Enzyme-Mediated Preparation of (+)- and (−)-*β*-Irone and (+)- and (−)-*cis*-*γ*-Irone from *Irone alpha*®

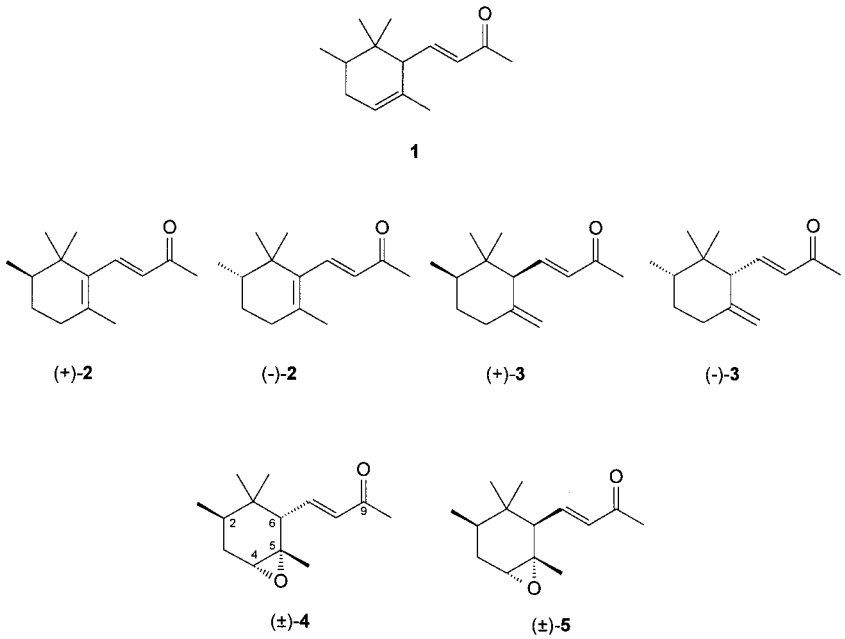
by **Elisabetta Brenna***, **Marco Delmonte**, **Claudio Fuganti**, and **Stefano Serra**

Dipartimento di Chimica del Politecnico di Milano, Centro CNR per lo Studio delle Sostanze Organiche Naturali, Via Mancinelli, 7, I-20131 Milano

The (−)- and (+)-*β*-irones ((−)- and (+)-**2**, resp.), contaminated with *ca.* 7–9% of the (+)- and (−)-*trans*-*α*-isomer, respectively, were obtained from racemic *α*-irone *via* the 2,6-*trans*-epoxide (±)-**4** (*Scheme 2*). Relevant steps in the sequence were the $LiAlH_4$ reduction of the latter, to provide the diastereoisomeric-4,5-dihydro-5-hydroxy-*trans*-*α*-irols (±)-**6** and (±)-**7**, resolved into the enantiomers by lipase-PS-mediated acetylation with vinyl acetate. The enantiomerically pure allylic acetate esters (+)- and (−)-**8** and (+)- and (−)-**9**, upon treatment with $POCl_3$/pyridine, were converted to the *β*-irol acetate derivatives (+)- and (−)-**10**, and (+)- and (−)-**11**, respectively, eventually providing the desired ketones (+)- and (−)-**2** by base hydrolysis and MnO_2 oxidation. The 2,6-*cis*-epoxide (±)-**5** provided the 4,5-dihydro-4-hydroxy-*cis*-*α*-irols (±)-**13** and (±)-**14** in a 3 : 1 mixture with the isomeric 5-hydroxy derivatives (±)-**15** and (±)-**16** on hydride treatment (*Scheme 1*). The $POCl_3$/pyridine treatment of the enantiomerically pure allylic acetate esters, obtained by enzymic resolution of (±)-**13** and (±)-**14**, provided enantiomerically pure *cis*-*α*-irol acetate esters, from which ketones (+)- and (−)-**22** were prepared (*Scheme 4*). The same materials were obtained from the (9*S*) alcohols (+)-**13** and (−)-**14**, treated first with MnO_2, then with $POCl_3$/pyridine (*Scheme 4*). Conversely, the dehydration with $POCl_3$/pyridine of the enantiomerically pure 2,6-*cis*-5-hydroxy derivatives obtained from (±)-**15** and (±)-**16** gave rise to a mixture in which the *γ*-irol acetates **25a** and **25b** and **26a** and **26b** prevailed over the *α*- and *β*-isomers (*Scheme 5*). The (+)- and (−)-*cis*-*γ*-irones ((+)- and (−)-**3**, resp.) were obtained from the latter mixture by a sequence involving as the key step the photochemical isomerization of the *α*-double bond to the *γ*-double bond. External panel olfactory evaluation assigned to (+)-*β*-irone ((+)-**2**) and to (−)-*cis*-*γ*-irone ((−)-**3**) the strongest character and the possibility to be used as dry-down note.

Introduction. – The synthesis of the enantiomerically pure isomers of irones (the C_{14} nor-terpenoid ketone components of the essential oil of *Iris* rhizomes [1]) starting from the components of the 'pool of chirality' [2] is still attracting a great deal of attention [3]. Recently, *Monti et al.* [4] obtained (+)-*cis*-*γ*-irone from naturally occurring (+)-(2*R*,5*R*)-*trans*-dihydrocarvone. Prompted by this report, we refer now on the synthesis of (+)- and (−)-*β*-irone ((+)- and (−)-**2**, resp.) and of (+)- and (−)-*cis*-*γ*-irone ((+)- and (−)-**3**, resp.) from *Irone alpha*®, the commercially available 55 : 45 mixture of racemic *trans*- and *cis*-*α*-irone **1**, containing 5% of the *β*-isomer. This is part of a wider study designed to obtain the olfactory active enantiomeric forms of potent odorants from readily available racemic materials [5][6] by enzymic procedures.

Relevant intermediates in the preparation of (+)- and (−)-**2** and (+)- and (−)-**3** were the 2,6-*trans*- and 2,6-*cis*-epoxides (±)-**4** and (±)-**5**, which we had already exploited in a previous synthesis of (+)- and (−)-*trans*-*α*-irone and (+)- and (−)-*cis*-*α*-irone from *Irone alpha*® (**1**) [6]. Indeed, direct peracid treatment of the *trans/cis* mixture **1** led to a mixture of (±)-**4** and (±)-**5**, which were separated by column chromatography (CC; SiO_2). The single enantiomers of the diastereoisomerically pure species (±)-**4** and (±)-**5** were prepared in a sequence starting with the acetylation by



vinyl acetate, in the presence of lipase PS, of the single diastereoisomeric alcohols obtained upon $NaBH_4$ reduction. The (9*R*)-allyl alcohols, obtained by hydrolysis of the enzymically generated esters, and the (9*S*)-enantiomers, recovered unreacted after acetylation, were oxidized with MnO_2, to afford (+)- and (−)-**4** and (+)- and (−)-**5**. These latter derivatives provided (+)- and (−)-*trans*-α-irone and (+)- and (−)-*cis*-α-irone, respectively, by a deoxygenation reaction.

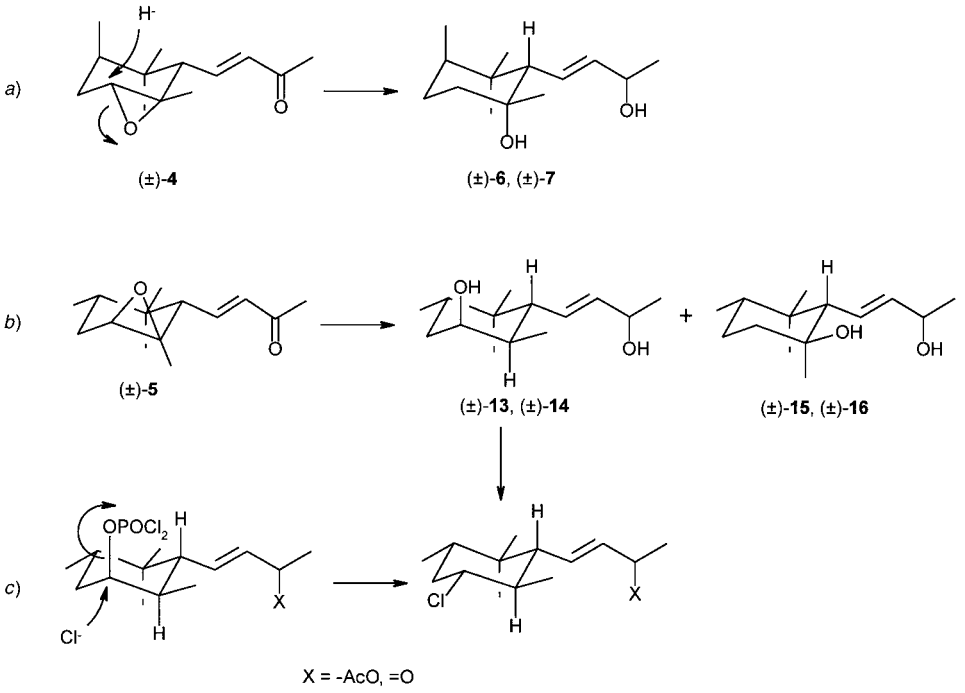
The access to (±)-**4** and (±)-**5** from *trans*/*cis*-α-irone **1** became much simpler thanks to the observation that (±)-**5** crystallized nicely from the crude oily epoxidation mixture by seeding at low temperature. Its recovery was then possible by filtration of the mixture taken up with cold pentane. This additional feature of a practical nature induced us to attempt the synthesis of some other naturally occurring irone isomers [7], *i.e.*, of *trans*- and *cis*-γ-irone and β-irone, starting from racemic *trans*- and *cis*-α-irone epoxide (±)-**4** and (±)-**5**. We report now the results of this study.

Results and Discussion. – To convert α-irone epoxides (±)-**4** and (±)-**5** to derivatives of the other skeletal series, *i.e.*, to *trans*- and *cis*-γ-irone and β-irone, which differ by the position of the C=C bond in the cyclohexane ring, we considered useful the reductive opening of the 4,5-oxirane moiety to the corresponding alcohols at position 5, followed by dehydration under conditions leading either to the exocyclic or to the more-substituted endocyclic 5,6-double bond.

*Enantiomeric β-Irones (+)- and (−)-***2** *from Racemic Epoxy*-trans-α-*irone (±)-***4**. Racemic (±)-**4** was refluxed in tetrahydrofuran (THF) in the presence of $LiAlH_4$ (5 mol-equiv.) for 48 h, affording diols (±)-**6** and (±)-**7** in a *ca.* 1:1 ratio (*Scheme 1*,*a*). These products crystallized nicely from hexane, once separated by CC (SiO_2). The

relative configuration at the stereocenters characterizing derivatives (±)-**6** and (±)-**7** was first assigned on the basis of the following considerations: *a*) Hydride attack at the less-substituted C-atom should afford the tertiary alcohol with the OH group on the same side as the side chain, through the highly favored *trans*-diaxial opening [8] of the oxirane ring (*Scheme 1*,*a*). This is in accordance with what was reported for the reduction of 4,5-epoxy-4,5-dihydro-α-ionone showing the same relative configuration at C(5) and C(6) [9]. *b*) The relative configuration at C(9) and C(6) was assigned by comparison of derivatives (±)-**6** and (±)-**7** with the same diols obtained by $LiAlH_4$ reduction of the known (2*RS*,4*RS*,5*SR*,6*SR*,9*SR*)-4,5-epoxy-4,5-dihydro-*trans*-α-irol and of its (9*RS*)-diastereoisomer [6].

