was dissolved in AcOEt (80 ml) and stirred with a sat. NaF soln. (25 ml) for 5 h. The precipitate formed was filtered and the filtrate evaporated. The residue was purified by CC (hexane/AcOEt 95:5) and bulb-to-bulb distillation: pure **5** (700 mg, 86%; 95% pure by GC, t_R 15.1). IR, ^{1}H-NMR, MS: in accordance with those reported [9b].

3. *Racemic 3,4-Didehydro-γ-ionone Isomers.* 3.1. cis/trans-*4-Hydroxy-γ-ionone* (*=(3*E*)-4-(*cis/trans-*5-Hydroxy-2,2-dimethyl-6-methylenecyclohexyl)but-3-en-2-one*; **10a**/**10b**). At −78°, 10M BuLi in hexane (55 ml) was added dropwise to $^iPr_2NH$ (58 g, 573 mol) in dry THF (300 ml) under N_2. The mixture was stirred at −78° for 30 min, then a soln. of **8a**/**8b** (52 g, 0.25 mol) in dry THF (60 ml) was added dropwise. The mixture was gradually warmed to r.t. (1 h) and then heated under reflux for 3 h (TLC monitoring). After cooling to r.t., the mixture was poured into a mixture of crushed ice and 5% HCl soln. (850 ml) and extracted with Et_2O (3×200 ml). The org. phase was successively washed with sat. aq. NH_4Cl soln. (100 ml) and brine, dried (Na_2SO_4), and evaporated. The residue was purified by CC (hexane/AcOEt 9:1 → hexane/AcOEt 1:1): **11** (3.1 g, 6%) followed by **10a**/**10b** (41.5 g, 80%).

Data of 1-(2,2-Dimethyl-8-methylene-6-oxabicyclo[3.2.1]oct-7-yl)propan-2-one (**11**): 98% pure by GC, t_R 15.4. Colorless oil. IR: 1716, 1366, 1159, 1059, 1013, 965, 892. ^{1}H-NMR: 4.97 (*s*, 1 H–C=C(8)); 4.78 (*s*, 1 H–C=C(8)); 4.58 (*t*, *J*=6.7, H–C(7)); 4.31 (*d*, *J*=4.5, H–C(5)); 2.69–2.60 (*dd*, *J*=16.1, 6.7, 1 H, CH_2COMe); 2.44–2.33 (*dd*, *J*=16.1, 6.7, 1 H, CH_2COMe); 2.14 (*s*, MeCO); 1.86 (*s*, H–C(1)); 1.81–1.73 (*m*, 1 H), 1.73–1.62 (*m*, 1 H), 1.60–1.49 (*m*, 1 H), 1.20 (*dd*, *J*=13.5, 5.5, 1 H) (CH_2(3) CH_2(4)); 1.03 (*s*, 1 Me–C(2)); 0.94 (*s*, 1 Me–C(2)). ^{13}C-NMR: 206.9; 149.2; 104.2; 77.7; 74.4; 57.8; 49.8; 35.3; 31.7; 31.4; 30.6; 28.3; 26.2. MS: 208 (1, M^+), 193 (5), 175 (2), 165 (6), 157 (1), 150 (30), 147 (10), 135 (20), 122 (10), 119 (9), 107 (36), 95 (20), 91 (18), 81 (18), 79 (19), 69 (13), 67 (11), 55 (17), 53 (12), 43 (100). Anal. calc. for $C_{13}H_{20}O_2$: C 74.96, H 9.68; found: C 75.05, H 9.70.

