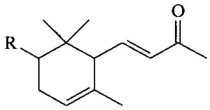
Synthesis and Olfactory Evaluation of (+)- and (−)-γ-Ionone

by **Claudio Fuganti**, **Stefano Serra***, and **Alessandro Zenoni**

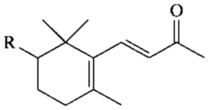
Dipartimento di Chimica del Politecnico, Centro CNR per la Chimica delle Sostanze Organiche Naturali, Via Mancinelli 7, I-20133 Milano

The synthesis of enantiomerically pure (+)- and (−)-γ-ionone **3** is reported. The first step in the synthesis is the diastereoisomeric enrichment of 4-nitrobenzoate derivatives of racemic γ-ionol **12**. The enantioselective lipase-mediated kinetic acetylation of γ-ionol **13b** afforded the acetate **14** and the alcohol **15**, which are suitable precursors of the desired products (−)- and (+)-**3**, respectively. The olfactory evaluation of the γ-ionone isomers shows a great difference between the two enantiomers both in fragrance response and in detection threshold. The selective reduction of (−)-**3** and (+)-**3** to the γ-dihydroionones (−)-(*R*)-**16** and (+)-(*S*)-**17**, respectively, allowed us to assign unambiguously the absolute configuration of the γ-ionones.

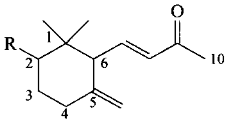
1. Introduction. – Ionones and irones are considered among the historically most important flavor and fragrance materials [1]. The distribution of these C_{13} and C_{14} norterpenoids, respectively, in Nature varies depending on the plant origin and also on the thermodynamic stability imparted by the substitution differences between ionones and irones. In particular, *cis*-γ-irone (**6**) is the main component of the *Iris* essential oil [2], where it is accompanied by the α-isomer **4** (*cis* > *trans*) and by minor quantities of the β-material **5**. On the other side, α- and β-ionone (**1** and **2**, resp.) have been found, usually as a mixture, in a number of plant materials [3]. Conversely, the natural occurrence of γ-ionone (**3**) is restricted to a Chinese rose oil [4]. Apart from this naturalistic curiosity, γ-ionone (**3**) and γ-irone (**6**) share the difficult accessibility by chemical synthesis, particularly in enantiomerically pure form [5][6]. In this context, the first preparation of partially enantiomerically enriched γ-ionone (**3**) goes back to the work of *Eugster*, *Ohloff*, and co-workers [7], designed to the stereochemical correlation of manool and ambrein with α- and ε-carotenes. These authors converted, by H_3PO_4 treatment, a sample of **3** showing $[\alpha]_D^{20} = -4.0$ ($CHCl_3$), obtained by partial resolution of the racemic material *via* crystallizations of the derivative with (−)-menthyl aminocarbamate, into (−)-α-ionone ($[\alpha]_D^{20} = -17$ (neat); -7.8 ($CHCl_3$)), of (*S*)-absolute configuration. By this correlation, the (*S*)-configuration is assigned to the enantiomer of **3** that shows a negative optical rotation. Subsequently, *Oritani* and *Yamashita* [6] revised this result, repeating the synthesis reported by *Ohloff* and *Mignat* [8] for racemic **3**, which provides from the acetate of 4′,5′-dihydro-5′-hydroxy-α-ionone, by thermal decomposition, a mixture of α- and γ-ionone (**1** and **3**, resp.). Indeed, starting from (+)-(*R*)-cyclogeranic acid ($[\alpha]_D^{20} = +320$ (EtOH)), they obtained a sample of γ-ionone (**3**), separated from the prevailing (+)-α-isomer **1**, possessing $[\alpha]_D^{21} = +241$ ($c = 2$, EtOH), by SiO_2 column chromatography in the presence of $AgNO_3$, showing $[\alpha]_D^{20} = -20$ ($c = 1.5$, $CHCl_3$) and -15.6 ($c = 1.6$, EtOH), respectively. Confirmatory evidence in favor of the stereochemical revision arose from the experiments performed on (−)-(*S*)-cyclogeranic acid, which led to (−)-(*S*)-*α*-ionone ($[\alpha]_D^{20} = -301$ ($c = 2$, EtOH)) and (+)-(*S*)-*γ*-ionone ($[\alpha]_D^{20} = +19.5$ ($c = 0.5$, EtOH)). Judging from the reported optical-rotation values, the enantiomeric purities of *α*-ionone (**1**)[1]) and of the accompanying *γ*-isomer **3**[2]) seem to be modest.



