Enzyme-Mediated Preparation of (+)- and (–)-*cis*-α-Irone and (+)- and (–)-*trans*-α-Irone

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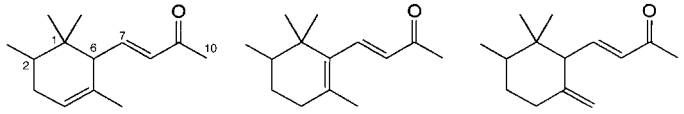
The preparation of (−)- and (+)-*trans*-α-irone (**1a** and **1b**, resp.) and of (+)- and (−)-*cis*-α-irone (**1c** and **1d**, resp.) from commercially available *Irone alpha* ® is reported. The relevant step in the synthetic sequence is the initial chromatographic separation of crystalline (±)-4,5-epoxy-4,5-dihydro-*cis*-α-irone ((±)-**5**) from oily (±)-4,5-epoxy-4,5-dihydro-*trans*-α-irone ((±)-**4**). The latter was subsequently converted, after $NaBH_4$ reduction, into the crystalline 3,5-dinitrobenzoate ester (±)-**8**, thus allowing a complete separation of the two corresponding diastereoisomeric alcohol derivatives. Suitable enantiomerically pure precursors of the desired products **1a**–**d** were obtained by kinetic resolution of the racemic allylic alcohols derived from (±)-**5** and (±)-**8**, mediated by lipase PS (*Amano*). The last steps consisted of MnO_2 oxidation and removal of the epoxy moiety with Me_3SiCl/NaI in MeCN. External panel olfactory evaluation showed that (−)-*cis*-α-irone (**1d**) has the finest and most distinct 'orris butter' character.

Introduction. – Irones **1**–**3** are the olfactory active components of *Iris* essential oil, one of the most precious raw materials in fine perfumery [1a]. These ketones are not present in fresh rhizomes, but they are slowly produced from two isomeric C_{31} precursors, after the harvesting and during ageing, through a still obscure oxidative mechanism. The manufacture of the essential oil begins with the rhizomes of three-years-old plants, which, once peeled, are kept in a dry and aerated environment for two to three years. The powdered material is then incubated with diluted sulfuric acid and steam-distilled to provide the 'orris butter', containing up to 90% myristic acid. The desired essential oil is finally recovered from the butter through delicate operations [2]. More recently, *Belcour et al.* reported on a new microbial process allowing the expression of up to 1 g of irones per kilogram of three-year-old rhizomes, instead of the 0.4 g provided by the traditional procedure [3].

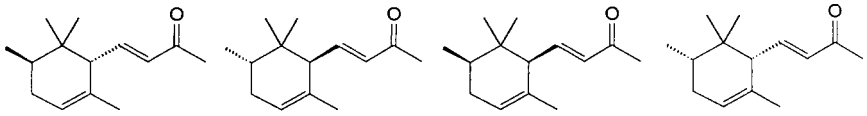
Irones were first isolated from *Iris* rhizomes by *Tiemann* more than one century ago [4], but the correct structural formula was assigned in 1947 by *Ruzicka* and *Naves* at the end of an extended degradative work [5][6]. The materials extracted from *Iris pallida* LEMARCK, and used by *Ruzicka* in the structure elucidation, were shown to possess (2*R*)-configuration through chemical correlation with (−)-camphor by *Rautenstrauch* and *Ohloff* in 1971 [7]. Not surprisingly, the set of chemically identical products isolated from *Iris germanica* LINNAEUS possess the opposite configuration [8]. Indeed, the configurational assignment explains, in terms of olfactory enantiodifferentiation, the defect in radiant power, long known to professional perfumers, of the *Iris germanica* extracts in comparison to those of *Iris pallida* and *Iris florentina* LINNAEUS. Similarly, the odor response of synthetic racemic α-irone was described to be different from that of the natural extract [1b].

Detailed comparative olfactory descriptions of all the stereoisomers of α-, β-, and γ-irones **1**–**3** are rather limited, since these materials are not easily accessible in enantiomerically enriched forms. Indeed, the number of syntheses of optically active irones is rather small [9], especially when compared to the number of the racemic modifications [10]. *Petrzilka* and co-workers reported the olfactory evaluation of the single enantiomers of irones **1**–**3** by chiral GC-sniff analyses of the corresponding racemic materials on modified cyclodextrins as stationary phases [11]. According to this study, with the exception of *trans*-α-irone, all the other pairs of enantiomers could be distinguished by the human nose. In particular, of *cis*-α-irone and *cis*-γ-irone, which constitute up to 80% of the essential oils of different origin in *ca.* equal ratio, only the (2*R*)-enantiomers appeared to be odor active, showing also the finest and most intense iris-like notes. Independently, *Ohloff* considered (2*R*)-*trans*-α-irone and (2*R*)-β-irone to possess the highest odor quality amongst the olfactorily active compounds known at the time [1b].

At the light of these observations, it seemed desirable to have access to substantial quantities of each stereoisomer of **1**–**3** in enantiomerically enriched forms through a general procedure from inexpensive readily available starting materials. We report now on the preparation of the (+)- and (−)-*trans*- and (+)- and (−)-*cis*-α-irones (**1a**–**d**) from *Irone alpha*®, a commercially available 55 : 45 mixture of racemic *trans*- and *cis*-α-irone, with 5% of β-isomer.



1 (trivial numbering) **2** **3**



1a ((-)-*trans*) **1b** ((+)-*trans*) **1c** ((+)-*cis*) **1d** ((-)-*cis*)

Results and Discussion. – To prepare the enantiomerically pure substrates **1a**–**d**, we first considered exploitation of the same procedure we had successfully developed for the resolution of racemic α-ionone [12a]. (*R*)- and (*S*)-α-Ionone were obtained by MnO_2 oxidation of enantiomerically pure α-ionols produced by lipase-mediated acetylation of the racemic materials and subsequent saponification. However, in the case of α-irone, the presence of one more Me group at C(2) gave rise to eight stereoisomers upon $NaBH_4$ reduction of commercial α-irone: eight peaks of nearly equal intensity were indeed observed by chiral GC analysis of the corresponding ironol acetates (see *Exper. Part*). Thus, a chemical separation of the two racemic diastereoisomers **1a**,**b** and **1c**,**d** was desirable before attempting enzymic resolution. Fortunately, a series of favorable circumstances greatly facilitated the achievement of this goal.

On the basis of an earlier experience with α- and β-ionone epoxides [12b], we found that key derivatives for the separation of *trans*- and *cis*-α-irone were the corresponding epoxides. The 3-chloroperbenzoic acid oxidation of *Irone alpha*® in CH_2Cl_2 afforded an oily mixture, showing two main well-resolved spots by TLC. Column chromatography (SiO_2, 10–15% AcOEt/hexane) gave, in order of elution, (±)-**4** and (±)-**5**. The latter was obtained in pure form since it crystallized nicely from hexane; X-ray single-crystal analysis (by *L.M.*) (*Fig. 1*) allowed the assignment of the structural formula of (±)-**5**. This crystalline material was found to be the diastereoisomerically pure epoxide derivative of *cis*-α-irone (**1c**,**d**) bearing the oxirane ring in '*anti*' position to the side chain at C(6), consistent with the following measured torsional angles: C(4)–C(5)–(6)–C(7) 150.0(1)°, O(1)–C(5)–C(6)–C(7) 143.6(1)°, and C(11)–C(5)–C(6)–C(7) 7.7(2)°.

