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Synthesis, olfactory evaluation and determination of the absolute configuration of the β- and γ-Iralia® isomers

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ABSTRACT

The regioselective synthesis of the methyl-ionone isomers **6**–**9** is described. The enantiomers of the γ-isomers **8** and **9** are prepared by enzyme-mediated resolution of the corresponding 4-hydroxy derivatives followed by reductive elimination of the hydroxy group. The absolute configuration of the latter compound is determined by chemical correlation with the known α-isomers. Since all the isomers obtained are components of the artificial violet odourants sold under the trade name of Iralia®, their odour properties are evaluated by professional perfumers.

1. Introduction

The industrial creation of new perfumes[1] requires two essential lines of research: the discovery of new odourous molecules and the reinvestigation or chemical modification of older commercial products. Due to the unpredictable relationship between chemical structure and odour,[2] the latter approach is particularly interesting from a chemical point of view. Indeed, many fragrances are sold as a mixture of isomers, whose specific contribution to the perceived odour may be very different. Moreover, enantiomer composition of a single chemical compound greatly affects the fragrance properties, either in terms of features or as odour thresholds.[3]

As part of a programme on the synthesis of enantioenriched odourants, we have previously prepared a large number of enantiomerically pure isomers of commercial fragrances and natural flavours by enzyme-mediated methods.[3,4] In this context, we have focused our attention on the odourants with the ionone framework[5] that are of pivotal relevance in industrial perfumery.

Methyl-ionone isomers **4**–**9** (Fig. 1) are relevant artificial violet odourants sold as a mixture of isomers under the trade name of Iralia®.[1a] The latter commercial product is prepared by condensation of citral with ethyl methyl ketone followed by acid-catalyzed cyclization. The first step proceeds without selectivity, whereas the second one shows a regioselectivity that depends on the kind of acid used. Concentrated phosphoric acid affords α-isomers with high selectivity, whereas sulfuric acid or Lewis acids afforded β- or γ-isomers, respectively, with low selectivity. As a consequence of this fact, the overall quality of the product is affected by the synthetic method used. Moreover, α- and γ-isomers are a mixture of enantiomers and the specific preparation of β- and γ-isomers has not yet been reported till now. Therefore, a comprehensive olfactory evaluation of each isomeric forms of Iralia® is still lacking (Fig. 1).

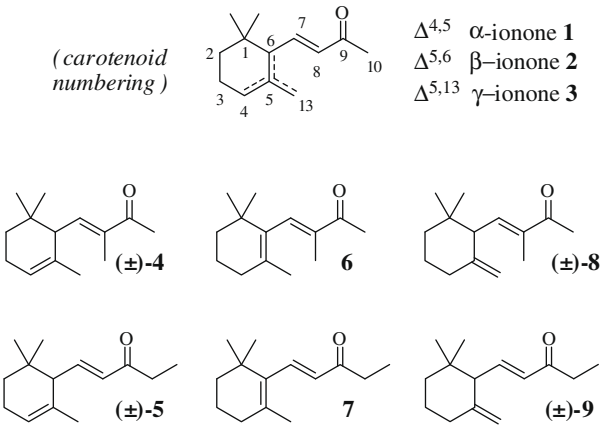

Figure 1.

Recently,[5f] we have described the preparation and odour evaluation of the enantiomeric forms of α-isomers **4** and **5**, which are the main components of commercial Iralia®. Otherwise, the impact of the minor components on the final odour could be relevant and their specific evaluation is highly desired. This aspect is particularly evident for γ-isomers of ionone[6] and methyl ionone[7] which have shown fragrance performances superior to those described for the corresponding α-isomers.

Herein we report on the stereoselective preparation of β- and γ-isomers **6**, **7** and **8**, **9**, respectively. In addition, we prepared the four enantiomeric forms of the latter γ-isomers and determined their absolute configuration by chemical correlation. All the

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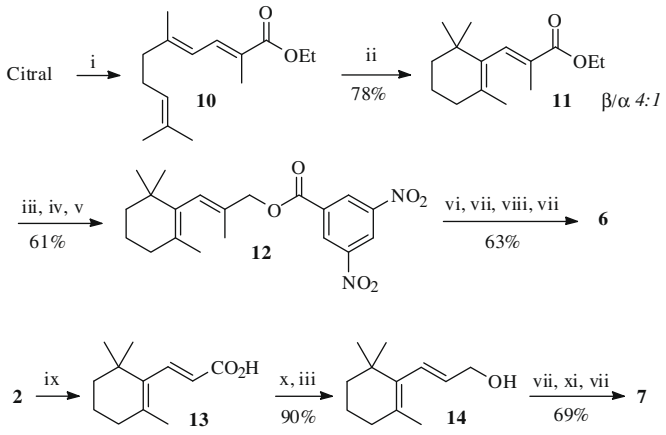
isomers obtained were evaluated by professional perfumers to achieve a complete description of each component of Iralia®.

2. Results and discussion

2.1. Preparation of β-isomers 6 and 7

As mentioned above, only compounds with high isomeric purity are suitable for a correct olfactory evaluation. This aspect is especially relevant for methyl-ionone isomers which are inseparable by the usual methodologies. We found that cyclization of methyl-pseudoionone isomers (3,6,10-trimethylundeca-3,5,9-trien-2-one and 7,11-dimethyldodeca-4,6,10-trien-3-one) affords β-isomers **6** or **7** contaminated with a substantial amount of the corresponding α-isomers. Therefore, we studied two different regiospecific pathways to these compounds (Scheme 1). 8-Methyl β-ionone **6** was prepared starting from citral. The Horner–Emmons reaction of the latter aldehyde with triethyl 2-phosphonopropionate afforded ester **10** that was cyclized using H_2SO_4 as an acid catalyst. The ester **11** obtained was reduced with $LiAlH_4$ to give the corresponding alcohol, which was converted into ester **12** by treatment with 3,5-dinitrobenzoyl chloride and pyridine.