Data of **10a/10b**: 96% pure by GC, t_R 20.8 (**10a**) and t_R 20.5 (**10b**), deduced from the mixture. IR: 3428, 1672, 1626, 1366, 1253, 1131, 1069, 1047, 998, 902. ^{1}H-NMR: *cis* isomer **10a**: 6.93 (*dd*, *J*=15.8, 10.3, H–C(7)); 6.08 (*d*, *J*=15.8, H–C(8)); 5.17 (br. *s*, 1 H–C=C(5)); 4.69 (br. *s*, 1 H–C=C(5)); 4.10–4.02 (*m*, H–C(4)); 2.56 (*d*, *J*=10.3, H–C(6)); 2.28 (*s*, Me(10)); 2.01–1.92 (*m*, 1 H), 1.64–1.50 (*m*, 2 H), 1.49–1.39 (*m*, 1 H) (CH_2(2), CH_2(3)); 0.89 (*s*, 1 Me–C(1)); 0.88 (*s*, 1 Me–C(1)); *trans*-isomer **10b**: 6.89 (*dd*, *J*=15.8, 9.9, H–C(7)); 6.14 (*dd*, *J*=15.8, 0.6, H–C(8)); 5.08–5.06 (*m*, 1 H–C=C(5)); 4.72 (br. *s*, 1 H–C=C(5)); 4.32–4.26 (*m*, H–C(4)); 2.98 (*d*, *J*=9.9, H–C(6)); 2.26 (*s*, Me(10)); 1.91–1.81 (*m*, 1 H), 1.74–1.57 (*m*, 2 H), 1.49–1.39 (*m*, 1 H) (CH_2(2), CH_2(3)); 0.94 (*s*, 1 Me–C(1)); 0.88 (*s*, 1 Me–C(1)). MS: 208 (3, M^+), 193 (8), 190 (4), 175 (12), 165 (100), 157 (3), 150 (39), 147 (78), 135 (29), 122 (43), 109 (40), 107 (69), 105 (43), 95 (58), 91 (59), 81 (39), 79 (41), 69 (41), 67 (32), 55 (36). Anal. calc. for $C_{13}H_{20}O_2$: C 74.96, H 9.68; found: C 75.10, H 9.65.

cis-*4-[(4-Nitrobenzoyl)oxy]-γ-ionone* (*=(3*E*)-4-{*cis-*5-[4-Nitrobenzoyl)oxy]-2,2-dimethyl-6-methylenecyclohexyl)but-3-en-2-one*; **12a**). A sample of **10a**/**10b** (7 g, 33.6 mmol) in CH_2Cl_2 (30 ml) was treated with 4-nitrobenzoyl chloride (7.6 g, 41 mmol) and pyridine (20 ml). After workup, the crude product was purified by CC (hexane/AcOEt 8:2): **12a** (11 g, 92%). Two crystallizations from MeOH afforded crystalline **12a** (4.9 g, yield of recrystallizations 41%; up to 98% pure by NMR). M.p. 101–102°. IR: 1724, 1671, 1605, 1526, 1357, 1278, 1104, 990, 904, 722. ^{1}H-NMR: 8.34–8.24 (*m*, 4 arom. H); 6.97 (*dd*, *J*=15.6, 10.1, H–C(7)); 6.16 (*d*, *J*=15.6, H–C(8)); 5.54–5.46 (*m*, H–C(4)); 5.12 (*s*, 1 H–C=C(5)); 4.81 (*s*, 1 H–C=C(5)); 2.72 (*d*, *J*=10.1, H–C(6)); 2.23 (*s*, Me(10)); 2.12–2.01 (*m*, 1 H), 1.94–1.82 (*m*, 1 H), 1.79–1.69 (*m*, 1 H), 1.60–1.49 (*m*, 1 H) (CH_2(2), CH_2(3)); 0.96 (*s*, 2 Me–C(1)). ^{13}C-NMR: 197.4; 163.5; 150.6;

144.7; 144.7, 135.5; 132.6; 130.7; 123.5; 110.2; 75.1; 55.8; 36.1; 35.2; 28.9; 28.5; 27.8; 22.7. MS: 357 (18, M^+), 342 (10), 207 (30), 190 (69), 175 (19), 149 (36), 147 (100), 134 (36), 121 (17), 105 (11), 91 (5), 69 (3), 43 (11). Anal. calc. for $C_{20}H_{23}NO_5$: C 67.21, H 6.49; found: C 67.35, H 6.50.

Alkaline Hydrolysis of **12a**. A soln. of **12a** (1 g, 2.8 mmol) in MeOH (20 ml) was treated with NaOH (1 g, 18 mmol) under reflux for 1 h. After workup, the crude product was purified by CC (hexane/AcOEt 9:1 → hexane/AcOEt 1:1): **11** (350 mg, 60%) and *cis*-isomer **10a** (150 mg, 26%). IR, ^{1}H-NMR, MS: in accordance with those reported above.