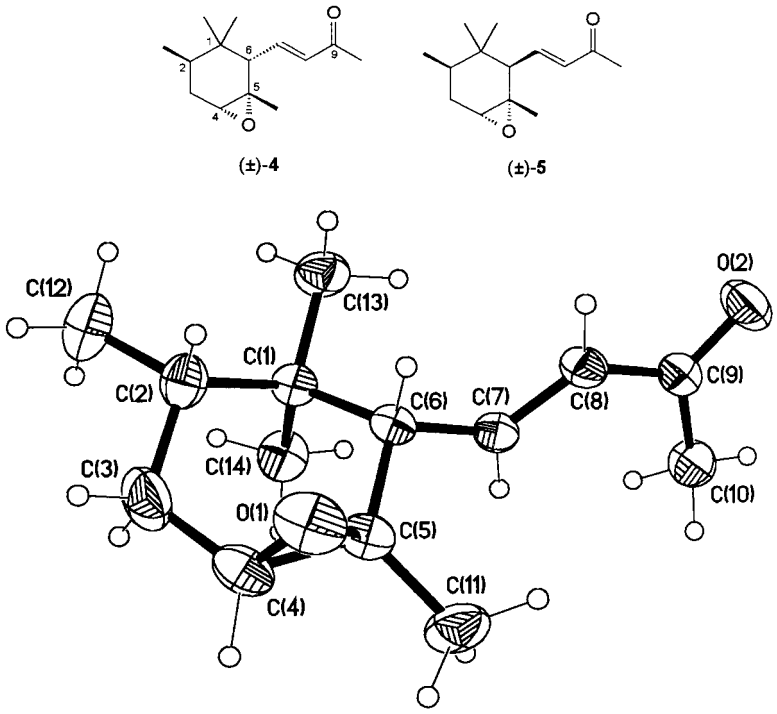


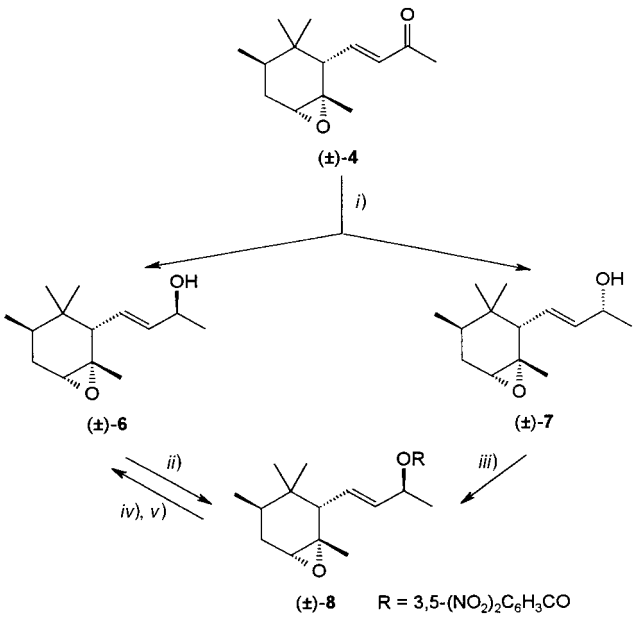
Fig. 1. *Molecular structure of (±)-***5** *with the atom-numbering scheme.* Displacement ellipsoids correspond to 30% probability; H-atoms are shown as spheres of arbitrary radius.

The first eluted fraction of the epoxidation mixture was composed mainly of (±)-epoxy-*trans*-α-irone (±)-**4**, with 20% of the other diastereoisomer of epoxy-*cis*-α-irone, *i.e.* the one obtained by reaction of the peracid on the same side of the substituent at C(6). As a matter of fact, the treatment of this chromatographic fraction with chlorotrimethylsilane and NaI in MeCN [13] afforded a 80 : 20 mixture of *trans*- and *cis*-α-irone. The configuration of the epoxy moiety of derivative (±)-**4** was determined by ^{1}H-NMR analysis of a suitable derivative.

It is worth noting that the steric course of the epoxidation of *cis*-α-irone was completely different from that we observed for *trans*-α-irone and the one *Eugster* reported for α-ionone [14], in complete accordance with the known '*anti*'-epoxidation of *cis*-α-sub-skeletons under the same reaction conditions [15].

Substrate (±)-**4**, contaminated with the *cis*-derivative, was reduced with $NaBH_4$ in CH_2Cl_2/MeOH 2:1 to provide, as major components, the two racemic diastereoisomeric alcohols (±)-**6** and (±)-**7** (1:1 ratio), which could be separated by column chromatography (SiO_2) (*Scheme 1*). The first-eluted alcohol (±)-**6**, containing over 90% of a single component, was obtained in pure form by crystallization of the corresponding 3,5-dinitrobenzoate ester (±)-**8** from EtOH. This material was assigned the shown relative configuration at the cyclic moiety by NMR data.

Scheme 1



i) $NaBH_4$, CH_2Cl_2/MeOH 2:1, column chromatography. *ii*) 3,5-$(NO_2)_2C_6H_3COCl$, pyridine, CH_2Cl_2. *iii*) *Mitsunobu*'s esterification. *iv*) Crystallization from EtOH. *v*) KOH, MeOH.

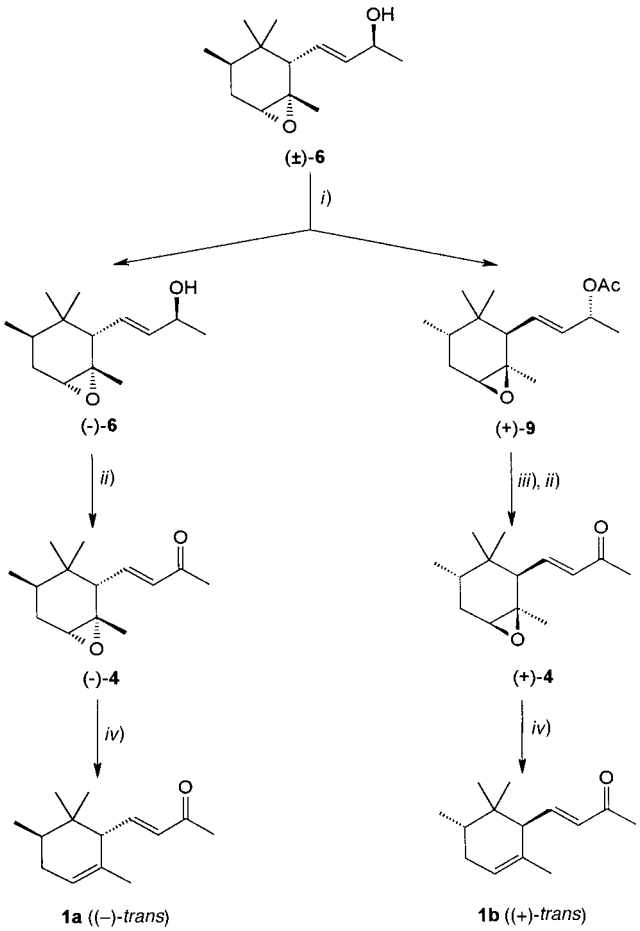
A strong NOE was observed between H–C(7) and H–C(2) of (±)-**8**, thus confirming the *trans*-configuration of Me–C(2) and the side chain. The oxirane ring was found to be on the same side of the substituent at C(6) on the basis of the clear NOEs between the axial Me–C(1) and H–C(4) and Me–C(5). Moreover, the values of the vicinal coupling constants J(H–C(4),H_{eq}–C(3)) and J(H–C(4),H_{ax}–C(3)) were rather low (1.7 and 2.4 Hz, resp.), in agreement with an equatorial location of H–C(4).

The relative configuration of the OH-bearing C-atom in the side chain was tentatively attributed by analogy to the first-eluted diastereoisomeric epoxy-α-ionol, showing '*anti*' relationship between the side chain and the OH group [12b]. This assignment was confirmed by the outcome of the synthetic sequence described below.

The 3,5-dinitrobenzoate of (±)-**7** was an oil. Crude (±)-**7** was then esterified with 3,5-dinitrobenzoic acid under *Mitsunobu* conditions [16] to provide (±)-**8**. The

crystalline ester (±)-**8**, pooled from the two reactions, was crystallized from EtOH and hydrolyzed under basic conditions to afford (±)-**6**. The homogeneity of the sample was verified by chiral GC analysis of the corresponding acetate (*Fig. 2*,*a*). The allylic alcohol (±)-**6** was straightforwardly converted to the (−)- and (+)-*trans*-α-irones (**1a** and **1b**, resp.) by the chemo-enzymatic process outlined in *Scheme 2* [12b]. Treatment of (±)-**6** with vinyl acetate in *t*-butyl methyl ether in the presence of lipase PS (*Amano*) afforded enantiomerically pure acetate (+)-**9** (see *Fig. 2*,*c*) and unreacted alcohol (−)-**6** showing an ee of 98% (GC of the corresponding acetate derivative, see *Fig. 2*,*b*; enantiomer ratio = 461 and conversion = 0.5, calculated according to [17]). The acetate (+)-**9** was then hydrolyzed under basic conditions, and the derived alcohol was oxidized with MnO_2 in CH_2Cl_2 to give epoxy ketone (+)-**4** (ee 98% by GC). Similarly, alcohol (−)-**6** afforded enantiomerically pure (GC) epoxy ketone (−)-**4**. Finally, (−)- and (+)-**4**

Scheme 2



i) Lipase PS (*Amano*), vinyl acetate, ^{t}BuOMe, column chromatography. *ii*) MnO_2, CH_2Cl_2. *iii*) KOH, MeOH. *iv*) Me_3SiCl, NaI, MeCN.