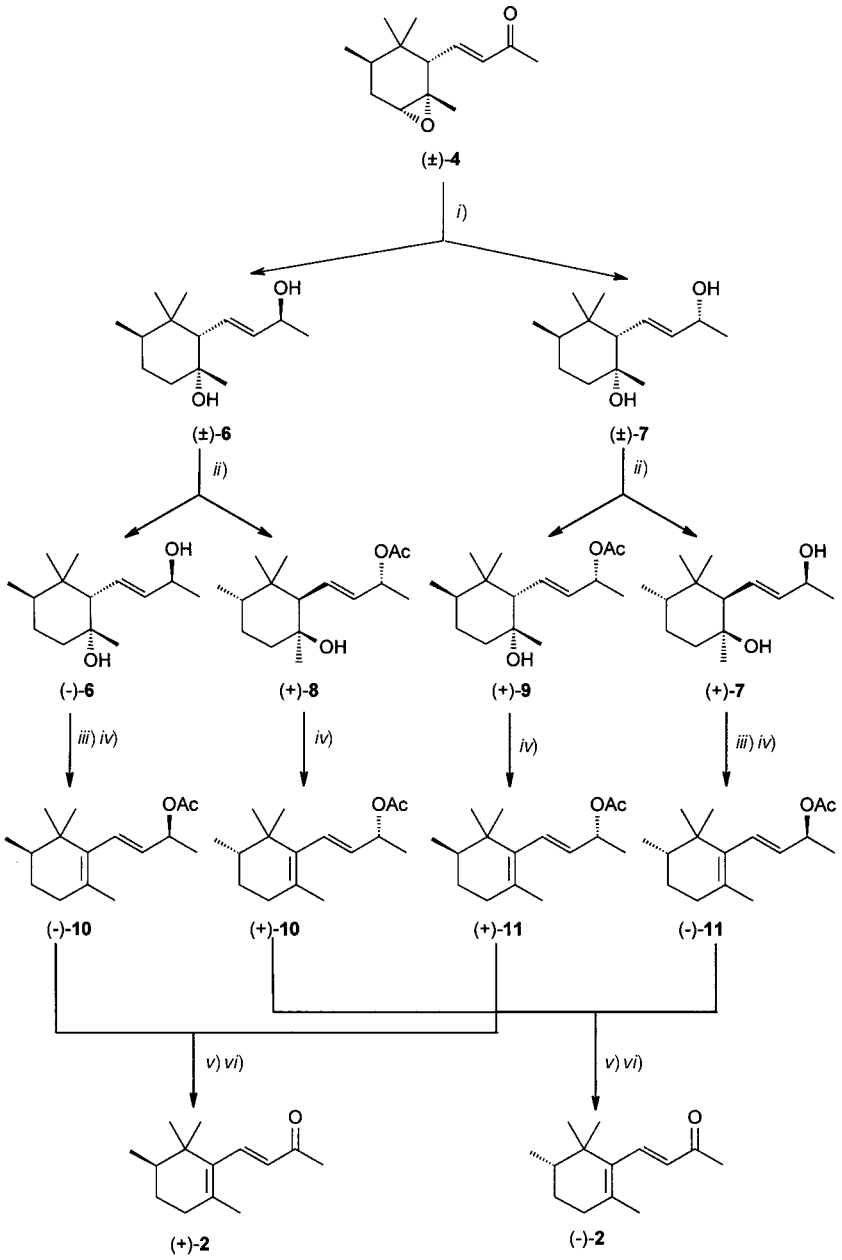
Scheme 1



This configurational assignment was confirmed by NOE experiments performed on (±)-**7**. The following strong and useful NOEs were observed: *i*) between Me–C(2) and H–C(6) (2,6-*trans*-configuration); *ii*) between Me–C(5) and H_{ax}–C(4) and H–C(6) (*anti* relation between Me–C(5) and the side chain at C(6)).

In enzymic acetylation experiments, diols (±)-**6** and (±)-**7** showed a behavior very similar to that of their 4,5-epoxy precursors [6]. As a matter of fact, they were converted to the corresponding (9*R*)-acetate esters (+)-**8** and (+)-**9**, respectively, upon treatment with vinyl acetate in the presence of lipase PS in *t*-butyl methyl ether (^{t}BuOMe) solution (*Scheme 2*). On the contrary, they did not react when *Candida cylindracea* lipase (CCL) or *Porcine pancreatic* lipase (PPL) were employed as catalysts.

Scheme 2



i) $LiAlH_4$, THF. *ii*) Lipase PS, ^{t}BuOMe, vinyl acetate; column chromatography. *iii*) Ac_2O, pyridine. *iv*) $POCl_3$, pyridine. *v*) KOH, MeOH. *vi*) MnO_2, CH_2Cl_2.

The (9*R*)-configuration was assigned to (+)-**8** and (+)-**9** on the basis of the preference shown by lipase PS for the acetylation of (*R*)-alcohols of this structural series [5][6]. The enantiomer excesses (ee) of acetyl derivatives (+)-**8** and (+)-**9** and of the surviving alcohols (−)-**6** and (+)-**7** were inferred from those of their transformation products, *i.e.* the β-irol acetates (+)-**10**, (+)-**11**, (−)-**10**, and (−)-**11**, respectively.

Products structurally similar to (+)-**8** and (+)-**9**, showing a C(Me)OH moiety at C(5) of a 1,1-dimethyl-6-alkyl-substituted cyclohexane ring, had been previously converted to exo-cyclic-methylene derivatives, for example, by *Ohloff* and *Mignat* [10] on thermal treatment of the corresponding tertiary acetate ester in the synthesis of dihydro-γ-ionone. We first investigated the dehydration of the tertiary-alcohol moiety of allylic monoacetates (+)-**8** and (+)-**9** by reaction with $POCl_3$ in pyridine, as it was reported to proceed with high stereo- and regioselectivity [11]. In the synthesis of isotheaspirane [12], by means of this reagent, *Weyerstahl* and co-workers converted an intermediate resembling (+)-**8** and (+)-**9** into a mixture of unsaturated products in which the ratio of the isomer with the exo-cyclic-methylene group to that possessing the 4,5-double bond was *ca.* 95 :5.

At room temperature, monoacetate (+)-**8** reacted slowly with $POCl_3$, the conversion being complete after one week. β-Irol acetate (+)-**10** (ee = 99% by chiral GC) was obtained in 90% yield, contaminated by 9% of the (−)-*trans*-α-isomer. The γ-isomer was not detected by GC/MS among the reaction products. The components of the oily mixture could not be separated by chromatography and the same was true for the alcohols obtained by basic hydrolysis. A purification of β-irol from the contaminating *trans*-α-isomer was attempted by fractional crystallization of the 4-nitrobenzoate ester, obtained as low melting crystals from cold hexane. However, the ratio of the isomers in the mixture recovered from the base hydrolysis of the ester (50% recovery from the crystallization solvent) was substantially unaltered with respect to that of the starting material.

The sequence described for (+)-**8** was extended (*Scheme 2*) to (+)-**9** and to the acetyl derivatives of (−)-**6** and (+)-**7**, which yielded a similar distribution of isomers. The (2*R*)-diastereoisomeric β-irol acetate esters (−)-**10** and (+)-**11** were then pooled, hydrolyzed, and oxidized with MnO_2 to provide (+)-(2*R*)-β-irone ((+)-**2**) in high yield. Similarly, from (+)-**10** and (−)-**11**, the (−)-(2*S*)-enantiomer (−)-**2** was obtained. Thus far, (+)-**2** and (−)-**2** prepared by this synthetic sequence were contaminated by (−)-*trans*-α-irone (9%, by GC/MS) and (+)-*trans*-α-irone (7%, by GC/MS), respectively. This made the definition of the enantiomer purity by optical measurements very difficult.

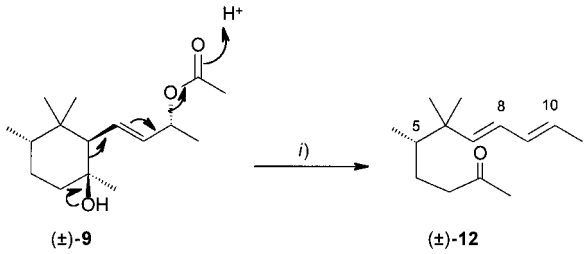
Reports on the characterization of the enantiomers of β-irone were scarce, despite of the fact that this compound is present in *Iris* extracts [7]. This is really a minor component. Mixtures highly enriched in β-irone could be obtained upon equilibration of the α- and γ-isomers [13] in basic medium. Thus, product (+)-**2**, containing a minute but definite amount of (+)-*cis*-γ-irone ((+)-**3**), obtained *via* base isomerization of the natural extract originally used by *Ruzicka* for the structure-elucidation studies, was assigned a specific optical rotation of +33 in CH_2Cl_2 (calculated value +59) as deduced by *Rautenstrauch* and *Ohloff* [13]. *Chapuis* and *Brauchli* [3d] found $[\alpha]_D^{20} = -65.0$ for the (−)-enantiomer (−)-**3** (86% ee), prepared by synthesis and purified by prep. GC. Unfortunately, our samples of (+)-**2** and (−)-**2** were contaminated with (−)-

and (+)-*trans*-α-irone, whose specific optical rotations ($[\alpha]_D^{20} = -420$ ($c = 0.98$, CH_2Cl_2) and $[\alpha]_D^{20} = +427$ ($c = 0.95$, CH_2Cl_2) [6]) were opposite in sign and of much higher numerical value than those of the β-irone enantiomers[1]).

The enantiomer purity of the two β-irone samples (+)- and (−)-**2** was then assessed by a spectroscopic NMR method based on the use of chiral shift reagents. In the ^{1}H-NMR spectrum of racemic β-irone, on progressive addition of [Eu(hfc)$_3$] (hfc = 3-[(heptafluoropropyl)hydroxymethylene]camphorate), the two *s* corresponding to Me−C(5) (δ(H) 1.73) and to one of the geminal Me−C(1) (δ(H) 1.06), were shifted downfield (δ(H) 2 and 1.8, resp.) and split into two lines each ($\Delta\delta = 0.01$ ppm for both signals, with chiral shift reagent/substrate 4.6:1). By this method, the two β-irone samples (+)- and (−)-**2** were found to be enantiomerically pure (see *Exper. Part* for details).

To verify whether a different regiochemical course of dehydration could be achieved, we experimented with reaction conditions other than the concerted elimination of phosphate ester promoted by $POCl_3$ and affording β-irone. Thus, the tertiary alcohol (±)-**9** did not react at room temperature by treatment either with pyridinium 4-toluenesulfonate in EtOH, or with 4-toluenesulfonic acid in toluene, or with thionyl chloride/pyridine in $CHCl_3$. However, it was soon converted to a complex mixture of decomposition products, by forcing the reaction conditions. Catalytic 85% perchloric acid in THF at 0° rapidly converted (±)-**9** to (7*E*,9*E*)-5,6,6-trimethylundeca-7,9-dien-2-one ((±)-**12**) (*Scheme 3*). The C-skeleton fragmentation thus described was likely initiated by the protonation of the allylic acetate at position 9.

Scheme 3



(±)-**9** (±)-**12**

i) Cat. 85% $HClO_4$ in THF.

Enantiomeric cis-α-*Irones (+)- and (−)-***22** *and Enantiomeric* cis-γ-*Irones (+)- and (−)-***3** *from Racemic Epoxy*-cis-α-*irone* (±)-**5**. When the sequence of chemo-enzymatic reactions was applied to epoxy-*cis*-α-irone (±)-**5**, a different synthetic course was observed: the final products were the enantiomerically enriched forms of *cis*-α-irone and *cis*-γ-irone.

The first difference between (±)-**4** and (±)-**5** was the mode of reaction with $LiAlH_4$. The reduction of (±)-**5** was much slower than that of (±)-**4**, and it afforded a *ca.* 3:1

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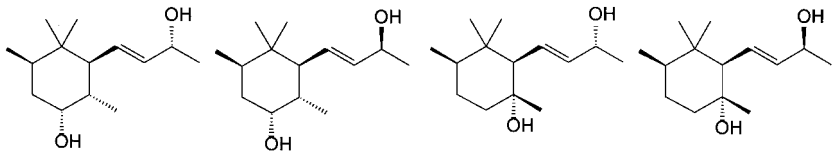
[1]) Taking into account the chemical composition of the two samples of β-irone ((+)-**2**: 91% of β-irone and 9% of (−)-*trans*-α-irone, by GC/MS; (−)-**2**: 93% of β-irone and 7% of (+)-*trans*-α-irone, by GC/MS), we determined an extrapolated value of specific optical rotation for enantiomerically pure β-irone of *ca.* ± 60 from the measured values of $[\alpha]_D^{20} = +17.1$ ($c = 1.45$, CH_2Cl_2) and $[\alpha]_D^{20} = -20.2$ ($c = 2.30$, CH_2Cl_2).

mixture of 4,5-dihydro-4-hydroxy-*cis*-α-irols (±)-**13** and (±)-**14** and 4,5-dihydro-5-hydroxy-*cis*-α-irols (±)-**15** and (±)-**16** (*Scheme 1*, *b*). Each component of the mixture was separated by column chromatography (SiO_2), the 4-hydroxy isomers (±)-**13** and (±)-**14** being eluted first.

In a previous work [6], we had shown by X-ray analysis that, in the derivative (±)-**5**, the oxirane ring was in '*anti*' relation to the side chain at C(6). Thus, this course of epoxide opening could be tentatively explained on the basis of a competition between the hydride attack at the most-hindered C-atom C(5), leading to a highly favored *trans*-diaxial opening in a chair-like transition state [8], and the reaction at the less substituted C-atom C(4) (*Scheme 1*, *b*). The resulting configurations of the favored (±)-**13** and (±)-**14** were confirmed by ^{1}H-NMR analysis.

