Enzyme-Mediated Syntheses of the Enantiomers of γ-Irones

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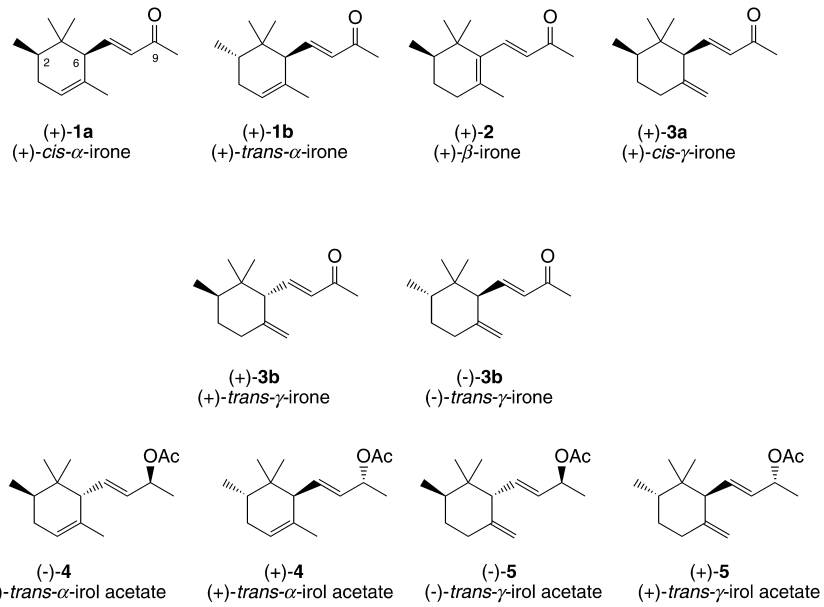
An enzymatic approach to the synthesis of all the possible stereoisomers of (*E*) and (*Z*), *cis* and *trans*-γ-irones in enantiomerically pure form from commercial *Irone Alpha*® is described. A very efficient resolution of racemic *trans*-γ-irone, affording both the enantiomers in high ee and chemical purity, is also presented. Olfactory evaluation of (+)- and (−)-**3b** and full configuration assignment of the irone isomers contained in samples of Italian iris oil are reported.

1. Introduction. – The essential oil known as 'orris root oil' or 'essence d'iris' is a rather precious ingredient of scents, perfumes, and other cosmetics [1]. Its odoriferous principle was first isolated by *Tiemann* in 1893 and named irone [2]. Forty years later *Ruzicka* and co-workers [3a] determined the correct elemental analysis of irone ($C_{14}H_{22}O$); then *Ruzicka* and *Naves* and co-workers [3b,c] independently found that at least three isomers of irone were present in natural iris oil, their structures being determined as **1**, **2**, and **3**. In 1971, *Rautenstrauch* and *Ohloff* [4] completed the structure determination by establishing the configuration of the irone isomers they had isolated from the Italian iris oil (probably from *Iris pallida*) first used by *Ruzicka* and co-workers. They found that the oil contained the following four isomers: (+)-*cis*-α-irone ((+)-**1a**), (+)-*trans*-α-irone ((+)-**1b**), (+)-β-irone ((+)-**2**), and (+)-*cis*-γ-irone ((+)-**3a**). Later, in the same oil, *Ohloff* and co-workers [5] were able to detect traces of the *trans*-γ-irone, together with some other isomers, probably showing (*Z*) configuration at the C=C bond in the side chain. The absolute configuration of the *trans*-γ-irone found in Italian iris oil is apparently still unknown.

In some previous reports [6], we described the enzyme-mediated syntheses of (+)- and (−)-*cis*-α-, (+)- and (−)-*trans*-α-, (+)- and (−)-*cis*-γ, and (+)- and (−)-β irone isomers, starting from *Irone Alpha*®, a 55:45 mixture of racemic *trans*-α- and *cis*-α-irone, with a 5% content of β-irone. We wish now to report on the enzymatic approach we have optimized to obtain the last isomers of the series, (+)- and (−)-*trans*-γ-irone ((+)- and (−)-**3b**), using once again commercial *Irone Alpha*® as a starting material. The key step is the photochemical isomerization of the C(4)=C(5) bond of enantiomerically pure *trans*-α-irol acetates (+)- and (−)-**4**, obtained by enzymic resolution, to afford *trans*-γ-irol acetates (+)- and (−)-**5**. We describe also an alternative biocatalysed synthetic path, which allowed us to prepare both the enantiomers from racemic *trans*-γ-irone in high chemical purity, in order to clarify the diverse values for the optical rotation reported in the literature for (+)- and (−)-**3b**. For this purpose, we optimized a large-scale synthesis of racemic *trans*-γ-irone. The external olfactory evaluation and the threshold values of the two enantiomers of *trans*-



γ-irone are reported. Full configuration assignment of the irone isomers found in four samples of Italian iris oil is also given.

2. Results and Discussion. – 2.1. *Syntheses.* Four different enantioselective syntheses [7a–d] of *trans*-γ-irone, from components of the so-called 'pool of chirality' as starting materials, were reported in the literature; none of them was applied to afford both the enantiomers[1]). A rough comparison of these publications put into evidence a certain disagreement in the determination of the optical rotatory power. We now devised two new synthetic approaches for the preparation of both enantiomerically pure (+)- and (−)-**3b**: in both cases optical activation was obtained by means of lipase-PS-mediated kinetic resolution of suitable intermediates.

Approach A. We had already reported [6a] on the possibility to prepare (+)-*trans*- and (−)-*trans*- and (+)-*cis*- and (−)-*cis*-α-irone stereoisomers from commercial *Irone Alpha*®, using as key intermediates the enantiomerically pure epoxy derivatives (−)-**6** and (+)-**7**, (+)-**8** and (+)-**9**, obtained by lipase-PS-mediated acetylation of (±)-**6** and (±)-**8**, respectively, in *tert*-butyl methyl ether (^{t}BuOMe) solution in the presence of vinyl acetate as an acyl donor. In this work we now report alcohol derivatives (+)- and (−)-**6** and (+)- and (−)-**8** were deoxygenated by reaction with Zn and NaI in AcOH at room temperature, to give (+)- and (−)-**4a** and (−)- and (+)-**10a**, respectively (*Schemes 1* and *2*, resp.). Acetylation of these derivatives in pyridine and Ac_2O afforded α-irol acetates (+)- and (−)-**4b** and (−)- and (+)-**10b**[2]), in the *trans* and *cis*

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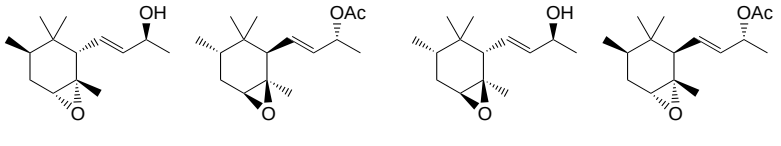
[1]) For a recent large-scale synthesis of both enantiomers of *cis*-γ-irone by chemical resolution, see [7m].

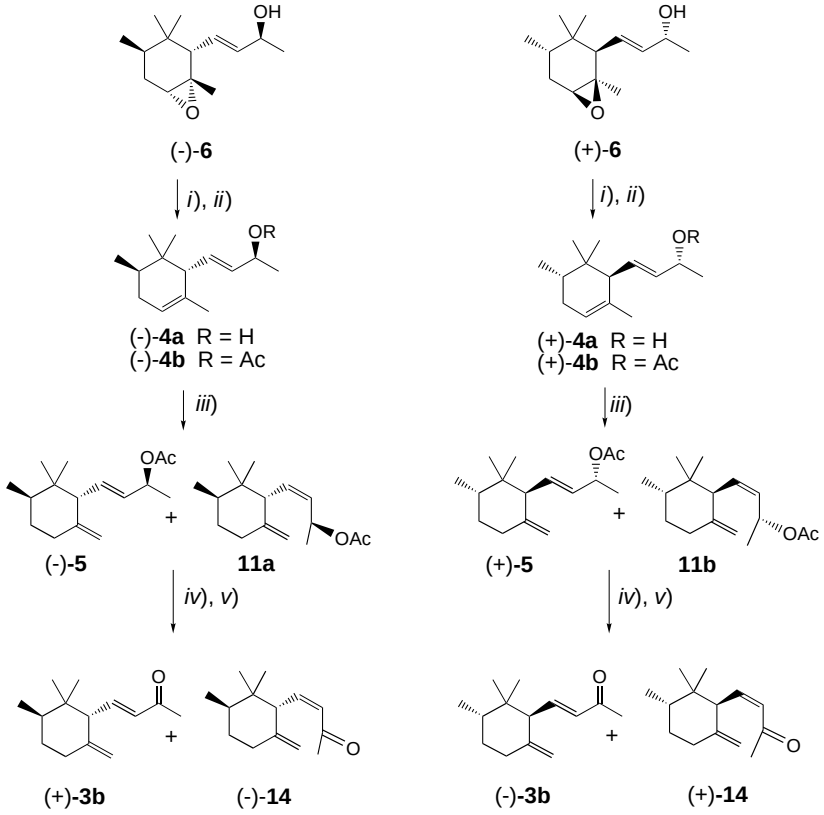
[2]) In [6c], we reported $[\alpha]_D^{20} = -73$ ($c = 1.50$, CH_2Cl_2) for a sample of (2*R*,6*S*,9*R*)-α-irol acetate with an impurity of 13% 4-chloro-4,5-dihydro-*cis*-α-irol acetate.

series, respectively. During the preparation of (+)- and (−)-*cis*-γ-irone [6c], we found that 4.5 : 2.5 : 2 mixtures of *cis*-γ-, *cis*-α-, and β-irol acetates can readily be converted into 78–82% of *cis*-γ-irol isomer by photoisomerization in ^{i}PrOH solution in the presence of xylene as a photosensitizer. Thus, we exploited this shift of the endocyclic double bond to convert the enantiomerically pure *trans*-α-irol acetates (+)- and (−)-**4b** into the *trans*-γ isomers (+)- and (−)-**5**. Simultaneously, in the same experimental apparatus (see *Exper. Part*), *cis*-α derivatives (+)- and (−)-**10b** were irradiated as well, in order to make a rough comparison between the photochemical isomerizations of the two sets of diastereoisomers (*cis*- and *trans*-α-irol acetates). In both cases, irradiation