1 R=H
4 R=Me



2 R=H
5 R=Me



3 R=H
6 R=Me
(trivial numbering)

In light of these observations, it seemed of interest to have access to the enantiomerically pure forms of **3** through a procedure not necessarily involving the troublesome separation from the accompanying isomer **1**. Recently, we succeeded in the separation of the enantiomers of *α*-ionone (**1**) [9] and of *cis*- and *trans*-*α*-irone **4** [10] through the enantioselective lipase-mediated acetylation of the diastereoisomerically pure allylic alcohols obtained upon $NaBH_4$ reduction of the racemic ketones, followed by MnO_2 oxidation. The latter approach to enantiomerically pure forms of odorants that possess the ionane skeleton seems rather flexible, since it was applied with success also to the preparation of the enantiomers of the structurally similar synthetic odorant *Timberol*® [11].

Accordingly, we extended the acquired enzymic methodology to the preparation of the enantiomers of *γ*-ionone (**3**) starting from the racemic material, and we report here the results. The study first involved the synthesis of racemic **3**, followed by the enzymic resolution of the corresponding diastereoisomerically pure alcohols. Of the single enantiomers of **3** obtained by this method, it is here also reported the olfactory evaluation, kindly provided by *Givaudan-Roure*. Moreover, the selective reduction of (−)- and (+)-*γ*-ionone gave the enantiomerically pure (−)-**16** and (+)-*γ*-dihydroionone **17**, respectively (*cf. Scheme 2*). Since our synthesis afforded these two compounds of known absolute configuration without formation of *α*- and/or *β*-isomers, the absolute configuration of the *γ*-ionones was assigned unambiguously.

2. Results. – 2.1. *Synthesis of Racemic γ-Ionone.* The preparation of enantiomerically pure (+)-**3** and (−)-**3** by our synthetic method required the availability of racemic *γ*-ionone. In addition, for the chemical and olfactory characterization of the title compounds, we needed a starting material without the presence of the accompanying *α*- and/or *β*-isomers. Many different approaches to *γ*-ionone are described in the literature. The most straightforward ones afforded the *γ*-ionone starting from a suitable and easily available C_{13} precursor, but, unfortunately, the mixture of the isomers [8] [12] was invariably obtained. The same difficulties were encountered in the preparation of the related *γ*-irones. In consideration of the solution adopted in this latter case [5b] [13], the construction of the *γ*-ionone framework by condensation of *γ*-

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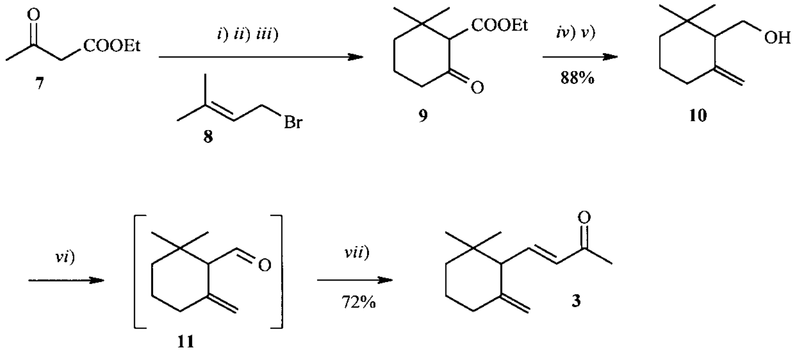
[1]) For optically pure **1**, $[\alpha]_D^{20} = +422$ ($c = 1$, $CHCl_3$), see [9a].

[2]) In this work, we found $[\alpha]_D^{20} = +30.2$ ($c = 0.5$, EtOH) for a sample of (+)-**3** showing 98% ee (chiral GC).

cyclocitral with (acetylmethylidene)triphenylphosphorane seems to be the most promising approach. The required aldehyde **11** was prepared combining some procedures reported in the literature. *Scheme 1* shows in detail our synthetic path to the monocyclic building block **11**. Alkylation of the dianion of ethyl acetoacetate (**7**) with dimethylallyl bromide (**8**), followed by cyclization with $SnCl_4$ afforded the β-keto ester (**9**)[3]) [14a], which was converted to the γ-cyclogeraniol (**10**)[4]) on *Wittig* methylenation[5]) of the ketone function, followed by $LiAlH_4$ reduction of the ester group. The *Swern* oxidation of the obtained alcohol **10** afforded pure γ-cyclocitral[6]) without isomerization of the exocyclic C=C bond. This latter compound was not purified but used directly for the synthesis of **3**. *Wittig* reaction of crude **11** with (acetylmethylidene)triphenylphosphorane in refluxing toluene gave racemic **3** and a small amount of isomerized β-cyclocitral. It is noteworthy that the γ-ionone is the exclusive condensation product, though β-cyclocitral was formed under these reaction conditions.