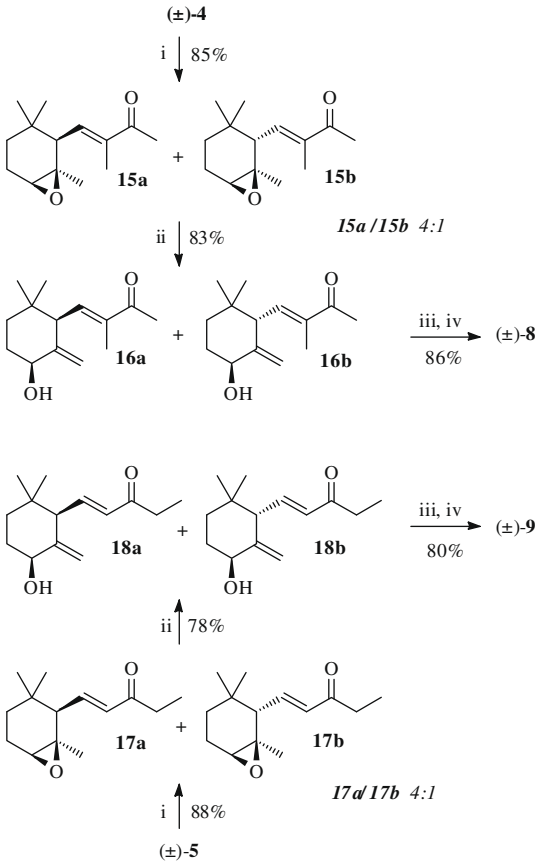
Scheme 1. Regioselective preparation of β-iralia isomers **6** and **7**. Reagents and conditions: (i) NaH, triethyl 2-phosphonopropionate, THF, reflux; (ii) H_2SO_4/AcOH, −5 °C; (iii) $LiAlH_4$, Et_2O, 0 °C; (iv) 3,5-dinitrobenzoyl chloride, Py/CH_2Cl_2; (v) two crystallizations from MeOH; (vi) NaOH, MeOH; (vii) MnO_2, $CHCl_3$, reflux; (viii) MeMgI, Et_2O; (ix) Br_2, NaOH/H_2O, dioxane; (x) MeOH/H_2SO_4; (xi) EtMgBr, Et_2O.

The latter compound was then purified by crystallization from methanol in order to remove all of the unwanted isomers. The pure ester was saponified and the alcohol oxidized by MnO_2. The lacking carbon atom was then introduced by treatment of the obtained aldehyde with methyl magnesium iodide, and the resulting ionol was converted into pure **6** by MnO_2 oxidation.

A different pathway was used for the preparation of isomer **7**. β-Ionone **2** is commercially available in good isomeric purity (up to 96%) and was used as a starting material. The haloform reaction (Br_2/NaOH) afforded acid **13**,[8] which was converted into alcohol **14** by esterification to the corresponding methyl ester followed by reduction with $LiAlH_4$. The latter allylic alcohol was oxidized and the aldehyde obtained was treated with ethyl magnesium bromide. The resulting ionol was then converted into pure **7** by MnO_2 oxidation.

2.2. Preparation of γ-isomers 8 and 9

As mentioned in the introduction, the specific preparation of γ-isomers **8** and **9** has not previously been reported although some studies on their isolation and characterization from the commercial product was described many years ago.[9] Indeed, the synthesis of γ-ionone derivatives by cyclization invariably afforded an inseparable mixture of regioisomers. Otherwise, α-isomers **4** and **5** are prepared on a large scale and in good isomeric purity by cyclization of 3,6,10-trimethyl-undeca-3,5,9-trien-2-one and from α-ionone **1**, respectively (Section 4.1). We have previously developed a stereoselective procedure that allows the conversion of α-ionone derivatives into γ-ionone derivatives.[5c,10] The regioselective base-mediated isomerization of 4,5-epoxy-4,5-dihydro-α-ionone followed by reductive elimination of the obtained allylic alcohols were the key steps of our syntheses. Therefore, we decided to apply the latter synthetic pathway for the conversion of compounds **4** and **5** into **8** and **9**, respectively (Scheme 2).



Scheme 2. Regioselective preparation of racemic γ-iralia isomers **8** and **9**. Reagents and conditions: (i) MCPBA, CH_2Cl_2, 0 °C; (ii) LDA, THF, −78 °C then reflux; (iii) Ac_2O/Py; (iv) HCOOH, Et_3N, PPh_3, $PdCl_2(PPh_3)_2$ cat., THF, reflux.

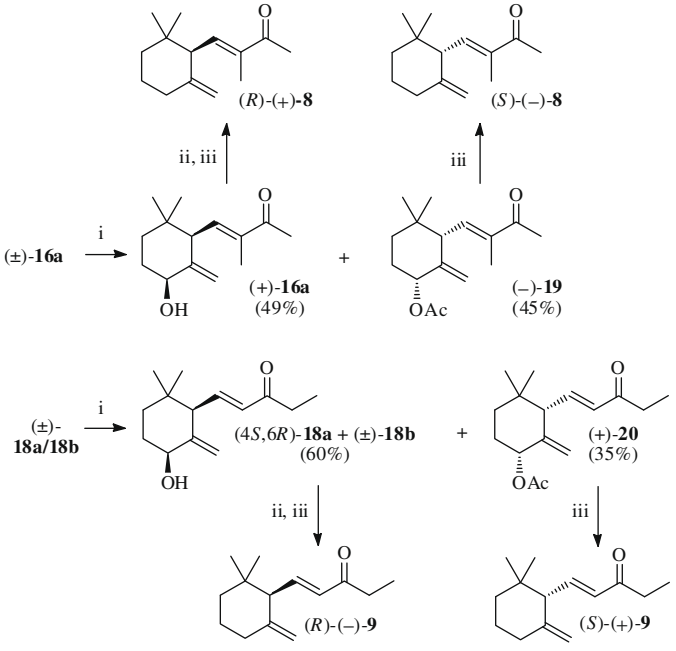
Accordingly, we submitted methyl ionones **4** and **5** to an epoxidation procedure with *m*-chloroperbenzoic acid to afford the *cis*/*trans* mixtures of epoxides **15a**/**15b** and **17a**/**17b**, respectively. The latter compounds were added to an excess (2.5–3 equiv, −78 °C) of LDA in THF and then warmed at reflux. After quenching, we obtained the *cis*/*trans* mixtures of alcohols **16a**/**16b** and **18a**/**18b**, respectively, showing the same diastereoisomeric ratio of the starting epoxides (*cis*/*trans* 4:1). The allylic alcohols obtained were acetylated, and then the acetate group was reductively removed by treatment with triethylammonium formate and a palladium catalyst to give 8-methyl γ-ionone **8** and 10-methyl γ-ionone **9**, respectively. As previously reported in the synthesis of γ-ionone, the latter reduction proceeds with good regioselectivity although with some slight differences among the isomers. The

above mentioned γ-ionones were obtained with the following isomeric purity: **3** (97%), **8** (96–97%) and **9** (94%).

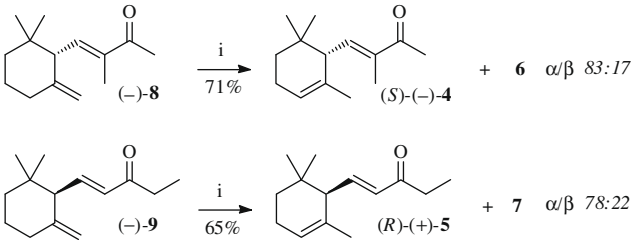
2.3. Synthesis of enantioenriched γ-iralia isomers (+) and (−)-8 and (+) and (−)-9

The aforementioned allylic alcohols **16** and **18** are suitable starting materials for the preparation of enantioenriched isomers **8** and **9**, respectively. Indeed, we have established[5c] that lipase-mediated acetylation of 4-hydroxy γ-ionone yielded enantiopure (4*R*,6*S*)-4-acetoxy-γ-ionone. The reaction proceeds with high enantioselectivity and with complete diastereoselectivity allowing the exclusive transformation of the *cis* isomers. Preliminary acetylation experiments confirmed that alcohols **16** and **18** showed the same behaviour.