In derivatives (±)-**13** and (±)-**14**, the H-atom at C(4) gave rise to a *q* at *ca.* 3.80 ppm with $J = 3$ Hz, in accordance with its equatorial arrangement and its coupling with $H_{ax}-C(3)$, $H_{eq}-C(3)$, and $H_{ax}-C(5)$ with low coupling constants. Moreover, H–C(6) gave a *dd* with $J = 10$ and 11.3 Hz at 1.83 ppm, thus sustaining the axial position of H–C(5).

Derivatives (±)-**13** to (±)-**16** were submitted to enzymic acetylation with vinyl acetate and lipase PS in ^{t}BuOMe solution, to provide (9*R*)-acetate esters (+)-**17**, (+)-**18**, (+)-**23**, (+)-**24**, respectively, and the (9*S*)-allylic alcohols (+)-**13**, (−)-**14**, (+)-**15**, and (+)-**16**, respectively (see below, *Schemes 4* and *5*). Interestingly enough, the enzyme-mediated transesterification of 4,9-diols (±)-**13** and (±)-**14** afforded only the allylic (9*R*)-acetate esters under these conditions. The assignment of the relative configuration and of the enantiomer purity of this set of materials was based on the direct comparison with the products of $LiAlH_4$ treatment of enantiomerically pure (9*R*)- and (9*S*)-diastereoisomeric epoxy-*cis*-α-irols [6].

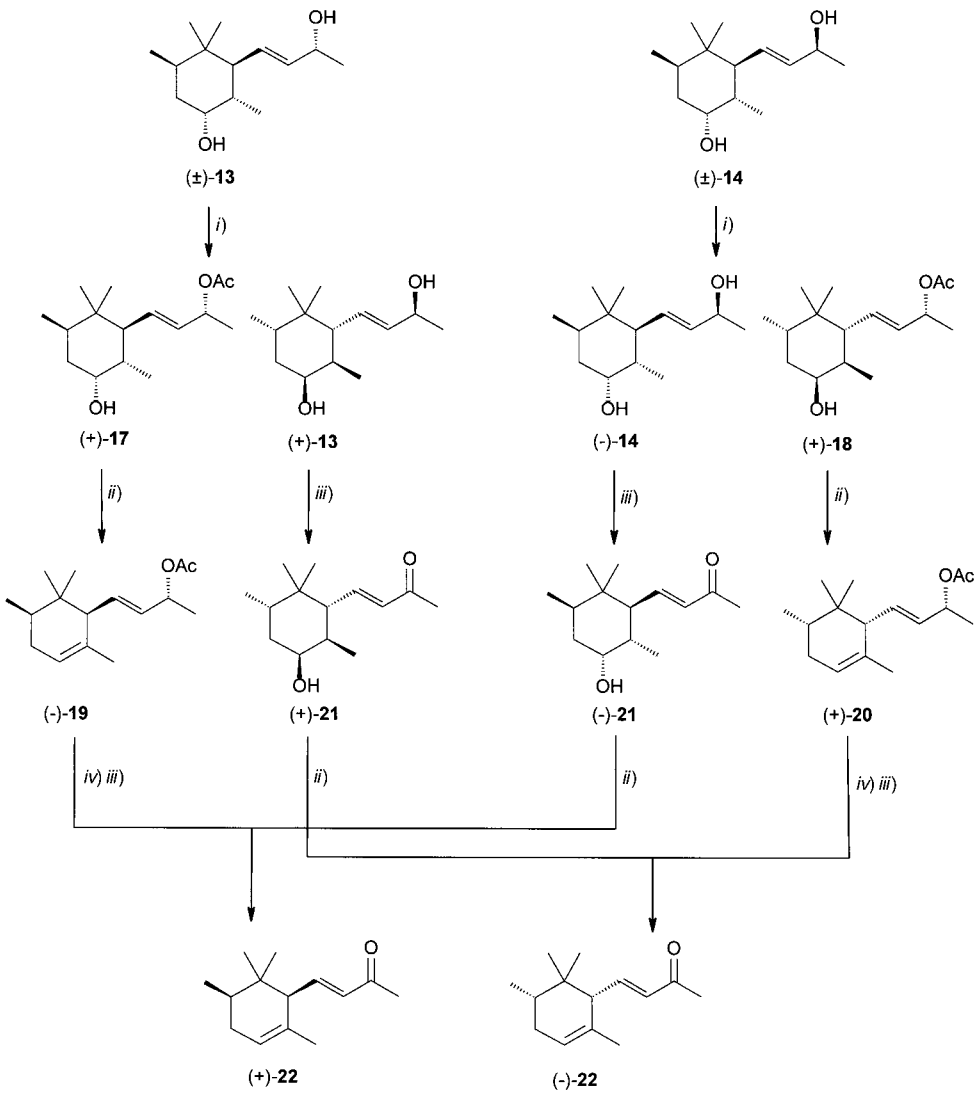


(±)-**13** (±)-**14** (±)-**15** (±)-**16**

The (9*R*)-4,5-dihydro-4-hydroxy-*cis*-α-irol acetate esters (+)-**17** and (+)-**18** and the corresponding (9*S*)-alcohols (+)-**13** and (−)-**14** were converted to *cis*-α-irones (−)- and (+)-**22** by the convergent sequences outlined in *Scheme 4*. Treatment of the acetate esters (+)-**17** and (+)-**18** with $POCl_3$ in pyridine at room temperature [14] provided, within a few minutes, the diastereoisomeric α-irol acetate esters (−)-**19** (ee = 98%, by chiral GC) and (+)-**20** (ee = 97%, by chiral GC) [6][15], respectively. These latter compounds were found to contain 13% (by GC/MS) and 28% (by GC/MS), respectively, of the corresponding 4-chloro derivatives, obtained by Cl-substitution of the intermediate phosphate ester (*Scheme 1*, *c*). Acetates (−)-**19** and (+)-**20** afforded the *cis*-α-irones (+)- and (−)-**22** by basic hydrolysis and MnO_2 oxidation, the purification of the α-irones being possible by CC (removal of the contaminating 4-chloro-4,5-dihydro ketone analogue). The conversion of the diastereoisomeric 4,9-diols (+)-**13** and (−)-**14** into (−)- and (+)-**22**, respectively, by the same route required the

regioselective chemical acetylation of the allylic alcohol. The attempt based on the use of Ac_2O and pyridine in CH_2Cl_2 failed: *ca.* 1:1 mixtures of 4- and 9-monoacetate esters were invariably obtained. However, by inverting the order of application of the reactions of *Scheme 4*, (+)-**13** and (−)-**14** were straightforwardly converted to (−)- and (+)-**22**, respectively. To this end, (+)-**13** and (−)-**14** were first oxidized with MnO_2 to the enantiomeric 4,5-dihydro-4-hydroxy-*cis*-α-irones (+)-**21** and (−)-**21** and then treated with $POCl_3$ in pyridine.

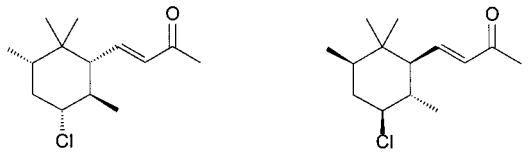
Scheme 4



i) Lipase PS, ^{t}BuOMe, vinyl acetate. *ii*) $POCl_3$, pyridine. *iii*) MnO_2, CH_2Cl_2. *iv*) KOH, MeOH.

This sequence would represent a new simple entry to enantiomerically pure forms of *cis*-α-irone from *Irone alpha*® *via* crystalline epoxy derivative (±)-**5** [6]. However, there is a drawback in the process. As a matter of fact, the $POCl_3$/pyridine treatment of the 4-hydroxy derivatives (+)-**17**, (+)-**18**, (+)-**21**, and (−)-**21** produced also the corresponding 4-chloro-4,5-dihydro analogues in small amounts by nucleophilic substitution, together with the desired dehydration products with the *cis*-α-irone skeleton. The chlorinated compounds were separated by CC and completely characterized as ketone derivatives (+)-**27** (from (+)-**17** and (−)-**21**) and (−)-**27** (from (+)-**18** and (+)-**21**). The configurations of (+)- and (−)-**27** were in accordance with the inversion of the configuration at C(4) promoted by the nucleophilic substitution of the phosphate ester by the Cl-ion (*Scheme 1*, *c*) and was confirmed by ^{1}H-NMR analysis.

The H-atom at C(4) of (−)- or (+)-**27** gave rise to a *ddd* with $J = 4.6, 10.7, 12.1$ Hz at *ca.* 3.5 ppm. This was in accordance with an axial arrangement of this H-atom, involved in two axial-axial couplings (with $H_{ax}-C(3)$ and $H_{ax}-C(5)$), and one axial-equatorial coupling (with $H_{eq}-C(3)$).



(-)-**27** (+)-**27**

The equatorially located Cl-atom could not be eliminated. Various reaction conditions were attempted: ^{t}BuOH/THF, DBU/$CHCl_3$, and 35% KOH/EtOH. Thus, the rapid dehydration of (+)-**17**, (+)-**18**, (+)-**21**, and (−)-**21** occurring by $POCl_3$/pyridine treatment was the result of the *anti*-periplanar elimination of the axially located phosphate ester, together with the axial H−C(5). The competing substitution of the phosphate ester by the Cl^- ion occurred with inversion of configuration at C(4), and the desired 4,5-dehydrohalogenation became very difficult for stereochemical reasons.

The (9*R*)-acetate esters (+)-**23** and (+)-**24** (see below, *Scheme 5*) and their (9*S*)-enantiomers (obtained upon treatment with Ac_2O/pyridine of the alcohols (+)-**15** and (+)-**16**) were also treated with $POCl_3$/pyridine. These materials reacted immediately with $POCl_3$, even at 0°, affording almost quantitatively mixtures of *cis*-γ-, *cis*-α-, and β-irol acetate diastereoisomers in a *ca.* 45 : 35 : 20 ratio. Chiral GC analysis of the reaction mixtures showed conservation of the enantiomer purity during the dehydration process.

The different regiochemistry of the $POCl_3$/pyridine-induced dehydration of the tertiary alcohols of the *trans*-series (derived from (±)-**6** and (±)-**7**; see *Scheme 2*) and of the *cis*-series (derived from (±)-**15** and (±)-**16**; see below, *Scheme 5*) could be tentatively explained, taking into account the precise stereochemical requisites of E_2 elimination. *Anti*-periplanar arrangement of the H-atom and of the other leaving group is required. In such cyclohexane derivatives, this steric condition is best satisfied when the H-atom and, in this case, the phosphate ester are in a *trans*-diaxial relation. The analysis of the chair conformations reported in *Scheme 1* allowed us to draw the following conclusions: *a*) In derivatives (±)-**6** and (±)-**7**, H−C(6) and OH−C(5) are in

trans-diaxial relation. Thus, dehydration of the corresponding allylic acetates to β-derivatives is highly favored. Traces of *trans*-α-irol acetate are due to a competing *anti*-periplanar elimination with the axial H–C(4). *b*) In derivatives (±)-**15** and (±)-**16**, OH–C(5) is equatorial and is eliminated to give *cis*-γ- and cis-α-derivatives preferentially. The distribution of the dehydration products might suggest an E_1 mechanism [16]. The elucidation of the mechanism of this kind of reaction far exceeds the purpose of this work.

The mixture of *cis*-γ-, *cis*-α-, and β-irol acetate diastereoisomers, prepared from (+)- and (−)-**23** and (+)- and (−)-**24**, as well as the alcohols obtained by base hydrolysis, were unseparable by CC (SiO_2). Thus, the amount of the γ-isomers present in the various mixtures was increased by photoisomerization, under conditions similar to those described in the synthesis of presiccanochromene A by *Nozoe* and *Hirai* [17] from an intermediate similar to our products. The irol acetate mixtures were thus irradiated with UV lamps, in ^{i}PrOH solution containing 10% xylene, while the course of the reaction was followed by GC/MS. Within 24 h, the *cis*-α-irol acetate was completely converted into the corresponding *cis*-γ analogue, while the β-isomer almost immediately disappeared, giving rise to various minor products, which were not characterized. As irradiation proceeded, before the conversion of the α-isomer could be completed, we noticed also the formation of the (7*Z*)-isomer of *cis*-γ-irol acetate. At the end of the photoisomerization, CC (SiO_2) allowed us to separate the mixture of (7*Z*)- and (7*E*) *cis*-γ-irol acetate from the more polar products of transformation of the β-isomer. No further purification of the irol mixture obtained by base hydrolysis of the latter acetate esters was possible by CC. During MnO_2 oxidation, (7*Z*)-*cis*-γ-irone [18] was formed together with the (*E*)-isomer, but it was the first to be eluted on CC (SiO_2, 3–4% AcOEt/hexane), thus a final complete separation was possible.