Scheme 1



i) THF, 1 equiv. NaH. *ii*) 1 Equiv. BuLi, then **8**. *iii*) $SnCl_4$, CH_2Cl_2. *iv*) Ph_3PCH_2, THF, reflux. *v*) $LiAlH_4$, THF. *vi*) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2. *vii*) $Ph_3PCHCOMe$, toluene, reflux.

2.2. *Enzymic Resolution of the Racemic γ-Ionone.* As in the case of α- and β-ionone, the $NaBH_4$ reduction of racemic **3** afforded **12** (*Scheme 2*) as a 1:1 mixture of two racemic diastereoisomers, inseparable by the usual chromatographic procedures. Moreover a preliminary enzymic esterification experiment on racemic **12**, in the presence of lipase *PS* (*Pseudomonas cepacia*), with vinyl acetate in *t*-BuOMe solution, provided a 1:1 mixture of enantiomerically pure acetate (GC analysis, second and fourth peaks). These observations show that the isomeric ionols display the same behavior toward the enzymic esterification. Since our resolution method is based on the enantioselective enzyme-mediated acetylation of the diastereisomerically pure allylic alcohols, we converted **12** to its *p*-nitrobenzoate derivative in order to separate the diastereoisomeric esters by fractional crystallization. Three crystallizations of the

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[3]) For an alternative synthesis of keto ester **9**, see [14b].

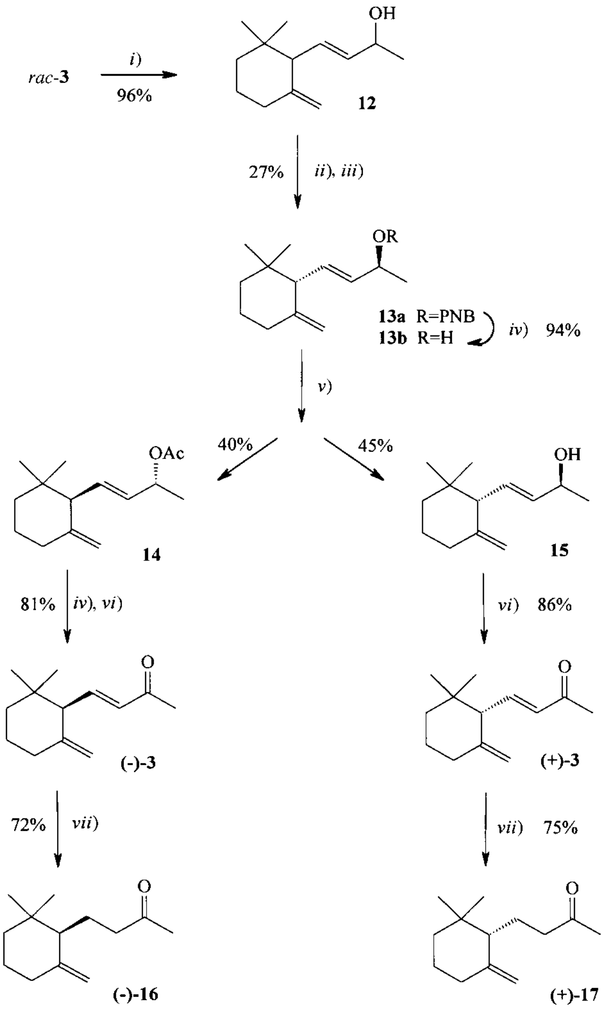
[4]) For optically pure **10**, see [15a,b].

[5]) For a similar *Wittig* reaction on the methyl ester of **9**, see [15a].

[6]) For optically pure **11**, see [15b].

mixture from hexane afforded **13a** (27% overall yield, 98% de), which was hydrolyzed with methanolic KOH to diastereomerically pure **13b**. This latter was treated with vinyl acetate in *t*-BuOMe solution in the presence of lipase *PS* (*Amano*) to afford acetate **14** and unreacted alcohol **15**. The acetate **14** was then hydrolyzed with methanolic KOH, and the derived alcohol was oxidized with MnO_2 in refluxing $CHCl_3$ to give enantiomerically pure (−)-γ-ionone **3**. Similarly, the oxidation of the alcohol **13** afforded enantiomerically pure (+)-γ-ionone **3**.