As a result, we performed the enzyme-mediated resolution of the above mentioned alcohols (Scheme 3). The described reductive elimination of the acetate group (Section 2.2) proceeds without racemization thus allowing the preparation of enantioenriched methyl-γ-ionone isomers. This is noteworthy, since the diastereoisomeric allylic alcohols **16a**/**16b** and **18a**/**18b** are not separable by chromatography, while the resolution procedure gives the corresponding acetylated compounds with high ee and de leaving unreacted alcohols with low de. Luckily, epoxide **15a** is separable from its diastereoisomer **15b**, and the following base-mediated isomerization afforded **16a** as the sole isomers. Accordingly, racemic alcohol **16a** was acetylated with vinyl acetate in the presence of lipase PS as catalyst. The reaction was interrupted at 50% of conversion to give unreacted alcohol (+)-**16a** (99% de, 87% ee) and acetate (−)-**19** (99% de, 99% ee). The reductive removal of the acetoxy group converted the latter compounds into (+)-8-methyl γ-ionone (87% ee) and (−)-8-methyl γ-ionone (99% ee), respectively. Otherwise, epoxides **17a** and **17b** are not separable; the 4:1 mixture of alcohols **18a** and **18b** was used in the resolution step. The latter racemic compounds were treated with vinyl acetate in the presence of lipase PS as a catalyst. The reaction was interrupted at 40% conversion to give acetate (+)-**20** (99% de, 99% ee) and an inseparable mixture of unreacted alcohols (4*S*,6*R*)-**18a** and racemic **18b** (50% de, 85% ee). As described above, the reductive removal of the acetoxy group converted the latter compounds into (+)-10-methyl γ-ionone (99% ee) and (−)-10-methyl γ-ionone (65% ee), respectively.



Scheme 3. Preparation of enantioenriched γ-iralia isomers **8** and **9**. Reagents and conditions: (i) vinyl acetate, *t*-BuOMe, lipase PS; (ii) Ac_2O/Py; (iii) HCOOH, Et_3N, PPh_3, $PdCl_2(PPh_3)_2$ cat., THF, reflux.



Scheme 4. Chemical correlation of enantioenriched γ-iralia isomers **8** and **9** with enantioenriched α-iralia isomers **4** and **5**. Reagent and condition: (i) 85% H_3PO_4.

2.4. Determination of the absolute configuration of γ-iralia isomers

The absolute configurations of the enantiomeric forms of **8** and **9** were unknown. In order to associate odour descriptions with the configuration of the γ-ionone isomers, we needed to assign these data. Since the absolute configuration of the enantiomers of α-isomers **4** and **5** was determined unambiguously,[5f] we decided to correlate the enantiomeric forms of **8** and **9** with the aforementioned α-isomers. Indeed, it is known[5c] that treatment of γ-ionone isomers with concentrated phosphoric acid gave isomerization of the exocyclic double bond without any racemization. Therefore, we treated a sample of compound (−)-**8** and of compound (−)-**9** with H_3PO_4 (Scheme 4). By this means we achieved complete isomerization of the starting γ-isomers to the α- and β-isomers. 8-Methyl γ-ionone (−)-**8** afforded a mixture of (*S*)-(−)-8-methyl α-ionone **4** and 8-methyl β-ionone **6**, whereas 10-methyl γ-ionone (−)-**9** afforded a mixture of (*R*)-(+)-10-methyl α-ionone **5** and 10-methyl β-ionone **7**. In conclusion, the absolute configuration of (−)-**8** and (−)-**9** was assigned unambiguously as (*S*) and (*R*), respectively.

2.5. Olfactory evaluation of the iralia isomers

The regioisomers of β-iralia and the enantiomerically enriched forms of γ- iralia were evaluated by qualified perfumers (Givaudan Schweiz AG, Fragrance Research). The following results were obtained:

8-Methyl β-ionone **6**—Floral-woody and powdery violet note with a more pronounced woody, powdery cedarwood character and fatty-buttery aspects. Weaker than **7** and β-ionone on the blotter, less dry than β-ionone. Dry down weak powdery-woody, and less substantive than **7**.

10-Methyl β-ionone **7**—Strong and typical floral-woody β-ionone note with a more pronounced floral violet side, less woody-powdery and stronger than **6** on blotter. Dry down floral-woody, typical β-ionone like, more substantive than **6**.

(*S*)-(−)-8-Methyl-γ-ionone **8**—Woody-ambery mix odour between methyl ionone and Iso E Super of dry character.

(*R*)-(+)-8-Methyl γ-ionone **8**—Rich and interesting woody-ambery leather odour with fruity-floral facets in the direction of irone and methyl ionone and additional green accents.

(*S*)-(+)-10-Methyl-γ-ionone **9**—Woody-floral odour in the direction of methyl ionone, with a fruity-floral violet inclination and facets of orris, but also an oily background.

(*R*)-(−)-10-Methyl γ-ionone **9**—Woody odour in the direction of methyl ionone with additional dry, leathery aspects.

3. Conclusions

A number of results have been achieved. We have reported a new regioselective synthesis of the methyl-ionones isomers **6**–**9**. The enantiomers of the γ-isomers **8** and **9** were prepared by a chemo-enzymatic approach, and their absolute configuration determined by chemical correlation with the known α-isomers. Finally, the odour properties of all the aforementioned compounds were evaluated by professional perfumers. In previous work, we reported the odour descriptions of the enantiomers of α-isomers **4** and **5**. Therefore, we have now achieved a complete description of each component of the commercial odourants Iralia®. The following considerations are noteworthy:

(a) All the isomeric forms show distinct olfactory features.
(b) For the methyl-ionone isomers, the difference between the α-isomers and the γ-isomers, although evident, is less pronounced than those reported for the ionone series.[5a]
(c) The difference between the enantiomers of γ-methyl-ionone isomers are much less pronounced than those reported for the ionone series.
(d) Overall, these data show that any structural modification to the ionone framework (methyl group introduction and position, double bond position absolute configuration) gives a definite and unpredictable modification to the odour.