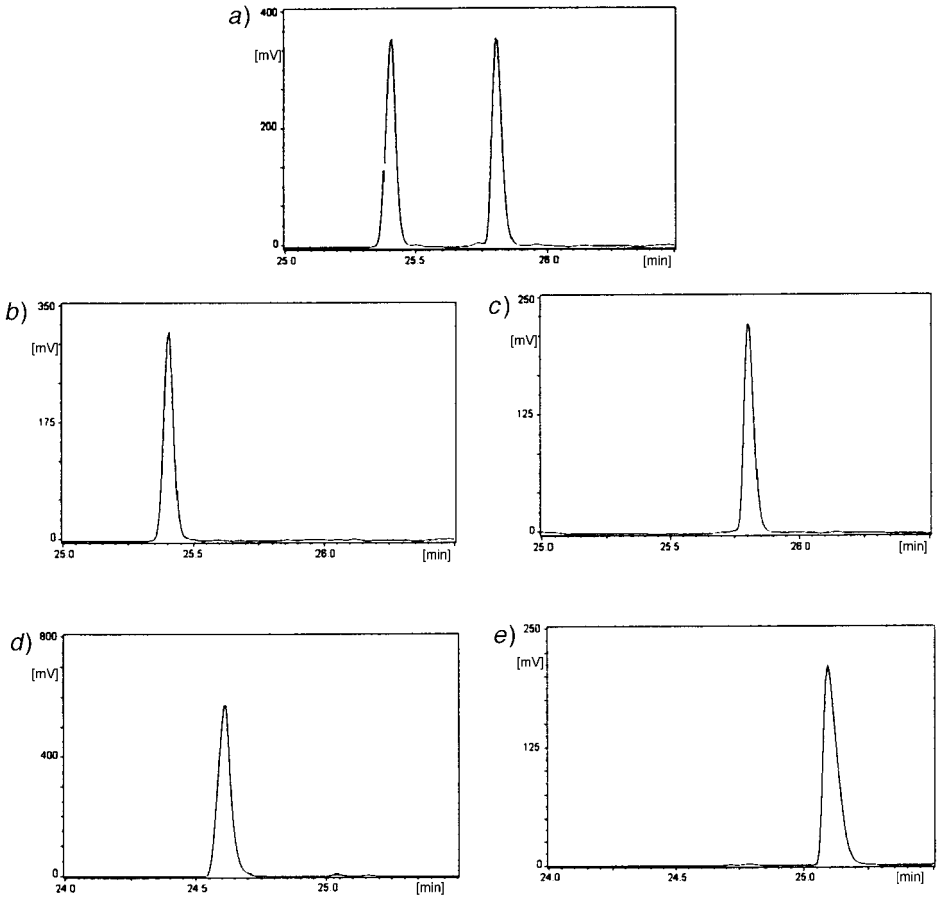


Fig. 2. *Chiral GC analyses* a) *of the acetate derivatives of* (±)-**6**, b) *of the acetate derivative of* (−)-**6**, c) *of* (+)-**9**, d) *of* (−)-**4**, *and* e) *of* (+)-**4**

were deoxygenated separately in good yields to (−)-*trans*-α-irone (**1a**; chemical purity 88% and ee 98% by GC) and (+)-*trans*-α-irone (**1b**; chemical purity 96% and ee 98% by GC). This deoxygenation process caused the formation of impurities which could not be easily separated from *trans*-α-irone (see *Fig. 3*,*d* and *e*).

Lipase PS (*Amano*) usually reacts with (*R*)-alcohols [12]; thus, the conversion of (−)-**6** and (+)-**6** into **1a** ((−)-*trans*) and **1b** ((+)-*trans*), respectively, supported the configurational assignment of (±)-**6** and (±)-**7**. Moreover, the conversion of (±)-**7** to (±)-**6** by *Mitsunobu*'s esterification and hydrolysis allowed us to resolve (±)-**4** in 33% overall yield without loss of material.

More direct was the access to the enantiomers **1c** and **1d** of *cis*-α-irone from the racemic *trans*/*cis* mixture thanks to the crystallinity of epoxy-*cis*-α-irone (±)-**5** (*Scheme 3*). This latter was reduced with $NaBH_4$ to afford a 1:1 mixture of the two diastereoisomeric alcohols (±)-**10** and (±)-**11**, which could be separated by column chromatography. The second-eluted alcohol (±)-**11** was then purified by crystallization

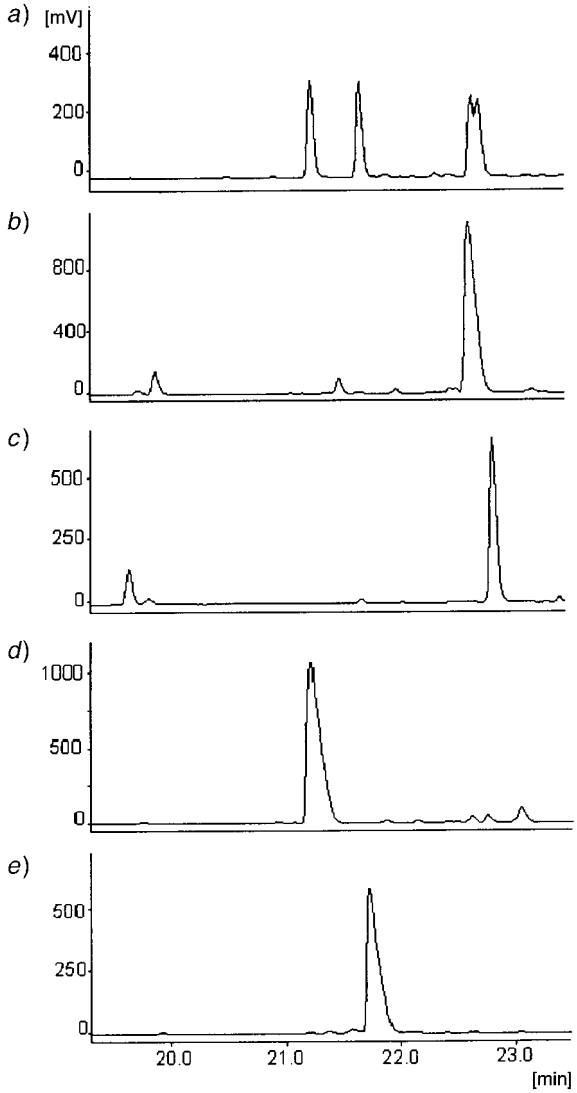
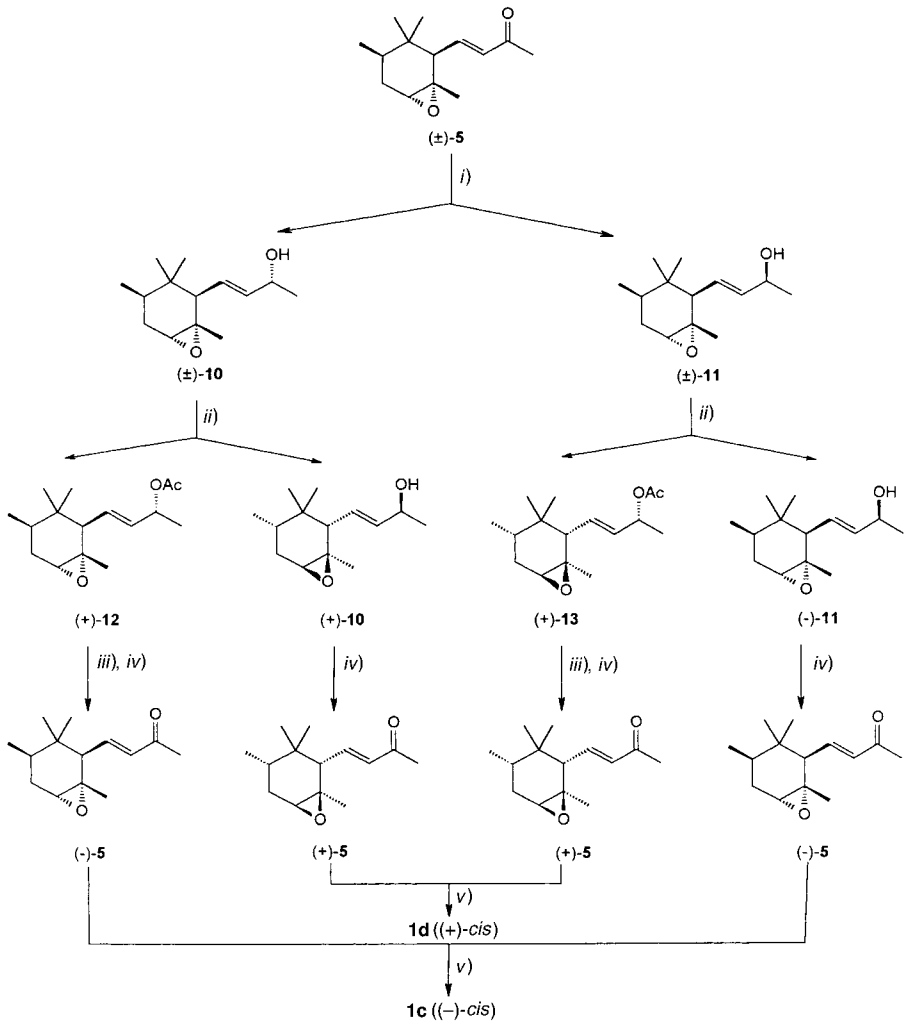