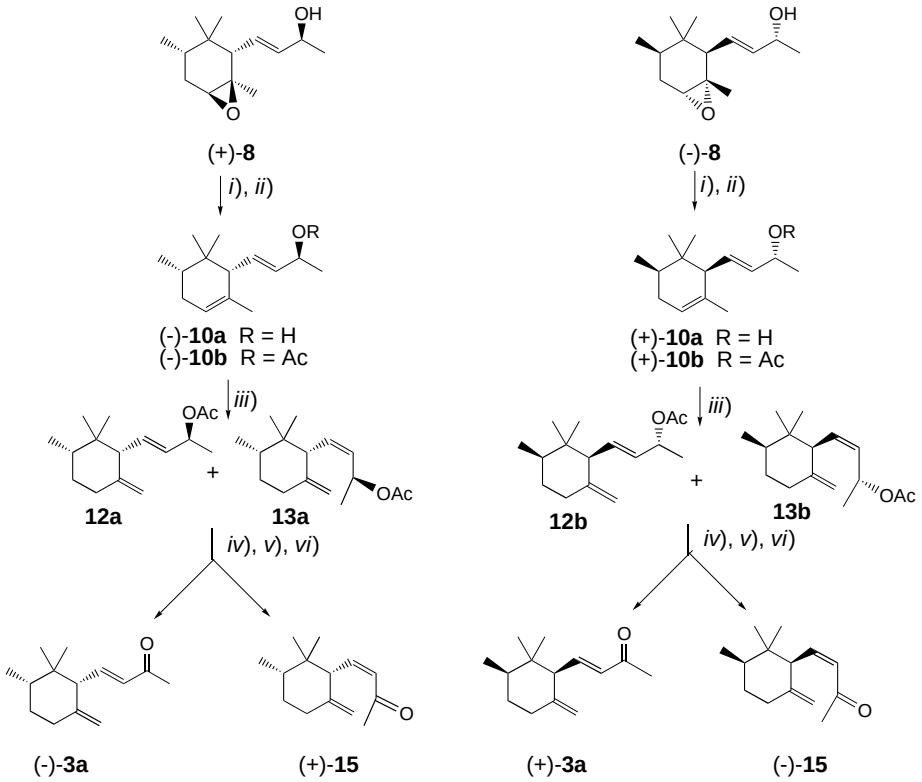
(-)-**6** (+)-**7** (+)-**8** (+)-**9**

Scheme 1



i) Zn, NaI, AcOH. *ii*) Ac_2O, pyridine. *iii*) *hv*, ^{i}PrOH, xylene. *iv*) KOH, MeOH. *v*) Manganese(IV) oxide, CH_2Cl_2.

Scheme 2



i) Zn, NaI, AcOH. *ii*) Ac_2O, pyridine. *iii*) *hν*, ^{i}PrOH, xylene. *iv*) KOH, MeOH. *v*) Manganese(IV) oxide, CH_2Cl_2. *vi*) Column chromatography.

was prolonged until the ratio between α- and γ-isomers, evaluated by GC/MS, did not change further.

Isomerization of *trans*-α-acetates (−)- and (+)-**4b** (0.04M solution in ^{i}PrOH with 10% of xylene, *Scheme 1*) took *ca.* twelve days: a photostationary equilibrium was reached, characterized by 2–7% of still unreacted α-isomer. The *trans*-γ-isomers obtained were found to be 1:1 mixtures of derivatives (−)- and (+)-**5** and of the corresponding (7*Z*) diastereoisomers **11a** and **11b**[3]) only when their ^{1}H-NMR spectra were recorded. As a matter of fact, no distinction was possible by GC/MS.

As for the *cis*-α derivatives (−)- and (+)-**10b** (0.04M solution in ^{i}PrOH with 10% of xylene, *Scheme 2*), after 5 h, *ca.* 40% of *cis*-γ-isomer **12a** or **12b** respectively[3]) was detected by GC, and no traces of (7*Z*) isomers, neither in the α nor in the γ series, were found. Within 27 h from the beginning, the *cis*-α-irol acetates had completely

[3]) We use the labels '**a**' and '**b**' to distinguish the two enantiomers of derivatives **11**–**13**. They could not be obtained as single pure compounds, so it was not possible to determine the right sign of the optical rotation for each of them.

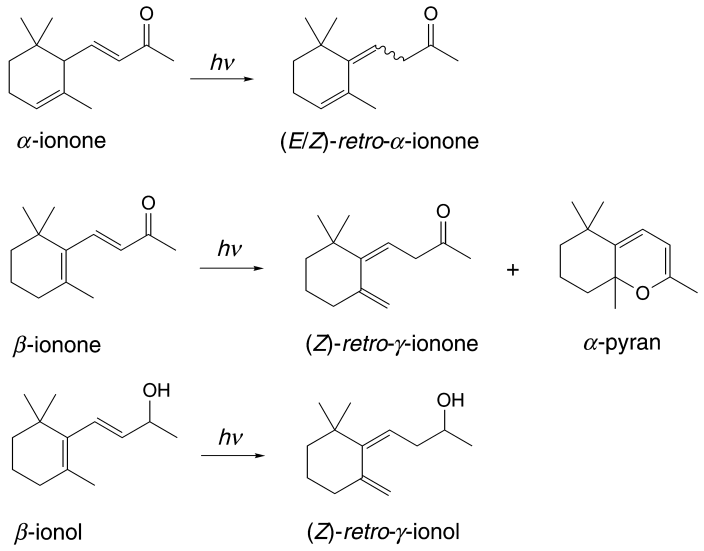
disappeared, and *ca.* 30% of (7*Z*) isomers **13a** and **13b**[3]) had formed. The appearance of (7*Z*)-isomers (5%) was first detected after an irradiation time of 7 h.

The rate constants for the photoisomerization processes were estimated from the disappearance of the corresponding α-irol acetate, as measured by GC/MS in the presence of *ca.* 5% of dodecane as an internal standard: $k_{trans} = 2 \cdot 10^{-6}$ s^{-1} and $k_{cis} = 6 \cdot 10^{-5}$ s^{-1}. Owing to inherent design limitations of the reactor, a constant temperature could not be maintained. A difference of *ca.* one order of magnitude was observed between the rate constants of *cis*- and *trans*-α-irol acetate isomerization. This could be tentatively attributed to the so-called 'steric factor'. This process is probably very sensitive to the molecular geometry of the substrate itself, since triplet-triplet transfer generally needs a collision between sensitizer and substrate.

Photosensitized irradiation of *cis*- and *trans*-α-irol acetates is similar to that described for dihydro-α-ionol acetate [8], which readily undergoes isomerization to the γ-isomer. The presence of the C(7)=C(8) bond does not inhibit $\alpha \rightarrow \gamma$ isomerization; this C=C bond is only involved in an $(E) \rightarrow (Z)$ process, which seems to happen after the C(4)=C(5) bond shift. This photochemical behavior somewhat resembles that of cycloalkenes. Several studies have established that transfer of triplet energy to acyclic or macrocyclic olefins from suitable photosensitizers results in *cis* → *trans* isomerization of the C=C bond [9]. By contrast, small-ring cyclic olefins, characterized by highly strained *trans* isomers, are known to undergo a different fate. For example, irradiation of 1-alkylcycloalkenes in the presence of aromatic-hydrocarbon photosensitizers induces isomerization to the analogous exocyclic olefins [9]. Our substrates show both a hindered endocyclic C=C bond responsible for γ-isomerization, and a C=C bond in the side chain suitable for $(E)/(Z)$ isomerization.

A completely different behavior is reported in the literature for ionone derivatives subjected to direct irradiation (*Scheme 3*). α-Ionone is known to afford (*E/Z*)-*retro*-α-

Scheme 3. *Products of Photochemical Irradiation of α-Ionone, β-Ionone, and β-Ionol*



ionone *via* γ-abstraction at $C_{(6)}$ [10], while β-ionone is described to give a mixture of *retro*-γ-ionone and an α-pyran isomer upon direct irradiation, and only this latter upon triplet-sensitized reaction [11]. Direct irradiation of β-ionol affords *retro*-γ-ionol [12].

The photoisomerization mixtures were hydrolysed in methanolic KOH solution, and the corresponding irol derivatives were oxidized in CH_2Cl_2 in the presence of manganese(IV) oxide. Both in the *trans* and in the *cis* series, (7*E*)-irone could be separated from the (7*Z*) diastereoisomer by column chromatography on SiO_2. The following products were thus obtained:

i) From (−)-**4b**: (+)-(7*E*)-*trans*-γ-irone ((+)-**3b**): $[\alpha]_D^{20} = +10$ ($c = 2.8$, CH_2Cl_2), chemical purity 74% (GC/MS), with 8% of (−)-*trans*-α-irone, ee 99% (HPLC); (−)-(7Z)-*trans*-γ-irone ((−)-**14**): $[\alpha]_D^{20} = -43.2$ ($c = 1.25$, CH_2Cl_2) [7c]: $[\alpha]_D^{20} = -42$ ($c = 0.4$, CH_2Cl_2; ee 76%), chemical purity 70 % (GC/MS).

ii) From (+)-**4b**: (−)-(7*E*)-*trans*-γ-irone ((−)-**3b**): $[\alpha]_D^{20} = -16$ ($c = 3.0$ CH_2Cl_2), chemical purity 79% (GC/MS), with 3% of *trans*-α-irone, ee 99% (HPLC); (+)-(7*Z*)-*trans*-γ-irone ((+)-**14**): $[\alpha]_D^{20} = +48.7$ ($c = 1.32$, CH_2Cl_2), chemical purity 76% (GC/MS).

iii) From (−)-**10b**: (−)-(7*E*)-*cis*-γ-irone ((−)-**3a**): $[\alpha]_D^{20} = -2.54$ ($c = 4.9$, CH_2Cl_2), chemical purity 96 % (GC/MS), ee 99% (GC); (+)-(7*Z*)-*cis*-γ-irone ((+)-**15**): $[\alpha]_D^{20} = +50.5$ ($c = 1.08$, CH_2Cl_2), chemical purity 90% (GC/MS).

iv) From (+)-**10b**: (+)-(7*E*)-*cis*-γ-irone ((+)-**3a**): $[\alpha]_D^{20} = +1.78$ ($c = 4.3$, CH_2Cl_2), chemical purity 93% (GC/MS), ee 99% (GC); (−)-(7*Z*)-*cis*-γ-irone ((−)-**15**): $[\alpha]_D^{20} = -48.3$ ($c = 1.2$, CH_2Cl_2), chemical purity 91% (GC/MS).

This approach allowed us to obtain all eight stereoisomers of (*E*)- and (*Z*)-*cis*- and (*E*)- and (*Z*)-*trans*-γ-irones from commercial *Irone Alpha*®. However, in the samples of (+)- and (−)-**3b**, the presence of α-isomers, showing high values of optical rotation of the opposite sign (see [6a]: (+)-**1b**, $[\alpha]_D^{20} = +427$ ($c = 0.95$, CH_2Cl_2); (−)-**1b**, $[\alpha]_D^{20} = -400$ ($c = 1.05$, CH_2Cl_2)) could not be avoided and strongly affected the values of the measured optical rotation. An alternative synthetic path affording enantiomerically pure (+)- and (−)-**3b** with high chemical purity was thus devised.