4. Experimental

4.1. General experimental

All moisture-sensitive reactions were carried out under a static atmosphere of nitrogen. All reagents were of commercial quality. Racemic α-iralia isomer **4** was prepared by acid-catalyzed cyclization of 3,6,10-trimethyl-undeca-3,5,9-trien-2-one in accord to the well-known procedure used in the synthesis of α-ionone from pseudoionone. Racemic α-iralia isomer **5** was prepared from α-ionone in accord to our previously reported procedure.[5f] Lipase from *Pseudomonas cepacia* (PS), Amano Pharmaceuticals Co., Japan, 30 units/mg was employed in this work. TLC: Merk Silica Gel 60 F_{254} plates. Column chromatography (CC): silica gel. GC–MS analyses: HP-6890 gas chromatograph equipped with a 5973 mass detector, using a HP-5MS column (30 m × 0.25 mm, 0.25 μm firm thickness; Hewlett Packard) with the following temp program: 60 °C (1 min)—6 °C/min—150 °C (1 min)—12 °C/min—280 °C (5 min); carrier gas, He; constant flow 1 mL/min; split ratio, 1/30; t_R given in min: t_R(**4**) 17.50, t_R(**5**) 18.28, t_R(**6**) 18.07, t_R(**7**) 19.39, t_R(**8**) 17.64, t_R(**9**) 18.59, t_R(**11**α) 19.23, t_R(**11**β) 19.55, t_R(**12**) 30.76, t_R(**14**) 15.88, t_R(**15a**) 19.31, t_R(**15b**) 19.73, t_R(**16a**) 21.16, t_R(**16b**) 20.80, t_R(**17a**) 20.19, t_R(**17b**) 20.27, t_R(**18a**) 21.73, t_R(**18b**) 21.45 t_R(**19**) 22.27, t_R(**20**) 22.61; mass spectra: *m/z* (rel.%). Chiral GC analyses: DANI-HT-86.10 gas chromatograph; enantiomer excesses determined on a CHIRASIL DEX CB-Column with the following temp program: compound **19**: 70 °C (1 min)—2 °C/min—150 °C (0 min)—30 °C/min—180 °C (0 min); t_R given in min: t_R((−)-**19**) 33.7, t_R((+)-**19**) 34.0; compound **20**: 70 °C (0 min)—2 °C/min—130 °C (0 min)—1 °C/min—140 °C (0 min)—30°/min—180 °C (0 min); t_R given in min: t_R((+)-**20**) 35.4, t_R((−)-**20**) 35.6. Optical rotations: Jasco-DIP-181 digital polarimeter. ^{1}H and ^{13}C Spectra: $CDCl_3$ solns at rt; Bruker-AC-400 spectrometer at 400 and 100 MHz, respectively; chemical shifts in ppm rel to internal $SiMe_4$ (=0 ppm), *J* values in Hertz. IR spectra were recorded on a Perkin–Elmer 2000 FT-IR spectrometer; *ν* in cm^{-1}. Melting points were measured on a Reichert apparatus, equipped with a Reichert microscope, and are uncorrected.

4.2. Synthesis of β-iralia isomers 6 and 7

4.2.1. 8-Methyl β-ionone = (*E*)-3-methyl-4-(2,6,6-trimethyl-cyclohex-1-enyl)-but-3-en-2-one 6

Triethyl 2-phosphonopropionate (38.1 g, 160 mmol) was added dropwise under nitrogen over a period of 1 h to a stirred suspension of NaH (7 g, 60% in mineral oil, 175 mmol) in dry THF (200 mL) at rt. To the resulting mixture citral (23 g, 151 mmol) in dry THF (100 mL) was added slowly and the reaction mixture was heated at reflux for 2 h. After cooling, the mixture was poured onto ice-water and extracted with diethyl ether (3 × 200 mL). The organic phase was washed with brine (2 × 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was diluted with hexane (30 mL) and, while stirring at −5 °C, a mixture of 120 g of concentrated sulfuric acid and 35 g of glacial acetic acid was added dropwise. After 1 h the reaction was quenched by addition of ice and extracted with hexane (2 × 200 mL). The combined organic phases were washed in turn with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by distillation to give pure ester **11** (27.9 g, 78% yield) as a 4:1 mixture of β/α-isomers.

Data for (*E*)-2-methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-acrylic acid ethyl ester **11** (β-isomer): colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (br s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 1.99 (br t, *J* = 6.0 Hz, 2H), 1.71 (d, *J* = 1.3 Hz, 3H), 1.68–1.60 (m, 2H), 1.55–1.45 (m, 2H), 1.47 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.98 (s, 6H). IR (film, cm^{-1}) 1711, 1635, 1366, 1245, 1112, 1033, 975, 743. GC–MS *m/z* (rel intensity) 236 (M^+, 68), 221 (100), 193 (35), 175 (51), 163 (29), 147 (91), 133 (18), 119 (24), 107 (59), 91 (31), 77 (17), 69 (10), 55 (9).

The above mentioned ester was added dropwise to a stirred and cooled (0 °C) suspension of $LiAlH_4$ (4.5 g, 119 mmol) in dry ether (200 mL). After work-up procedure, the crude alcohol was dissolved in pyridine (30 mL) and treated with a solution of 3,5-dinitrobenzoyl chloride (29 g, 126 mmol) in dry CH_2Cl_2 (100 mL). After complete conversion of the starting alcohol, the mixture was diluted with water (200 mL) and extracted with CH_2Cl_2 (2 × 250 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution, brine and then dried over Na_2SO_4. Concentration at reduced pressure gave an oil that was purified by CC (hexane/Et_2O 9:1) and crystallized twice from methanol to afford pure **12** (28.2 g, 61% yield).

Data for 3,5-dinitrobenzoic acid (*E*)-2-methyl-3-(2,6,6-trimethyl-cyclohex-1-enyl)-allyl ester **12**: colourless crystals, mp 69–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (m, 1H), 9.16 (m, 2H), 6.13 (s, 1H), 4.94 (s, 2H), 1.99 (br t, *J* = 6.0 Hz, 2H), 1.69–1.59 (m, 2H), 1.65 (d, *J* = 1.1 Hz, 3H), 1.52 (s, 3H), 1.51–1.45 (m, 2H), 0.97 (s, 6H). ^{13}C NMR (100 MHz) δ 162.3, 148.8, 134.6, 134.2, 131.5, 129.5, 129.3, 129.1, 122.2, 72.2, 39.1, 34.6, 31.9, 28.2, 20.9, 19.3, 15.5. IR (Nujol, cm^{-1}) 1716, 1630, 1551, 1294, 1167, 952, 727. GC–MS *m/z* (rel intensity) 388 (M^+, 9), 373 (23), 207 (7), 195 (25), 176 (16), 161 (100), 149 (17), 133 (30), 119 (52), 105 (59), 91 (29), 75 (14), 55 (13).