Fig. 3. *Chiral GC analyses* a) *of commercial α-irone*, b) *of (+)*-cis-*α-irone* (**1c**), c) *of (−)*-cis-*α-irone* (**1d**), d) *of (−)*-trans-*α-irone* (**1a**), *and* e) *of (+)*-trans-*α-irone* (**1b**)

from hexane. The configurational assignment of (±)-**10** and (±)-**11** was based on the same arguments given for (±)-**6** and similarly confirmed by the synthetic sequence. In separate experiments, (±)-**10** and (±)-**11** were submitted to lipase PS mediated acetylation in ^{t}BuOMe solution in the presence of vinyl acetate to provide, after column chromatography, acetates (+)-**12** (ee 98%, by GC, see *Fig. 4,e*) and (+)-**13** (ee 98%) by GC see *Fig. 4,f*), respectively, and unreacted alcohols (+)-**10** (ee 98% by GC of the corresponding acetate derivative, see *Fig. 4,g*) and (−)-**11** (ee 98% by GC of the corresponding acetate derivative, see *Fig. 4,h*), respectively (enantiomer ratio = 461,

Scheme 3



i) $NaBH_4$, CH_2Cl_2/MeOH 2:1. *ii*) Lipase PS (*Amano*), vinyl acetate, ^{t}BuOMe, column chromatography. *iii*) KOH, MeOH. *iv*) MnO_2, CH_2Cl_2. *v*) Me_3SiCl, NaI, MeCN.

conversion = 0.5 for both the kinetic resolutions; see [17]). Acetate (+)-**12** gave, upon hydrolysis and oxidation with MnO_2 the same enantiomeric epoxy-irone (−)-**5** as obtained by direct oxidation of (−)-**11**. The two samples of (−)-**5** were combined (ee 98% by GC, see *Fig. 4,i*) and submitted to deoxygenation with chlorotrimethylsilane and NaI in MeCN, to give (+)-*cis*-α-irone (**1c**, chemical purity 81% and ee = 98% by GC, see *Fig. 3,b*). Derivative (+)-**5** (ee 98% by GC, see *Fig. 4,j*), prepared both from acetate (+)-**13** and from alcohol (+)-**10**, was transformed according to the same deoxygenation procedure into (−)-*cis*-α-irone (**1d**; chemical purity 85% and ee 98% by GC, see *Fig. 3,c*). Thus, enantiospecific acetylation of the two diastereoisomeric

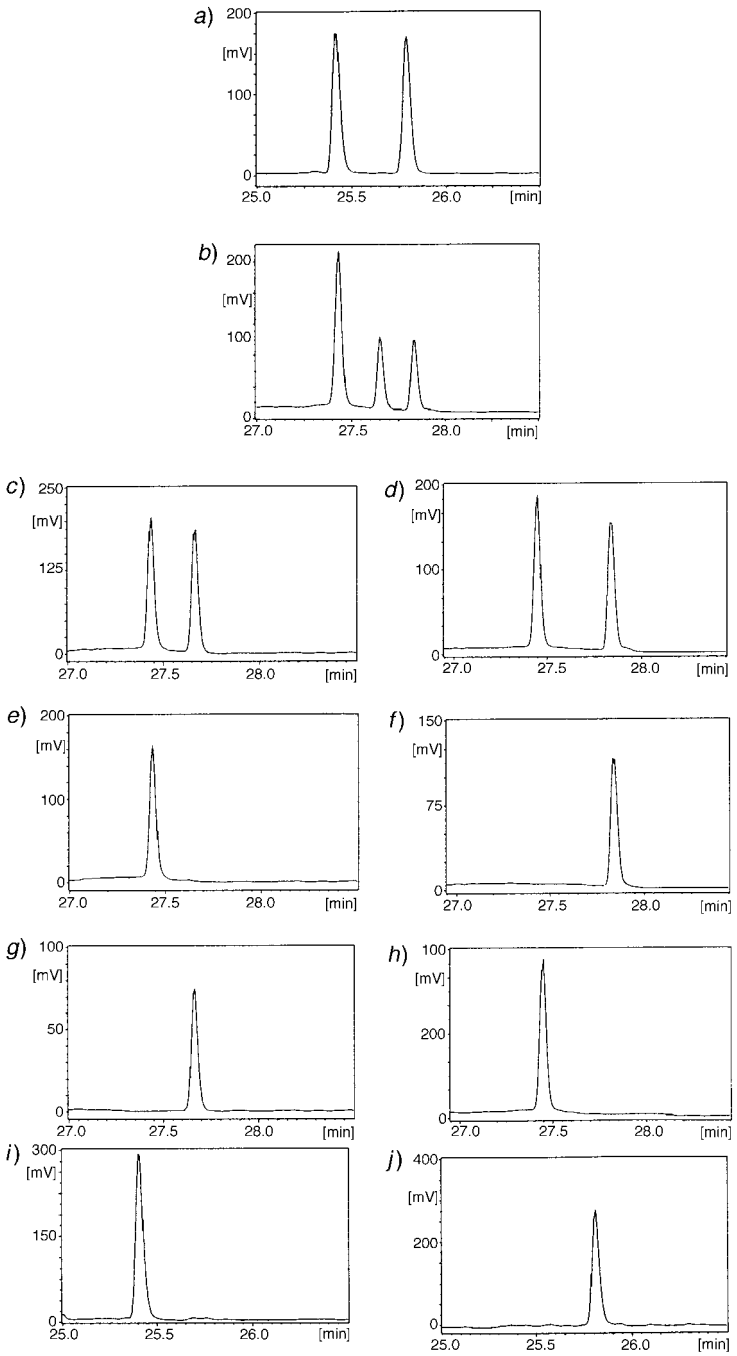


Fig. 4. *Chiral GC analyses* a) *of* (±)-**5**, b) *of the acetate derivatives of* (±)-**10**/(±)-**11** *1 : 1*, c) *of the acetate derivatives of* (±)-**10**, d) *of the acetate derivatives of* (±)-**11**, e) *of* (+)-**12**, f) *of* (+)-**13**, g) *of the acetate derivative of* (+)-**10**, h) *of the acetate derivative of* (−)-**11**, i) *of* (−)-**5**, *and* j) *of* (+)-**5**

alcohols (±)-**10** and (±)-**11** allowed us to convert both acetates and unreacted alcohols to (−)- and (+)-**5**, precursors of the valuable (+)- and (−)-*cis*-α-irones, allowing a formal resolution of epoxy-*cis*-α-irone (±)-**5** in 49% overall yield. The weak point of the sequence was again the deoxygenation process, in which some impurities not easily separable were produced, thus lowering the chemical purity of the samples.