Scheme 2



i) $NaBH_4$, MeOH. *ii*) 4-Nitrobenzoyl chloride (PNB-Cl), pyridine, CH_2Cl_2. *iii*) Three crystallizations from hexane. *iv*) KOH, MeOH. *v*) Vinyl acetate, *t*-BuOMe, lipase *PS*. *vi*) MnO_2, $CHCl_3$, reflux. *vii*) Bu_3SnH, $(Ph_3P)_2PdCl_2$, THF.

2.3. *Olfactory Evaluation of (+)- and (−)-γ-Ionone.* The olfactory evaluation of (+)- and (−)-γ-ionone **3** was performed together with that of (+)- and (−)-α-ionone **1**[7] (*Givaudan-Roure Research Ltd.*, Dübendorf, Switzerland). The results are described in the *Table* and suggest some interesting considerations: *a*) (+)- and (−)-γ-ionone **3** show very different olfactory features, and the (+)-(*S*)-γ-ionone is the most pleasant and powerful of the ionone isomers. *b*) The two isomeric α-ionones show similar odor description and the olfactory threshold is almost the same. Otherwise, (+)-γ-ionone is *ca.* 150 time more powerful than the (−)-isomer.

Table. *Olfactory Evaluation of α- and γ-Ionone Isomers*

Ionone isomer	Olfactory evaluation	Odor threshold [ng/l of air]
(+)-(*R*)-α	Linear woody, floral odor, with an additional honey aspect. Its odor remains linear within 10 h, but is weaker than that of the (*S*)-isomer.	3.2
(+)-(*S*)-γ	Linear, very pleasant, floral, green, woody odor with a very natural violet tonality. On the blotter, it is the most powerful and pleasant of the isomers. After 10 h, slightly earthy nuances are also detectable in the scent.	0.07
(−)-(*S*)-α	Floral, woody, with an additional honey aspect. More powerful than the (*R*)-isomer, though, after 10 h on blotter, the odors of both isomers are quite similar.	2.7
(−)-(*R*)-γ	Weak green, fruity, pineapple-like odor with metallic aspects, quite different from the typical ionone odor. It is, however, also slightly woody, ionone-type. With the time this woody-ionone tonality comes more and more to the fore, but fruity aspects remain present, even after 10 h.	10.8

2.4. *Correlation of (+)- and (−)-γ-Ionone with (+)- and (−)-γ-Dihydroionone.* As mentioned in the *Introduction*, the absolute configuration of (+)- and (−)-**3** was first assigned by *Eugster*, *Ohloff*, and co-workers [7], and then corrected by *Oritani* and *Yamashita* [6]. Moreover, in the light of our results, the optical-rotation values obtained by the latter authors are modest. Though the sense and the amplitude of the chiroptical properties reported by *Oritani* and *Yamashita* seem to be sufficient to determine the absolute configuration of γ-ionone, we decided to verify this assignment with our enantiomerically pure (+)- and (−)-γ-ionone free of any α- and/or β-isomers. Consequently, we decided to reduce (+)-**3** and (−)-**3** to the related dihydroionones **16** and **17**, respectively, of known absolute configuration [17]. A preliminary hydrogenation experiment, performed with *Raney*-Ni as catalyst, was unsatisfactory for our purpose. In effect, partial isomerization of the double bond occurred, and a small amount (< 10%) of the α-dihydroionone was formed. To develop a regiospecific path to γ-dihydroionone, we used a radical reduction method that was previously employed [18] in the reduction of dehydroionones. Accordingly, we found that Bu_3SnH and catalytic amounts of $(Ph_3P)_2PdCl_2$ converted the (−)-γ-ionone and the (+)-γ-ionone to the enantiomerically pure (−)-γ-dihydroionone ((−)-**16**) and (+)-γ-dihydroionone

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[7] For earlier evaluation of (+)- and (−)-α-ionone, see [16]. For a pronounced aptitude to perceive either one or the other enantiomer of α-ionone, see [16d].

((+)-**17**), respectively, without isomerization of the C=C bond. The measured optical rotation values ($[\alpha]_D^{20} = -19.8$ ($c = 1.3$, $CHCl_3$) and $[\alpha]_D^{20} = +19.4$ ($c = 1.2$, $CHCl_3$), resp.) are in good agreement with those reported for the natural [17] (+)-(*S*)-γ-dihydroionone ($[\alpha]_D^{20} = +20.9$ ($c = 10.4$, $CHCl_3$)). In conclusion, the absolute configurations of the (+)-γ-ionone and (−)-γ-ionone were assigned unambiguously as (*S*) and (*R*), respectively.