A sample of **12** (25 g, 64.4 mmol) was treated with a solution of NaOH (5 g, 125 mmol) in methanol (150 mL) and stirring at rt until no more starting acetate was detected by TLC analysis. The mixture was diluted with water (300 mL) and extracted with diethyl ether (2 × 150 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in $CHCl_3$ (200 mL) and treated with MnO_2 (30 g, 345 mmol) under stirring at reflux for 6 h. The mixture was then cooled, filtered and the organic phase concentrated under reduced pressure to afford an oil (13 g). The latter was dissolved in dry diethyl ether (150 mL) and treated under stirring with an excess of methylmagnesium iodide (100 mL of a 1 M solution in ether) keeping the

reaction temperature under 5 °C by external cooling (ice bath). The usual work-up afforded crude carbinol that was dissolved in $CHCl_3$ (200 mL) and treated with MnO_2 (30 g, 345 mmol) under stirring at reflux for 12 h. After filtration and concentration, the crude ketone was purified by chromatography (hexane/Et_2O 95:5) and bulb to bulb distillation (oven temperature 105 °C, 0.4 mmHg) to afford pure **6** (8.4 g, 63% yield).

Data for 8-methyl β-ionone **6**: colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1H), 2.36 (s, 3H), 2.01 (t, J = 6.2 Hz, 2H), 1.70–1.61 (m, 2H), 1.66 (d, J = 1.2 Hz, 3H), 1.53–1.48 (m, 2H), 1.46 (s, 3H), 0.99 (s, 6H); ^{13}C NMR (100 MHz) δ 199.9, 140.6, 139.5, 134.8, 129.7, 39.0, 34.7, 31.8, 28.3, 25.6, 21.1, 19.1, 12.9. IR (film, cm^{-1}) 1670, 1625, 1431, 1384, 1363, 1251, 1101, 1034, 997, 897. GC–MS *m/z* (rel intensity) 206 (M^+, 2), 191 (100), 176 (5), 163 (4), 149 (12), 136 (7), 123 (8), 105 (5), 91 (9), 77 (5), 69 (2), 55 (3).

4.2.2. 10-Methyl β-ionone = (*E*)-1-(2,6,6-trimethyl-cyclohex-1-enyl)-pent-1-en-3-one 7

A solution of (*E*)-3-(2,6,6-trimethyl-cyclohex-1-enyl)-acrylic acid **13** (20 g, 103 mmol) in methanol (100 mL) was treated with concentrated sulfuric acid (25 mL) and then heated under reflux for 1 h. The reaction mixture was then cooled, poured in ice and extracted with ether (2 × 150 mL). The organic phase was washed in turn with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The obtained ester was added dropwise to a stirred and cooled (0 °C) suspension of $LiAlH_4$ (2.95 g, 78 mmol) in dry ether (150 mL). After work-up procedure, the crude alcohol was purified by chromatography (hexane/AcOEt 95:5) to afford pure **14** (16.8 g, 90% yield).

Data for (*E*)-3-(2,6,6-trimethyl-cyclohex-1-enyl)-prop-2-en-1-ol **14**: colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (d, J = 16.0 Hz, 1H), 5.61 (dt, J = 16.0, 6.0 Hz, 1H), 4.19 (br s, 2H), 1.98 (br t, J = 6.2 Hz, 2H), 1.67 (s, 3H), 1.65–1.53 (m, 2H), 1.49–1.41 (m, 2H), 1.31 (br s, 1H), 1.00 (s, 6H). ^{13}C NMR (100 MHz) δ 136.8, 132.4, 129.8, 129.1, 64.2, 39.7, 34.0, 32.8, 28.7, 21.3, 19.3. IR (film, cm^{-1}) 3351, 1360, 1094, 1011, 972. GC–MS *m/z* (rel intensity) 180 (M^+, 79), 165 (86), 147 (100), 137 (14), 121 (65), 105 (81), 91 (75), 81 (50) 67 (25), 55 (39), 41 (42).

A solution of alcohol **14** (12.5 g, 69.3 mmol) in $CHCl_3$ (200 mL) was treated with MnO_2 (25 g, 287 mmol) with stirring at reflux for 5 h. The mixture was then cooled, filtered and the organic phase concentrated under reduced pressure to afford an oil (12 g). The latter was dissolved in dry diethyl ether (150 mL) and treated under stirring with an excess amount of ethylmagnesium bromide (100 mL of a 0.9 M solution in ether) keeping the reaction temperature under 5 °C by external cooling (ice bath). After the usual work-up, the crude carbinol obtained was dissolved in $CHCl_3$ (200 mL) and was treated with MnO_2 (30 g, 345 mmol) under stirring at reflux for 12 h. Filtration and concentration afforded the crude ketone that was purified by chromatography (hexane/Et_2O 95:5) and bulb to bulb distillation (oven temperature 115 °C, 0.9 mmHg) to give pure **7** (9.9 g, 69% yield).

Data for (*E*)-1-(2,6,6-trimethyl-cyclohex-1-enyl)-pent-1-en-3-one **7**: colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, J = 0.7, 16.4 Hz, 1H), 6.12 (d, J = 16.4 Hz, 1H), 2.57 (q, J = 7.4 Hz, 2H), 2.06 (t, J = 6.2 Hz, 2H), 1.75 (d, J = 0.7 Hz, 3H), 1.67–1.58 (m, 2H), 1.52–1.46 (m, 2H), 1.13 (t, J = 7.4 Hz, 3H), 1.07 (s, 6H); ^{13}C NMR (100 MHz) δ 200.8, 141.8, 136.3, 135.2, 130.5, 39.9, 34.1, 33.7, 33.5, 28.8, 21.6, 19.0, 8.3. IR (film, cm^{-1}) 1694, 1673, 1607, 1459, 1376, 1361, 1195, 1114, 1037, 980. GC–MS *m/z* (rel intensity) 206 (M^+, 7), 191 (100), 177 (7), 163 (4), 149 (15), 135 (6), 121 (10), 107 (9), 91 (11), 77 (7), 57 (13).

4.3. Synthesis of racemic γ-iralia isomers 8 and 9

4.3.1. General procedure for epoxidation of α-iralia isomers

m-Chloroperbenzoic acid (12 g, of 75% wet acid, 52.1 mmol) was added to a solution of racemic α-iralia isomer **4** or **5** (10 g, 48.5 mmol) in methylene chloride (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then filtered in order to remove the *m*-chlorobenzoic acid precipitate. The organic phase was washed in turn with saturated Na_2SO_3 solution and saturated $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane/Et_2O 9:1) to give the corresponding α-epoxy-derivatives.

Epoxide **15** (85% yield) **15a**:**15b** = 4:1 separable by chromatography. Both colourless oils.

Epoxide **17** (88% yield) **17a**:**17b** = 4:1; inseparable mixture. Colourless oil.