Approach B. This approach was based on the resolution of (±)-*trans*-γ-irone by enzymic methods. We thus optimized a large-scale synthesis of this racemic material[4]), which is depicted in *Scheme 4*. Commercial 2,3-dimethylbut-2-ene was brominated with *N*-bromosuccinimide (NBS) in CCl_4 solution, in the presence of catalytic amounts of dibenzoyl peroxide, to give bromo derivative **16** [13]. This latter was employed as an alkylating agent of ethyl acetoacetate (=ethyl 3-oxobutanoate) to afford **17**[5]), according to a general procedure for the alkylation of dianions of β-keto esters reported in [14b]. Cyclization of substrate **17** with $SnCl_4$ in CH_2Cl_2 (see, *e.g.*, [15]) allowed us to obtain the known cyclic keto ester **18** [16] as a 2:1 mixture of *trans/cis* diastereoisomers, which had been previously used in a synthesis of racemic *trans*-γ-irone [7k]. This derivative was subjected[6]) to reaction with $PPh_3{=}CH_2$, followed by reduction of the ester function with $LiAlH_4$, to afford *trans*-6-methyl-γ-cyclogeraniol (**19**)[7]) as a single diastereoisomer (GC/MS, ^{1}H-NMR). Oxidation to the corresponding

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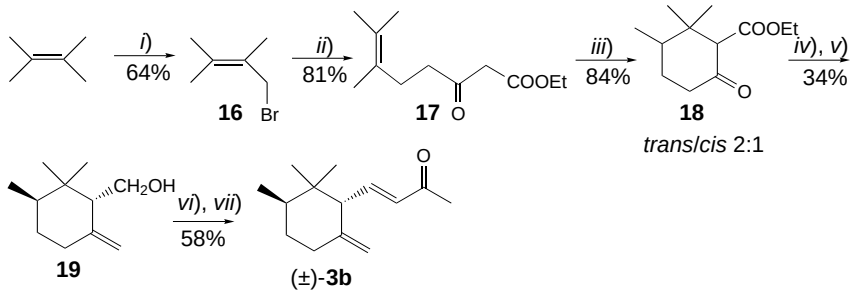
4) For previous syntheses of racemic *trans*-γ-irone, see [7e–k].

5) For an analogous terminal olefinic acetoacetate derivative, see [14a].

6) For a similar synthetic procedure, see [17b].

7) For optically active **19**, see [7b].

Scheme 4



i) NBS, CCl_4, benzoyl peroxide. *ii*) Ethyl acetoacetate, 1 equiv of NaH, THF; then 1 equiv of BuLi, 0°. *iii*) $SnCl_4$, CH_2Cl_2. *iv*) $PPh_3=CH_2$, THF, reflux. *v*) $LiAlH_4$, THF, 0°. *vi*) ClCOCOCl, DMSO; Et_3N, CH_2Cl_2. *vii*) $PPh_3=CHCOMe_3$, toluene, reflux.

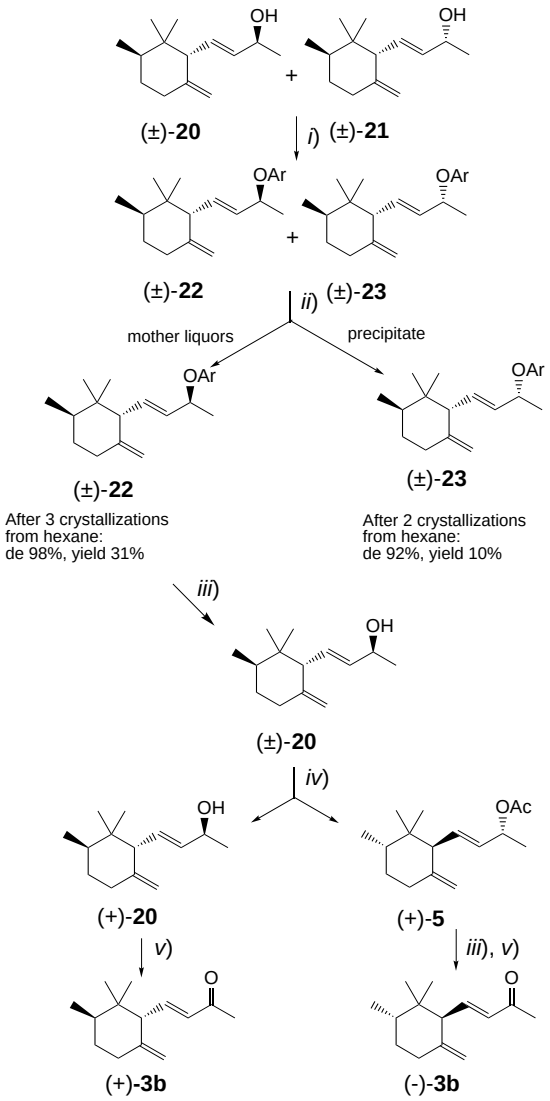
aldehyde and condensation with $PPh_3=CHCOMe_3$, by analogy with [7b,i], completed the synthetic path to racemic *trans*-γ-irone (±)-**3b** (only 2% of *cis*-γ isomer, GC/MS).

As for the resolution of the so-obtained (±)-*trans*-γ-irone (±)-**3b** (*Scheme 5*), we took advantage of a scheme we had already exploited for α- and γ-ionone [17]. Reduction with $NaBH_4$ afforded a 1:1 mixture of γ-irols (±)-**20** and (±)-**21**, which were converted to the corresponding crystalline 4-nitrobenzoates (±)-**22** and (±)-**23** (*Scheme 5*). These latter derivatives could be separated by fractional crystallization from hexane. The less soluble diastereoisomer (±)-**23**, obtained as a precipitate from the first crystallization, was crystallized twice and reached a de of 92% (GC/MS). The mother liquors from the first crystallization, surprisingly, afforded diastereoisomer (±)-**22** with a de of 98% (GC/MS) after four recrystallizations. This latter was the major product, and was then hydrolysed to give (±)-**20**. The relative configuration depicted in structural formula (±)-**20** was deduced from the outcome of the synthetic sequence, as we will explain below.

After four days, lipase-PS-mediated acetylation of racemic γ-irol (±)-**20** in ^{t}BuOMe in the presence of vinyl acetate gave γ-irol acetate (+)-**5**, and left unreacted alcohol (+)-**20**. Hydrolysis of (+)-**5**, followed by manganese(IV) oxide oxidation afforded (−)-*trans*-γ-irone (−)-**3b** with an $[\alpha]_D^{20}=-81$ ($c=1$, CH_2Cl_2), a chemical purity of 99% (GC/MS), and an ee >99% (chiral HPLC). Oxidation of the unreacted alcohol (+)-**20** allowed us to obtain (+)-*trans*-γ-irone (+)-**3b** with an $[\alpha]_D^{20}=+76.4$ ($c=1.2$, CH_2Cl_2), a chemical purity of 99% (GC/MS), and an ee >99% (chiral HPLC). The reference values of $[\alpha]_D^{20}$ reported in the literature for (+)- and (−)-**3b** are rather low and not fully comparable: *a*) (−)-**3b**, ee 70% (NMR with chiral shift reagents), $[\alpha]_D^{20}=-43.3$ ($c=0.8$, CH_2Cl_2) [7a]; *b*) (−)-**3b**, ee 76% (ee of the starting material), $[\alpha]_D^{20}=-53.4$ ($c=2.34$, $CHCl_3$) [7b]; *c*) (+)-**3b**, ee 80% (ee of the starting material), $[\alpha]_D^{20}=+57$ ($c=0.33$, CH_2Cl_2) [7c]; *d*) (+)-**3b**, ee 99% (HPLC), $[\alpha]_D^{20}=+59.4$ ($c=1.2$, $CHCl_3$) [7d].

We have previously observed and experimentally verified that lipase PS usually reacts with (*R*) alcohols [6][17][18]: we thus assumed that acetate (+)-**5** had (*R*) configuration at C(9). As (+)-**5** is the precursor of (−)-**3b**, (*S*) configuration was assigned to both C(2) and C(6). The configurations of the compounds reported in *Scheme 4* are thus justified.

Scheme 5



i) 4-Nitrobenzoyl chloride, pyridine. *ii*) Fractional crystallization from hexane. *iii*) KOH, MeOH. *iv*) Lipase PS, vinyl acetate, ^{t}BuOMe, column chromatography. *v*) MnO_2 in CH_2Cl_2.

2.2. *Olfactory Evaluation.* Thanks to the synthetic *Approach B*, we had in our hands enantiomerically pure samples of (+)- and (−)-*trans*-γ-irone of high chemical purity suitable for odor evaluation and threshold determination. This work was performed at *Givaudan Dübendorf AG,* Fragrance Research (Dübendorf, Switzerland). Thus, (+)-*trans*-γ-irone ((+)-**3b**) is very weak, of a woody odor tonality with a threshold value of

113.5 ng/l; (−)-*trans*-γ-irone ((−)-**3b**) is also not very powerful, but it possesses a soft orris-butter-type odor, with a threshold value of 26.35 ng/l.

2.3. *Determination of Irone-Isomer and -Enantiomer Distributions in Italian Iris-Oil Samples.* Having accomplished the syntheses described in *Sect. 2.1*, we had in our hands all ten possible irone isomers in enantiomerically pure form, and had optimized chiral GC and HPLC methods to distinguish them. We then had the chance to determine the configuration of the irone isomers generated from fresh Italian iris rhizomes by an accelerated procedure, based on an enzymatic process [19].

It is well-known that freshly harvested rhizomes do not contain irones, but their triterpenoid precursors called 'iridals' [20]. According to the traditional procedure, decorticated rhizomes are kept in a dry and aerated environment for 2–3 years, then powdered, incubated with diluted sulfuric acid, and finally steam-distilled to provide the precious 'orris butter'. The mechanism of the oxidative degradation affording irones from iridals is still unknown.

Ten years ago, *Gil et al.* patented an enzymatic procedure for the development of irones [19]. The ethanolic extract of fresh rhizomes is treated with a lipoxydase under O_2, in the presence of linoleic acid as a hydroperoxide donor. Steam distillation of the reaction mixture affords, after extraction with CH_2Cl_2 and evaporation, a residue containing various irone isomers. The isomer and enantiomer composition of the iris oil prepared according to this accelerated method has never been fully characterized.

We had a generous gift of four batches (*a*–*d*) of fresh iris rhizomes, sold by *Aboca* (Sansepolcro, Toscana, Italy) as *Iris pallida.* Rhizomes were cut into slices and extracted according to the procedure described in the *Exper. Part*. The residue was suspended in H_2O in the presence of soy bean flour as a source of lipoxidase and of linoleic acid. The reaction mixture was vigorously stirred at room temperature under O_2 for 24 h. Steam distillation allowed the recovery of an odorous oil, which was chromatographed (silica gel) to isolate the fraction containing irone isomers. The four irone samples thus obtained were submitted to GC and HPLC analysis (see *Table*).