3.2. *Pd-Mediated Elimination of* **10a**/**10b** via **12b** *to 3,4-Didehydro-γ-ionone* (*=(3*E*)-4-(2,2-Dimethyl-6-methylenecyclohex-4-en-1-yl)but-3-en-2-one*; **6**) *and 1,6,7,8-Tetrahydro-3,6,6-trimethyl-2-benzoxepine*; **15**). A sample of **10a**/**10b** (3 g, 14.4 mmol) was converted to the corresponding acetate by treatment with pyridine (20 ml) and Ac_2O (20 ml) at r.t. for 24 h. The crude **12b** was dissolved in dioxane (30 ml) and treated with $Pd(OAc)_2$ (50 mg, 0.2 mmol), $CaCO_3$ (2 g, 20 mmol), and PPh_3 (0.53 g, 2 mmol). The resulting heterogeneous mixture was stirred under reflux under N_2 for 4 h (TLC monitoring). Then, the mixture was cooled to r.t., diluted with Et_2O (100 ml), and filtered. The filtrate was washed successively with sat. aq. $NaHCO_3$ soln. (50 ml) and brine, dried (Na_2SO_4), and evaporated and the residue purified by CC (hexane → hexane/Et_2O 8:2). The first-eluted fractions afforded, after bulb-to-bulb distillation (oven temp. 95–100°/0.05 Torr), pure **15** (0.49 g, 18%; 99% pure by GC, t_R 16.4). The last-eluted fractions gave, after bulb-to-bulb distillation (oven temp. 100–105°/0.05 Torr), **6** (2.14 g, 78%; 98% pure by GC, t_R 15.3).

Data of **15**: Colorless oil. IR: 1648, 1626, 1589, 1446, 1394, 1361, 1331, 1214, 1196, 1054, 1029, 943, 848, 810. ^{1}H-NMR: 5.59 (br. *d*, *J*=8.6, H–C(5)); 5.56 (br. *t*, *J*=4.0, H–C(9)); 4.93 (*dd*, *J*=8.6, 0.7, H–C(4)); 4.41 (*d*, *J*=0.7, CH_2(1)); 2.25–2.18 (*m*, CH_2(8)); 1.87 (*s*, Me–C(3)); 1.53 (*t*, *J*=6.2, CH_2(7)); 1.04 (*s*, 2 Me–C(6)). ^{13}C-NMR: 158.6; 143.8; 133.8; 128.9; 116.3; 101.2; 74.4; 36.8; 34.2; 27.2; 27.2; 23.2; 21.6. MS: 191 (15, $[M+1]^+$), 190 (100, M^+), 175 (38), 157 (11), 147 (40), 134 (89), 119 (83), 117 (22), 115 (22), 105 (48), 91 (49), 79 (24), 77 (23), 65 (14), 55 (13), 43 (87). Anal. calc. for $C_{13}H_{18}O$: C 82.06, H 9.53; found: C 81.95, H 9.50.

Data of **6**: Colorless oil. IR: 1674, 1620, 1426, 1366, 1253, 990, 890, 733. ^{1}H-NMR: 6.70 (*dd*, *J*=15.8, 9.2, H–C(7)); 6.16 (*dt*, *J*=9.9, 1.8, H–C(4)); 6.09 (*d*, *J*=15.8, H–C(8)); 5.74 (*dt*, *J*=9.9, 3.6, H–C(3)); 4.95 (*s*, 1 H–C=C(5)); 4.80 (*s*, 1 H–C=C(5)); 2.72 (*d*, *J*=9.2, H–C(6)); 2.24 (*s*, Me(10)); 2.09–1.88 (*m*, CH_2(2)); 0.93 (*s*, 2 Me–C(1)). ^{13}C-NMR: 198.0; 147.0; 143.2; 132.2; 127.8; 127.5; 114.0; 54.8; 37.6; 33.1; 27.9; 26.9; 25.9. MS: 191 (1, $[M+1]^+$), 190 (8, M^+), 175 (9), 157 (8), 147 (32), 131 (20), 119 (19), 105 (48), 91 (42), 79 (16), 77 (21), 65 (15), 55 (15), 43 (100). Anal. calc. for $C_{13}H_{18}O$: C 82.06, H 9.53; found: C 82.15, H 9.50.

3.3. *Pd-Mediated Elimination of 4-Nitrobenzoate* **12a** *to* **6** *and* **15**. As described in *Exper. 3.2* with **12a** (1.1 g, 3.1 mmol), $Pd(AcO)_2$ (25 mg, 0.1 mmol), $CaCO_3$ (0.5 g, 5 mmol), and PPh_3 (0.26 g, 1 mmol): **15** (0.11 g, 19%; 98% pure by GC) and **6** (0.42 g, 71%; 97% pure by GC).