Olfactory Evaluation. – Olfactory evaluation of irones **1a**–**d** was performed by twelve trained evaluators (*Robertet S.A.*, Grasse, France) using 0.1% solutions in EtOH. The following results were obtained: *a*) The *trans* enantiomers **1a** and **1b** did not possess the characteristic 'orris' odor. The (−)-enantiomer **1a** showed a weak violet/wood/red berry character, while the (+)-enantiomer **1b** was defined as the weakest isomer by unanimous decision. *b*) (+)-*cis*-α-Irone (**1c**) was violet-like, with woody, methylionone undertones. (−)-*cis*-α-Irone (**1d**) was slightly stronger with a distinct 'orris-butter' character (iris-like).

The olfactory detection threshold (triangular test) was *ca.* 10 ppm for **1d** and *ca.* 100 ppm for **1c** (in H_2O). As for derivatives **1c** and **1d**, remarkable differences were observed with respect to the olfactory evaluation of *cis*-α-irone enantiomers reported by *Petrzilka* and co-workers [11]. In contrast with our results, by GC-sniff analysis of racemic *cis*-α-irone, the (−)-enantiomer was found to be odorless, and the (+)-enantiomer was described as floral, fruity, with a woody ionone and sweet irone odor.

Conclusions. – The preparation of enantiomerically pure irones **1a**–**d** from the commercially available mixture of *trans*- and *cis*-α-irone **1** (*Irone alpha*®) might be of some utility. The enzyme-mediated kinetic resolution of allylic alcohols (±)-**6,** (±)-**10**, and (±)-**11** was an extension of some previous findings [12]. However, the success of these bio-catalyzed reactions was based on the simple, and still unknown, separation of racemic *trans*-α-irone from racemic *cis*-α-irone through their epoxide derivatives. The crystallinity of epoxide (±)-**5** was of great help in this separation process. Moreover, the conversion of both (±)-**6** and (±)-**7** to (±)-**8**, which was easily purified by crystallization, was another key step in the synthetic sequence.

Thus, the unexceptional reactions described in this work might be of some significance in the chemistry of irones, a class of compounds that have been known for more than one century, but which are still subject to new chemical investigations.

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Experimental Part

1. *General. Irone alpha*® was purchased from *IES*, Allauch, France. Lipase PS *Pseudomonas cepacia* (*Amano Pharmaceuticals Co.*, Japan) was employed in this work. TLC: *Merck* silica gel *60* F_{254} plates. Column chromatography (CC): silica gel. Chiral GC analysis: *DANI-HT-86.10* gas chromatograph; enantiomer and diastereoisomer excesses determined on a *Chirasil DEX CB* column (25 m × 0.25 mm; *Chrompack*) temp. program 70° (3 min) −3.5°/min −140° −8°/min −180° (1 min); analysis of α-ironol acetates on a *Hydrodex-β-PM* column (50 m × 0.25 mm; *Superchrom*), temp. program 70° (3 min) −1°/min −150° (10 min) −1°/min −160° (1 min) −10°/min −200° (1 min): t_R 84.10, 84.61, 84.96, 85.24, 90.32, 90.54, 91.07, and 91.57; mass-detection limit for anal. GC *ca.* 10 ng for an injected volume of 1 µl; t_R in min. Optical rotations: *Jasco-DIP-181* digital polarimeter. ^{1}H-NMR Spectra: $CDCl_3$ solns. at r.t., unless otherwise stated; *Bruker-AC-250* spectrometer

at 250 MHz (^{1}H); chemical shifts in ppm rel. to internal $SiMe_4$ (= 0 ppm), J values in Hz. Microanalyses were determined on an analyzer *1106* from *Carlo Erba*.

2. *X-Ray Crystal-Structure Determination of (±)-***5**. A colorless crystal, suitable for X-ray analysis, with the shape of a hexagonal prism, was obtained by crystallization from hexane. For crystal data and measurement conditions, see *Table*. Diffraction data were collected on a *Siemens-P4* diffractometer with graphite monochromated Cu-$K\alpha$ radiation (λ 1.54179 Å) by the $\theta/2\theta$ scan technique. Unit-cell parameters were determined using 48 reflections in the range $18° \leq 2\theta \leq 80°$. Empirical adsorption correction was applied by means of the ψ-scan methods; no decay correction was deemed necessary. The structure was solved by direct methods with SIR97 [18] and refined with SHELXL97 [19] programs. All H-atoms were located from a difference electron density map, and their positions were allowed to refine together with individual isotropic temp. factors. The six-membered ring has a slightly distorted envelope form, with the C(1) atom at 0.690(2) Å out of the best plane of the other five-ring C-atoms; the O(1) atom lies at 1.283 Å on the opposite side of the plane. Crystallographic data for (±)-**5** have been deposited at the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC 132368.

Table. *Crystal Data and Structure Refinement of (±)-***5**

Empirical formula	$C_{14}H_{22}O_2$	θ Range [°]	5.27 to 67.96
M_r	222.32	Index ranges	$-10 \leq h \geq 10$, $-15 \leq k \geq 16$, $-12 \leq l \geq 12$
Crystal system	monoclinic	Reflect. collected	4552
Space group	$P2_1/c$	Independent reflect.	2309 (R(int) = 0.081)
Unit cell dimension a[Å]	9.131(5)	Completeness to $2\theta = 67.96$	91.0%
b[Å]	14.912(5)	Refinement method	full-matrix least-squares on F^2
c[Å]	10.734(5)	Data/restraints/parameters	2309/0/234
β[°]	111.71(1)	Goodness of fit on F^2	1.068
Volume [Å^3]	1343.0(11)	Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0492$, $wR_2 = 0.1250$
Z	4	R indices (all data)	$R_1 = 0.0541$, $wR_2 = 0.1296$
Density calc. [Mg m^{-3}]	1.100	Largest difference peaks and hole [e · Å^{-3}]	0.158 and −0.144
Adsorption coeff. [mm^{-1}]	0.560		
F(000)	488		
Crystal size [mm]	0.8 × 0.6 × 0.3		

3. *(±)-(2*RS*,4*RS*,5*SR*,6*SR*)-4,5-Epoxy-4,5-dihydro-α-irone* (= *(*E*)-4-[(1*RS*,2*RS*,4*SR*,6*SR*)-1,3,3,4-Tetramethyl-7-oxabicyclo[4.1.0]hept-2-yl]but-3-en-2-one*; (±)-**4**) *and (±)-(2*RS*,4*RS*,5*SR*,6*RS*)-4,5-Epoxy-4,5-dihydro-α-irone* (= *(*E*)-4-[(1*RS*,2*SR*,4*SR*,6*SR*)-1,3,3,4-Tetramethyl-7-oxabicyclo[4.1.0]hept-2-yl]but-3-en-2-one*; (±)-**5**). To a soln. of racemic α-irone (**1**; *ca.* 55 : 45 *trans*/*cis* mixture; 50 g, 0.24 mol) in CH_2Cl_2 (450 ml) at 0°, 3-chloroperbenzoic acid (62 g, 0.36 mol) was added. The mixture was stirred at 0° for 2 h, then poured into H_2O. The org. phase was washed with sat. $NaHCO_3$ soln., dried (Na_2SO_4) and evaporated. The residue was submitted to CC (hexane/AcOEt 9 : 1): (±)-**4** (18.6 g, 35%) and then pure (±)-**5** (10.1 g, 19%; after crystallization).

*Data of (±)-***4** (containing 20% (GC, ^{1}H-NMR) of isomer (±)-(2*RS*,4*SR*,5*RS*,6*RS*)-4,5-epoxy-4,5-dihydro-α-irone): Chiral GC: t_R 24.58, 24.96; isomer (20%) at t_R 25.41, 25.78. ^{1}H-NMR: 6.76 (*dd*, J = 15.7, 10.0, H−C(7)); 6.10 (*d*, J = 15.7, H−C(8)); 3.11 (*m*, H−C(4)); 2.30 (*s*, Me(10)); 2.11 (*d*, J = 10, H−C(6)); 2.01 (*m*, 1 H); 1.59 (*m*, 2 H); 1.27 (*s*, Me−C(5)); 0.83 (*s*, 1 Me−C(1)); 0.81 (*d*, J = 6, Me−C(2)); 0.70 (3 H, *s*, 1 Me−C(1)); isomer (20%) at 3.07 (*d*, J = 6, H−C(4)). Anal. calc. for $C_{14}H_{22}O_2$: C 75.63, H 9.97; found: C 75.69, H 9.91.