Table. *Isomer and Enantiomer Distribution of Irone-Oil Samples*

	trans-α-Irone			*trans*-γ-Irone			*cis*-α-Irone			*cis*-γ-Irone			β-Irone	Others[a])
	% GC	main enantiomer	% ee[b])	% GC	main enantiomer	% ee[c])	% GC	main enantiomer	% ee[b])	% GC	main enantiomer	% ee[b])	% GC	% GC
Sample *a:* $[\alpha]_D^{20} = +6$ ($c = 0.55$[d]))	3.0	(+)	99	0.61	(−)	99	39.6	(−)	26	39.8	(+)	99	0.38	16.6
Sample *b:* $[\alpha]_D^{20} = +25$ ($c = 0.88$[d]))	3.4	(+)	99	0.52	(−)	99	29.9	(+)	26	48.5	(+)	99	–	17.7
Sample *c:* $[\alpha]_D^{20} = +11$ ($c = 1.2$[d]))	5.6	(+)	99	0.56	(−)	99	29.1	(+)	65	55.6	(+)	99	0.28	8.86
Sample *d:* $[\alpha]_D^{20} = +26$ ($c = 0.54$[d]))	4.0	(+)	99	0.49	(−)	99	28.0	(+)	99	55.3	(+)	99	–	12.2

[a]) Unidentified irone components. [b]) Chiral GC. [c]) Chiral HPLC. [d]) In CH_2Cl_2 solution.

GC Analysis (*HP5* column) allowed us to recognize irone isomers by comparison with the corresponding synthesized samples: traces of *trans*-γ-irone could be revealed. The abundances of the main irone isomers **1**–**3** in the four samples were determined. The corresponding percentages calculated from GC-peak integrals are reported in the *Table*.

The two enantiomers of *trans*-α-, *cis*-α, and *cis*-γ-irone could be distinguished by chiral GC analysis, while HPLC was employed to separate the two antipodes of *trans*-γ-irone. No chromatographic method was found for the separation of the β-irone enantiomers.

The average composition of the irone oil produced by the employed enzymatic method was the following: 4% of (+)-*trans*-α-irone (ee 99%), 0.6% of (−)-*trans*-γ-irone (ee 99%), 31.6% of prevalently dextrorotatory *cis*-α-irone, 49.8% of (+)-*cis*-γ-irone (ee 99%), traces of β-irone, and 13.8% of other unidentified components. Among the latter, traces of (7*Z*)-*cis*-γ-irone were identified by GC. This composition is quite similar to the one reported for *Iris pallida* butter obtained *via* the classical method [21]. In these extracts, we found only the laevorotatory *trans*-γ-irone, that is to say, the enantiomer showing at the stereogenic atoms C(2) and C(6) the same configuration (2*S*,6*S*) as naturally occurring (+)-*trans*-α-irone. We could suppose that the 0.6% of γ-isomer might derive from partial isomerization of the corresponding α-isomer.

3. Conclusions. – In this report, we have described the synthesis of enantiomerically pure (*E*/*Z*)-*trans*-γ-irone isomers starting from *Irone Alpha*®. We have thus completed a series of studies devoted to the preparation of all ten stereoisomers of (*E*)-irones from the commercial mixture of racemic *trans*- and *cis*-α-irone. The synthetic procedure took advantage of the lipase-mediated kinetics resolution of some epoxy intermediates, and of the photoisomerization of the endocyclic α- to exocyclic γ-double bond. The behavior of *trans*-α-irol acetates under triplet-excited irradiation, which had never been investigated, was studied and compared from kinetics point of view to that shown by *cis*-α-irol derivatives. A difference of one order of magnitude was found between the two rate constants. The samples of *trans*-γ-irone obtained by this method could not be purified from the starting α-isomers. A more efficient procedure for the preparation of *trans*-γ-irones of higher purity was thus devised. This latter consisted of separating of *trans*-γ-irol diastereoisomers (±)-**20** and (±)-**21** *via* fractional crystallization of the corresponding 4-nitrobenzoate esters. Diastereoisomerically pure (±)-**20** was then recovered and submitted to lipase-PS-mediated kinetics resolution. At the end of this sequence, chemically pure (+)- and (−)-**3b** showing an ee higher than 99% were obtained. These samples allowed us to describe precise optical-rotation values of both the enantiomers and to give the complete odor description.

The experience we had collected during the last three years in the analytical identification of irone isomers induced us to try the complete characterization of irone-oil samples prepared according to the enzymatic procedure of *Gil et al.* This work allowed us to identify the so-called 'missing γ-irone' [5] and to assess its configuration. In the extracts produced by the action of lipoxydase on irone precursors, we could detect (−)-*trans*-γ-irone, the one described to possess a soft orris-butter-type odor, according to Swiss researchers (see *Sect. 2.2*).

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Experimental Part

General. Epoxy derivatives (−)-**6**, (+)-**7**, (+)-**8**, and (+)-**9** are described in [6a]; 1-bromo-2,3-dimethyl-but-2-ene (**16**) was prepared according to [13]. *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: t_R in min. Optical rotations: *Dr. Kernchen-Propol* digital automatic polarimeter. IR: in cm^{-1}. ^{1}H-NMR Spectra: $CDCl_3$ solns. at r.t. unless otherwise stated; *Bruker-AC-250* spectrometer (250 MHz ^{1}H); chemical shifts δ in ppm rel. to internal $SiMe_4$, *J* values in Hz. GC/MS: in *m*/*z* (rel. %); t_R in min. Microanalyses were determined on a *Carlo Erba Analyzer 1106*.

1. *Deoxygenation of Epoxy Derivatives* **6** *and* **8**. 1.1. *General Procedure 1 (GP 1)*. NaI (3.20 g, 0.21 mol) was added to a stirred mixture of the suitable epoxy-α-irol (2.24 g, 0.010 mol), Zn powder (0.788 g, 0.012 mol), and NaOAc (2.34 g, 0.029 mol) in AcOH (50 ml) at r.t. The mixture was stirred at r.t. for 2–24 h, diluted with hexane/AcOEt 1:1, and filtered. The filtrate was treated with H_2O, and sat. $NaHCO_3$ soln., the org. phase dried and evaporated, and the residue submitted to CC (hexane/AcOEt 95:5).

1.2 *(2*R,*6*R,*9*S*)-α-Irol* (=*(2*S,*3*E*)-4-[(1*R,*5*R*)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-ol*; (−)-**4a**). According to *GP 1*, (−)-**6** (5 g, 0.022 mol) gave, after 24 h, (−)-**4a** (2.83 g, 61%). $[\alpha]_D^{20} = -94$ (*c* = 0.51, CH_2Cl_2); ee > 99% by chiral GC of the corresponding acetate (t_R = 20.74). Chemical purity 93% by GC/MS (t_R 16.06), with 7% of *cis*-α-irol (t_R 16.77). ^{1}H-NMR: 5.55 (*m*, H−C(8), H−C(7)); 5.36 (*m*, H−C(4)); 4.29 (*quint.*, *J* = 6, C*H*OH); 2.10–1.50 (*m*, 4 H); 1.55 (*m*, Me−C(5)); 1.26 (*d*, *J* = 6.5, MeCHOH); 0.81 (*d*, *J* = 6.5, Me−C(2)); 0.80 (s, 1 Me−C(1)); 0.77 (*s*, 1 Me−C(1)). ^{13}C-NMR: 136.9; 135.9; 131.2; 121.4; 68.9; 56.1; 35.2; 34.6; 29.7; 26.50; 22.7; 22.4; 15.1; 14.0. GC/MS: 95 (100), 138 (46), 190 (1), 208 (0.6). Anal. calc. for $C_{14}H_{24}O$: C 80.71, H 11.61; found: C 80.65, H 11.57.

1.3. *(2*S,*6*S,*9*R*)-α-Irol* (=*(2*R,*3*E*)-4-[(1*S,*5*S*)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-ol*; (+)-**4a**). According to *GP 1*, (+)-**6** (5 g, 0.022 mol) gave, after 24 h, (+)-**4a** (2.97 g, 65%). $[\alpha]_D^{20} = +90.7$ (*c* = 0.38, CH_2Cl_2); ee > 99% by chiral GC of the corresponding acetate (t_R 21.38). Chemical purity 91% by GC/MS (t_R 16.06), with 9% *cis*-α-irol (t_R 16.77). MS and ^{1}H-NMR: in accordance with those of (−)-**4a**. Anal. calc. for $C_{14}H_{24}O$: C 80.71, H 11.61; found: C 80.79, H 11.67.

1.4. *(2*S,*6*R,*9*S*)-α-Irol* (=*(2*S,*3*E*)-4-[(1*R,*5*S*)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-ol*; (−)-**10a**). According to *GP 1*, (+)-**8** (5 g, 0.022 mol) gave, after 2 h, (−)-**10a** (3.29 g, 72%). $[\alpha]_D^{20} = -55.5$ (*c* = 1.0, CH_2Cl_2); ee > 99% by chiral GC of the corresponding acetate (t_R 22.40). Chemical purity 98% by GC/MS (t_R 16.79). ^{1}H-NMR: 5.59 (*dd*, *J* = 6.3, 15.2, H−C(8)); 5.43 (*dd* + *m*, *J* = 10, 15.2, H−C(7), H−C(4)); 4.34 (*quint.*, *J* = 6.3, C*H*OH); 2.35 (*m*, 1 H); 1.89 (*m*, 1 H); 1.69 (*m*, 1 H); 1.51 (*m*, Me−C(5)); 1.45 (*m*, 1 H); 1.29 (*d*, *J* = 6.3, *Me*CHOH); 0.85 (*d* + *s*, *J* = 6.5, Me−C(2), 1 Me−C(1)); 0.65 (*s*, 1 Me−C(1)). ^{13}C-NMR: 137.7; 133.8; 130.5; 121.8; 68.8; 55.6; 38.2; 35.1; 31.9; 26.4; 23.5; 22.9; 15.5; 14.6. GC/MS: 95 (100), 138 (42), 190 (1), 208 (0.5). Anal. calc. for $C_{14}H_{24}O$: C 80.71, H 11.61; found: C 80.65, H 11.68.

1.5. *(2*R,*6*S,*9*R*)-α-Irol* (=*(2*R,*3*E*)-4-[(1*S,*5*R*)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-ol*; (+)-**10a**). According to *GP 1*, (−)-**8** (5 g, 0.022 mol) gave, after 2 h, (+)-**10a** (3.16 g, 69%). $[\alpha]_D^{20} = +53.5$ (*c* = 1.1, CH_2Cl_2); ee > 99% by chiral GC of the corresponding acetate (t_R 22.9). Chemical purity 98% by GC/MS (t_R 16.77). MS and ^{1}H-NMR: in accordance with those of (−)-**10a**. Anal. calc. for $C_{14}H_{24}O$: C 80.71, H 11.61; found: C 80.76, H 11.54.