All the mixtures originated from the $POCl_3$/pyridine treatment of (+)- and (−)-**23** and (+)- and (−)-**24** were UV-irradiated (→ **25** and **26**, resp.), pooled according to the configuration at C(2) and C(6), hydrolyzed in alcoholic KOH solution, and then submitted to MnO_2 oxidation and CC purification (*Scheme 5*). The following samples of *cis*-γ-irone were obtained (*Scheme 5*): *a*) (+)-*cis*-γ-irone ((+)-**3**; 96% ee, by chiral GC), containing 5% of (+)-*cis*-α-irone ((+)-**22**) and 3% of (+)-β-irone ((+)-**2**), with $[\alpha]_D^{20} = +9.5$ ($c = 2.15$, CH_2Cl_2), and *b*) (−)-*cis*-γ-irone ((−)-**3**; 97% ee by chiral GC), containing 4.5% of (−)-*cis*-α-irone ((−)-**22**) and 1.5% of (−)-β-irone ((−)-**2**), with $[\alpha]_{20}^D = -6.3$ ($c = 1.05$, CH_2Cl_2). Some discrepancies could be observed in the magnitude of the specific rotations of *cis*-γ-irone reported[2]). It was only possible to conclude that optically pure *cis*-γ-irone was characterized by a very low specific rotation. Our values, however, were altered by the presence of traces of *cis*-α-irone and β-irone showing specific rotations of the same sign. Enantiomer purity was then determined by chiral GC analysis.

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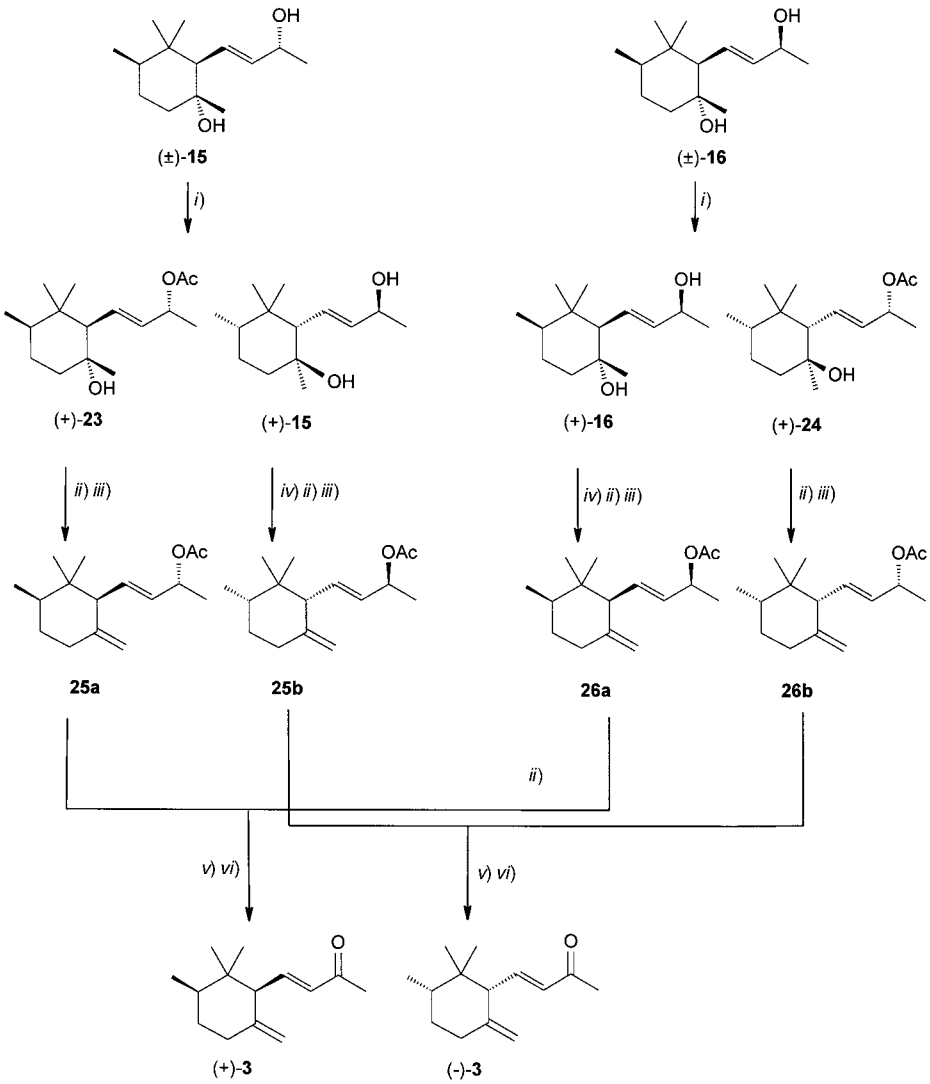
[2]) The following solution data for $[\alpha]$ were available: *i*) [19]: (−)-*cis*-γ-irone, chemical purity (GC) 99%, $[\alpha]_{578}^{20} = -1$ ($c = 0.5$, CH_2Cl_2); (+)-*cis*-γ-irone, chemical purity (GC) 99%, $[\alpha]_{578}^{20} = +2$ ($c = 0.5$, CH_2Cl_2); *ii*) [13a]: (+)-*cis*-γ-irone, $[\alpha]_D^{20} = (+)\text{-}2$ ($c = 0.443$, CH_2Cl_2); *iii*) [3d]: (−)-*cis*-γ-irone, purified from (−)-*trans*-γ-irone by prep. GC, ee 76%, $[\alpha]_D^{20} = -5.3$ ($c = 1.66$, CH_2Cl_2); *iv*) [20]: (−)-*cis*-γ-irone $[\alpha]_D^{20} = -5.3$ ($c = 0.75$, $CHCl_3$); *v*) [4]: (+)-*cis*-γ-irone, de 99%, ee 99%, $[\alpha]_D^{20} = +0.4$ ($c = 3$, $CHCl_3$).

Scheme 5



i) Lipase PS, ^{t}BuOMe, vinyl acetate. *ii*) $POCl_3$, pyridine. *iii*) *hv*, xylene/^{i}PrOH. *iv*) Ac_2O, pyridine. *v*) KOH, MeOH. *vi*) MnO_2, CH_2Cl_2.

Olfactory Evaluation. – The odor descriptions of samples (+)- and (−)-**2** and (+)- and (−)-**3** were performed at *Givaudan-Roure Research Ltd*. (Dübendorf, Switzerland):

(+)-β-Irone ((+)-**2**) (91% chemical purity) possesses a β-ionone-type odor of warm floral-woody tonality with green and anisic aspects. The odor is linear, and the tenacity

of the note is good. It can be considered a dry-down note. This compound is the strongest of the series.

(−)-β-Irone ((−)-**2**) (93% chemical purity) has a woody odor with a distinct honey note, that is quite sweet. Besides, it shows floral ionone-type facets, and a fruity tonality, but also an unpleasant smokey character. It belongs to the ionone-type family, without being very close to β-ionone.

(−)-cis-*γ-Irone* ((−)-**3**) (94% chemical purity) exhibits a β-ionone-type odor of warm floral-woody tonality, and green aspects are present, too. Instead of anisic attributes, the compound shows some fruity nuances, reminiscent of pineapples. The odor is linear; it is the second strongest compound of this series, and it can also be considered a dry-down note. Odor threshold (chiral GC olfactometry): 0.75 ng/l.

(+)-cis-*γ-Irone* ((+)-**3**) shows a floral, fatty, sweet, and woody odor character, an ionone-type odor with slightly sweet aspects. Odor threshhold (chiral GC olfactometry): > 100 ng/l.

Conclusions. – The chemo-enzymatic sequence described here allowed us to prepare enantiomerically enriched samples of six of the ten stereoisomers of irone, starting from the commercial 55 : 45 mixture of racemic *trans*- and *cis*-α-irone **1**. The (+)- and (−)-β-irone, (+)- and (−)-*cis*-α-irone, and (+)- and (−)-*cis*-γ-irone were obtained and fully characterized. The two samples of (+)-β-irone ((+)-**2**) and (−)-*cis*-γ-irone ((−)-**3**) were found to be the strongest of the series, to be eventually used as a dry-down note.

The key intermediates were the two epoxide derivatives (±)-**4** and (±)-**5**, readily prepared from *Irone alpha*®. The different arrangement of the oxirane moiety in relation to the side chain at C(6) was responsible for the different regiochemical course of $LiAlH_4$ reduction of the two epoxides. Thus, (±)-**4** afforded almost exclusively the diastereoisomeric tertiary alcohols (±)-**6** and (±)-**7**, while (±)-**5** provided both the secondary alcohols (±)-**13** and (±)-**14** and the tertiary derivatives (±)-**15** and (±)-**16**.

The axial OH group at C(5) of (±)-**6** and (±)-**7** was lost in the dehydration process affording β-analogues. A completely different and unexpected regiochemical course was observed when the dehydration process involved the equatorial OH group at C(5) of (±)-**15** and (±)-**16**: a mixture of *cis*-α-, *cis*-γ-, and β-irol acetates was obtained, and then enriched in the *cis*-γ-derivative by photoisomerization. Access to the *cis*-γ-analogues was thus found.

$POCl_3$ Treatment of secondary alcohols (±)-**13** and (±)-**14** allowed us to find a route to the *cis*-α-irones alternative to that described in [6].

Work is now in progress to prepare both the enantiomers of *trans*-γ-irone by enzymatic resolution of a suitable derivative obtained from *Irone alpha*®.

The authors are indebted to Dr. *Philip Kraft*, Dr. *Caroline Denis*, and Dr. *Heinz Koch* (*Givaudan-Roure Research Ltd.*, Switzerland) for the odour descriptions and thresholds evaluation of the irone samples. The authors would like to thank *CNR-Progetto Finalizzato Biotecnologie* for financial support.

Experimental Part

General. Irone alpha® was purchased from *IES* (Allauch, France). Lipase PS from *Pseudomonas cepacia* (*Amano Pharmaceuticals Co.*, Japan), *Candida cylindracea* lipase (CCL; *Sigma*, type VII, 900 U mg^{-1}), and porcine pancreatic lipase (PPL, *Sigma*, type II) were employed in this work. Chiral GC analysis: *Chirasil-*

DEX-CB (*Chrompack*) column (25 m × 0.25 mm), *DANI-HT-86.10* gas chromatograph; temp. program: 70° (3 min), then 3.5°/min → 140°, then 8°/min → 180° (1 min). Anal. GC: mass-detection limit *ca.* 10 ng for an injected volume of 1 µl; t_R in min. TLC: *Merck* silica-gel *60 F_{254}* plates. Column chromatography (CC): silica gel. Optical rotations: *Jasco DIP-181* digital polarimeter. ^{1}H-NMR Spectra: $CDCl_3$ solns. at r.t. unless otherwise stated; *Bruker ARX-400* spectrometer (400 MHz ^{1}H); δ in ppm rel. to $SiMe_4$, *J* in Hz, chx = cyclohexane moiety. GC/MS: *HP 6890* gas chromatography, 5773 mass detector, *HP 5MS* column (30 m × 0.25 mm × 0.25 µm); temp. program: 60° (1 min), then 6°/min → 150° (1 min), then 12°/min → 280° (5 min); *m/z* (rel. %). Microanalyses were determined on an analyzer *1106 from Carlo Erba*.

1. *Lithium Aluminium Hydride Reduction of Epoxy-α-irones.* 1.1. *General Procedure 1* (*GP 1*). A mixture of the suitable epoxy-α-irone (30 g, 0.135 mol) and $LiAlH_4$ (25.7 g, 0.676 mol) in THF (500 ml) was refluxed. The mixture was treated with AcOEt and MeOH and then diluted with H_2O. After concentration under reduced pressure, the aq. layer was extracted with AcOEt, the org. phase dried and evaporated, and the residue submitted to CC (hexane/AcOEt 7:3).