3. Conclusion. – The preparation of enantiomerically pure (+)- and (−)-γ-ionone was achieved by the lipase-mediated kinetic resolution of allylic alcohol **13b**. This synthetic path was an extension of a previously developed method that shows great versatility. However, the high-quality results obtained in terms of chemical and enantiomeric purity of the products are superior to those previously reported for the synthesis of (+)- and (−)-γ-ionone. These results allowed the olfactory evaluation of the γ-ionone isomers and a strict confirmation of their absolute configuration by conversion in the related γ-dihydroionone isomers.

The authors would like to thank Dr. *Philip Kraft*, *Givaudan-Roure Research Ltd.*, Dübendorf, Switzerland, for his kind co-operation. We gratefully acknowledge *Caroline Denis*, for the olfactory descriptions and *Heinz Koch* for the threshold determinations. We thank *MURST* for partial financial support.

Experimental Part

1. *General.* Lipase *PS Pseudomonas cepacia* (*Amano Pharmaceuticals Co.*, Japan) was employed. TLC: *Merck* silica gel *60 F₂₅₄* plates. Column chromatography (CC): silica gel. GC: *DANI-HT-86.10* gas chromatography; ee and de values were determined on a *Chirasil DEX CB* column (25 m × 0.25 mm; *Chrompack*) with the following temp. program 70° (3 min) – 3.5°/min – 140° – 8°/min – 180° (2 min); analysis of γ-ionol acetates: t_R 19.05, 19.19, 19.26, 19.72; analysis of γ-ionones: t_R 17.10, 17.41; analysis of γ-dihydroionones: t_R 16.32, 16.59; t_R in min. 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-250* spectrometer at 250 MHz (^1H); chemical shifts (δ) in ppm rel. to internal Me_4Si (=0 ppm), *J* values in Hz. MS: *Finnigan-Mat TSQ 70* spectrometer; *m*/*z* (rel.%). Microanalyses: analyzer *1106* from *Carlo Erba*.

2. *(±)-γ-Cyclogeraniol* ((±)-**10**). BuLi (30.1 ml of a 10M soln. in hexane) was added dropwise to a cooled (−78°) suspension of $Ph_3P^+MeBr^-$ (110 g, 0.307 mol) in dry THF (300 ml). The resulting mixture was warmed to r.t. and stirred at this temp. until the phosphonium salt disappeared almost completely. The keto ester **9** (50 g, 0.252 mol) was added to the resulting soln. of ylide and the mixture was heated at reflux for 2 h. After cooling, the mixture was poured into H_2O and extracted with Et_2O. The org. phase was successively washed with sat. NH_4Cl soln. and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in hexane, and the triphenylphosphine oxide was eliminated by crystallization (ice-bath cooling). The liquid phase was diluted with dry THF (300 ml), was cooled (0°), and $LiAlH_4$ (9 g, 0.237 mol) was added under stirring. After reduction of the ester, workup afforded the crude product. Purification by distillation under reduced pressure (b.p. 95°/10 mm) gave (±)-**10** (34 g, 0.221 mol; 88%); 97% chemical purity (GC). IR: 3371, 2932, 1648, 1441, 1029, 889. ^1H-NMR: 4.96 (*m*, H−CH=C(5)); 4.76 (*m*, H−CH=C(5)); 3.76–3.67 (*dd*, *J* = 10.4, 4.9, H−C(7)); 3.62 (*t*, *J* = 10.4, H−C(7)); 2.18–2.08 (*m*, CH_2(4)); 2.08–2.00 (*dd*, *J* = 10.9, 4.9, H−C(6)); 1.64–1.20 (*m*, CH_2(2), CH_2(3)); 1.49 (*s*, OH); 0.95 (*s*, Me−C(1)); 0.87 (*s*, Me−C(1)). MS: 154 (1, M^+), 136 (36), 123 (49), 121 (64), 109 (51), 93 (94), 81 (70), 69 (100), 55 (31), 41 (53). Anal. calc. for $C_{10}H_{18}O$: C 77.87, H 11.76; found: C 77.95, H 11.70.

3. *(±)-γ-Ionone* ((±)-**3**). DMSO (25 g, 0.320 mol) was added dropwise to a cooled soln. (−78°) of ClCOCOCl (21 g, 0.165 mol) in CH_2Cl_2 (200 ml). Alcohol **10** (20 g, 0.130 mol) was then added, and the mixture was stirred for 15 min at the same temp. The resulting suspension was treated with Et_3N (50 g, 0.494 mol), and the mixture was allowed to warm to r.t. After 2 h, the mixture was diluted with CH_2Cl_2 and washed with H_2O. The org. phase was dried (Na_2SO_4), and the solvent was evaporated. The obtained crude γ-cyclocitral (92% chemical purity (GC)) was dissolved in toluene (150 ml) and treated with (acetylmethylidene)triphenylphosphorane (50 g, 0.157 mol) under reflux for 8 h. After cooling, hexane was added to the mixture, and the Ph_3PO