2. *Acetylation of Irol Derivatives* **4a** *and* **10a**. 2.1. *General Procedure 2* (*GP 2*). All irol derivatives (2.08 g, 0.01 mol) were acetylated by treatment with Ac_2O (0.05 mol) and pyridine (5 ml) in excess.

2.2 *(2*R,*6*R,*9*S*)-α-Irol Acetate* (=*(2*S,*3*E*)-4-[(1*R,*5*R*)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-ol Acetate*; (−)-**4b**). According to *GP 2*, (−)-**4a** gave (−)-**4b** (3.09 g, 95 %). $[\alpha]_D^{20} = -58$ (*c* = 1.2, CH_2Cl_2); ee > 99% by chiral GC (t_R 20.74). Chemical purity 94% by GC/MS (t_R 18.44), with 6% of *cis*-α-irol acetate (t_R 19.06). ^{1}H-NMR: 5.60–5.30 (*m*, H−C(7), H−C(8), H−C(9), H−C(4)); 2.04 (*s*, MeCO); 1.90–1.50 (*m*, 4 H); 1.56 (*m*, Me−C(5)); 1.30 (*d*, *J* = 6.1, *Me*CHOAc); 0.81 (*d*, *J* = 6.7, Me−C(2)); 0.79 (*s*, Me−C(1)); 0.76 (*s*, Me−C(1)). ^{13}C-NMR: 170.4; 132.5; 131.2; 131.1; 121.6; 70.9; 56.1; 37.8; 33.6; 32.4; 26.4; 22.6; 21.38; 20.9; 15.20; 14.1. GC/MS: 95 (54), 105 (100), 120 (81), 138 (46), 180 (48), 190 (27). Anal. calc. for $C_{16}H_{26}O_2$: C 76.75, H 10.47; found: C 76.69, H 10.42.

2.3 *(2S,6S,9R)-α-Irol Acetate* (=*(2R,3E)-4-[(1S,5S)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-ol Acetate*; (+)-**4b**). According to *GP 2*, (+)-**4a** (2.80 g, 0.013 mol) gave (+)-**4b** (3.06 g, 91%). $[\alpha]_D^{20} = +56$ ($c = 1.1$, CH_2Cl_2); ee >99% by chiral GC (t_R 21.38). Chemical purity 91% by GC/MS (t_R 18.44), with 9% of *cis*-α-irol acetate (t_R 19.05). MS and ^{1}H-NMR: in accordance with those of (−)-**4b**. Anal. calc. for $C_{16}H_{26}O_2$: C 76.75, H 10.47; found: C 76.79, H 10.52.

2.4 *(2S,6R,9S)-α-Irol Acetate* (=*(2S,3E)-4-[(1R,5S)-2,5,6,6-Tetramethylcyclohex-2-en-1-yl]but-3-en-2-ol Acetate*; (−)-**10b**). According to *GP 2*, (−)-**10a** (3.20 g, 0.015 mol) gave (−)-**10b** (3.38 g, 90%). $[\alpha]_D^{20} = -105$ ($c = 1.41$, CH_2Cl_2); ee >99% by chiral GC (t_R 22.40). Chemical purity 98% by GC/MS (t_R 19.05). ^{1}H-NMR: 5.50 (*m*, 2 H); 5.47 (*m*, 1 H); 5.36 (*m*, H−C(9)); 2.32 (*m*, 1 H); 2.04 (*s*, MeCO); 1.90 (*m*, 1 H); 1.70 (*m*, 1 H); 1.50 (*m*, Me−C(5)); 1.44 (*m*, 1 H), 1.32 (*d*, $J = 6.5$, MeCHOAc); 0.85 (*d* + *s*, $J = 6.7$, Me−C(2), Me−C(1)), 0.65 (*s*, 1 Me−C(1)). ^{13}C-NMR: 170.3; 133.6; 133.2; 132.8; 122.0; 71.0; 55.8; 38.1; 35.2; 31.9; 26.3; 22.7; 21.26; 15.53; 14.47. GC/MS: 105 (100), 120 (80), 138 (44), 180 (57), 190 (20). Anal. calc. for $C_{16}H_{26}O_2$: C 76.75, H 10.47; found: C 76.81, H 10.39.

2.5 *(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*; (+)-**10b**). According to *GP 2*, (+)-**10a** (3.10 g, 0.015 mol) gave (+)-**10b** (3.32 g, 89%). $[\alpha]_D^{20} = +107$ ($c = 1.55$, CH_2Cl_2) ([6c]: $[\alpha]_D^{20} = -73$ ($c = 1.50$, CH_2Cl_2; sample containing 13% of 4-chloro-4,5-dihydro-*cis*-α-irol acetate); ee >99% by chiral GC (t_R 22.9). Chemical purity 98% by GC/MS (t_R 19.05). MS and ^{1}H-NMR: in accordance with those of (−)-**10b**. Anal. calc. for $C_{16}H_{26}O_2$: C 76.75, H 10.47; found: C 76.68, H 10.39.

3. *Photochemical Isomerization of* **4b** *or* **10b**. 3.1. *General Procedure 3 (GP 3)*. A soln. of the suitable irol acetate (1.0 g, 0.004 mol) in ^{i}PrOH (90 ml) in the presence of xylene (10 ml) as photosensitizer was irradiated in quartz vessels, in a *Rayonet* photochemical reactor equipped with ten 8-W high-pressure Hg lamps. The soln. was evaporated and the residue purified by CC (hexane/AcOEt 95:5).

3.2 *(2R,6R,7E,9S)-γ-Irol Acetate* (=*(2S,3E)-4-[(1R,3R)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol Acetate*; (−)-**5**) *and (2R,6R,7Z,9S)-γ-Irol Acetate* (=*(2S,3Z)-4-[(1R,3R)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol*) *Acetate*; **11a**). According to *GP 3*, (−)-**4b** (1.0 g, 0.004 mol) gave a 1:1 mixture (^{1}H-NMR) (−)-**5**/**11a** (0.89 g, 89%). Chemical purity 61% by GC/MS (t_R 18.69). FT-IR (neat): 1738, 1645, 1455, 1371, 1250, 1135. ^{1}H-NMR of the mixture: 5.97 (*dd*, $J = 9$, 15, H−C(7) (*E*)-isomer); 5.82 (*t*, $J = 11$, H−C(7) (*Z*) isomer); 5.76 (*m*, H−C(9) (*Z*) isomer); 5.44 (*m*, H−C(8) (*Z*) and (*E*) isomers); 5.32 (*quint.*, $J = 6$, H−C(9) (*E*) isomer); 4.67 (*m*, 1 H of C=CH$_2$ *E* isomer, C=CH$_2$ (*Z*) isomer); 4.60 (*m*, 1 H of C=CH (*E*) isomer); 2.97 (*d*, $J = 11$, H−C(6) (*Z*) isomer); 2.46 (*d*, $J = 9$, H−C(6) (*E*) isomer); 2.10–2.30 (*m*, 4 H); 2.03 (*s*, MeCO (*E*) isomer); 1.99 (*s*, MeCO (*Z*) isomer); 1.40–1.60 (*m*, 4 H); 1.29 (*m*, 8 H); 0.80–0.87 (*m*, 15 H); 0.76 (*s*, Me−C(1) (*E*) isomer). GC/MS: 83 (100), 105 (97), 123 (66), 175 (62), 190 (60), 250 (5).

3.3 *(2S,6S,7E,9R)-γ-Irol Acetate* (=*(2R,3E)-4-[(1S,3S)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol Acetate*; (+)-**5**) and *(2S,6S,7Z,9R)-γ-Irol Acetate* (=*(2R,3Z)-4-[(1S,3S)-2,2,3-Trimethyl-6-methylidene cyclohexyl]but-3-en-2-ol Acetate*; **11b**). According to *GP 3*, (+)-**4b** (1.0 g, 0.004 mol) gave a 1:1 mixture (^{1}H-NMR) (+)-**5**/**11b** (0.85 g, 85%). Chemical purity 65% by GC/MS ($t_R = 18.69$). MS and ^{1}H-NMR: in accordance with those of the corresponding enantiomers.

3.4 *(2S,6R,7E,9S)-γ-Irol Acetate* (=*(2S,3E)-4-[(1R,3S)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol Acetate*; **12a**) *and (2S,6R,7Z,9S)-γ-Irol Acetate* (=*(2S,3Z)-4-[(1R,3S)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol Acetate*; (**13a**)). According to *GP 3*, (−)-**10b** (1.0 g, 0.004 mol) gave a 2:1 mixture (GC/MS) **12a**/**13a** (0.91 g, 91%). Chemical purity 95% by GC/MS (t_R (**13a**) 18.53, t_R (**12a**) 19.22). FT-IR (neat): 1734, 1648, 1451, 1370, 1254, 1131. ^{1}H-NMR: **12a**: 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*, 1 H, C=CH); 4.45 (*m*, 1 H, C=CH); 2.32 (*m*, 2 H); 2.03 (*s* + *m*, Ac + 1 H); 1.67–1.15 (*d* + *m*, $J = 6.5$, Me−C(9) + 3 H); 0.86 (*d* + *s*, $J = 7$, Me−C(2), 1 Me−C(1)); 0.63 (*s*, 1 Me−C(1)); **13a**: 4.74 (*m*, 1 H, C=C*H*); 4.50 (*m*, 1 H, C=C*H*). GC/MS: **13a**: 83 (94), 91 (100), 105 (95), 175 (83), 190 (60), 232 (2), 250 (3); **12a**: 83 (96), 91 (100), 105 (91), 175 (64), 190 (64), 232 (3), 250 (5).

3.5 *(2R,6S,7E,9R)-γ-Irol Acetate* (=*(2R,3E)-4-[(1S,3R)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol Acetate*; **12b**) and *(2R,6S,7Z,9R)-γ-Irol Acetate* (=*(2R,3Z)-4-[(1S,3R)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol Acetate*; **13b**). According to *GP 3*, (+)-**10b** (1 g, 0.004 mol) gave a 2:1 mixture (GC/MS) **12b**/**13b** (0.95 g, 95%). Chemical purity 95% by GC/MS. MS and ^{1}H-NMR: in accordance with those of the corresponding enantiomers.

4. *Saponification of the (E)/(Z) Mixtures of γ-Irol Acetates*. 4.1. *General Procedure 4* (*GP 4*). A soln. of the suitable mixture of γ-irol acetates (1.64 g, 6.56 mmol) in MeOH (10 ml) in the presence of KOH (0.551 g, 9.84 mmol) was stirred at r.t. for 2 h. The mixture was diluted with H_2O and extracted with AcOEt. The org. phase was dried (Na_2SO_4) and evaporated and the residue purified by CC (hexane/AcOEt 7:3).