Data for (4*SR*,5*RS*,6*RS*)-4,5-epoxy-4,5-dihydro-8-methyl α-ionone **15a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (dd, J = 10.8, 1.3 Hz, 1H), 3.08 (s, 1H), 2.50 (d, J = 10.8 Hz, 1H), 2.36 (s, 3H), 2.05–1.88 (m, 2H), 1.85 (d, J = 1.3 Hz, 3H), 1.45 (ddd, J = 13.7, 9.8, 5.7 Hz, 1H), 1.23 (s, 3H), 1.02 (dt, J = 13.7, 5.1 Hz, 1H), 0.96 (s, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz) δ 199.8, 141.6, 138.8, 59.6, 59.2, 47.6, 31.8, 29.0, 28.3, 26.4, 25.5, 24.1, 21.7, 11.8. IR (film, cm^{-1}) 1670, 1368, 1253, 1177, 1095, 910. GC–MS *m/z* (rel intensity) 222 (M^+, 2), 207 (5), 193 (10), 179 (16), 165 (9), 153 (12), 137 (30), 123 (100), 109 (53), 95 (17), 81 (16), 69 (15), 55 (16).

Data for (4*SR*,5*RS*,6*SR*)-4,5-epoxy-4,5-dihydro-8-methyl α-ionone **15b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (dd, J = 11.6, 1.4 Hz, 1H), 3.00 (s, 1H), 2.69 (d, J = 11.6 Hz, 1H), 2.35 (s, 3H), 2.05 (dm, J = 15.5 Hz, 1H), 1.97–1.87 (m, 1H), 1.86 (d, J = 1.4 Hz, 3H), 1.50–1.36 (m, 1H), 1.20–1.12 (m, 1H), 1.17 (s, 3H), 0.89 (s, 3H), 0.79 (s, 3H). ^{13}C NMR (100 MHz) δ 199.4, 140.8, 139.7, 59.7, 58.1, 49.5, 32.8, 32.5, 29.4, 25.7, 23.3, 21.5, 21.4, 11.8. IR (film, cm^{-1}) 1672, 1368, 1250, 1154, 1067, 908. GC–MS *m/z* (rel intensity) 222 (M^+, 2), 207 (5), 189 (3), 179 (14), 165 (15), 153 (10), 137 (15), 123 (100), 109 (55), 95 (14), 79 (13), 69 (14), 55 (16).

Data for (4*SR*,5*RS*,6*RS*)-4,5-epoxy-4,5-dihydro-10-methyl α-ionone **17a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (dd, J = 16.1, 10.3 Hz, 1H), 6.04 (d, J = 16.1 Hz, 1H), 3.01 (s, 1H), 2.68–2.48 (m, 2H), 2.01 (d, J = 10.3 Hz, 1H), 1.98–1.78 (m, 2H), 1.43–1.26 (m, 1H), 1.18 (s, 3H), 1.05 (t, J = 7.3 Hz, 3H), 0.94 (dt, J = 13.6, 4.9 Hz, 1H), 0.86 (s, 3H), 0.69 (s, 3H). GC–MS *m/z* (rel intensity) 222 (M^+, 3), 207 (4), 193 (72), 179 (8), 165 (54), 147 (19), 137 (20), 123 (100), 109 (72), 95 (60), 81 (28), 69 (35), 57 (69).

Data for (4*SR*,5*RS*,6*SR*)-4,5-epoxy-4,5-dihydro-10-methyl α-ionone **17b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (dd, J = 15.7, 11.2 Hz, 1H), 6.10 (d, J = 15.7 Hz, 1H), 2.93 (s, 1H), 2.68–2.48 (m, 2), 2.25 (d, J = 11.2 Hz, 1H), 1.98–1.78 (m, 2H), 1.43–1.26 (m, 1H), 1.14–1.00 (m, 1H), 1.12 (s, 3H), 1.06 (t, J = 7.3 Hz, 3H), 0.79 (s, 3H), 0.74 (s, 3H). GC–MS *m/z* (rel intensity) 222 (M^+, 8), 207 (9), 193 (19), 179 (13), 165 (60), 147 (21), 137 (22), 123 (100), 109 (77), 95 (49), 81 (23), 69 (32), 57 (85).

IR (for **17a**/**17b** mixture, film, cm^{-1}) 1699, 1675, 1627, 1379, 1367, 1204, 991.

4.3.2. General procedure for conversion of epoxides 15 and 17 into allylic alcohols 16 and 18, respectively

BuLi (5.5 mL of a 10 M solution in hexane) was added dropwise to a cooled (−78 °C) solution of iPr$_2$NH (5.8 g, 57.3 mmol) in dry THF (90 mL) under nitrogen. The mixture was stirred at this temperature for 30 min then a solution of the epoxide **15** or **17** (4.5 g, 20.2 mmol) in dry THF (20 mL) was added dropwise. The reaction mixture was gradually warmed to rt (1 h) and then was heated at reflux until no more starting epoxide was detected by TLC analysis (3 h). After cooling to rt, the mixture was poured into a mixture of crushed ice and 5% HCl soln (80 mL) and extracted

with Et_2O (3×200 mL). The organic phase was successively washed with satd aq NH_4Cl soln (100 mL), brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (eluting from hexane/AcOEt 9:1 to hexane/AcOEt 1:1) to give allylic alcohol **16** (**16a**:**16b** = 4:1, 83% yield) or allylic alcohol **18** (**18a**:**18b** = 4:1, 78% yield).

Data for (4*SR*,6*RS*)-4-hydroxy-8-methyl γ-ionone **16a**: colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (dd, J = 9.9, 1.3 Hz, 1H), 5.15 (s, 1H), 4.65 (s, 1H), 4.10 (m, 1H), 2.86 (d, J = 9.9 Hz, 1H), 2.37 (s, 3H), 2.04–1.93 (m, 1H), 1.74 (d, J = 1.3 Hz, 3H), 1.66–1.45 (m, 3H), 0.90 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (100 MHz) δ 199.7, 149.5, 141.4, 139.0, 106.6, 72.6, 51.3, 38.0, 36.0, 32.2, 29.4, 25.6, 21.2, 11.4. GC–MS *m/z* (rel intensity) 222 (M^+, 2), 204 (11), 189 (13), 179 (100), 161 (53), 148 (13), 135 (18), 123 (33), 109 (30), 91 (24), 79 (19), 69 (15), 55 (16).

Data for (4*SR*,6*SR*)-4-hydroxy-8-methyl γ-ionone **16b**: colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, J = 10.0, 1.3 Hz, 1H), 5.03 (s, 1H), 4.67 (s, 1H), 4.31 (br t, J = 4.6 Hz, 1H), 3.33 (d, J = 10.0 Hz, 1H), 2.34 (s, 3H), 2.08–1.80 (m, 3H), 1.80–1.67 (m, 1H), 1.78 (d, J = 1.3 Hz, 3H), 0.95 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (100 MHz) δ 199.6, 149.4, 141.4, 139.2, 110.1, 71.6, 49.6, 35.7, 34.5, 30.5, 29.0, 25.7, 22.4, 11.4. GC–MS *m/z* (rel intensity) 222 (M^+, 2), 204 (8), 189 (13), 179 (100), 161 (55), 148 (14), 135 (19), 123 (32), 109 (28), 96 (26), 81 (18), 69 (15), 55 (17).