was eliminated by crystallization (ice-bath cooling). The liquid phase was concentrated under reduced pressure and submitted to CC (hexane/AcOEt 9.1). The eluted fractions provided β-cyclocitral (2.5 g, 16 mmol) and γ-ionone, which was then further purified by distillation under reduced pressure to give pure (±)-**3** (18.1 g, 94 mmol; 72%; 98% chemical purity (GC)). IR: 2932, 1675, 1364, 1254, 990, 895. ^{1}H-NMR: 6.93 (*dd*, *J* = 15.7, 10.1, H−C(7)); 6.08 (*d*, *J* = 15.7, H−C(8)); 4.78 (*s*, H−CH=C(5)); 4.53 (*s*, H−CH=C(5)); 2.57 (*d*, *J* = 10.1, H−C(6)); 2.33 – 2.18 (*m*, H−C(4)); 2.26 (*s*, Me(10)); 2.13 – 1.97 (*m*, H−C(4)); 1.67 – 1.26 (*m*, $CH_2(3)$, $CH_2(2)$); 0.89 (*s*, Me−C(1)); 0.85 (*s*, Me−C(1)). ^{13}C-NMR: 198.3; 148.4; 147.2; 132.7; 109.6; 57.6; 38.6; 35.6; 34.1; 29.2; 27.3; 23.9; 23.1. MS: 192 (10, *M*$^+$), 177 (31), 164 (13), 159 (14), 149 (100), 135 (13), 121 (70), 109 (54), 91 (27), 81 (49), 69 (48), 43 (57). Anal. calc. for $C_{13}H_{20}O$: C 81.20, H 10.48; found: C 81.25, H 10.50.

(±)-γ-Ionol ((±)-**12**). $NaBH_4$ (2.5 g, 66 mmol) reduction of racemic **3** (20 g, 104.2 mmol) in MeOH (100 ml) afforded, after purification by CC (hexane/AcOEt 8 : 2), **12** (19.5 g, 100.5 mmol, 96%) as a 1 : 1 mixture of two racemic diastereoisomers; 97% chemical purity (GC). Chiral GC (corresponding acetates): t_R 19.05, 19.19, 19.26, 19.72.

Fractional Crystallization of the 4-Nitrobenzoates of (±)-**12** (4 stereoisomers). The ionol **12** (16 g, 82.5 mmol) in CH_2Cl_2 was treated with 4-nitrobenzoyl chloride (18.2 g, 98 mmol) and pyridine (20 ml). After workup, the crude product was purified by CC (hexane/AcOEt 9 : 1) to give a racemic mixture of 4-nitrobenzoates (25.9 g, 75.5 mmol; 91%). Three crystallizations from hexane afforded the crystalline racemic 4-nitrobenzoate **13a** (7.9 g, yield of recrystallizations 30%). M.p. 74°. GC (corresponding acetates): t_R 19.05, 19.19; de 98%. IR: 3418, 2927, 1717, 1524, 1338, 1277, 1104, 1037, 717. ^{1}H-NMR: 8.34 – 8.15 (*m*, 4 arom. H); 6.02 – 5.90 (*dd*, *J* = 14.7, 9.4, H−C(7)); 5.71 – 5.51 (*m*, H−C(8), H−C(9)); 4.75 (*s*, H−CH=C(5)); 4.53 (*s*, H−CH=C(5)); 2.43 (*d*, *J* = 9.4, H−C(6)); 2.34 – 2.21 (*dt*, *J* = 13.5, 5.2, H−C(4)); 2.10 – 1.95 (*m*, H−C(4)); 1.63 – 1.24 (*m*, $CH_2(3)$, $CH_2(2)$); 1.49 (*d*, *J* = 6, Me(10)); 0.86 (*s*, Me−C(1)); 0.79 (*s*, Me−C(1)). MS: 343 (3, *M*$^+$), 300 (22), 270 (3), 216 (6), 193 (19), 176 (40), 161 (41), 150 (100), 133 (37), 120 (83), 105 (51), 91 (63), 79 (34), 69 (74). Anal. calc. for $C_{20}H_{25}NO_4$: C 69.95, H 7.34, N 4.08; found: C 70.05, H 7.38, N 4.15.