3.4. *$POCl_3$-Mediated Elimination of* **10a**/**10b** *to* **6** *and* **13**/**14a**/**14b**. A soln. of $POCl_3$ (2.6 ml, 27.9 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a cooled (0°) soln. of **10a**/**10b** (3 g, 14.4 mmol) in CH_2Cl_2 (20 ml) and pyridine (20 ml). The mixture was stirred for 3 h, then diluted with Et_2O (100 ml) and added to a mixture of crushed ice and sat. aq. $NaHCO_3$ soln. (50 ml). The org. phase was washed with brine, dried (Na_2SO_4), and evaporated and the residue purified by CC (hexane → hexane/Et_2O 8:2). The first-eluted fractions afforded, after bulb-to-bulb distillation **6** (0.74 g, 27%; 99% pure by GC). The last-eluted fractions gave **13**/**14a**/**14b** in a 2:1:1 (1.4 g, 43%; 98% pure by GC, t_R 19.7 (**13**), 19.5 (**14a**), and 19.1 (**14b**)). MS: 228 (2, $[M+2]^+$), 226 (9, M^+), 211 (1), 191 (12), 183 (13), 170 (12), 157 (6), 147 (36), 135 (88), 121 (100), 105 (15), 91 (65), 79 (12), 77 (14), 65 (9), 53 (6). Anal. calc. for $C_{13}H_{19}ClO$: C 68.86, H 8.45, Cl 15.64; found: C 69.00, H 8.50, Cl 15.60.

Data of 5-methyl-*Chloro-α-ionone* (*=(3*E*)-4-[2-(Chloromethyl)-6,6-dimethylcyclohex-2-enyl)but-3-en-2-one*; **13**): ^{1}H-NMR: 6.61 (*dd*, *J*=15.8, 9.6, H–C(7)); 6.11 (*d*, *J*=15.8, H–C(8)); 5.94 (br. *t*, *J*=3.7, H–C(4)); 3.95–3.87 (*m*, CH_2Cl); 2.74 (*d*, *J*=9.6, H–C(6)); 2.25 (*s*, Me(10)); 2.22–1.87 (*m*), 1.55–1.22 (*m*) (CH_2(2), CH_2(3)); 0.96 (*s*, 1 Me–C(1)); 0.91 (*s*, 1 Me–C(1)).

Data of cis-*4-Chloro-γ-ionone* (*=(3*E*)-4-(*cis-*5-Chloro-2,2,-dimethyl-6-methylenecyclohexyl)but-3-en-2-one*; **14a**): ^{1}H-NMR: 7.03 (*dd*, *J*=15.8, 10.3, H–C(7)); 6.07 (*d*, *J*=15.8, H–C(8)); 5.36 (*s*, 1 H–

C=C(5)); 4.85 (*s*, 1 H–C=C(5)); 4.48 (*dd*, *J*=8.9, 4.8, H–C(4)); 2.64 (*d*, *J*=10.3, H–C(6)); 2.28 (*s*, Me(10)); 2.22–1.87 (*m*), 1.74 (*ddd*, *J*=14.0, 6.5, 4.1, 1 H), 1.55–1.22 (*m*) (CH_2(2), CH_2(3)); 0.90 (*s*, 2 Me–C(1)).

Data of trans-*4-Chloro-γ-ionone* (=*(3*E*)-4-(*trans-*5-Chloro-2,2-dimethyl-6-methylenecyclohexyl)-but-3-en-2-one*; **14b**): ^{1}H-NMR: 6.81 (*dd*, *J*=15.8, 9.9, H–C(7)); 6.20 (*d*, *J*=15.8, H–C(8)); 5.16 (br. *s*, 1 H–C=C(5)); 4.77 (br. *t*, *J*=3.5, H–C(4)); 4.71 (br. *d*, *J*=1.5, 1 H–C=C(5)); 3.15 (*d*, *J*=9.9, H–C(6)); 2.27 (*s*, Me(10)); 2.22–1.87, 1.55–1.22 (2*m*, CH_2(2), CH_2(3)); 0.95 (*s*, 1 Me–C(1)); 0.86 (*s*, 1 Me–C(1)).