4.2 *(2*R,*6*R,*7*E,*9*S*)-γ-Irol* (=*(2*S,*3*E*)-4-[(1*R,*3*R*)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol*; (+)-**20**) *and (2*R,*6*R,*7*Z,*9*S*)-γ-Irol* (=*(2*S,*3*Z*)-4-[(1*R,*3*R*)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol*). According to *GP 4*, the 1:1 mixture (−)-**5** and **11a** (1.64 g, 9.84 mmol) gave a 1:1 mixture (GC/MS) of the corresponding irol derivatives (1.23 g, 90%). ^{1}H-NMR: 5.92 (*dd*, *J* = 8.6, 15.1, H−C(7) (*E*) isomer); 5.79 (*t*, *J* = 11, H−C(7) (*Z*) isomer); 5.51 (*m*, H−C(8) of (*Z*) and (*E*) isomers); 4.73 (*m*, H−C(9) (*Z*) isomer); 4.67 (*m*, 1 H of C=CH$_2$ (*E*) isomer, C=CH$_2$ (*Z*) isomer); 4.60 (*m*, 1 H of C=CH$_2$ (*E*) isomer); 4.28 (*quint.*, *J* = 6, H−C(9) (*E*) isomer); 2.94 (*d*, *J* = 11, H−C(6) (*Z*) isomer); 2.48 (*d*, *J* = 8.6, H−C(6) (*E*) isomer); 2.10–2.30 (*m*, 4 H); 1.40–1.60 (*m*, 4 H); 1.25 (*m*, 8 H), 0.77–0.88 (*m*, 18 H)). GC/MS: *(2*R,*6*R,*7*Z,*9*S*)-γ-irol* (t_R 16.20): 107 (100), 135 (56), 175 (48), 190 (13); *(2*R,*6*R,*7*E,*9*S*)-γ*-irol (t_R 16.46): 107 (100), 135 (56), 175 (33), 190 (10).

4.3. *(2*S,*6*S,*7*E,*9*R*)-γ-Irol* (=*(2*R,*3*E*)-4-[(1*S,*3*S*)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol* (−)-**20**) *and (2*S,*6*S,*7*Z,*9*R*)-γ-Irol* (=*(2*R,*3*Z*)-4-[(1*S,*3*S*)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol*). According to *GP 4*, the 1:1 mixture (+)-**5**/**11b** (1.61 g, 6.44 mmol) gave a 1:1 mixture (GC/MS) of the corresponding irol derivatives (1.51 g, 94%). GC/MS and ^{1}H-NMR: in accordance with those of the corresponding enantiomers.

4.4. *(2*S,*6*R,*7*E,*9*S*)-γ-Irol* (=*(2*S,*3*E*)-4-[(1*R,*3*S*)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol*) *and (2*S,*6*R,*7*Z,*9*S*)-γ-Irol* (=*(2*S,*3*Z*)-4-[(1*R,*3*S*)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol*). According to *GP 4*, the 2:1 mixture **12a**/**13a** (2.61 g, 0.010 mol) gave a 2:1 mixture (GC/MS) of the corresponding irol derivatives (1.94 g, 89%). ^{1}H-NMR (selection of signals of the main (7*E*) isomer): 5.75 (*ddd*, *J* = 0.95, 9.8, 15.3, H−C(7)); 5.52 (*dd*, *J* = 6.7, 15.3, H−C(8)); 4.74 (*m*, 1 H, C=C*H*); 4.47 (*m*, 1 H, C=C*H*); 4.35 (*quint.*, *J* = 0.95, 6.7, C*H*OH); 1.29 (*d*, *J* = 6.7, MeCHOH); 0.90 (*s*, 1 Me−C(1)); 0.85 (*d*, *J* = 6.3, Me−C(2)); 0.64 (*s*, 1 Me−C(1)); selection of signals of the (7*Z*) isomer: 5.61 (*m*, 2 H); 4.77 (*m*, 1 H, C=C*H*); 4.60 (*m*, 1 H, C=C*H*); 4.54 (*m*, C*H*OH); 1.24 (*d*, *J* = 6.7, MeC*H*CHOH); 0.87 (*s*, 1 Me−C(1)); 0.86 (*d*, *J* = 6.3, Me−C(2)); 0.64 (*s*, Me−C(1)). GC/MS: *(2*S,*6*R,*7*Z,*9*S*)-γ*-irol (t_R 16.46): 107 (100), 123 (61), 135 (65), 150 (39), 175 (65), 190 (11), 208 (7); (2*S*,6*R*,7*E*,9*S*)-γ-irol (t_R 17.00): 107 (100), 123 (69), 135 (65), 150 (72), 175 (31), 190 (7), 208 (2).

4.5. *(2*R,*6*S,*7*E,*9*R*)-γ-Irol* (=*(2*R,*3*E*)-4-[(1*S,*3*R*)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol*) *and (2*R,*6*S,*7*Z,*9*R*)-γ-Irol* (=*(2*R,*3*Z*)-4-[(1*S,*3*R*)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-ol*). According to *GP 4*, the 2:1 mixture **12b**/**13b** (2.47 g, 9.88 mmol) gave a 2:1 mixture (GC/MS) of the corresponding irol derivatives (1.79 g, 87%). GC/MS and ^{1}H-NMR: in accordance with those of the corresponding enantiomers.

5. *Manganese(IV) Oxide Oxidation.* 5.1. *General Procedure 5 (GP 5).* A mixture of the suitable γ-irols (1.50 g, 7.21 mmol) in CH_2Cl_2 (25 ml) in the presence of manganese(IV) oxide (1.5 equiv.) was refluxed for 4 h. The mixture was filtered, the filtrate evaporated, and the residue purified by CC (hexane/AcOEt 97:3).

5.2. *(2*R,*6*R,*7*E*)-γ-Irone* (=*(3*E*)-4-[(1*R,*3*R*)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-one*; (+)-**3b**) *and (2*R,*6*R,*7*Z*)-γ-Irone* (=*(3*Z*)-4-[(1*R,*3*R*)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-one*; (−)-**14**). According to *GP5*, the 1:1 mixture *(2*R,*6*R,*7*E,*9*S)-γ-irol/(2*R*,*6*R*,*7*Z*,*9*S*)-γ-irol (1.13 g, 5.43 mmol) gave (+)-**3b** (0.358 g, 32%) and (−)-**14** (0.324 g, 29%).

Data of (+)-**3b**: ee > 99% by chiral HPLC (t_R 24.54). Chemical purity 74% by GC/MS (t_R 17.57), with impurities of 8% (−)-*trans*-α-irone (t_R 17.25) and 5% (+)-*cis*-γ-irone (t_R 17.90). $[\alpha]_D^{20} = +10$ (*c* = 2.8, CH_2Cl_2). ^{1}H-NMR: 7.07 (*dd*, *J* = 9.4, 15.6, H−C(7)); 6.10 (*dd*, *J* = 1.1, 15.6, H−C(8)); 4.76 (*m*, 1 H, C=CH$_2$); 4.67 (*m*, 1 H, C=CH$_2$); 2.64 (*d*, *J* = 9.4, H−C(6)); 2.25 (*s*, MeCO); 2.22 (*m*, 2 H); 1.61 (*m*, 2 H); 1.31 (*m*, 1 H); 0.90 (*s*, 1 Me−C(1)); 0.86 (*d*, *J* = 6.7, Me−C(2)); 0.81 (*s*, 1 Me−C(1)). GC/MS: 121 (100), 149 (40), 163 (57), 178 (14), 191 (11), 206 (8). Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.59, H 10.70.

Data of (−)-**14:** Chemical purity 70% by GC/MS (t_R 15.97). $[\alpha]_D^{20} = -43.2$ (*c* = 1.25, CH_2Cl_2). ^{1}H-NMR: 6.35 (*t*, *J* = 12.1, H−C(7)); 6.17 (*d*, *J* = 12.1, H−C(8)); 4.75 (*m*, 1 H, C=CH$_2$); 4.71 (*m*, 1 H, C=CH$_2$); 4.06 (*d*, *J* = 12.1, H−C(6)); 2.21 (*s*, MeCO); 2.20–1.20 (*m*, 5 H); 0.88 (*d*, *J* = 6.3, *Me*−C(2)); 0.87 (*s*, 1 Me−C(1)); 0.82 (*s*, 1 Me−C(1)). ^{13}C NMR: 199.0; 148.6; 146.9; 127.4; 110.1; 51.9; 37.8; 35.8; 31.9; 31.6; 31.3; 25.8; 21.8; 15.5. GC/MS: 121 (95), 149 (44), 163 (67), 173 (11), 191 (100), 206 (10). Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.44, H 10.64.

5.3. *(2*S,*6*S,*7*E*)-γ-Irone* (=*(3*E*)-4-[(1*S,*3*S*)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-one*; (−)-**3b**) *and (2*S,*6*S,*7*Z*)-γ-Irone* (=*(3*Z*)-4-[(1*S,*3*S*)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en -2-one*; (+)-**14**). According to *GP 5*, the 1:1 mixture (2*S*,6*S*,7*E*,9*R*)-γ-irol and *(2*S,*6*S,*7*Z,*9*R*)-γ-irol (1.40 g, 6.73 mmol) gave (−)-**3b** (0.388 g, 28%) and (+)-**14** (0.332 g, 24%). Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.57, H 10.69.

Data of (−)-**3b**: ee > 99% by chiral HPLC (t_R 27.46). Chemical purity 79% by GC/MS (t_R 17.57), with impurities of 3% (+)-*trans*-α-irone and 5% (−)-*cis*-γ-irone. $[\alpha]_D^{20} = -16$ (*c* = 3.0, CH_2Cl_2). MS and ^{1}H-NMR: in

accordance with those of the corresponding enantiomer. Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.43, H 10.81.

Data of (+)-**14**: Chemical purity 76% by GC/MS (t_R 15.97). $[\alpha]_D^{20} = 48.7$ ($c = 1.32$, CH_2Cl_2). MS and ^{1}H-NMR: in accordance with those of the corresponding enantiomer. Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.41, H 10.68.

5.4. *(2S,6R,7E)-γ-Irone* (=*(3E)-4-[(1R,3S)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-one*; (−)-**3a**) *and (2S,6R,7Z)-γ-Irone* (=*(3Z)-4-[(1R,3S)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-one*; (+)-**15**). According to *GP 5*, the 2:1 mixture (2*S*,6*R*,7*E*,9*S*)-γ-irol/(2*S*,6*R*,7*Z*,9*S*)-γ-irol (1.84 g, 8.84 mmol) gave (−)-**3a** (0.765 g, 42%) and (+)-**15** (0.346 g, 19%).