*(±)-(6*RS*,9*RS*)-γ-Ionol* ((±)-**13b**). The crystalline 4-nitrobenzoate **13a** (7.7 g, 22.5 mmol) was treated with KOH (3 g, 53.5 mmol) in MeOH (60 ml) under reflux for 2 h. After the usual workup, the alcohol obtained was purified by CC (hexane/AcOEt 8 : 2) to afford (±)-**13b** (4.1 g, 21.1 mmol; 94%). GC (corresponding acetates): t_R 19.05, 19.19; de 98%. IR: 3341, 2930, 1643, 1366, 1060, 980, 890. ^{1}H-NMR: 5.81 – 5.72 (*dd*, *J* = 15.3, 9.4, H−C(7)); 5.58 – 5.50 (*dd*, *J* = 15.3, 6.3, H−C(8)); 4.72 (*s*, H−CH=C(5)); 4.53 (*s*, H−CH=C(5)); 4.32 (*quint.*, *J* = 6.3, H−C(9)); 2.41 (*d*, *J* = 9.4, H−C(6)); 2.30 – 2.22 (*dt*, *J* = 13.4, 5.4, H−C(4)); 2.07 – 1.98 (*m*, H−C(4)); 1.65 – 1.43 (*m*, 3 H); 1.46 (*s*, OH); 1.36 – 1.26 (*m*, 1 H); 1.27 (*d*, *J* = 6.4, Me(10)); 0.9 (*s*, Me−C(1)); 0.81 (*s*, Me−C(1)). ^{13}C-NMR: 203.8; 190.1; 182.9; 161.9; 130.9; 130.6; 130.3; 122.5; 110.8; 92.7; 88.8; 88.2; 83.1. MS: 194 (1, *M*$^+$), 176 (17), 161 (35), 136 (100), 121 (87), 109 (60), 93 (65), 79 (44), 69 (72), 55 (25), 43 (78). Anal. calc. for $C_{13}H_{22}O$: C 80.35, H 11.41; found: C 80.43, H 11.48.

*Enzymic Acetylation of (±)-***13b**. A mixture of (±)-**13b** (4 g, 20.6 mmol; de 99%), lipase *PS* (*Pseudomonas cepacia*; 4 g), and vinyl acetate (20 ml) in *t*-BuOMe (100 ml) was stirred at r.t. for 72 h. After filtration and evaporation of the filtrate, the residue was chromatographed (hexane/AcOEt 9 : 1). The first-eluted fractions afforded *(6*R*,9*R*)-γ-ionol acetate* (**14**; 1.95 g, 8.3 mmol; 40%; 97% chemical purity (GC)). Chiral GC: t_R 19.19; ee 99%. $[\alpha]^{20}_{D} = +77.3$ ($c = 2$, $CHCl_3$). IR: 2932, 1739, 1369, 1241, 1044, 890. ^{1}H-NMR: 5.88 – 5.76 (*dd*, *J* = 14.5, 9.7, H−C(7)); 5.51 – 5.29 (*m*, H−C(8), H−C(9)); 4.73 (*s*, H−CH=C(5)); 4.51 (*s*, H−CH=C(5)); 2.39 (*d*, *J* = 9.7, H−C(6)); 2.32 – 2.20 (*dt*, *J* = 13.9, 5.2, H−C(4)); 2.11 – 1.94 (*m*, H−C(4)); 2.04 (*s*, MeCOO); 1.68 – 1.24 (*m*, $CH_2(3)$, $CH_2(2)$); 1.31 (*d*, *J* = 6.6, Me(10)); 0.87 (*s*, Me−C(1)); 0.79 (*s*, Me−C(1)). MS: 236 (2, *M*$^+$), 203 (3), 193 (21), 176 (56), 161 (63), 133 (50), 119 (35), 105 (85), 91 (100), 79 (65), 69 (64), 55 (23), 43 (86). Anal. calc. for $C_{15}H_{24}O_2$: C 76.23, H 10.24; found: C 76.35, H 10.16.

The last-eluted fractions gave *(6*S*,9*S*)-γ-ionol* (**15**; 1.8 g, 9.3 mmol; 45%; 96% chemical purity (GC)). Chiral GC (corresponding acetate): t_R 19.05; ee 95%. $[\alpha]^{20}_{D} = +2.2$ ($c = 2$, $CHCl_3$). IR, ^{1}H-NMR, MS: in accordance with those of (±)-**13b**. Anal. calc. for $C_{13}H_{22}O$: C 80.35, H 11.41; found: C 80.30, H 11.45.