3.5. *3,4-Didehydro-7,8-dihydro-γ-ionone* (=*4-(6,6-Dimethyl-2-methylenecyclohex-3-en-1-yl)butan-2-one*; **7**). As described in *Exper. 2.2*, with **6** (0.9 g, 4.7 mmol), Bu_3SnH (2.75 g, 9.4 mmol), [$PdCl_2(PPh_3)_2$] (140 mg, 0.2 mmol), NH_4Cl (600 mg, 11.3 mmol), H_2O (0.2 ml, 11.2 mmol), and THF (50 ml). Bulb-to-bulb distillation (oven temp. 90–95°/0.02 Torr) gave **7** (0.82 g, 91%; 98% pure by GC, t_R 13.9). IR: 1719, 1638, 1599, 1430, 1364, 1273, 1161, 995, 884, 782. ^{1}H-NMR: 5.99 (*dd*, *J*=9.8, 2.0, H–C(4)); 5.67–5.61 (*m*, H–C(3)); 4.88 (*s*, 1 H–C=C(5)); 4.67 (*s*, 1 H–C=C(5)); 2.46 (*ddd*, *J*=17.2, 9.2, 5.4, 1 H–C(8)); 2.33 (*ddd*, *J*=17.2, 9.2, 6.6, 1 H–C(8)); 2.10 (*s*, Me(10)); 2.09 (br. *d*, *J*=17.5, H–C(6)); 1.89–1.79 (*m*, 1 H–C(7)); 1.77–1.67 (*m*, CH_2(2)); 1.31–1.18 (*m*, 1 H–C(7)); 1.00 (*s*, 1 Me–C(1)); 0.86 (*s*, 1 Me–C(1)). ^{13}C-NMR: 209.1; 145.4; 128.0; 126.9; 112.7; 50.9; 42.1; 36.2; 32.7; 29.9; 28.1; 27.5; 21.9. MS: 192 (1, M^+), 174 (6), 159 (24), 149 (1), 144 (1), 134 (61), 121 (33), 119 (100), 107 (21), 105 (19), 93 (12), 91 (30), 79 (12), 77 (13), 71 (4), 65 (5), 55 (5), 43 (31). Anal. calc. for $C_{13}H_{20}O$: C 81.20, H 10.48; found: C 81.15, H 10.50.

3.6. *Hydrogenation of* **15** *to Decahydro-3,6,6-trimethyl-2-benzoxepine* (**16**) *and Tetrahydroionone* (=*4-(2,2,6-trimethylcyclohexyl)butan-2-one*; **17**). A soln. of **15** (300 mg, 1.6 mmol) in AcOEt (50 ml) was treated with 5% Pd/$BaCO_3$ (70 mg) and hydrogenated at 1 atm. for 2 days. The catalyst was then filtered off and the filtrate evaporated. The residue was purified by CC (hexane → hexane/Et_2O 8:2): **16** (210 mg, 67%; 95% pure by GC (4 peaks); t_R 14.1, 14.2, 14.3, 14.5) followed by **17** as a 2:1 *cis*/*trans* mixture (25 mg, 8%; 93% pure by GC; t_R 15.1, 15.3) whose identity was confirmed by comparison with an authentic sample.

Data of **16**: IR: 1466, 1377, 1366, 1271, 1250, 1110. ^{1}H-NMR: 3.96–3.36 (*m*, 3 H); 1.90–1.20 (*m*, 12 H); 1.16–0.72 (*m*, 9 H). MS: 196 (9, M^+), 181 (71), 163 (38), 154 (24), 137 (34), 123 (23), 109 (100), 95 (49), 81 (58), 67 (45), 55 (30), 41 (33). Anal. calc. for $C_{13}H_{24}O$: C 79.53, H 12.32; found: C 79.40, H 12.30.