Data of (−)-**3a**: ee >99% by chiral GC. (t_R 20.86). Chemical purity 96% by GC/MS (t_R 17.90). $[\alpha]_D^{20} = -2.54$ ($c = 4.9$, CH_2Cl_2). ^{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*, 1 H, C=CH$_2$); 4.43 (*m*, 1 H, C=CH$_2$); 2.55 (*d*, *J* = 10.3, H−C(6)); 2.35 (*ddd*, *J* = 2.5, 4.4, 13.3, 1 H); 2.28 (*s*, MeCO); 2.10 (*m*, 1 H); 1.60–1.20 (*m*, 3 H); 0.87 (*s* + *d*, *J* = 7, 1 Me−C(1), Me−C(2)); 0.73 (*s*, Me−C(1)). GC/MS: 121 (100), 149 (41), 163 (29), 191 (8), 206 (3). Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.45, H 10.77.

Data of (+)-**15**: Chemical purity 90% by GC/MS (t_R 16.33). $[\alpha]_D^{20} = +50.5$ ($c = 1.08$, CH_2Cl_2). ^{1}H-NMR: 6.29 (*d* , *J* = 11.8, H−C(8)); 6.20 (*dd*, *J* = 10.3, 11.8, H−C(7)); 4.72 (*m*, 1 H, C=CH$_2$); 4.42 (*m*, 1 H, C=CH$_2$); 3.85 (*d*, *J* = 10.3, H−C(6)); 2.30 (*m*, 1 H); 2.18 (*s* + *m,* MeCO + 1 H); 1.51 (*m*, 2 H); 1.27 (*m*, 1 H); 0.88 (*s*, 1 Me−C(1)); 0.84 (*d*, *J* = 6.4, Me−C(2)); 0.68 (*s*, 1 Me−C(1)). ^{13}C-NMR: 199.4; 149.1; 146.7; 128.8; 107.5; 51.5; 41.9; 38.8; 36.3; 31.9; 31.6; 26.9; 15.9; 13.7. GC/MS: 149 (30), 191 (100), 206 (5). Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.43, H 10.78.

5.5. *(2R,6S,7E)-γ-Irone* (=*(3E)-4-[(1S,3R)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-one*; (+)-**3a**) *and (2R,6S,7Z)-γ-Irone* (=*(3Z)-4-[(1S,3R)-2,2,3-Trimethyl-6-methylidenecyclohexyl]but-3-en-2-one*; (−)-**15**). According to *GP 5*, the 2:1 mixture (2*R*,6*S*,7*E*,9*R*)-γ-irol/(2*R*,6*S*,7*Z*,9*R*)-γ-irol (1.65 g, 7.93 mmol) gave (+)-**3a** (0.751 g, 46%) and (−)-**15** (0.294 g, 18%).

Data of (+)-**3a**: ee >99% by chiral GC (t_R 20.56). Chemical purity 93% by GC/MS (t_R 17.90). $[\alpha]_D^{20} = +1.78$ ($c = 4.3$, CH_2Cl_2). MS and ^{1}H-NMR: in accordance with those of the enantiomer. Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.42, H 10.74.

Data of (−)-**15**: Chemical purity 91% by GC/MS (t_R 16.33). $[\alpha]_D^{20} = -48.3$ ($c = 1.2$, CH_2Cl_2). MS and ^{1}H-NMR: in accordance with those of the enantiomer. Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.57, H 10.68.

6. *6,7-Dimethyl-3-oxooct-6-enoic Acid Ethyl Ester* (**17**). Ethyl acetoacetate (50.4 g, 0.388 mol) was added dropwise to a suspension of NaH (60% mineral oil; 18.6 g, 0.466 mol) in THF (250 ml) at 0°. The colorless soln. was stirred at 0° for 10 min. To this mixture, 10M BuLi in hexane (46.6 ml, 0.466 mol) was added, and the yellow-orange soln. was stirred at 0° for 10 min. A soln. of bromo derivative **16** (60.0 g, 0.368 mol) in THF (100 ml) was then added, and the mixture was stirred for 30 min, while temp. was allowed to reach 20°. The reaction was quenched with conc. HCl soln. in H_2O and Et_2O. The aq. phase was extracted with Et_2O, the combined org. extract washed with H_2O until neutral, dried (Na_2SO_4), and evaporated, and the residue distilled: **17** (63.2 g, 81%). ^{1}H-NMR: 4.20 (*q*, *J* = 7, COO*CH*$_2$Me); 3.45 (*s*, CO*CH*$_2$COOEt); 2.58, 2.32 (2*m*, CH$_2$CH$_2$); 1.63 (*m*, Me$_2$C=CMe); 1.28 (*t*, *J* = 7, COOCH$_2$Me). ^{13}C-NMR: 203; 167.1; 125.4; 61.2; 49.2; 41.4; 28.2; 20.4; 19.9; 17.9; 13.9. Anal. calc. for $C_{12}H_{20}O_3$: C 67.89, H 9.50; found: C 67.78, H 9.45.

7. *2,2,3-Trimethyl-6-oxocyclohexanecarboxylic Acid Ethyl Ester* (**18**). Tin(IV) chloride (114 g, 0.283 mol) was added to a soln. of **17** (60.0 g, 0.283 mol) in CH_2Cl_2 (300 ml) at 0°. The mixture was stirred at r.t. for 1 h, poured into H_2O, and extracted with CH_2Cl_2. The org. extracts were washed with sat. $NaHCO_3$ soln., then with H_2O, dried (Na_2SO_4), and evaporated. The residue was distilled at 110°, 8 Torr to afford derivative **18** (50.4 g, 84%) as a 2:1 mixture of *trans* and *cis* diastereoisomers, which was submitted directly to the subsequent reaction. ^{1}H-NMR: 4.15 (*m*, COOC*H*$_2$Me); 3.11 (*m*, CO*CH*COOEt); 2.32 (*m*, C*H*$_2$CO); 1.90 (m, Me*CH*); 1.65 (*m*, CH$_2$); 1.28 (*m*, COOCH$_2$*Me*); 1.2–0.90 (*m*, 3 Me). GC/MS: *trans*-**18** (t_R 15.49): 55 (100), 83 (76), 114 (28), 167 (29), 194 (40), 212 (5); *cis*-**18** (t_R 16.28): 55 (100), 83 (78), 114 (29), 167 (30), 194 (24), 212 (5). Anal. calc. for $C_{12}H_{20}O_3$: C 67.89, H 9.50; found: C 67.53, H 9.85.

8. *(1RS,3RS)-2,2,3-Trimethyl-6-methylidenecyclohexane-1-methanol* (**19**). At −78°, 10M BuLi in hexane (28.6 ml, 0.287 mol) was added dropwise to a suspension of $(Ph_3PMe)^+Br^-$ (102.8 g, 0.287 mol) in dry THF (300 ml) at −78°. The mixture was warmed to r.t. and stirred until almost complete disappearance of the phosphonium salt. The cyclic keto ester **18** (50.0 g, 0.235 mol) was added, and the mixture was refluxed for 2 h. After cooling, the mixture was poured into H_2O and extracted with Et_2O. The org. phase was washed with sat. NH_4Cl soln. and brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in hexane and the triphenylphosphine oxide eliminated by crystallization. The mother liquors were diluted with dry THF (300 ml)

and cooled to 0°. $LiAlH_4$ (9.50 g, 0.250 mol) was added under stirring. The mixture was diluted with H_2O and extracted with Et_2O. The org. phase was dried (Na_2SO_4) and evaporated. Purification of the residue by distillation under reduced pressure gave **19** [7b] (13.4 g, 34%). ^{1}H-NMR: in accordance with that reported in [7b]; GC/MS (t_R 12.18): 83 (100), 95 (90), 107 (92), 137 (70), 150 (40), 168 (5). Anal. calc. for $C_{11}H_{20}O$: C 78.51, H 11.98; found: C 78.58, H 11.92.

9. *(±)-trans-γ-Irone* ((±)-**3b**). DMSO (14.7 g, 0.189 mol) was added dropwise to a soln. of ClCOCOCl (12.5 g, 0.098 mol) in CH_2Cl_2 (100 ml) at −78°. Then **19** [7b] (13.0 g, 0.077 mol) was added and the mixture stirred for 15 min at the same temp. The suspension was treated with Et_3N (30 g, 0.293 mol) and allowed to warm to r.t. After 2 h, the mixture was diluted with CH_2Cl_2 and washed with H_2O. The org. phase was dried (Na_2SO_4) and evaporated. The obtained crude residue was dissolved in toluene (100 ml) and treated with (acetylmethylene)triphenylphosphorane (30 g, 0.093 mol). The mixture was refluxed for 8 h. Triphenylphosphine oxide was eliminated by crystallization from hexane. The mother liquors were evaporated and submitted to CC (hexane/AcOEt 95:5): (±)-**3b** (9.19 g, 58%). Chemical purity 98% by GC/MS (t_R 17.57), with 2% *cis-γ*-irone. ^{1}H-NMR: in accordance with that of (+)-**3b** (see above). Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.58, H 10.68.

10. *(±)-(2*RS,*6*RS,*9*SR)*-γ-Irol 4-Nitrobenzoate* ((±)-**22**) *and (±)-(2*RS,*6*RS,*9*RS)*-γ-Irol 4-Nitrobenzoate* ((±)-**23**). Derivative (±)-**3b** (9.10 g, 0.044 mol) was reduced with $NaBH_4$. The resulting mixture of the two racemic alcohol diastereoisomers (8.60 g, 0.041 mol) was dissolved in pyridine (30 ml) and treated with 4-nitrobenzoyl chloride (9.12 g, 0.0492 mol). After the usual workup, the residue was crystallized from hexane. The crystalline precipitate was crystallized twice from hexane to afford (±)-**23** (1.47 g, 10%). The mother liquors were evaporated, and the residue was crystallized thrice from hexane to afford derivative (±)-**22** (4.54 g, 31%).

Data of (±)-**23**: M.p. 57°. GC/MS: (t_R 27.82, de 92%). ^{1}H-NMR: 8.24 (*m*, arom. H); 6.07 (*m*, H−C(7)); 5.60 (*m*, H−C(8), H−C(9)); 4.67 (*m*, 1 H, C=CH_2); 4.61 (*m*, 1 H, C=CH_2); 2.51 (*d*, *J* = 9, H−C(6)); 2.18 (*m*, 2 H); 1.57 (*m*, 2 H); 1.46 (*d*, *J* = 6, *Me*CHOAr); 1.27 (*m*, 1 H); 0.86 (*s*, 1 Me−C(1)); 0.84 (*d*, *J* = 6, Me−C(2)); 0.77 (*s*, 1 Me−C(1)). ^{13}C-NMR: 163.8; 150.4; 149.3; 136.2; 133.2; 130.6; 130.0; 123.3; 109.1; 73.1; 58.6; 37.2; 36.2; 31.4; 31.3; 26.7; 21.9; 20.5; 15.4. GC/MS: 91 (79), 120 (100), 150 (75), 190 (44), 207 (22), 284 (10), 314 (17), 357 (2). Anal. calc. for $C_{21}H_{27}NO_4$: C 70.56, H 7.61, N 3.92; found: C 70.49, H 7.68, N 3.87.