1.2. *(±)-(2*RS*,5*RS*,6*SR*,9*SR*)-4,5-Dihydro-5-hydroxy*-trans-*α-irol* (= *(1*RS*,2*SR*,4*RS*)-2-[(1*E*,3*SR*)-3-Hydroxybut-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (±)-**6**) *and (±)-(2*RS*,5*RS*,6*SR*,9*RS*)-4,5-Dihydro-5-hydroxy*-trans-*α-irol* (= *(1*RS*,2*SR*,4*RS*)-2-*[(1E,*3*RS*)-3-Hydroxybut-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (±)-**7**). According to *GP 1*, (±)-(2*RS*,4*RS*,5*SR*,6*SR*)-4,5-epoxy-*trans*-α-irone ((±)-**4**; 30 g, 0.135 mol) gave, after 48 h, the less polar (±)-**6** (12.5 g, 41%) and the more polar (±)-**7** (13.1 g, 43%).

*Data of (±)-***6**: ^{1}H-NMR: 5.76 (*ddd*, *J* = 0.9, 10.3, 15.7, H–C(7)); 5.53 (*dd*, *J* = 6.4, 15.7, H–C(8)); 4.35 (*quint. d*, *J* = 0.9, 6.4, H–C(9)); 2.09 (*tt*, *J* = 4, 13.4, H_{ax}–C(3)); 1.81 (*d*, *J* = 10.3, H–C(6)); 1.64 (*td*, *J* = 4, 13.4, 13.4, H_{ax}–C(4)); 1.55 (*m*, H–C(2)); 1.45 (*dt*, *J* = 4, 4, 13.4, H_{eq}–C(4)); 1.29 (*d*, *J* = 6.4, Me–C(9)); 1.24 (*dq*, *J* = 4, 4, 4, 13.4, H_{eq}–C(3)); 1.10 (*s*, Me–C(5)); 1.09 (*s*, Me_{ax}–C(1)); 0.92 (*d*, *J* = 7, Me–C(2)); 0.78 (*s*, Me_{eq}–C(1)). Anal. calc. for $C_{14}H_{26}O_2$: C 74.29, H 11.58; found: C 74.25, H 11.62.

*Data of (±)-***7**: ^{1}H-NMR: 5.75 (*dd*, *J* = 10.2, 15.2, H–C(7)); 5.50 (*dd*, *J* = 6.4, 15.2, H–C(8)); 4.33 (*quint. J* = 6.4, H–C(9)); 2.07 (*tt*, *J* = 4.3, 13.8, H_{ax}–C(3)); 1.80 (*d*, *J* = 10.2, H–C(6)); 1.62 (*td*, *J* = 4.3, 13.8, 13.8, H_{ax}–C(4)); 1.54 (*m*, H–C(2)); 1.48 (*dt*, *J* = 4.3, 4.3, 13.8, H_{eq}–C(4)); 1.28 (*d*, *J* = 6.4, Me–C(9)); 1.24 (*dq*, *J* = 4.3, 4.3, 4.3, 13.8, H_{eq}–C(3)); 1.14 (*s*, Me–C(5)); 1.07 (*s*, Me_{ax}–C(1)); 0.91 (*d*, *J* = 7, Me–C(2)); 0.75 (*s*, Me_{eq}–C(1)). Anal. calc. for $C_{14}H_{26}O_2$: C 74.29, H 11.58; found: C 74.33, H 11.54.

1.3. *(±)-(2*RS*,5*RS*,6*RS*,9*RS*)-4,5-Dihydro-5-hydroxy*-cis-*α-irol* (= *(1*RS*,2*RS*,4*RS*)-2-[(1*E*,3*RS*)-3-Hydroxybut-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (±)-**15**), *(±)-(2*RS*,5*RS*,6*RS*,9*SR*)-4,5-Dihydro-5-hydroxy*-cis-*α-irol* (= *(1*RS*,2*RS*,4*RS*)-2-[(1*E*,3*SR*)-3-Hydroxybut-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (±)-**16**), *(±)-(2*RS*,4*RS*,5*SR*,6*SR*,9*RS*)-4,5-Dihydro-4-hydroxy*-cis-*α-irol* (= *(1*RS*,2*SR*,3*SR*,5*RS*)-3-[(1*E*,3*RS*)-3-Hydroxybut-1-enyl]-2,4,4,5-tetramethylcyclohexanol*; (±)-**13**), *(±)-(2*RS*,4*RS*,5*SR*,6*SR*,9*SR*)-4,5-Dihydro-4-hydroxy*-cis-*α-irol* (= *(1*RS*,2*SR*,3*SR*,5*RS*)-3-[(1*E*,3*SR*)-3-Hydroxybut-1-enyl]-2,4,4,5-tetramethylcyclohexanol*; (±)-**14**). According to *GP 1*, (±)-(2*RS*,4*RS*,5*SR*,6*RS*)-4,5-epoxy-*cis*-α-irone ((±)-**5**; 40 g, 0.180 mol) gave, after 96 h, the less polar (±)-**13** (13.4 g, 33%), then in this elution order (±)-**14** (11.80 g, 29%), (±)-**15** (4.07 g, 10%), and (±)-**16** (4.48 g, 11%).

*Data of (±)-***13**: ^{1}H-NMR: 5.50 (*dd*, *J* = 6.4, 15.2, H–C(8)); 5.34 (*dd*, *J* = 10, 15.2, H–C(7)); 4.30 (*quint.*, *J* = 6.4, H–C(9)); 3.80 (*q*, *J* = 3, H–C(4)); 1.83 (*dd*, *J* = 10, 11.5, H–C(6)); 1.68 (*m*, 1 H); 1.65–1.45 (*m*, 3 H); 1.27 (*d*, *J* = 6.4, (Me–C(9)); 0.87 (*s*, Me–C(1)); 0.83 (*d*, *J* = 7, Me–C(2), Me–C(5)); 0.69 (*s*, Me_{eq}–C(1)). Anal. calc. for $C_{14}H_{26}O_2$: C 74.29, H 11.58; found: C 74.32, H 11.56.

*Data of (±)-***14**. ^{1}H-NMR: 5.50 (*dd*, *J* = 6.4, 15.7, H–C(7)); 5.34 (*dd*, *J* = 10, 15.7, H–C(7)); 4.30 (*quint. J* = 6.4, H–C(9)); 3.81 (*q*, *J* = 3, H–C(4)); 1.83 (*dd*, *J* = 10, 11.8, H–C(6)); 1.68 (*m*, 1 H); 1.65–1.45 (*m*, 3 H); 1.28 (*d*, *J* = 6.4, Me–C(9)); 0.88–0.80 (2*d*, *s*, *J* = 7, Me–C(5), Me–C(2), Me–C(1)); 0.67 (*s*, Me–C(1)). Anal. calc. for $C_{14}H_{26}O_2$: C 74.29, H 11.58; found: C 74.27, H 11.65%.

*Data of (±)-***15**: ^{1}H-NMR: 5.69 (*m*, H–C(7), H–C(8)); 4.35 (*m*, H–C(9)); 1.77 (*m*, 2 H); 1.45 (*m*, 2 H); 1.30 (*d*, *J* = 6.4, Me–C(9)); 1.22 (*m*, 2 H); 1.15 (*s*, Me–C(5)); 0.84 (*s*, *d*, *J* = 7, Me–C(1), Me–C(2)); 0.75 (*s*, Me–C(1)). Anal. calc. for $C_{14}H_{26}O_2$: C 74.29, H 11.58; found: C 74.34, H 11.61.

*Data of (±)-***16**: ^{1}H-NMR: 5.69 (*m*, H–C(7), H–C(8)); 4.35 (*m*, H–C(9)); 1.77 (*m*, 2 H); 1.46 (*m*, 2 H); 1.30 (*d*, *J* = 6.4, Me–C(9)); 1.23 (*m*, 2 H); 1.15 (*s*, Me–C(5)); 0.84 (*s*, *d*, *J* = 7, Me–C(1), Me–C(2)); 0.75 (*s*, Me–C(1)). Anal. calc. for $C_{14}H_{26}O_2$: C 74.29, H 11.58; found: C 74.30, H 11.53.

2. *Lipase PS-Mediated Acetylation.* 2.1. *General Procedure (GP 2).* A mixture of the suitable allyl alcohol (10 g, 0.044 mol), lipase PS (*Pseudomonas cepacia*; 10 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).

2.2. *(−)-(2*R*,5*R*,6*S*,9*S*)-4,5-Dihydro-5-hydroxy*-trans-*α-irol* (*=(1*R*,2*S*,4*R*)-2-[(1*E*,3*S*)-3-hydroxybut-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (−)-**6**) *and (+)-(2*S*,5*S*,6*R*,9*R*)-4,5-Dihydro-5-hydroxy*-trans-*α-irol Acetate* (*=(1*S*,2*R*,4*S*)-2-[(1*E*,3*R*)-3-(Acetyloxy)but-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (+)-**8**). According to *GP 2*, (±)-**6** (12.5 g, 0.055 mol) gave the less polar (+)-**8** (6.08 g, 41%) and the more polar (−)-**6** (4.75 g, 38%).

*Data of (+)-***8**: $[\alpha]_{20}^{D} = +102.6$ ($c = 0.62$, CH_2Cl_2). ^{1}H-NMR: 5.83 (*ddd*, $J = 0.9$, 10.3, 15.2, H−C(7)); 5.45 (*dd*, $J = 6.4$, 15.2, H−C(8)); 5.35 (*quint. d*, $J = 0.9$, 6.4, H−C(9)); 2.09 (*tt*, $J = 4$, 13.2, H_{ax}−C(3)); 2.03 (*s*, MeCOO); 1.79 (*d*, $J = 10.3$, H−C(6)); 1.63 (*td*, $J = 4$, 13.2, 13.2, H_{ax}−C(4)); 1.54 (*m*, H−C(2)); 1.44 (*dt*, $J = 4$, 4, 14.2, H_{eq}−C(4)); 1.32 (*d*, $J = 6.4$, Me−C(9)); 1.24 (*dq*, $J = 4$, 4, 4, 14.2, H_{eq}−C(3)); 1.10 (*s*, Me−C(5)); 1.08 (*s*, Me−C(1)); 0.91 (*d*, $J = 7$, Me−C(2)); 0.75 (*s*, Me−C(1)). Anal. calc. for $C_{16}H_{28}O_3$: C 71.60, H 10.52; found: C 71.55, H 10.54%.

*Data of (−)-***6**: $[\alpha]_{20}^{D} = -66.8$ ($c = 0.75$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (±)-**6**.

2.3. *(+)-(2*S*,5*S*,6*R*,9*S*)-4,5-Dihydro-5-hydroxy*-trans-*α-irol* (*=(1*S*,2*R*,4*S*)-2-[(1*E*,3*S*)-3-Hydroxybut-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (+)-**7**) *and (+)-(2*R*,5*R*,6*S*,9*R*)-4,5-Dihydro-5-hydroxy*-trans-*α-irol Acetate* (*=(1*R*,2*S*,4*R*)-2-[(1*E*,3*R*)-3-(Acetyloxy)but-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (+)-**9**). According to *GP 2*, (±)-**7** (13.1 g, 0.058 mol) gave the less polar (+)-**9** (6.52 g, 42%) and the more polar (+)-**7** (5.37 g, 41%).

*Data of (+)-***9**: $[\alpha]_{20}^{D} = +25.5$ ($c = 0.38$, CH_2Cl_2). ^{1}H-NMR: 5.82 (*ddd*, $J = 0.9$, 10.3, 15.2, H−C(7)); 5.44 (*dd*, $J = 6.4$, 15.2, H−C(8)); 5.32 (*quint. d*, $J = 0.9$, 6.4, H−C(9)); 2.07 (*tt*, $J = 4.4$, 13.3, H_{ax}−C(3)); 2.03 (*s*, MeCOO); 1.79 (*d*, $J = 10.3$, H−C(6)); 1.70–1.40 (*m*, 3 H); 1.32 (*d*, $J = 6.4$, Me−C(9)); 1.23 (*m*, 1 H); 1.10 (*s*, Me−C(5)); 1.05 (*s*, Me−C(1)); 0.90 (*d*, $J = 7$, Me−C(2)); 0.75 (*s*, Me−C(1)). Anal. calc. for $C_{16}H_{28}O_3$: C 71.60, H 10.52; found: C 71.64, H 10.48.

*Data of (+)-***7**: $[\alpha]_{20}^{D} = +48.6$ ($c = 0.90$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (±)-**7**.

2.4. *(+)-(2*S*,4*S*,5*R*,6*R*,9*S*)-4,5-Dihydro-4-hydroxy*-cis-*α-irol* (*=(1*S*,2*R*,3*R*,5*S*)-3-[(1*E*,3*S*)-3-Hydroxybut-1-enyl]-2,4,4,5-tetramethylcyclohexanol*; (+)-**13**) *and (+)-(2*R*,4*R*,5*S*,6*S*,9*R*)-4,5-Dihydro-4-hydroxy*-cis-*α-irol Acetate* (*=(1*R*,2*S*,3*S*,5*R*)-3-[(1*E*,3*R*)-3-(Acetyloxy)but-1-enyl]-2,4,4,5-tetramethylcyclohexanol*; (+)-**17**). According to *GP 2* (±)-**13** (13.4 g, 0.059 mol) gave the less polar (+)-**17** (6.19 g, 39%) and the more polar (+)-**13** (4.96 g, 37%).

