Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: *Asymmetry* 18 (2007) 2573–2580
Tetrahedron: *Asymmetry*

Chemoenzymatic resolution of *cis*- and *trans*-3,6-dihydroxy-α-ionone. Synthesis of the enantiomeric forms of dehydrovomifoliol and 8,9-dehydrotheaspirone

Stefano Serra,* Assem Barakat and Claudio Fuganti

C.N.R. Istituto di Chimica del Riconoscimento Molecolare, Presso Dipartimento di Chimica, Materiali ed Ingegneria Chimica del Politecnico, Via Mancinelli 7, 20131 Milano, Italy

Received 20 September 2007; accepted 10 October 2007
Available online 5 November 2007

Abstract—A straightforward synthesis of both enantiomers of *cis*- and *trans*-3-acetoxy-6-hydroxy-α-ionone is described. The title compounds are prepared by resolution of the diastereoisomerically pure racemic 3,6-dihydroxy-α-ionone isomers. The latter process is based on two steps. The first is the enantio- and regioselective lipase-mediated acetylation of diols to afford the corresponding 3-acetoxy-derivatives. The second is the fractional crystallization of the latter compounds that increase their enantiomeric purity. These building blocks were used for the synthesis of both enantiomeric forms of the natural norterpenoids dehydrovomifoliol **3** and 8,9-dehydrotheaspirone **5**. The latter compound is a natural flavor and its odor properties were evaluated by professional perfumers.

1. Introduction

Ionone isomers and their hydroxylated derivatives are important starting materials for the synthesis of several natural products. Since many of the latter compounds show biological activity, which is strictly related to their absolute configuration, their synthesis requires optically active starting materials.[1] Therefore the enantioselective preparation of these chiral building blocks has become an important research topic. In this context, we have been working on the enantioselective synthesis of different norterpenoid compounds, such as ionone,[2] irone,[3] damascone,[4] and 7,11-epoxymegastigma-5(6)-en-9-one[5] isomers. Our general approach consists of the preparation of diastereoisomerically pure racemic ionol isomers and then their resolution by means of lipase-mediated enantioselective acetylation. Recently,[2b,4,5] we found that different hydroxylated ionone derivatives are good substrates in this resolution protocol. In order to exploit the synthetic significance of the method, we herein report a study on the resolution of 3,6-dihydroxy-α-ionone isomers. The latter derivatives are potential building blocks for the stereospecific synthesis of compounds of the general structures **1**, **4**, and **5** (Fig. 1).

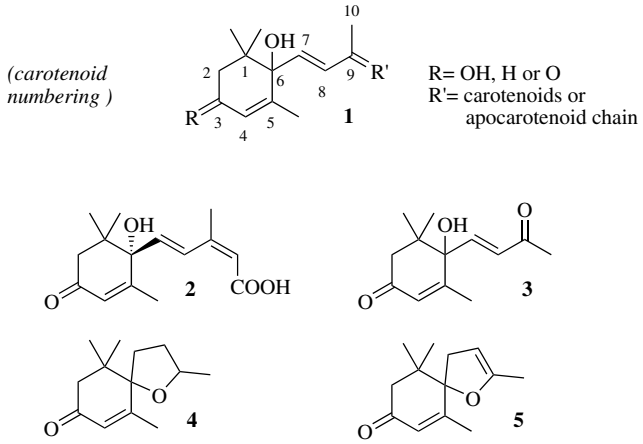


Figure 1.

Carotenoids and apocarotenoids of type **1** have been isolated[6] from different natural sources; the most well known is (+)-abscisic acid **2**, which is well established as an important growth regulator in most plants.[7] (+)-Dehydrovomifoliol **3** occurs in Nature[8] but its relevance is due to its use as penultimate precursor in the well established synthesis of **2**.[9]

* Corresponding author. Tel.: +39 02 2399 3076; fax: +39 02 2399 3080; e-mail: stefano.serra@polimi.it

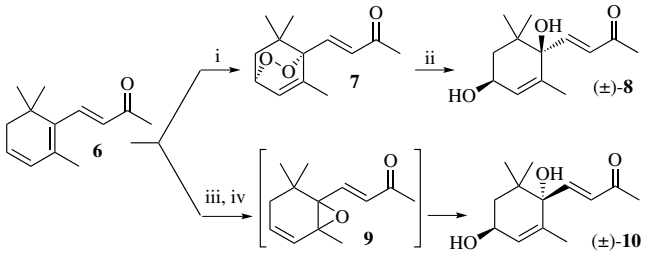
0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.10.014