4. *Enantiomer-Enriched 3,4-Didehydroionone Isomers*. 4.1. *Lipase-Mediated Resolution of* cis/trans-*4-Hydroxy-γ-ionone* (**10a**/**10b**). A mixture of racemic **10a**/**10b** (*cis*/*trans* 4:1; 40 g, 192 mmol), lipase PS (15 g), vinyl acetate (45 ml), and ^{t}BuOMe (250 ml) was stirred at r.t. for 5 days. After filtration and evaporation of the filtrate, the residue was subjected to CC (hexane/AcOEt 8:2). The first-eluted fractions afforded *(+)-(4*R,*6*S*)-4-(acetyloxy)-γ-ionone* ((+)-**12b**; 14.6 g, 30%; 98% pure; 99% de (GC), t_R 20.8). Chiral GC: t_R 32.5; ee 99%. $[\alpha]_D^{20} = +22.8$ (c=3, $CHCl_3$). IR: 1742, 1698, 1674, 1629, 1367, 1239, 1174, 1038, 994, 905. ^{1}H-NMR: 6.92 (*dd*, *J*=15.8, 10.2, H–C(7)); 6.10 (*d*, *J*=15.6, H–C(8)); 5.25–5.14 (*m*, H–C(4)); 5.02 (*s*, 1 H–C=C(5)); 4.71 (*s*, 1 H–C=C(5)); 2.63 (*d*, *J*=10.2, H–C(6)); 2.28 (*s*, Me(10)); 2.11 (*s*, MeCOO); 1.99–1.82 (*m*, 1 H), 1.78–1.57 (*m*, 2 H), 1.56–1.38 (*m*, 1 H) (CH_2(2), CH_2(3)); 0.91 (*s*, 1 Me–C(1)); 0.89 (*s*, 1 Me–C(1)). ^{13}C-NMR: 197.4; 169.5; 145.1; 145.0; 132.6; 109.1; 73.3; 55.7; 36.4; 35.1; 28.9; 28.5; 27.2; 22.2; 20.9. MS: 250 (1, M^+), 235 (5), 208 (26), 190 (33), 175 (19), 165 (31), 157 (6), 149 (51), 147 (100), 134 (32), 121 (31), 105 (34), 91 (34), 79 (14), 69 (14), 55 (12). Anal. calc. for $C_{15}H_{22}O_3$: C 71.97, H 8.86; found: C 72.10, H 8.85.

The last-eluted fractions gave a mixture of *(+)-(4*S,*6*R*)-4-hydroxy-γ-ionone* ((+)-**10a**) and *(4*RS,*6*RS*)-4-hydroxy-γ-ionone* ((±)-**10b**) (26.9 g, 67%; 98% pure; 55% de (GC)). Chiral GC (corresponding acetate): t_R 32.65; ee 70%. $[\alpha]_D^{20} = +4.9$ (c=3, $CHCl_3$). IR, ^{1}H-NMR, MS: in accordance with that of racemic **10a**/**10b**.

Repeating the lipase mediated resolution with (+)-**10a**/(±)-**10b** (8 days of reaction) afforded further (+)-**12b** (6.6 g; 98% pure; 99% de (GC); ee 76% (chiral GC); $[\alpha]_D^{20} = +16.9$ (c=2, $CHCl_3$)) and a mixture of (+)-**10a** and (±)-**10b** (20.2 g; 98% pure; 35% de (GC); ee 79% (chiral GC (corresponding acetate); $[\alpha]_D^{20} = +5.8$ (c=3, $CHCl_3$).

4.2. *(+)-(6*S*)- and (−)-(6*R*)-3,4-Didehydro-γ-ionone* ((+)- and (−)-**6**, resp.) *by Pd-Mediated Elimination*. As described in *Exper. 3.2*, with (+)-**12b** (0.8 g, 3.2 mmol; 98% pure; 99% de (NMR), 99% ee

(chiral GC)) $Pd(AcO)_2$ (25 mg, 0.1 mmol), $CaCO_3$ (0.64 g, 6.4 mmol), and PPh_3 (0.26 g, 1 mmol): **15** (0.1 g, 16%; 98% pure by GC) and (+)-**6** (0.47 g, 77%; 97% pure by GC). (+)-**6**: $[\alpha]_D^{20} = +11.1$ ($c = 2$, $CHCl_3$). IR, ^{1}H-NMR, MS: in accordance with that of (±)-**6**.

The same method was applied to the elimination of (+)-**10a**/(±)-**10b** (0.66 g, 3.2 mmol; 97% pure by GC; 55% de (NMR); 79% ee (chiral GC)), after conversion to the corresponding acetate: **15** (0.11 g, 18%; 98% pure by GC) and (−)-**6** (0.43 g, 71%; 98% pure by GC). (−)-**6**: $[\alpha]_D^{20} = -3.4$ ($c = 2$, $CHCl_3$).

4.3. *(−)-3,4-Didehydro-γ-ionone* ((−)-**6**) *by $POCl_3$-Mediated Elimination*. As described in *Exper. 3.4*, with (+)-**10a**/(±)-**10b** (1.5 g, 7.2 mmol; 96% pure by GC; 55% de (GC); 79% ee (chiral GC)): (−)-**6** (0.33 g, 24%; 99% pure by GC); $[\alpha]_D^{20} = -5.7$ ($c = 2$, $CHCl_3$)) and **13**/**14a**/**14b** 2.5 : 1 : 1 (0.65 g, 40%; 98% pure by GC).