*Data of (+)-***17**: $[\alpha]_{20}^{D} = +42.8$ ($c = 0.90$, CH_2Cl_2). ^{1}H-NMR: 5.40 (*m*, H−C(7), H−C(8)); 5.32 (*m*, H−C(9)); 3.80 (*q*, $J = 3$, H−C(4)); 2.02 (*m*, *s*, MeCOO, 1 H of chx); 1.81 (*m*, 1 H); 1.70–1.40 (*m*, 3 H); 1.29 (*d*, $J = 6.4$, Me−C(9)); 0.84–0.80 (2*d*, s, Me−C(5), Me−C(2), Me−C(1)); 0.67 (*s*, Me−C(1)). Anal. calc. for $C_{16}H_{28}O_3$: C 71.60, H 10.52; found: C 71.63, H 10.47.

*Data of (+)-***13**: $[\alpha]_{20}^{D} = +26.7$ ($c = 0.40$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (±)-**13**.

2.5. *(+)-(2*R*,4*R*,5*S*,6*S*,9*S*)-4,5-Dihydro-4-hydroxy*-cis-*α-irol* (*=(1*R*,2*S*,3*S*,5*R*)-3-[(1*E*,3*S*)-3-Hydroxybut-1-enyl]-2,4,4,5-tetramethylcyclohexanol*; (−)-**14**) *and (+)-(2*S*,4*S*,5*R*,6*R*,9*R*)-4,5-Dihydro-4-hydroxy*-cis-*α-irol Acetate* (*=(1*S*,2*R*,3*R*,5*S*)-3-[(1*E*,3*R*)-3-(Acetyloxy)but-1-enyl]-2,4,4,5-tetramethylcyclohexanol*; (+)-**18**). According to *GP 2*, (±)-**14** (11.80 g, 0.052 mol) gave the less polar (+)-**18** (5.18 g, 37%) and the more polar (−)-**14** (5.07 g, 43%).

*Data of (+)-***18**: $[\alpha]_{20}^{D} = +93.8$ ($c = 1.35$, CH_2Cl_2). ^{1}H-NMR: 5.40 (*m*, H−C(7), H−C(8)); 5.33 (*m*, H−C(9)); 3.80 (*q*, $J = 3$, H−C(4)); 2.02 (*m*, *s*, MeCOO, 1 H of chx); 1.80 (*m*, 1 H); 1.75–1.40 (*m*, 3 H); 1.31 (*d*, $J = 6.4$, Me−C(9)); 0.82 (2*d*, *s*, Me−C(5), Me−C(2), Me−C(1)); 0.66 (*s*, Me−C(1)). Anal. calc. for $C_{16}H_{28}O_3$: C 71.60, H 10.52; found: C 71.61, H 10.57.

*Data of (−)-***14**: $[\alpha]_{20}^{D} = -37.9$ ($c = 0.50$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (±)-**14**.

2.6. *(+)-(2*R*,5*R*,6*R*,9*R*)-4,5-Dihydro-5-hydroxy*-cis-*α-irol Acetate* (*=(1*R*,2*R*,4*R*)-2-[(1*E*,3*R*)-3-(Acetyloxy)-but-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (+)-**23**) *and (+)-(2*S*,5*S*,6*S*,9*S*)-4,5-Dihydro-5-hydroxy*-cis-*α-irol* (*=(1*S*,2*S*,4*S*)-2-[(1*E*,3*S*)-3-Hydroxybut-1-enyl]-1,3,3,4-tetramethylcyclohexanol* (+)-**15**). According to *GP 2* (±)-**15** (4.07 g, 0.018 mol) gave the less polar (+)-**23** (1.93 g, 40%) and the more polar (+)-**15** (1.75 g, 43%).

*Data of (+)-***23**: $[\alpha]_{20}^{D} = +33.7$ ($c = 0.55$, CH_2Cl_2). ^{1}H-NMR: 5.74 (*dd*, $J = 10.3$, 15.2, H−C(7)); 5.61 (*dd*, $J =$ 6.4, 15.2, H−C(8)); 5.36 (*quint.* $J = 6.4$, H−C(9)); 2.04 (*s*, MeCOO); 1.82–1.74 (*m*, *d*, $J = 10.3$, H−C(6), 1 H of chx); 1.47 (*m*, 2 H); 1.35 (*d*, $J = 6.4$, Me−C(9)); 1.26 (*m*, 2 H); 1.14 (*s*, Me−C(5)); 0.85 (*d*, $J = 6$, Me−C(2)); 0.82 (*s*, Me−C(1)); 0.75 (*s*, Me−C(1)). Anal. calc. for $C_{16}H_{28}O_3$: C 71.60, H 10.52; found: C 71.61, H 10.48.

*Data of (+)-***15**: $[\alpha]_{20}^{D} = +9.8$ ($c = 1.50$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (±)-**15**.

2.7. *(+)-(2*S*,5*S*,6*S*,9*R*)-4,5-Dihydro-5-hydroxy*-cis-*α-irol Acetate* (*=(1*S*,2*S*,4*S*)-2-[(1*E*,3*R*)-3-(Acetyloxy)-but-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (+)-**24**) *and (+)-(2*R*,5*R*,6*R*,9*S*)-4,5-Dihydro-5-hydroxy*-cis-*α-irol* (*=(1*R*,2*R*,4*R*)-2-[(1*E*,3*S*)-3-Hydroxybut-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (+)-**16**. According to *GP 2*, (±)-**16** (4.48 g, 0.020 mol) gave the less polar (+)-**24** (2.28 g, 43%) and the more polar (+)-**16** (1.75 g, 39%).

*Data of (+)-***24**: $[\alpha]_{20}^{D} = +47$ ($c = 0.18$, CH_2Cl_2). ^{1}H-NMR: 5.73 (*dd*, $J = 10.3$, 15.3, H−C(7)); 5.61 (*dd*, $J =$ 6.4, 15.3, H−C(8)); 5.36 (*quint.*, $J = 6.4$, H−C(9)); 2.04 (*s*, MeCOO); 1.81–1.75 (*m*, *d*, $J = 10.3$, H−C(6), 1 H of

chx); 1.47 (*m*, 2 H); 1.35 (*d*, *J* = 6.4, Me–C(9)); 1.26 (*m*, 2 H); 1.14 (*s*, Me–C(5)); 0.85 (*d*, *J* = 6, Me–C(2)); 0.82 (*s*, Me–C(1)); 0.76 (*s*, Me–C(1)). Anal. calc. for $C_{16}H_{28}O_3$: C 71.60, H 10.52; found: C 71.64, H 10.49.

*Data of (+)-***16**: $[\alpha]_{20}^{D} = +9.5$ ($c = 0.81$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (±)-**16**.

2.8. *(−)-(2*R*,5*R*,6*S*,9*S*)-4,5-Dihydro-5-hydroxy*-trans-*α-irol Acetate* (= *(1*R*,2*S*,4*R*)-2-[(1*E*,3*S*)-3-(Acetoxy)-but-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (−)-**8**). Treatment of (−)-**6** (4.65 g, 0.021 mol) with Ac_2O in pyridine gave (−)-**8** (5.40 g, 98%). $[\alpha]_{20}^{D} = -100.1$ ($c = 0.74$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (+)-**8**.

2.9. *(−)-(2*S*,5*S*,6*R*,9*S*)-4,5-Dihydro-5-hydroxy*-trans-*α-irol Acetate* (= *(1*S*,2*R*,4*S*)-2-[(1*E*,3*S*)-3-(Acetoxy)-but-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (−)-**9**). Treatment of (+)-**7** (5.25 g, 0.023 mol) with Ac_2O in pyridine gave (−)-**9** (6.04 g, 97%). $[\alpha]_{20}^{D} = -24.3$ ($c = 0.41$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (+)-**9**.

2.10. *(−)-(2*S*,5*S*,6*S*,9*S*)-4,5-Dihydro-5-hydroxy*-cis-*α-irol Acetate* (= *(1*S*,2*S*,4*S*)-2-[(1*E*,3*S*)-3-(Acetyloxy)-but-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (−)-**23**). Treatment of (+)-**15** (1.68 g, 7.43 mmol) with Ac_2O in pyridine gave (−)-**23** (1.91 g, 96%). $[\alpha]_{20}^{D} = -31.6$ ($c = 0.42$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (+)-**23**.

2.11. *(−)-(2*R*,5*R*,6*R*,9*S*)-4,5-Dihydro-5-hydroxy*-cis-*α-irol Acetate* (= *(1*R*,2*R*,4*R*)-2-[(1*E*,3*S*)-3-(Acetoxy)-but-1-enyl]-1,3,3,4-tetramethylcyclohexanol*; (−)-**24**). Treatment of (+)-**16** (2.15 g, 9.51 mmol) with Ac_2O in pyridine gave (−)-**24** (2.50 g, 98%). $[\alpha]_{20}^{D} = -45.8$ ($c = 0.32$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (+)-**24**.

2.12. *(+)-(2*S*,4*S*,5*R*,6*S*)-4,5-Dihydro-4-hydroxy*-cis-*α-irone* (= *(3*E*)-4-[(1*S*,3*S*,5*S*,6*R*)-5-Hydroxy-2,2,3,6-tetramethylcyclohexyl]but-3-en-2-one*; (+)-**21**). A mixture of (+)-**13** (4.84 g, 0.021 mol) and MnO_2 (1.5 equiv.) in CH_2Cl_2 (30 ml) was stirred at r.t. for 3 h. The mixture was filtered, the filtrate evaporated, and the residue purified by CC (hexane/AcOEt 8:2): (+)-**21** (4.31 g, 90%). $[\alpha]_{20}^{D} = +57$ ($c = 0.61$, CH_2Cl_2). ^{1}H-NMR: 6.58 (*dd*, *J* = 10.3, 15.7, H–C(7)); 6.08 (*d*, *J* = 15.7, H–C(8)); 3.83 (*q*, *J* = 2.5, H–C(4)); 2.25 (*s*, MeCO); 2.08 (*t*, *J* = 10.3, H–C(6)); 1.79–1.67 (*m*, H–C(2), H–C(5)); 1.64 (*dt*, *J* = 3.4, 3.4, 14.2, H_{eq}–C(3)); 1.52 (*ddd*, *J* = 3.4, 13.1, 14.2, H_{ax}–C(3)); 0.88–0.81 (*s*, 2 *d*, *J* = 7, Me–C(1), Me–C(2), Me–C(5)); 0.76 (*s*, Me–C(1)). Anal. calc. for $C_{14}H_{24}O_2$: C 74.95, H 10.78; found: C 74.90, H 10.82.

2.13. *(−)-(2*R*,4*S*,5*S*,6*R*)-4,5-Dihydro-4-hydroxy*-cis-*α-irone* (= *(3*E*)-4-[(1*R*,3*R*,5*R*,6)-5-Hydroxy-2,2,3,6-tetramethylcyclohexyl]but-3-en-2-one*; (−)-**21**). As described in *2.12*, with (−)-**14** (4.90 g, 0.022 mol) and MnO_2 (1.5 equiv.). (−)-**21** (4.32 g, 89%). $[\alpha]_{20}^{D} = -54.3$ ($c = 0.84$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (+)-**21**.

3. *Dehydration with Phosphorous Oxychloride in Pyridine.* 3.1. *General Procedure 3* (*GP 3*). A mixture of the suitable alcohol derivative (3 g, 0.011 mol), $POCl_3$ (2.57 g, 0.017 mol), and pyridine (15 ml) was stirred at r.t. The mixture was treated with H_2O and then extracted with AcOEt. After evaporation, the residue was purified by CC (hexane/AcOEt 9:1).