IR (for **16a**/**16b** mixture, film, cm^{-1}) 3424, 1666, 1387, 1368, 1250, 1071, 1049, 993, 900.

Data for (4*SR*,6*RS*)-4-hydroxy-10-methyl-ionone **18a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (dd, J = 15.8, 10.3 Hz, 1H), 6.09 (d, J = 15.8 Hz, 1H), 5.16 (s, 1H), 4.69 (s, 1H), 4.05 (m, 1H), 2.58 (q, J = 7.4 Hz, 2H), 2.55 (d, J = 10.3 Hz, 1H), 2.00–1.91 (m, 1H), 1.75–1.35 (m, 4H), 1.12 (t, J = 7.4 Hz, 3H), 0.89 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (100 MHz) δ 200.8, 150.4, 144.8, 132.0, 107.0, 72.4, 55.7, 37.9, 35.6, 33.5, 32.1, 29.6, 21.5, 8.1. GC–MS *m/z* (rel intensity) 222 (M^+, 6), 207 (8), 189 (7), 175 (13), 165 (99), 147 (71), 135 (29), 122 (36), 107 (55), 91 (43), 81 (30), 69 (31), 57 (100).

Data for (4*SR*,6*SR*)-4-hydroxy-10-methyl γ-ionone **18b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (dd, J = 15.9, 9.9 Hz, 1H), 6.15 (d, J = 15.9 Hz, 1H), 5.06 (s, 1H), 4.72 (s, 1H), 4.28 (br s, 1H), 2.96 (d, J = 9.9 Hz, 1H), 2.58 (q, J = 7.4 Hz, 2H), 1.90–1.80 (m, 1H), 1.75–1.35 (m, 4H), 1.11 (t, J = 7.4 Hz, 3H), 0.94 (s, 3H), 0.87 (s, 3H). GC–MS *m/z* (rel intensity) 222 (M^+, 5), 207 (6), 189 (7), 175 (12), 165 (99), 147 (100), 135 (23), 123 (27), 105 (36), 91 (41), 81 (28), 69 (30), 57 (87).

IR (for **18a**/**18b** mixture, film, cm^{-1}) 3408, 1715, 1675, 1627, 1206, 1049, 989, 902.

4.3.3. General procedure for the reduction of allylic alcohols 16 and 18 to γ-iralia isomers 8 and 9, respectively

A sample of compound **16** or **18** (3 g, 13.5 mmol) was converted in the corresponding acetate by treatment with pyridine (20 mL) and Ac_2O (20 mL) at rt for 24 h. The crude product was added to a solution of formic acid (1.2 g, 26 mmol), Et_3N (2.7 g, 26.7 mmol), $(PPh_3)_2PdCl_2$ (280 mg, 0.4 mmol) and triphenylphosphine (0.5 g, 1.9 mmol) in dry THF (60 mL). The mixture was refluxed under a static nitrogen atmosphere until reduction was complete (2 h, TLC analysis). The reaction mixture was then diluted with ether (150 mL) and washed with water (50 mL), 5% HCl soln (50 mL), satd aq $NaHCO_3$ soln (50 mL), and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (hexane/Et_2O 95:5) and bulb-to-bulb distillation to give γ-iralia isomers **8** (86% yield, 97% isomeric purity (GC)) or **9** (80% yield, 94% isomeric purity (GC)), respectively.

Data for 8-methyl γ-ionone = (*E*)-4-(2,2-dimethyl-6-methylene-cyclohexyl)-3-methyl-but-3-en-2-one (±)-**8**: colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (dd, J = 10.1, 1.3 Hz, 1H), 4.77 (s, 1H), 4.51 (s, 1H), 2.88 (d, J = 10.1 Hz, 1H), 2.36–2.25 (m, 1H), 2.35 (s, 3H), 2.12–2.02 (m, 1H), 1.77 (d, J = 1.3 Hz, 3H), 1.68–1.52 (m, 3H), 1.45–1.35 (m, 1H), 0.92 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (100 MHz) δ 199.6, 147.6, 142.2, 138.7, 109.0, 53.1, 39.1, 35.9, 34.5, 29.2, 25.5, 23.2, 22.9, 11.4. IR (film, cm^{-1}) 1670, 1645, 1439, 1386, 1367, 1262, 1233, 889. GC–MS *m/z* (rel intensity) 206 (M^+, 17), 191 (25), 178 (15), 163 (100), 149 (16), 135 (93), 123 (70), 107 (22), 95 (36), 77 (17), 69 (26), 55 (9).

Data for 10-methyl γ-ionone = (*E*)-1-(2,2-dimethyl-6-methylene-cyclohexyl)-pent-1-en-3-one (±)-**9**: colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (dd, J = 9.9, 15.7 Hz, 1H), 6.11 (dd, J = 15.7, 0.6 Hz, 1H), 4.78 (s, 1H), 4.55 (s, 1H), 2.62–2.53 (m, 1H), 2.58 (q, J = 7.4 Hz, 2H), 2.27 (dt, J = 13.5, 5.8 Hz, 1H), 2.06 (dt, J = 13.5, 6.7 Hz, 1H), 1.65–1.55 (m, 2H), 1.55–1.47 (m, 1H), 1.40–1.30 (m, 1H), 1.11 (t, J = 7.4 Hz, 3H), 0.91 (s, 3H), 0.86 (s, 3H). ^{13}C NMR (100 MHz) δ 200.6, 148.5, 145.7, 131.5, 109.5, 57.6, 38.6, 35.5, 34.1, 33.6, 29.1, 23.9, 23.1, 8.1. IR (film, cm^{-1}) 1695, 1677, 1626, 1460, 1366, 1207, 1187, 990, 891. GC–MS *m/z* (rel intensity) 206 (M^+, 25), 191 (26), 178 (38), 163 (99), 149 (92), 135 (100), 123 (47), 109 (57), 93 (41), 81 (59), 69 (63), 57 (47).

4.4. Synthesis of enantioenriched γ-iralia isomers (+) and (−)-8 and (+) and (−)-9

4.4.1. Lipase-mediated resolution of alcohols 16 and 18

Diastereoisomerically pure alcohol **16a** (obtained from epoxide **15a**) and the *cis*/*trans* 4:1 mixture of **18a**/**18b** were employed in the resolution procedure. A sample of the above mentioned racemic material (5 g, 22.5 mmol), lipase PS (5 g), vinyl acetate (25 mL) and *t*BuOMe (100 mL) was stirred at rt, and the formation of the acetate was monitored by TLC analysis. The reaction was stopped at about 50% of conversion when the substrate was **16a** and at 40% of conversion when the substrate was the **18a**/**18b** mixture. The enzyme was then filtered, and the solvent was evaporated at reduced pressure after which the residue was purified by chromatography (eluting from hexane/AcOEt 9:1 to hexane/AcOEt 1:1). The first-eluted fractions afforded derivatives (−)-**19** (45% yield) and (+)-**20** (35% yield), respectively. The last eluted fractions afforded derivatives (+)-**16a** (49% yield) and a mixture of (4*S*,6*R*)-**18a** and racemic **18b** (60% yield), respectively.