*Data of (±)-***5**: Crystallization from hexane. M.p. 65°. Chiral GC: t_R 25.41, 25.78. ^{1}H-NMR 6.71 (*dd*, J = 11.2, 15.5, H−C(7)); 6.16 (*d*, J = 15.5, H−C(8)); 3.00 (*m*, H−C(4)); 2.30 (*s* + *d*, J = 11.2, MeCO, H−C(6)); 2.01 (*ddd*, J = 14.7, 3.9, 1.2, H_{eq}−C(3)); 1.59 (*td*, J = 14.7, 1.9, H_{ax}−C(3)); 1.45 (*m*, H−C(2)); 1.22 (*s*, Me−C(5)); 0.82 (*d*, J = 6.5, Me−C(2)); 0.74 (*s*, 2 Me−C(1)). Anal. calc. for $C_{14}H_{22}O_2$: C 75.63, H 9.97; found: C 75.59, H 9.93.

4. *(±)-(2*RS*,4*RS*,5*SR*,6*SR*,9*SR*)-4,5-Epoxy-4,5-dihydro-α-ironol* (= *(2*RS*,*E*)-4-[(1*RS*,2*RS*,4*SR*,6*SR*)-1,3,3,4-Tetramethyl-7-oxabicyclo[4.1.0]hept-2-yl]but-3-en-2-ol*; (±)-**6**) *and (±)-(2*RS*,4*RS*,5*SR*,6*SR*,9*RS*)-4,5-Epoxy-4,5-dihydro-α-ironol* (= *(2*RS*,*E*)-4-[(1*SR*,2*SR*,4*RS*,6*RS*)-1,3,3,4-Tetramethyl-7-oxabicyclo[4.1.0]hept-2-*

yl]but-3-en-2-ol; (±)-**7**). Reduction of (±)-**4** (18.0 g, 0.081 mol) with $NaBH_4$ (3.7 g, 0.097 mol) in CH_2Cl_2/MeOH 2 : 1 (100 ml) gave, after the usual workup, (±)-**6**/(±)-**7** 1 : 1 (GC) which was chromatographed (hexane/AcOEt 8 : 2): (±)-**6** (7.4 g, 41%) and (±)-**7** (6.9 g, 38%).

Data of (±)-**6** (containing 5% (GC) of isomer (±)-(2*RS*,4*SR*,5*RS*,6*RS*,9*RS*)-4,5-epoxy-4,5-dihydro-α-ironol): Chiral GC (corresponding acetate): t_R 25.41, 25.80, isomer (5%) at t_R 26.15, 26.51. ^{1}H-NMR: 5.63 (*m*, 2 olef. H); 4.34 (*quint.*, $J = 6$, H–C(9)); 3.07 (*m*, H–C(4)); 1.94 (*m*, 2 H); 1.55 (*m*, 2 H); 1.29 (*d*, $J = 6$, Me(10)); 1.25 (*s*, Me–C(5)); 0.78 (*s*, Me–C(1)); 0.76 (*d*, $J = 6$, Me–C(2)). Anal. calc. for $C_{14}H_{24}O_2$: C 74.95, H 10.78; found: C 74.99, H 10.71.

Data of (±)-**7** (containing 6% (^{1}H-NMR) of isomer (±)-(2*RS*,4*SR*,5*RS*,6*RS*,9*SR*)-4,5-epoxy-4,5-dihydro-α-ironol): Chiral GC (corresponding acetate): t_R 25.80, 26.01. ^{1}H-NMR: 5.63 (*m*, 2 olef. H); 4.34 (*m*, H–C(9)); 3.08 (*m*, H–C(4)); 1.91 (*d*, $J = 9$, H–C(6)); 1.2–1.7 (*m*, 3 H); 1.29 (*d*, $J = 6$, Me(10)); 1.25 (*s*, Me–C(5)); 0.78 (*s*, Me–C(1)); 0.76 (*d*, $J = 6$, Me–C(2)); 0.69 (*s*, Me–C(1)); isomer (6%) at 3.01 (*d*, $J = 6$, H–C(4)). Anal. calc. for $C_{14}H_{24}O_2$: C 74.95, H 10.78; found: C 74.91, H 10.82.

5. *(±)-(2*RS,*4*RS,*5*SR,*6*SR,*9*SR*)-4,5-Epoxy-4,5-dihydro-α-ironol 3,5-Dinitrobenzoate* (±-**8**). *From (±)*-**6**: A soln. of (±)-**6** (7.0 g, 0.031 mol) in CH_2Cl_2 (70 ml) was treated with 3,5-dinitrobenzoyl chloride (8.5 g, 0.037 mol) in the presence of pyridine (10 ml). After the usual workup, purification of the residue by CC (hexane/AcOEt 9 : 1) gave (±)-**8** which was crystallized from EtOH: diastereoisomerically pure (GC) (±)-**8** (9.2 g, 71%). M.p. 89°. ^{1}H-NMR (C_6D_6): 8.69 (*d*, $J = 2.1$, 2 arom. H); 8.42 (*t*, $J = 2.1$, 1 arom. H); 6.05 (*ddd*, $J(7,6) = 10.4$, $J(7,8) = 15.7$, $J(7,9) = 0.95$, H–C(7)); 5.54 (*qd*, $J(9,Me) = 6.2$, $J(9,8) = 7.1$, H–C(9)); 5.42 (*dd*, $J(8,7) = 15.7$, $J(8,9) = 7.1$, H–C(8)); 2.75 (*t*, $J(4,3ax) = J(4,3eq) = 1.9$, H–C(4)); 1.79 (*ddd*, J (3eq,3ax) = 15.1, $J(3eq,2) = 4.7$, $J(3eq,4) = 1.6$, H_{eq}–C(3)); 1.76 (*d*, $J(6,7) = 10.4$, H–C(6)); 1.57 (*dqd*, $J(2,Me) = 6.9$, $J(2,3ax) = 11.2$, $J(2,3eq) = 4.7$, H–C(2)); 1.23 (*ddd*, $J(3ax,3eq) = 15.1$, $J(3ax,2) = 11.2$, $J(3ax,4) = 2.4$, H_{ax}–C(3)); 1.23 (*d*, $J = 6.4$, Me(10)); 1.16 (*s*, Me–C(5)); 0.70 (*s*, Me_{eq}–C(1)); 0.63 (*d*, $J = 6.9$, Me–C(2)); 0.60 (*s*, Me_{ax}–C(1)). Anal. calc. for $C_{21}H_{26}N_2O_7$: C 60.28, H 6.26; found: C 60.21, H 6.32.

From (±)-**7** *by* Mitsunobu's *Esterification:* a soln. of (±)-**7** (6.0 g, 0.027 mmol) and PPh_3 (8.49 g, 0.032 mol) in THF (30 ml) was added dropwise into a soln. of diisopropyl azodicarboxylate (6.54 g, 0.032 mmol) and 3,5-dinitrobenzoic acid (6.8 g, 0.032 mol) in THF (30 ml). The mixture was stirred at r.t. for 4 h and then evaporated, the residue poured into H_2O and extracted with AcOEt, the org. layer dried (Na_2SO_4) and evaporated, the residue chromatographed (hexane/AcOEt 9 : 1) and the product crystallized from EtOH: diastereoisomerically pure (±)-**8** (6.54 g, 58%). Anal. and spectral data: in accordance with those of the sample obtained from (±)-**6**.

6. *(±)-(2*RS,*4*RS,*5*SR,*6*SR,*9*SR*)-4,5-Epoxy-4,5-dihydro-α-ironol* ((±)-**6**). Diastereoisomerically pure (GC) (±)-**6** (6.11 g, 88%) was obtained by hydrolysis of (±)-**8** (13 g, 0.031 mol) with 85% KOH (2.45 g, 0.037 mol) in MeOH soln. (50 ml): Chiral GC (corresponding acetate): t_R 25.41, 25.80. ^{1}H-NMR: in accordance with that described above.

7. *(−)-(2*R,*4*R,*5*S,*6*S,*9*S*)-4,5-Epoxy-4,5-dihydro-α-ironol* ((−)-**6**) and *(+)-(2*S,*4*S,*5*R,*6*R,*9*R*)-4,5-Epoxy-4,5-dihydro-α-ironol Acetate* ((+)-**9**). A mixture of (±)-**6** (de > 99%; 6 g, 0.026 mol), lipase PS (*Pseudomonas cepacia*; 6 g), and vinyl acetate (10 ml) in ^{t}BuOMe (80 ml) was stirred at r.t. for 24 h. The residue obtained upon evaporation of the filtered mixture was chromatographed (hexane/AcOEt 7 : 3): (+)-**9** (3.11 g, 45%) and (−)-**6** (2.44 g, 42%).