3.2. *(+)-(2*S*,9*R*)-β-Irol Acetate* (= *(2*R*,3*E*)-4-[(5*S*)-2,5,6,6-Tetramethylcyclohex-1-en-1-yl]but-3-en-2-ol Acetate*; (+)-**10**). According to *GP 3*, (+)-**8** (5.90 g, 0.022 mol) gave, at r.t. after 7 days, (+)-**10** (4.29 g, 78%). $[\alpha]_{20}^{D} = +57$ ($c = 0.95$, CH_2Cl_2); ee 99% by chiral GC (t_R 22.74); 91% chemical purity, 9% *trans*-α-irol acetate. ^{1}H-NMR: 6.10 (*d*, *J* = 15, H–C(7)); 5.38 (*m*, H–C(8), H–C(9)); 2.03 (*s*, *m*, MeCOO, 2 H of chx); 1.63 (*s*, Me–C(5)); 1.55–1.20 (*d*, *m*, *J* = 6.1, Me–C(9), 3 H of chx); 0.98 (*s*, Me–C(1)); 0.88 (*d*, *J* = 6, Me–C(2)); 0.82 (*s*, Me–C(1)). GC/MS: t_R 19.44; 250 (4.9), 208 (6.1), 190 (46.5), 175 (100), 133 (78.9), 119 (77.0). Anal. calc. for $C_{16}H_{26}O_2$: C 76.75, H 10.47; found: C 76.70, H 10.52.

3.3. *(+)-(2*R*,9*S*)-β-Irol Acetate* (= *(2*S*,3*E*)-4-[(5*R*)-2,5,6,6-Tetramethylcyclohex-1-en-1-yl]but-3-en-2-ol Acetate*; (−)-**10**. As described in *3.2*, with (−)-**8** (5.30 g, 0.020 mol): (−)-**10** (3.86 g, 78%). $[\alpha]_{20}^{D} = -54$ ($c = 1.5$, CH_2Cl_2); ee 99% by chiral GC (t_R 22.57); 92% chemical purity, 8% *trans*-α-irol acetate. GC/MS: t_R 19.44. ^{1}H-NMR: in accordance with that of (+)-**10**.

3.4. *(+)-(2*R*,9*R*)-β-Irol Acetate* (= *(2*R*,3*E*)-4-[(5*R*)-2,5,6,6-Tetramethylcyclohex-1-en-1-yl]but-3-en-2-ol Acetate* (+)-**11**). As described in *3.2* with (+)-**9** (6.40 g, 0.024 mol): (+)-**11** (4.48 g, 75%). $[\alpha]_{20}^{D} = +111.7$ ($c = 0.69$, CH_2Cl_2); ee 90% by chiral GC (t_R 21.47); 95% chemical purity, 5% *trans*-α-irol acetate. ^{1}H-NMR: 6.10 (*d*, *J* = 15, H–C(7)); 5.38 (*m*, H–C(8), H–C(9)); 2.03 (*s*, *m*, MeCOO, 2 H of chx); 1.63 (*s*, Me–C(5)); 1.55–1.20 (*d*, *m*, *J* = 6.1, Me–C(9), 3 H of chx); 0.97 (*s*, Me–C(1)); 0.88 (*d*, *J* = 6, Me–C(2)); 0.83 (*s*, Me–C(1)). GC/MS: t_R 19.44; 250 (5.0), 208 (6.5), 190 (55.0), 175 (100), 133 (66), 119 (65). Anal. calc. for $C_{16}H_{26}O_2$: C 76.75, H 10.47; found: C 76.80, H 10.42.

3.5. *(+)-(2*S*,9*S*)-β-Irol Acetate* (= *(2*S*,3*E*)-4-[(5*S*)-2,5,6,6-Tetramethylcyclohex-1-en-1-yl]but-3-en-2-ol Acetate*; (−)-**11**). As described in *3.2*, with (−)-**9** (5.90 g, 0.022 mol): (−)-**11** (4.18 g, 76%). $[\alpha]_{20}^{D} = -108.2$ ($c = 0.75$, CH_2Cl_2); ee 90% by chiral GC (t_R 21.27); 93% chemical purity, 7% *trans*-α-irol acetate. GC/MS: t_R 19.44. ^{1}H-NMR: in accordance with that of (+)-**11**.

3.6. *(2R,6S,9R)-γ-Irol Acetate* (= *(2R,3E)-4-[(1S,3R)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol Acetate*; **25a**), *(2R,6S,9R)-α-Irol Acetate* ((−)-**19**), *and (2R,9R)-β-Irol Acetate* ((+)-**11**). According to *GP 3*, (+)-**23** (1.85 g, 6.90 mmol) gave, at 0°, **25a**/(−)-**19**/(+)-**11** (1.52 g, 88%). GC/MS: (−)-**19** (t_R 19.19, 35%): 190 (25.7), 180 (84.5), 138 (65.2), 120 (73.5), 105 (100), 95 (75.5); **25a** (t_R 19.37, 46%): 250 (3.6), 232 (2.5), 217 (4.6), 207 (30.8), 190 (40.5), 175 (43.3), 43 (100); (+)-**11**: t_R 19.44, 19%.

3.7. *(2S,6R,9S)-γ-Irol Acetate* (= *(2S,3E)-4-[(1R,3S)-2,2,3-Trimethyl-6-methylidenecyclohexylbut-3-en-2-ol Acetate*; **25b**), *(2S,6R,9S)-α-Irol Acetate* ((+)-**19**), *and (2S,9S)-β-Irol Acetate* ((−)-**11**). As described in *3.6*, with (−)-**23** (1.80 g, 6.71 mmol): **25b**/(+)-**19**/(−)-**11** (1.49 g, 89%). GC/MS: (+)-**19**: t_R 19.19, 35%; **25b**: t_R 19.37, 46%; (−)-**11**: t_R 19.44, 19%.

3.8. *(2S,6R,9R)-γ-Irol Acetate* (= *(2R,3E)-4-[(1R,3S)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol Acetate*; **26b**), *(2S,6R,9R)-α-Irol Acetate* ((+)-**20**), *and (2S,9R)-β-Irol Acetate* ((+)-**10**). As described in *3.6*, with (+)-**24** (1.62 g, 6.05 mmol): **26b**/(+)-**20**/(+)-**10** (1.34 g, 89%). GC/MS: (+)-**20** (t_R 19.28, 36%): 190 (28), 180 (82.5), 138 (67.9), 120 (72.3), 105 (100), 95 (78.9); **26b**/(+)-**10**: t_R 19.44, 64%.

3.9. *(2R,6S,9S)-γ-Irol Acetate* (= *(2S,3E)-4-[(1S,3R)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol Acetate*; **26a**), *(2R,6S,9S)-α-Irol Acetate* ((−)-**20**), *and (2R,9S)-β-Irol Acetate* ((−)-**10**). As described in *3.6*, with (−)-**24** (2.40 g, 8.95 mmol): **26a**/(−)-**20**/(−)-**24** (1.92 g, 86%). GC/MS: (−)-**20**: t_R 19.28, 34%; **26a**/(+)-**10**: t_R 19.44, 66%.

3.10. *(2R,6S,9R)-α-Irol Acetate* (= *(2R,3E)-4-[(1S,5R)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-ol Acetate*; (−)-**19**). According to *GP 3*, (+)-**17** (6.00 g, 0.022 mol) gave, at r.t. after 15 min, (−)-**19** (4.42 g, 79%). $[\alpha]_{20}^{D} = -73$ ($c = 1.5$, CH_2Cl_2); ee 98% by chiral GC (t_R 20.56). ^{1}H-NMR: 5.50 (*m*, H−C(7)); 5.38 (*m*, H−C(8), H−C(9), H−C(4)); 2.33 (*m*, 1 H); 2.05 (*s*, MeCOO); 1.90 (*m*, 1 H); 1.65 (*m*, 1 H); 1.49 (*m*, Me−C(5)); 1.40 (*m*, 1 H); 1.32 (*d*, $J = 6.4$, Me−C(9)); 0.84 (*s*, *d*, $J = 7$, Me−C(1), Me−C(2)); 0.64 (*s*, Me−C(1)). GC/MS: (−)-**19** ($t_R = 19.19$, 87%); 4-chloro-4,5-dihydro-*cis*-α-irol acetate (t_R 21.85 min, 13%): 286 (0.5), 246 (4.1), 244 (12.6), 228 (6.0), 226 (16.9, 124 (57.0), 107 (74.1), 95 (86.0), 43 (100).

3.11. *(2S,6R,9R)-α-Irol Acetate* (= *(2R,3E)-4-[(1R,5S)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-ol Acetate* (+)-**20**). According to *GP 3*, (+)-**18** (5.00 g, 0.018 mol) gave, at r.t. after 15 min, (+)-**20** (3.59 g, 77%). $[\alpha]_{20}^{D} = +9.5$ ($c = 0.21$, CH_2Cl_2); ee 97% by chiral GC (t_R 20.78). ^{1}H-NMR: 5.49 (*m*, H−C(7)); 5.38 (*m*, H−C(8), H−C(9), H−C(4)); 2.32 (*m*, 1 H); 2.05 (*s*, MeCOO); 1.90 (*m*, 1 H); 1.70 (*m*, 1 H); 1.51 (*m*, Me−C(5)); 1.42 (*m*, 1 H); 1.33 (*d*, $J = 6.4$, Me−C(9)); 0.84 (*s*, *d*, $J = 7$, Me−C(1), Me−C(2)); 0.62 (*s*, Me−C(1)). GC/MS: (+)-**20** (t_R 19.28, 72%); 4-chloro-4,5-dihydro-*cis*-α-irol acetate (t_R 21.95, 28%): 246 (3.1), 244 (10.7), 226 (15.6), 211 (22.8), 191 (24.1), 124 (51.1), 107 (70.6), 95 (79.1), 43 (100).

3.12. *(2S,6R)*-cis-α-*Irone* (= *(3E)-4-[(1R,5S)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-one* (−)-**22**) *and (2S,4R,5R,6R)-4-Chloro-4,5-dihydro-α-irone* (= *(3E)-4-[(1R,3S,5R,6R)-5-Chloro-2,2,3,6-tetramethylcyclohexyl]but-3-en-2-one*; (−)-**27**). According to *GP 3*, (+)-**21** (4.20 g, 0.019 mol) gave (−)-**22** (2.24 g, 58%) and (−)-**27** (0.68 g, 15%).

*Data of (−)-***22**: $[\alpha]_{20}^{D} = -121$ ($c = 1.55$, 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); 2.10 (*m*, 1 H); 1.80–1.50 (*m*, 2 H); 1.53 (*m*, Me−C(5)); 1.46 (*m*, 1 H); 0.88 (*d*, $J = 7$, Me−C(2)); 0.86 (*s*, Me−C(1)); 0.71 (*s*, Me−C(1)). GC-MS: t_R 17.87, 95% pure; 206 (14.4), 191 (20.3), 136 (52.4), 121 (100), 93 (56.7).

*Data of (−)-***27**: $[\alpha]_{20}^{D} = -53.8$ ($c = 0.41$, CH_2Cl_2). ^{1}H-NMR: 6.53 (*dd*, $J = 10.4, 16$, H−C(7)); 6.03 (*d*, $J = 16$, H−C(8)); 3.50 (*ddd*, $J = 4.6, 10.7, 12.4$, H−C(4)); 2.26 (*s*, MeCO); 2.00 (*ddd*, $J = 3.9, 4.9, 13.4$, H_{eq}−C(3)); 1.78 (*m*, 1 H); 1.74 (*q*, $J = 12.4$, H_{eq}−C(3)); 1.63 (*t*, $J = 10.4$, H−C(6)); 1.38 (*m*, 1 H); 0.98 (*d*, $J = 6.4$, 3 H); 0.90 (*d*, $J = 7$, 3 H); 0.83 (*s*, Me−C(1)); 0.81 (*s*, Me−C(1)). GC/MS: t_R 21.00, 97% pure; 244 (1.0), 242 (3.1), 227 (1.9), 206 (14.2), 191 (24.5), 121 (97.6), 111 (100). Anal. calc. for $C_{14}H_{23}ClO$: C 69.26, H 9.55, Cl 14.60; found: C 69.21, H 9.49, Cl 14.65.

3.13. *(2R,6S)*-cis-α-*Irone* (= *(3E)-4-[(1S,5R)-2,5.6,6-Tetramethylcyclohex-2-en-1-yl]but-3-3-en-2-one* (+)-**22**) *and (2R,4S,5S,6S)-4-Chloro-4,5-dihydro-α-irone* (= *(3E)-4-[(1S,3R,5S,6S)-5-chloro-2,2,3,6-tetramethylcyclohexyl]but-3-en-2-one* (+)-**27**). According to *GP 3* (−)-***21*** (4.20 g, 0.019 mol) gave (+)-**22** (2.12 g, 55%) and (+)-**27** (0.82 g, 18%).

*Data of (+)-***22**: $[\alpha]_{20}^{D} = +118$ ($c = 1.45$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (−)-**22**. GC/MS: 93% pure, t_R 17.87.

*Data of (+)-***27**: $[\alpha]_{20}^{D} = +57$ ($c = 0.41$, CH_2Cl_2). ^{1}H-NMR: in accordance with that of (−)-**27**. GC/MS: 96% pure, t_R 21.00.