The same method was applied to a different sample of (+)-**10a**/(±)-**10b** (0.8 g, 3.8 mmol; 97% pure by GC); 25% de (NMR); 90% ee (chiral GC)); (−)-**6** (0.17 g, 23%; 98% pure by GC); $[\alpha]_D^{20} = -7.5$ ($c = 2$, $CHCl_3$)) and **13**/**14a**/**14b** 3 : 2 : 1 (0.43 g, 50%; 98% pure by GC).

4.4. *(+)-(6S)- and (−)-(6R)-3,4-Didehydro-7,8-dihydro-γ-ionone* ((+)- and (−)-**7**, resp.). As described in *Exper. 3.5*, with (+)-**6** (0.9 g, 4.7 mmol; 96% pure by GC; $[\alpha]_D^{20} = +11.1$ ($c = 2$, $CHCl_3$)): (+)-**7** (0.8 g, 89%; 97% pure by GC). $[\alpha]_D^{20} = +79.5$ ($c = 2$, $CHCl_3$). IR, ^{1}H-NMR, MS: in accordance with that of (±)-**7**.

The same method was applied to (−)-**6** (0.7 g, 3.7 mmol; 97% pure by GC; $[\alpha]_D^{20} = -7.5$ ($c = 2$, $CHCl_3$)): (−)-**7** (0.62 g, 87%; 97% pure by GC). $[\alpha]_D^{20} = -55.5$ ($c = 2$, $CHCl_3$). IR, ^{1}H-NMR, MS: in accordance with that of (±)-**7**.

5. *Conversion of Acetate (+)-***12b** *to (+)-(6S)-γ-Ionone* ((+)-**3**) *and (−)-(6S)-α-Ionone ((−)-***1**. 5.1. *Reduction of (+)-***12b**. A soln. of (+)-**12b** (1.6 g, 6.4 mmol; 98% pure by GC; 99% ee (chiral GC)), formic acid (0.6 g, 13 mmol), Et_3N (1.4 g, 13.8 mmol), $[PdCl_2(PPh_3)_2]$ (140 mg, 0.2 mmol), and PPh_3 (0.25 g, 0.9 mmol) in THF (30 ml) was refluxed under N_2 for 2 h (TLC monitoring). Then mixture was diluted with Et_2O (100 ml) and washed with H_2O (50 ml), 5% HCl soln. (50 ml), sat. aq. $NaHCO_3$ soln. (50 ml), and brine. The org. phase was dried (Na_2SO_4) and evaporated and the residue purified by CC (hexane/Et_2O 9 : 1) and bulb-to-bulb distillation: ionone mixture (+)-**3**/(−)-**1**/**2** (1.07 g, 87%; 98% pure; ratio $\gamma/\alpha/\beta$ 97 : 2.5 : 0.5; t_R 15.2 (γ), 15.1 (α), 16.3 (β)); $[\alpha]_D^{20} = +25.2$ (c = 2, $CHCl_3$); 99% ee for the γ isomer ((+)-**3**) (chiral GC [5]). (+)-**3**: IR, ^{1}H-NMR, MS: in accordance with that reported for enantiomerically pure (+)-(6*S*)-γ-ionone.

5.2. Isomerization of *(+)-(6S)-γ-Ionone* ((+)-**3**) *to (−)-(6S)-α-Ionone* ((−)-**1**). A sample of the above obtained (+)-**3** (0.4 g, 2.1 mmol; containing α- and β-*ionone*) was stirred in 85% H_3PO_4 soln. (2 ml) at r.t. for 2 h (GC monitoring). The mixture was then poured onto crushed ice and extracted with Et_2O (2 × 60 ml). The org. phase was washed with sat. aq. $NaHCO_3$ soln. (60 ml) and brine, dried (Na_2SO_4), and evaporated, and the residue purified by CC (hexane/Et_2O 9 : 1) and bulb-to-bulb distillation to give α/β-ionone ((−)-**1**/**2**; (0.25 g, 62%; 98% pure; α/β 64 : 36), $[\alpha]_D^{20} = -251.2$ ($c = 2$, $CHCl_3$).

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