Data of (+)-**9**: Chiral GC: t_R 25.80; enantiomerically pure. $[\alpha]_D^{20} = +218.8$ ($c = 0.95$, CH_2Cl_2). ^{1}H-NMR: 5.72 (*dd*, $J = 15$, 10, H–C(7)); 5.51 (*dd*, $J = 15$, 6.2, H–C(8)); 5.35 (*quint.*, $J = 6.2$, H–C(9)); 3.05 (*m*, H–C(4)); 2.03 (*s*, MeCOO); 1.95 (*dd*, $J = 10$, 1, 1 H); 1.88 (*d*, $J = 10$, H–C(6)); 1.53 (*m*, 2 H); 1.32 (*d*, $J = 6.2$, Me(10)); 1.24 (*s*, Me–C(5)); 0.77 (*s*, Me–C(1)); 0.76 (*d*, $J = 6.2$, Me–C(2)); 0.66 (*s*, Me–C(1)). Anal. calc. for $C_{16}H_{26}O_2$: C 72.14, H 9.84; found: C 72.09, H 9.92.

Data of (−)-**6**: Chiral GC (corresponding acetate): t_R 25.41; ee 98%. $[\alpha]_D^{20} = -280$ ($c = 0.45$, CH_2Cl_2). ^{1}H-NMR: consistent with that of the racemic starting material.

8. *(−)-(2*R,*4*R,*5*S,*6*S*)-4,5-Epoxy-4,5-dihydro-α-irone* ((−)-**4**). At r.t. (−)-**6** (ee 98% by GC; 2.40 g, 0.011 mol) was oxidized with MrO_2 (0.017 mol, 1.48 g) in CH_2Cl_2 (30 ml). The crude material was purified by CC (hexane/AcOEt 9 : 1): (−)-**4** (1.97 g, 83%). Chiral GC: t_R 24.58; ee 97%. $[\alpha]_D^{20} = -258$ ($c = 1.0$ CH_2Cl_2). ^{1}H-NMR: in accordance with that of (±)-**4**.

9. *(+)-(2*S,*4*S,*5*R,*6*R,*9*R*)-4,5-Epoxy-4,5-dihydro-α-ironol* ((+)-**6**). Enantiomerically pure acetate (+)-**9** (3.0 g, 0.011 mol) was hydrolyzed with 85% KOH (1.09 g, 0.017 mol) in MeOH (30 ml), to afford, after CC, enantiomerically pure (+)-**6** (2.24 g, 91%). $[\alpha]_D^{20} = +270$ ($c = 0.7$ CH_2Cl_2). ^{1}H-NMR: in accordance with that of (±)-**6**.

10. *(+)-(2S,4S,5R,6R)-4,5-Epoxy-4,5-dihydro-α-irone* ((+)-**4**). According to *Exper. 8*, with (+)-**6** (2.20 g, 0.010 mol), MnO_2 (0.015 mol, 1.30 g), and CH_2Cl_2 (30 ml): (+)-**4** (2.02 g, 91%). Chiral GC: t_R 24.96; ee 98%. $[\alpha]_D^{20} = +260$ ($c = 1.15$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (±)-**4**.

11. *(±)-(2RS,4RS,5SR,6RS,9RS)-4,5-Epoxy-4,5-dihydro-α-ironol* ((±)-**10**) *and (±)-(2RS,4RS,5SR,6RS,9SR)-4,5-Epoxy-4,5-dihydro-α-irone* ((+)-**11**). According to *Exper. 4*, with (±)-**5** (15.0 g, 0.068 mol), $NaBH_4$ (3.1 g, 0.081 mol), and CH_2Cl_2/MeOH 2:1 (100 ml). CC (hexane/AcOEt 8:2) of (±)-**10**/(±)-**11** 1:1 (GC) gave (±)-**10** (6.4 g, 42%) and (±)-**11** (5.6 g, 37%; after crystallization from hexane).

Data of (±)-**10**: Chiral GC (corresponding acetate): t_R 27.43, 27.65. ^{1}H-NMR: 5.56 (*m*, 2 olef. H); 4.36 (*m*, H–C(9)); 2.97 (*m*, H–C(4)); 2.14 (*d*, $J = 10$, H–C(6)); 1.97 (*ddd*, $J = 14.6$, 3.9, 1.2, H_{eq}–C(3)); 1.52 (*td*, $J = 14.6$, 1.9, H_{ax}–C(3)); 1.40 (*m*, H–C(2)); 1.30 (*d*, $J = 6$, Me(10)); 1.16 (*s*, Me–C(5)); 0.80 (*d*, $J = 7$, Me–C(2)); 0.76 (*s*, Me–C(1)); 0.67 (*s*, Me–C(1)). Anal. calc. for $C_{14}H_{24}O_2$: C 74.95, H 10.78; found: C 74.88, H 10.71.

Data of (±)-**11**: M.p. 64°. Chiral GC (corresponding acetate): t_R 27.43, 27.83. ^{1}H-NMR: 5.57 (*m*, 2 olef. H); 4.35 (*m*, H–C(9)); 2.97 (*m*, H–C(4)); 2.14 (*d*, $J = 9.6$, H–C(6)); 1.97 (*ddd*, $J = 14.7$, 4.2, 1.6, H_{eq}–C(3)); 1.52 (*td*, $J = 14.7$, 1.9, H_{ax}–C(3)); 1.40 (*m*, H–C(2)); 1.30 (*d*, $J = 6.5$, Me(10)); 1.19 (*s*, Me–C(5)); 0.80 (*d*, $J = 7$, Me–C(2)); 0.73 (*s*, Me–C(1)); 0.66 (*s*, Me–C(1)). Anal. calc. for $C_{14}H_{24}O_2$: C 74.95, H 10.78; found: C 75.01, H 10.75.

12. *(+)-(2R,4R,5S,6R,9R)-4,5-Epoxy-4,5-dihydro-α-ironol Acetate* ((+)-**12**) *and (+)-(2S,4S,5R,6S,9S)-4,5-epoxy-4,5-dihydro-α-ironol* ((+)-**10**). According to *Exper. 7*, with (±)-**10** (6 g, 0.026 mol), lipase PS (*Pseudomonas cepacia*; 6 g), vinyl acetate (10 ml), and ^{t}BuOMe (80 ml). (+)-**12** (3.22 g, 46%) and (+)-**10** (2.39 g, 41%).

Data of (+)-**12**: Chiral GC: t_R 27.43; enantiomerically pure. $[\alpha]_D^{20} = +58$ ($c = 1.8$, CH_2Cl_2). ^{1}H-NMR: 5.57 (*m*, 2 olef. H); 5.36 (*quint.*, $J = 6.5$, H–C(9)); 2.96 (*m*, H–C(4)); 2.12 (*d*, $J = 10$, 1 H); 2.04 (*s*, MeCOO); 1.96 (*ddd*, $J = 14.5$, 4.2, 1.2, H_{eq}–C(3)); 1.52 (*td*, $J = 14.5$, 2 H_{ax}–C(3)); 1.40 (*m*, 1 H); 1.35 (*d*, $J = 6.5$, Me(10)); 1.15 (*s*, Me–C(5)); 0.80 (*d*, $J = 6.5$, Me–C(2)); 0.71 (*s*, Me–C(1)); 0.66 (*s*, Me–C(1)). Anal. calc. for $C_{16}H_{26}O_2$: C 72.14, H 9.84; found: C 72.08, H 9.81.

Data of (+)-**10**: Chiral GC (corresponding acetate): t_R 27.65; ee 98%. $[\alpha]_D^{20} = +16$ ($c = 1.0$, CH_2Cl_2). ^{1}H-NMR: consistent with that of the racemic starting material.

13. *(−)-(2R,4R,5S,6R,9R)-4,5-Epoxy-4,5-dihydro-α-ironol* ((−)-**10**). (+)-**12** (3.2 g, 0.012 mol) was hydrolyzed with 85% KOH (1.18 g, 0.018 mol) in MeOH (25 ml), to afford, after CC (hexane/AcOEt 7:3), enantiomerically pure (−)-**10** (2.39 g, 89%), $[\alpha]_D^{20} = -14$ ($c = 1.05$, CH_2Cl_2). ^{1}H-NMR: consistent with that of (±)-**10**.