4. *Photoisomerization of Irol Acetate Derivatives.* 4.1. *General Procedure 4* (*GP 4*). A soln. of the suitable irol acetate (2 g, 8 mmol) in ^{i}PrOH (150 ml) and xylene (15 ml) was irradiated for 24 h in a *Rayonet*

photochemical reactor with a 120-W high-pressure Hg lamp. The soln. was evaporated, and the residue purified by CC (hexane/AcOEt 9:1).

4.2. *(2R,6S,9R)-γ-Irol Acetate* (**25a**). According to *GP 4*, **25a** (−)-**19**/(+)-**11** (1.70 g, 6.8 mmol) was converted to **25a** (1.45 g, 85%), containing 20% (^{1}H-NMR) of the (7*Z*)-diastereoisomer (C=CH_2 at δ 4.73 and 4.50); ee 98% by chiral GC (t_R 20.97). ^{1}H-NMR: 5.81 (*dd*, *J* = 10, 15, H−C(7)); 5.45 (*dd*, *J* = 6.5, 10, H−C(8)); 5.38 (*quint.*, *J* = 6.5, H−C(9)); 4.73 (*m*, C=CH); 4.45 (*m*, C=CH); 2.32 (*m*, 2 H); 2.03 (*s* + *m*, MeCOO, 1 H of chx); 1.67 – 1.15 (*d*, *m*, *J* = 6.5, Me−C(9), 3 H of chx); 0.86 (*d*, *s*, *J* = 7, Me−C(2), Me−C(1)); 0.63 (*s*, Me−C(1)).

4.3. *(2S,6R,9S)-γ-Irol Acetate* (**25b**). According to *GP 4*, **25b**/(+)-**19**/(−)-**11** (1.35 g, 5.4 mmol) was converted to **25b** (1.16 g, 86%), containing 18% (^{1}H-NMR) of the (7*Z*) diastereoisomer; ee 98% by chiral GC (t_R 21.25). ^{1}H-NMR: in accordance with that of **25a**.

4.4. *(2S,6R,9R)-γ-Irol Acetate* (**26b**). According to *GP 4* **26b**/(+)-**20**/(+)-**10** (1.25 g, 5.0 mmol) was converted into **26b** (1.05 g, 84%), containing 22% (^{1}H-NMR) of the (7*Z*) diastereoisomer (C=CH_2 at δ 4.73 and 4.50); ee 98% by chiral GC (t_R 21.62). ^{1}H-NMR: 5.82 (*dd*, *J* = 10, 15, H−C(7)); 5.45 (*dd*, *J* = 6.5, 10, H−C(8)); 5.38 (*quint.*, *J* = 6.5, H−C(9)); 4.73 (*m*, C=CH); 4.46 (*m*, C=CH); 2.32 (*m*, 2 H); 2.04 (*s*, *m*, MeCOO, 1 H of chx); 1.67 – 1.15 (*d*, *m*, *J* = 6.5, Me−C(9), 3 H of chx); 0.86 (*d*, *s*, *J* = 7, Me−C(2), Me−C(1)); 0.64 (*s*, Me−C(1)).

4.5. *(2R,6S,9S)-γ-Irol Acetate* (**26a**). According to *GP 4*, **26a**/(−)-**20**/(−)-**10** (1.85 g, 7.4 mmol) was converted into **26a** (1.61 g, 87%), containing 19% (^{1}H-NMR) of the (7*Z*) diastereoisomer; ee 98% by chiral GC (t_R 20.98). ^{1}H-NMR: in accordance with that of **26b**.

5. *Manganese(IV) Oxide Oxidation*. 5.1. *General Procedure 5* (*GP 5*). The suitable irol acetate derivatives were pooled, saponified by reaction with KOH in MeOH, and then directly submitted to oxidation in CH_2Cl_2 soln. in the presence of MnO_2 (1.5 equiv.) at r.t. The mixture was filtered, the filtrate evaporated, and the residue purified by CC (hexane/AcOEt 97:3). All the samples of irone isomers were distilled bulb-to-bulb before analysis and optical-rotation measurement.

5.2. *(+)-(R)-β-Irone* (=*(3E)-4-[(5R)-2,5,6,6-Tetramethylcyclohex-1-en-1-yl]but-3-en-2-one*; (+)-**2**). According to *GP 5*, (−)-**10** (3.70 g, 0.015 mol) and (+)-**11** (4.30 g, 0.018 mol) gave (+)-**2** (6.07 g, 88%). $[\alpha]_{20}^{D}$ = +17.1 (*c* = 1.45, CH_2Cl_2); ee 98% by ^{1}H-NMR (chiral shift reagents). ^{1}H-NMR: 7.25 (*dm*, *J* = 16, H−C(7)); 6.08 (*d*, *J* = 16, H−C(8)); 2.30 (*s*, MeCO); 2.07 (*m*, 2 H); 1.73 (*s*, Me−C(5)); 1.65 – 1.34 (*m*, 3 H); 1.06 (*s*, Me−C(1)); 0.91 (*s*, *d*, *J* = 7, Me−C(1), Me−C(2)). GC/MS: (+)-**2**: t_R 18.55, 91%; 206 (4.0), 191 (100), 149 (12.4), 121 (15.4); (−)-*trans*-α-irone: t_R 17.37, 9%; 206 (17.0), 191 (6.5), 136 (54.2), 121 (100), 93 (60.2).

5.3. *(−)-(S)-β-Irone* (=*(3E)-4-[(5S)-2,5,6,6-Tetramethylcyclohex-1-en-1-yl]but-3-en-2-one*; (−)-**2**). According to *GP 5*, (+)-**10** (4.10 g, 0.016 mol) and (−)-**11** (4.00 g, 0.016 mol) gave (−)-**2** (5.27 g, 80%). $[\alpha]_{20}^{D}$ = −20.2 (*c* = 2.30, CH_2Cl_2); ee 98% by ^{1}H-NMR (chiral shift reagents). ^{1}H-NMR: in accordance with that of (+)-**2**. GC/MS: (−)-**2**: t_R 18.55, 93%; (+)-*trans*-α-irone: t_R 17.37, 7%.

5.4. *(+)-(2R,6S)-γ-Irone* (=*(3E)-4-[(1S,3R)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-one*; (+)-**3**). According to *GP 5*, **25a** (1.30 g, 5.2 mmol) and **26a** (1.50 g, 6.0 mmol) gave (+)-**3** (1.24 g, 54%): $[\alpha]_{20}^{D}$ = +9.5 (*c* = 2.15, CH_2Cl_2): ee 96% by chiral GC (t_R 19.70). ^{1}H-NMR: 6.93 (*dd*, *J* = 15.8, 10.3, H−C(7)); 6.09 (*d*, *J* = 15.8, H−C(8)); 4.80 (*m*, C=CH); 4.43 (*m*, C=CH); 2.55 (*d*, *J* = 10.3, H−C(6)); 2.35 (*ddd*, *J* = 2.5, 4.4, 13.3, H_{ax}−C(4)); 2.28 (*s*, MeCO); 2.10 (*m*, 1 H); 1.60 – 1.20 (*m*, 3 H); 0.87 (*s*, *d*, *J* = 7, Me−C(1), Me−C(2)); 0.73 (*s*, Me−C(1)). GC/MS: (+)-**3**: 92%, t_R 18.08; 206 (2.9), 191 (8.9), 173 (5.4), 163 (31.2), 149 (41.9), 121 (100), 83 (23.8)); (+)-(2*R*,6*S*)-*cis*-α-irone ((+)-**22**): 5%, t_R 17.89; (+)-(2*R*)-β-irone ((+)-**2**): 3%, t_R 18.59.

An anal. sample of (2*R*,6*S*,7*Z*)-γ-irone was recovered: ^{1}H-NMR: 6.30 (*d*, *J* = 11.8, H−C(8)); 6.21 (*dd*, *J* = 11.8, 10.3, H−C(7)); 4.73 (*m*, C=CH); 4.42 (*m*, C=CH); 3.86 (*d*, *J* = 10.3, H−C(6)); 2.19 (*s*, *m*, MeCO, 1 H of chx); 1.60 – 1.20 (*m*, 3 H); 0.89 (*s*, Me−C(1)); 0.84 (*d*, *J* = 7, Me−C(2)); 0.68 (*s*, Me−C(1)). Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.46, H 10.71.

5.5. *(−)-(2S,6R)-γ-Irone* (=*(3E)-4-[(1R,3S)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-one*; (−)-**3**). According to *GP 5*, **25b** (1.00 g, 4.0 mmol) and **26b** (0.90 g, 3.6 mmol) gave (−)-**3** (0.892 g, 57%). $[\alpha]_{20}^{D}$ = −6.3 (*c* = 1.05, CH_2Cl_2); ee 97% by chiral GC (t_R 20.08). GC/MS: (−)-**3**: 94%, t_R = 18.08; (−)-(2*S*,6*R*)-*cis*-α-irone ((−)-**22**): t_R 17.89, 4.9%; (−)-(2*S*)-β-irone ((−)-**2**): 1.5%, t_R 18.59. ^{1}H-NMR: in accordance with that of (+)-**3**.

5.6. *(+)-(2R,6S)-α-Irone* ((+)-**22**). According to *GP 5*, (−)-**19** (4.30 g, 0.017 mol) gave (+)-**22** (2.41 g, 68%). $[\alpha]_{20}^{D}$ = +108 (*c* = 1.5, CH_2Cl_2); optical purity 97%. ^{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); 2.10 (*m*, 1 H); 1.80 – 1.50 (*m*, 2 H); 1.53 (*m*, Me−C(5)); 1.46 (*m*, 1 H); 0.88 (*d*, *J* = 7, Me−C(2)); 0.86 (*s*, Me−C(1)); 0.71 (*s*, Me−C(1)). GC/MS: 97% pure, t_R 17.87. Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.53, H 10.82.

5.7. *(−)-(2S,6R)-α-Irone* ((−)-**22**). According to *GP 5*, (+)-**20** (3.40 g, 0.014 mol) gave (−)-**22** (1.71 g, 61%). $[\alpha]_{20}^{D} = -115$ ($c = 1.05$, CH_2Cl_2); optical purity 97%. ^{1}H-NMR: in accordance with that of (+)-**22**. GC/MS: 96% pure t_R 17.87.

5.8. *(7E,9E)-5,6,6-Trimethylundeca-7,9-dien-2-one* ((±)-**12**). Treatment of (±)-**9** (2 g, 7.46 mmol) with cat. 85% perchloric acid in THF (20 ml) at 0° afforded, after evaporation and purification of the residue by CC (hexane/AcOEt 9:1), (±)-**12** (0.85 g, 55%). ^{1}H-NMR: 6.03 (*ddq*, $J = 1.4, 15, 10.3$, H−C(9)); 5.92 (*dd*, $J = 15, 10$, H−C(8)); 5.60 (*dq*, $J = 15$, 7, H−C(10)); 5.50 (*d*, $J = 15$, H−C(7)); 2.48 (*ddd*, $J = 5$, 10, 16.7, CHCO); 2.31 (*ddd*, $J = 6.4, 8, 15.7$), 2.12 (*s*, MeCO); 1.73 (*dd*, $J = 1.4$, 7, Me−C(10)); 1.20–1.10 (*m*, 2 H); 0.97 (*s*, Me−C(6)); 0.96 (*s*, Me−C(6)); 0.80 (*d*, $J = 6.4$, Me−C(5)). GC/MS: t_R 17.68; 208 (5.1), 109 (100), 99 (14.1), 67 (20.9). Anal. calc. for $C_{14}H_{24}O$: C 80.71, H 11.61; found: C 80.76, H 11.57.

6. *Determination of the Optical Purity of β-Irone Samples.* The ^{1}H-NMR spectrum of (±)-β-irone was recorded in $CDCl_3$ soln. at r.t. On progressive addition of [Eu(hfc)$_3$], the two *s* corresponding to Me−C(5) (δ(H) 1.73) and to one of the geminal Me−C(1) (δ(H) 1.06) were shifted downfield (δ(H) 2 and 1.8, resp.), and splitted into two lines each ($\Delta\delta = 0.01$ ppm for both signals; chiral shift reagent/substrate 4.6:1). The same chiral shift reagent/sample ratio was used to record ^{1}H-NMR spectra of (+)-**2**, (−)-**2**, and of two mixtures of the single enantiomer with the racemate in a 2:1 ratio: (*R*)-β-irone gave rise to the lines at δ(H) 2.080 and 1.86, (*S*)-β-irone to those at δ(H) 2.070 and 1.87.

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