Data of (±)-**22**: M.p. 73°. GC/MS: (t_R 27.87, de 98%). ^{1}H-NMR: 8.24 (*m*, arom. H); 6.11 (*dd*, *J* = 9, 14.3, H−C(7)); 5.58 (*m*, H−C(8), H−C(9)); 4.69 (*m*, 1 H, C=CH_2); 4.62 (*m*, 1 H, C=CH_2); 2.50 (*d*, *J* = 9, H−C(6)); 2.18 (*m*, 2 H); 1.58 (*m*, 2 H); 1.45 (*d*, *J* = 6, MeCHOAr); 1.38 (*m*, 1 H); 0.84 (*d*, *J* = 6, Me−C(2)); 0.82 (*s*, 1 Me−C(1)); 0.76 (*s*, 1 Me−C(1)). ^{13}C-NMR: 163.9; 150.4; 149.5; 136.3; 133.9; 130.6; 129.9; 123.5; 109.1; 73.3; 58.8; 37.2; 36.1; 31.5; 31.4; 26.7; 21.7; 20.4; 15.5. GC/MS: 91 (100), 120 (94), 150 (86), 190 (51), 207 (30), 284 (7), 314 (19). Anal. calc. for $C_{21}H_{27}NO_4$: C 70.56, H 7.61, N 3.92; found: C 70.62, H 7.56, N 4.05.

11. *(±)-(2*RS,*6*RS,*9*SR)*-γ-Irol* ((±)-**20**). Saponification of (±)-**22** (4.54 g, 0.013 mol) according to *GP 4* afforded (±)-**20** (2.51 g, 95%). Chemical purity 98% by GC/MS (t_R 16.46). ^{1}H-NMR: 5.92 (*ddd*, *J* = 1.1, 8.6, 15.1, H−C(7)); 5.54 (*ddd*, *J* = 0.7, 6, 15.1, H−C(8)); 4.66 (*m*, 1 H, C=CH_2); 4.60 (*m*, 1 H, C=CH_2); 4.28 (*quint.*, *J* = 6, H−C(9)); 2.48 (*d*, *J* = 8.6, H−C(6)); 2.18 (*m*, 2 H); 1.59 (*m*, 2 H); 1.25 (*d* + *m*, *J* = 6.4, MeCHOH + 1 H); 0.86 (*s*, 1 Me−C(1)); 0.83 (*d*, *J* = 6.7, 1 Me−C(2)); 0.77 (*s*, 1 Me−C(1)). ^{13}C-NMR: 150.0; 135.6; 129.7; 108.7; 68.8; 58.9; 37.1; 36.0; 31.7; 31.4; 26.8; 23.4; 21.7; 15.6. GC/MS: 107 (100), 135 (56), 175 (33), 190 (10). Anal. calc. for $C_{14}H_{24}O$: C 80.71, H 11.61; found: C 80.65, H 11.55.

12. *(+)-(2*S,*6*S,*9*R)*-γ-Irol Acetate* ((+)-**5**) *and (+)-(2*R,*6*R,*9*S)*-γ-Irol* ((+)-**20**). A mixture of derivative (±)-**20** (2.50 g, 0.012 mol) and lipase PS (2.50 g) in ^{t}BuOMe (30 ml) in the presence of vinyl acetate (5 ml) was stirred at r.t. for 4 days. The enzyme was filtered off, the filtrate evaporated, and the residue chromatographed (hexane/AcOEt): (+)-**5** (1.26 g, 42%), followed by (+)-**20** (1.02 g, 41%).

Data of (+)-**5**: B.p. 90–100°/0.2 Torr. Chemical purity 98% by GC/MS (t_R 18.69). $[\alpha]_D^{20} = +46.6$ (*c* = 1.2, CH_2Cl_2). ^{1}H-NMR: 5.97 (*dd*, *J* = 9, 15, H−C(7)); 5.44 (*ddd*, *J* = 0.7, 7, 15, H−C(8)); 5.32 (*quint.*, *J* = 6, H−C(9)); 4.67 (*m*, 1 H, C=CH_2); 4.60 (*m*, 1 H, C=CH_2); 2.46 (*d*, *J* = 9, H−C(6)); 2.18 (*m*, 2 H); 2.03 (*s*, MeCO); 1.58 (*m*, 2 H); 1.29 (*d* + *m*, *J* = 7, MeCHOAc + 1 H); 0.83 (*s* + *d*, *J* = 6.7, 1 Me−C(1), Me−C(2)); 0.76 (*s*, Me−C(1)). ^{13}C-NMR: 170.3; 149.5; 132.5; 130.7; 108.7; 71.2; 58.7; 37.1; 36.0; 31.5; 31.3; 26.7; 21.7; 21.5; 20.3; 15.6. GC/MS: 91 (100), 105 (91), 123 (56), 175 (62), 190 (65), 250 (7). Anal. calc. for $C_{16}H_{26}O_2$: C 76.75, H 10.47; found: C 76.81, H 10.49.

Data of (+)-**20**: B.p. 95–100°/0.2 Torr. Chemical purity 98% by GC/MS (t_R 16.46). $[\alpha]_D^{20} = +38.2$ (*c* = 1.0, CH_2Cl_2). GC/MS and ^{1}H-NMR: in accordance with those of the corresponding racemate. Anal. calc. for $C_{14}H_{24}O$: C 80.71, H 11.61; found: C 80.64, H 11.69.

13. *(−)-(2*S,*6*S,*9*R)*-γ-Irol* ((−)-**20**). Saponification of (+)-**5** (1.20 g, 4.8 mmol) according to *GP 4* gave alcohol (−)-**20** (0.938 g, 94%). Chemical purity 97% by GC/MS (t_R 16.46). $[\alpha]_D^{20} = -39.8$ (*c* = 1.0, CH_2Cl_2). MS

and ^{1}H-NMR: in accordance with those of the racemate. Anal. calc. for $C_{14}H_{24}O$: C 80.71, H 11.61; found: C 80.81, H 11.58.

14. *(+)-(2*R*,6*R*)*-Trans-*γ*-*Irone* ((+)-**3b**). According to *GP 5*, alcohol (+)-**20** (0.95 g, 4.56 mmol) gave (+)-**3b** (0.760 g, 81%): ee >99% by chiral HPLC (t_R 24.54). Chemical purity 99% by GC/MS (t_R 17.57). $[\alpha]_D^{20} = +76.4$ ($c = 1.0$, CH_2Cl_2). MS and ^{1}H-NMR: in accordance with those described above. Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.41, H 10.68.

15. *(−)-(2*S*,6*S*)-trans-*γ*-Irone* ((−)-**3b**). According to *GP 5* alcohol (−)-**20** (0.90 g, 4.37 mmol) gave (−)-**3b** (0.648 g, 72%): ee >99% by chiral HPLC (t_R 27.46). Chemical purity 99% by GC/MS (t_R 17.57). $[\alpha]_D^{20} = -81$ ($c = 1.0$, CH_2Cl_2). MS and ^{1}H-NMR: in accordance with those already described above. Anal. calc. for $C_{14}H_{22}O$: C 81.50, H 10.75; found: C 81.43, H 10.81.

16. *Preparation of Irone Oil Samples from Fresh Rhizomes.* Fresh rhizomes (*Iris pallida*) of four different batches were obtained from *Aboca* (Toscana, Italy), cut into slices, and extracted with acetone at r.t. (4 l of acetone/1 kg of fresh rhizomes). The acetone extracts were evaporated, and the residue was suspended in H_2O and extracted with hexane/AcOEt. The combined org. extract was washed with sat. $NaHCO_3$ soln. and H_2O, dried (Na_2SO_4), and evaporated, and the residue submitted to the enzymatic procedure for the preparation of irone oil as described in [19]. Soybean flour was employed as a source of lipoxydase.

17. *Irone-Isomer and -Enantiomer Distributions in Italian Iris Oil Samples.* 17.1. Irone-isomer distribution was determined by achiral GC analysis of irone oil samples on a *HP-5MS* column (30 m × 0.25 mm × 0.25 μm), installed in a *HP-6890* gas chromatograph equipped with a FID detector and a *5973* mass detector. The following temp. program was employed: 60° (1 min), then 6°/min to 150° (1 min), then 12°/min to 280° (5 min). Identification of irone isomers was achieved by comparison with pure synthetic samples. The following retention times were observed: (*Z*)-*cis*-*γ*-irone, t_R 16.41; *trans*-*α*-irone, t_R 17.90; *trans*-*γ*-irone, t_R 18.19; *cis*-*α*-irone, t_R 18.35; *cis*-*γ*-irone, t_R 18.51; *β*-irone, t_R 19.08.

17.2 The enantiomer excesses of *trans*-*α*-irone, *cis*-*α*-irone, and *cis*-*γ*-irone, and *α*-irol acetates were determined by chiral GC analysis with a *Chirasil DEX CB*, 25 m × 0.25 mm (*Chrompack*) column, installed in a *DANI-HT-86.10* gas chromatograph, with the following temp. program: 70° (3 min); then 3.5°/min to 140°, then 8°/min to 180° (1 min). The following retention times were observed: (−)-*trans*-*α*-irone, t_R 18.61; (+)-*trans*-*α*-irone, t_R 19.01; *trans*-*γ*-irone, t_R 19.30; (+)-*cis*-*α*-irone, t_R 19.89; (−)-*cis*-*α*-irone, t_R 19.98; (+)-*cis*-*γ*-irone, t_R 20.56; (−)-*cis*-*γ*-irone, t_R 20.86; *β*-irone, t_R 21.56.

17.3. The enantiomer excess of *trans*-*γ*-irone was determined by chiral HPLC analysis with a *Chiralcel OD* column (*Daicel*, Japan) installed in a *Merck-Hitachi L-6200* apparatus; UV detector (254 nm), hexane/^{i}PrOH 99:1 with the addition of one drop of Et_3N *per* 100 ml of eluent, 0.6 ml/min. The following retention times were observed: *cis*-*α*-irone, t_R 17.98; (−)-*trans*-*α*-irone, t_R 19.14; (+)-*trans*-*α*-irone, t_R 20.53; (+)-*trans*-*γ*-irone, t_R 24.54; (+)-*cis*-*γ*-irone, t_R 26.46; (−)-*trans*-*γ*-irone, t_R 27.46; (−)-*cis*-*γ*-irone, t_R 30.48.

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