14. *(+)-(2S,4S,5R,6S,9R)-4,5-Epoxy-4,5-dihydro-α-ironol Acetate* ((+)-**13**) *and (−)-(2R,4R,5S,6R,9S)-4,5-Epoxy-4,5-dihydro-α-ironol* ((−)-**11**). According to *Exper. 7*, with (±)-**11** (5.5 g, 0.025 mol), lipase PS (*Pseudomonas cepacia*; 6 g), vinyl acetate (10 ml), and ^{t}BuOMe (80 ml): (+)-**13** (2.72 g, 41%) and (−)-**11** (2.13 g, 38%).

Data of (+)-**13**: Chiral GC: t_R 27.83; enantiomerically pure. $[\alpha]_D^{20} = 89$ ($c = 1.55$, CH_2Cl_2). ^{1}H-NMR: 5.58 (*m*, 2 olef. H); 5.37 (*quint.*, $J = 6.5$, H–C(9)); 2.97 (*m*, H–C(4)); 2.11 (*d*, $J = 10$, 1 H); 2.04 (*s*, MeCOO); 1.96 (*ddd*, $J = 14.4$, 4.1, 1.1, H_{eq}–C(3)); 1.51 (*td*, $J = 14.4$, 2.1, H_{ax}–C(3)); 1.40 (*m*, H–C(2)); 1.35 (*d*, $J = 6.5$, Me(10)); 1.15 (*s*, Me–C(5)); 0.80 (*d*, $J = 7$, Me–C(2)); 0.73 (*s*, Me–C(1)); 0.66 (*s*, Me–C(1)). Anal. calc. for $C_{16}H_{26}O_2$: C 72.14, H 9.84; found: C 72.19, H 9.93.

Data of (−)-**11**: Chiral GC (corresponding acetate): t_R 27.43; ee 98%. $[\alpha]_D^{20} = -38$ ($c = 0.95$, CH_2Cl_2). ^{1}H-NMR: consistent with that of the racemic starting material.

15. *(+)-(2S,4S,5R,6S,9R)-4,5-Epoxy-4,5-dihydro-α-ironol* ((+)-**11**). Acetate (+)-**13** (2.7 g, 0.010 mol) was hydrolyzed with 85% KOH (1.0 g, 0.015 mol) in MeOH (25 ml), to afford, after CC (hexane/AcOEt 7:3), enantiomerically pure (+)-**11** (1.93 g, 86%). $[\alpha]_D^{20} = +32$ ($c = 1.2$, CH_2Cl_2): ^{1}H-NMR: consistent with that of (±)-**11**.

16. *(−)-(2R,4R,5S,6R)-4,5-Epoxy-4,5-dihydro-α-irone* ((−)-**5**). In separate experiments, (−)-**10** (2.3 g, 0.010 mol) and (−)-**11** (2.10 g, 0.0094 mol) were oxidized with MnO_2 (0.015 mol, 1.30 g) in CH_2Cl_2 (30 ml), to afford the same enantiomer (−)-**5**. The two samples of (−)-**5** were combined (3.77 g, 0.017 mol), thus providing an overall yield from (±)-**5** of 25%. (−)-**5**: Chiral GC: t_R 25.41; ee 98%. $[\alpha]_D^{20} = -18$ ($c = 1.45$, CH_2Cl_2).

17. *(+)-(2S,4S,5R,6S)-4,5-Epoxy-4,5-dihydro-α-irone* ((+)-**5**). In separate experiments, (+)-**10** (2.3 g, 0.010 mol) and (+)-**11** (1.90 g, 0.0085 mol) were oxidized with MnO_2 (0.015 mol, 1.30 g) in CH_2Cl_2 (30 ml), to afford the same enantiomer (+)-**5**. The two samples of (+)-**5** were combined (3.55 g, 0.016 mol), thus providing an overall yield from (±)-**5** of 24%. (+)-**5**: Chiral GC: t_R 25.78; ee 98%. $[\alpha]_D^{20} = +21$ ($c = 1.15$, CH_2Cl_2).

18. *General Procedure for the Conversion of Epoxy-α-irones to α-Irones.* In separate experiments, epoxy-α-irone (−)-**4**, (+)-**4**, (−)-**5**, or (+)-**5** was deoxygenated according to the following procedure to afford α-irone **1a** ((−)-*trans*)), **1b** ((+)-*trans*), **1c** ((+)-*cis*), or **1d**, ((−)-*cis*), respectively. Chlorotrimethylsilane (1.63 g, 0.015 mol)

was added dropwise to a soln. of NaI (4.5 g, 0.03 mol) in dry MeCN (10 ml) under N_2. After a few min, a soln. of epoxy-α-irone (2.22 g, 0.01 mol) in MeCN (5 ml) was added. After stirring at r.t. for 30 min, the mixture was poured into 4N sodium thiosulfate and extracted with AcOEt. The org. layer was dried (Na_2SO_4) and evaporated, and the residue chromatographed (hexane): **1a**–**d**.

Data of (−)-trans-α-Irone (=*(*E*)-4-[(1*R*,5*R*)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-one*; **1a**): Yield 60%. After bulb-to-bulb distillation, 88% chemical purity (GC). Chiral GC: t_R 21.28; ee 98%. $[\alpha]_D^{20} = -400$ ($c = 1.05$, CH_2Cl_2) [7a]: $[\alpha]_D^{20} = -420$ ($c = 0.98$, CH_2Cl_2)). ^{1}H-NMR: 6.67 (*dd*, *J* = 15, 10, H−C(7)); 6.01 (*d*, *J* = 15, H−C(8)); 5.47 (*m*, H−C(4)); 2.30 (*m*, 1 H); 2.26 (*s*, MeCO); 2.05 (*m*, 1 H); 1.71 (*m*, 1 H), 1.64 (*m*, 1 H); 1.55 (*m*, Me−C(5)); 0.88 (*s*, Me−C(1)); 0.85 (*d*, *J* = 7, Me−C(2)); 0.82 (*s*, Me−C(1)).

Data of (+)-trans-α-Irone (=*(*E*)-4-[(1*S*,5*S*)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-one*; **1b**): Yield 57%. After bulb-to-bulb distillation, 96% chemical purity (GC). Chiral GC: t_R 21.72; ee 98%. $[\alpha]_D^{20} = +427$ ($c = 0.95$, CH_2Cl_2) ([9a]: $[\alpha]_D^{20} = +432$ ($c = 2.85$, CH_2Cl_2; 86% ee)). ^{1}H-NMR: in accordance with that of **1a**.

Data of (+)-cis-*α-Irone* (=*(*E*)-4-[(1*S*,5*R*)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-one*; **1c**): Yield 63%. After bulb-to-bulb distillation, 81% chemical purity (GC). Chiral GC: t_R 22.69; ee 98%. $[\alpha]_D^{20} = +117$ ($c = 1.5$, CH_2Cl_2) ([7a]: $[\alpha]_D^{20} = +111$ ($c = 0.92$, CH_2Cl_2)). ^{1}H-NMR: 6.65 (*dd*, *J* = 15.7, 11, H−C(7)); 6.12 (*d*, *J* = 15.7, H−C(8)); 5.52 (*m*, H−C(5)); 2.55 (*m*, 1 H); 2.28 (*s*, MeCO); 1.5–1.8 (*m*, 2 H); 1.53 (*m*, Me−C(5)); 1.46 (*m*, 1 H); 0.88 (*d*, *J* = 6, Me−C(2)); 0.86 (*s*, Me−C(1)); 0.71 (*s*, Me−C(1)).

Data of (−)-cis-*α-Irone* (=*(*E*)-4-[(1*R*,5*S*)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-one*; **1d**): Yield 55%. After bulb-to-bulb distillation, 85% chemical purity (GC). Chiral GC: t_R 22.77; ee 98%. $[\alpha]_D^{20} = -130$ ($c = 1.55$, CH_2Cl_2) ([9a]: $[\alpha]_D^{20} = -103.7$ ($c = 0.65$, $CHCl_3$; 86% ee)). ^{1}H-NMR: in accordance with that of **1c**.

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