(−)-γ-Ionone ((−)-**3**). A sample of **14** (1 g, 4.2 mmol) was hydrolyzed with KOH (1 g, 18 mmol) in MeOH (30 ml). The crude ionol obtained was then oxidized with MnO_2 (2 g, 23 mmol) in $CHCl_3$ (50 ml) under reflux for 4 h. After filtration and evaporation of the filtrate, the residue was chromatographed (hexane/AcOEt 9 : 1). Bulb-to-bulb distillation of the product afforded pure (−)-**3** (650 mg, 3.4 mmol; 81%; 98% chemical purity (GC)). Chiral GC: t_R 17.10; ee 99%. $[\alpha]^{20}_{D} = -37.4$ ($c = 1$, $CHCl_3$), $[\alpha]^{20}_{D} = -30.9$ ($c = 0.5$, EtOH). IR, ^{1}H-NMR, ^{13}C-NMR, MS: in accordance with those of (±)-**3**. Anal. calc. for $C_{13}H_{20}O$: C 81.20, H 10.48; found: C 81.25, H 10.50.

(+)-γ-Ionone ((+)-**3**). A sample of **15** (1 g, 5.1 mmol) was oxidized with MnO_2 (3 g, 34 mmol) in $CHCl_3$ (50 ml) under reflux for 4 h. After filtration and evaporation of the filtrate, the residue was chromatographed

(hexane/AcOEt 9 : 1). Bulb-to-bulb distillation of the product afforded pure (+)-**3** (850 mg, 4.4 mmol; 86%; 98% chemical purity (GC)). Chiral GC: t_R 17.41; ee 98%. $[\alpha]_D^{20} = +36.2$ ($c = 1$, $CHCl_3$), $[\alpha]_D^{20} = +30.2$ ($c = 0.5$, EtOH). IR, ^{1}H-NMR, ^{13}C-NMR, MS: in accordance with those of (±)-**3**. Anal. calc. for $C_{13}H_{20}O$: C 81.20, H 10.48; found: C 81.28, H 10.45.

(−)-γ-Dihydroionone ((−)-**16**). Bu_3SnH (1.22 g, 4.2 mmol) was added dropwise to a stirred soln. of (−)-**3** (400 mg, 2.1 mmol), $(Ph_3P)_2PdCl_2$ (70 mg, 0.1 mmol), NH_4Cl (250 mg, 4.7 mmol), and H_2O (0.1 ml, 5.6 mmol) in 20 ml of THF under N_2. After 3 h, Et_2O (60 ml) was added, and the soln. was washed with brine and then concentrated *in vacuo*. The residue was dissolved in AcOEt (40 ml) and stirred with a sat. soln. of NaF (10 ml) for 5 h. The precipitate formed was filtered, and the org. phase was separated and evaporated. The residue was chromatographed (hexane/AcOEt 95 : 5) on an alumina column (activity grade 1). Bulb-to-bulb distillation of the product afforded pure (−)-**16** (295 mg, 1.5 mmol; 72% yield; 95% chemical purity (GC)). Chiral GC: t_R 16.31; ee 99%. $[\alpha]_D^{20} = -19.8$ ($c = 1.3$, $CHCl_3$). IR: 2934, 2868, 1717, 1645, 1363, 1162, 890, 757. ^{1}H-NMR: 4.77 (*t*, $J = 1.1$, H−CH=C(5)); 4.52 (*d*, $J = 2.2$, H−CH=C(5)); 2.48 – 2.16 (*m*, CH_2(8)); 2.09 (*s*, Me(10)); 2.03 – 1.90 (*m*, CH_2(4)); 1.84 – 1.36 (*m*, 6 H), 1.28 – 1.06 (*m*, 1 H) (CH_2(3), CH_2(2), CH(6), CH_2(7)); 0.89 (*s*, Me−C(1)); 0.84 (*s*, Me−C(1)). ^{13}C-NMR: 209.4; 149.0; 109.4; 53.3; 42.3; 35.6; 34.7; 31.9; 30.1; 28.2; 26.5; 23.4; 20.2. MS: 194 (3, M^+), 176 (38), 161 (51), 136 (100), 121 (97), 109 (46), 93 (61), 81 (36), 69 (63), 55 (18), 43 (88). Anal. calc. for $C_{13}H_{22}O$: C 80.35, H 11.41; found: C 80.40, H 10.45.

(+)-γ-Dihydroionone ((+)-**17**). The same procedure described above was applied to reduce (+)-**3** and afforded (+)-**17** in 75% yield and 95% chemical purity (GC). Chiral GC: t_R 16.59; ee 98%. $[\alpha]_D^{20} = +19.4$ ($c = 1.2$, $CHCl_3$). IR, ^{1}H-NMR, ^{13}C-NMR, MS: in accordance with those of (−)-**16**. Anal. calc. for $C_{13}H_{22}O$: C 80.35, H 11.41; found: C 80.45, H 10.40.

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