Data for (4*R*,6*S*)-4-acetoxy-8-methyl γ-ionone (−)-**19**: colourless oil; 98% chemical purity, 99% de (GC); 99% ee (chiral GC); $[\alpha]_D^{20} = -17.1$ (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (dd, J = 10.0, 1.4 Hz, 1H), 5.28–5.19 (m, 1H), 5.01 (s, 1H), 4.67 (s, 1H), 2.93 (d, J = 10.0 Hz, 1H), 2.36 (s, 3H), 2.10 (s, 3H), 2.00–1.90 (m, 1H), 1.76 (d, J = 1.4 Hz, 3H), 1.73–1.61 (m, 2H), 1.59–1.47 (m, 1H), 0.92 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (100 MHz) δ 199.3, 169.7, 144.4, 140.5, 139.1, 108.3, 73.6, 51.4, 37.3, 35.7, 29.1, 28.8, 25.6, 21.6, 21.1, 11.5. IR (film, cm^{-1}) 1743, 1674, 1652, 1369, 1240, 1041, 998, 900. GC–MS *m/z* (rel intensity) 264 (M^+, 1), 249 (9), 222 (19), 204 (55), 189 (34), 179 (59), 161 (100), 148 (50), 135 (35), 123 (36), 105 (34), 91 (29), 77 (17), 69 (12), 55 (13).

Data for (4*R*,6*S*)-4-acetoxy-10-methyl γ-ionone (+)-**20**: colourless oil; 98% chemical purity, 99% de (GC); 99% ee (chiral GC); $[\alpha]_D^{20} = +27.1$ (*c* 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (dd, J = 15.7, 10.3 Hz, 1H), 6.12 (d, J = 15.7 Hz, 1H), 5.22–5.16 (m, 1), 5.02 (s, 1H), 4.71 (s, 1H), 2.61 (d, J = 10.3 Hz, 1H), 2.57 (q, J = 7.4 Hz, 2H), 2.10 (s, 3H), 1.96–1.85 (m, 1H), 1.78–1.58 (m, 2H), 1.52–1.38 (m, 1H), 1.12 (t, J = 7.4 Hz, 3H), 0.90 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (100 MHz) δ 200.3, 169.8, 145.3, 144.0, 131.7, 109.1, 73.5, 55.9, 36.8, 35.3, 34.0, 29.2, 28.7, 22.2, 21.1, 8.0. IR (film, cm^{-1}) 1743, 1677, 1630, 1369, 1264, 1125, 1040, 996, 898. GC–MS *m/z* (rel intensity) 264 (M^+, 1), 249 (6), 222 (24), 204 (36), 189 (14), 175 (30), 163 (63), 147 (100), 135 (29), 119 (25), 105 (35), 91 (37), 79 (15), 69 (16), 57 (52).

Data for (4*S*,6*R*)-4-hydroxy-8-methyl γ-ionone (+)-**16a**: 96% chemical purity, 99% de (GC); 87% ee (chiral GC); $[\alpha]_D^{20} = +32.6$ (*c* 2, $CHCl_3$); IR, ^1H NMR, MS: in accordance with that of (±)-**16a.**

Data for (4*S*,6*R*)-4-hydroxy-10-methyl γ-ionone (4*S*,6*R*)-**18a**: 96% chemical purity, 50% de (GC); 85% ee (chiral GC). IR, ^1H NMR, MS: in accordance with that of (±)-**18a.** Optical rotation power of this compound is near to 0. Therefore we describe the optical rotation value of the corresponding acetylated (Ac_2O/Py) derivative: $[\alpha]_D^{20} = -12.6$ (*c* 1.5, $CHCl_3$).

4.4.2. Preparation of enantioenriched γ-iralia isomers

The above obtained compounds (−)-**19**, (+)-**20**, (+)-**16** and (4*S*,6*R*)-**18a** were submitted to the reductive deoxygenation procedure described in Section 4.4.3 to afford γ-iralia isomers (−)-**8**, (+)-**9**, (+)-**8** and (−)-**9**, respectively. The latter compounds showed the following analytical data:

(*S*)-(−)-8-Methyl-γ-ionone (−)-**8**: 99% chemical purity, 96% regioisomeric purity (GC); $[\alpha]_D^{20} = -19.8$ (*c* 1, $CHCl_3$); IR, ^1H NMR, MS: in accordance with that of (±)-**8**.

(*S*)-(+)-10-Methyl-γ-ionone (+)-**9**: 99% chemical purity, 94% regioisomeric purity (GC); $[\alpha]_D^{20} = +18.7$ (*c* 1, $CHCl_3$); IR, ^1H NMR, MS: in accordance with that of (±)-**9**.

(*R*)-(+)-8-Methyl-γ-ionone (+)-**8**: 98% chemical purity, 96% regioisomeric purity (GC); $[\alpha]_D^{20} = +16.4$ (*c* 2, $CHCl_3$); IR, ^1H NMR, MS: in accordance with that of (±)-**8**.

(*R*)-(−)-10-Methyl-γ-ionone (−)-**9**: 98% chemical purity, 94% regioisomeric purity (GC); $[\alpha]_D^{20} = -13.8$ (*c* 1, $CHCl_3$); IR, ^1H NMR, MS: in accordance with that of (±)-**9**.

4.4.3. General procedure for isomerization of γ-iralia isomers to α and β-iralia isomers

γ-Iralia isomers (0.25 g, 1.2 mmol) were stirred in 85% H_3PO_4 (2 mL) at rt until no more starting γ-isomer was detected by GC analysis (2 h). The reaction mixture was poured onto crushed ice and the products were extracted with ether (2 × 40 mL). The organic phase was washed with satd aq $NaHCO_3$ soln (60 mL), and brine. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure and the residue was purified by CC (hexane/Et_2O 9:1) and bulb-to-bulb distillation to give a α/β-iralia isomers mixture. According to the above described procedure compound (−)-**8** ($[\alpha]_D^{20} = -19.8$ (*c* 1, $CHCl_3$)) afforded a mixture of (−)-**4** and **6** (71% yield, 98% chemical purity, α/β 83:17, $[\alpha]_D^{20} = -401.8$ (*c* 1, $CHCl_3$)), whereas compound (−)-**9** ($[\alpha]_D^{20} = -8.2$ (*c* 1, $CHCl_3$)) afforded a mixture of (+)-**5** and **7** (65% yield, 98% chemical purity, α/β 78:22, $[\alpha]_D^{20} = +97.2$ (*c* 1, $CHCl_3$)).

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