Moreover, spiroderivatives **4** and **5** are important flavors. Theaspirone **4** is a component of the thea scent[10] whereas the less well known dehydrotheaspirone **5** has received increasing attention after its isolation from tobacco,[11] Riesling wine,[12] nectarines,[13] honey,[8c] and *Reseda odorata* flowers.[14] All of the above-mentioned compounds share the same difficult accessibility by chemical synthesis, particularly in their enantiomerically pure forms. Within this topic, the known procedures are based essentially on three approaches: resolution of the enantiomers, the asymmetric synthesis, and the use of two easily available C-9 chiral building blocks. The first method[13,15] proved to be unsuitable for preparative purposes and is applied in only a few analytical studies dedicated to the evaluation of the physical[15a,b] or organoleptic[13,15c] properties of compounds **2** and **5**, respectively. Concerning the second pathway,[16] some leading methods exploited the Sharpless epoxidation[16a] and chiral bicyclic lactam[16b] or ketal[16c] alkylation procedure as a key step in the formation of the quaternary asymmetric center. The chiral intermediates obtained were then manipulated in order to obtain derivatives **2** and **3**. On the other hand, the third pathway is based on the use of (4*R*,6*R*)- and (4*R*,6*S*)-isomers of 4-hydroxy-2,2,6-trimethylcyclohexanone[1,17] that are in turn obtained in high enantiomeric excess by microbial reduction of oxoisophorone and by fractional crystallization of its diastereoisomeric esters, respectively. The latter two compounds were used as starting materials in a number of carotenoid syntheses involving the preparation of compounds of type **1**–**3**. As described above, we propose a different approach to the synthesis of enantioenriched derivatives **1**–**5** based on the lipase-mediated resolution of diastereoisomerically pure 3,6-dihydroxy-α-ionone isomers. Herein, we report the accomplishment of our plan by the stereoselective preparation of the four isomers of 3-acetoxy-6-hydroxy-α-ionone. The synthetic relevance of the latter compounds is demonstrated by their transformation in the enantiomeric forms of dehydrovomifoliol **3** and dehydrotheaspirone **5**.

2. Results and discussion

2.1. Preparation of racemic diols 8 and 10

As part of a program aimed at the preparation of enantiopure odorants,[18] we have previously shown the efficiency of lipase-mediated kinetic resolutions of racemic materials.[19] Accordingly, we extended this flexible enzymic methodology to the resolution of 3,6-dihydroxy-α-ionone derivatives. Our study first needed a valuable amount of racemic starting materials. Preliminary experiments demonstrated that different lipases catalyze the irreversible kinetic acetylation of the 3-hydroxy group of the above-mentioned isomers with complete regioselectivity and with very low diastereoselectivity. Therefore, we selected two diastereoselective preparations of racemic *cis*- and *trans*-3,6-dihydroxy-α-ionone **8** and **10**, respectively (Scheme 1). In accordance with previously reported methods, both diols were prepared by starting from the easily available 3,4-dehydroxy-β-ionone **6**. Treatment of the latter compound with oxygen and visible light in the presence of rose bengal as a photosensitizer[15a] provided the stable peroxy-



Scheme 1. Preparation of racemic diols **8** and **10**. Reagents and conditions: (i) Rose Bengal, O_2, MeOH; (ii) thiourea, MeOH, rt, 56% (two steps); (iii) MCPBA, Et_2O, 0 °C; (iv) $NaHCO_3$, H_2O, rt, then crystallization from hexane/AcOEt, 59% (two steps).

derivative **7**, which was reduced with thiourea[20] to give the *cis*-3,6-dihydroxy-α-ionone **8**. Conversely, the oxidation of **6** with MCPBA afforded the epoxy-derivative **9**, which is not stable in the reaction environment and rearranged to give a 5:1 mixture of diols **10** and **8**, respectively.[21] Due to the different crystal properties of the latter compounds, the crystallization of the crude reaction mixture afforded pure diol **10**.

2.2. Lipase-mediated resolution of diols 8 and 10

Each of the two diastereoisomerically pure diols **8** and **10** was treated with vinyl acetate in *t*-BuOMe solution in the presence of lipases (PS, CRL, and PPL). The reactivity of each substrate toward the irreversible acetylation was tested by monitoring at regular time intervals the product distribution by GC analysis. After interruption of the reaction, the products were isolated and their ee and absolute configuration determined by specific rotation values measurements and chemical correlation with the known dehydrovomifoliol **3**, respectively (see Section 2.3). The results of this study are collected in Table 1 and allow some interesting considerations.

Table 1. Results of the enzyme-mediated acetylation of diols (±)-**8** and (±)-**10**

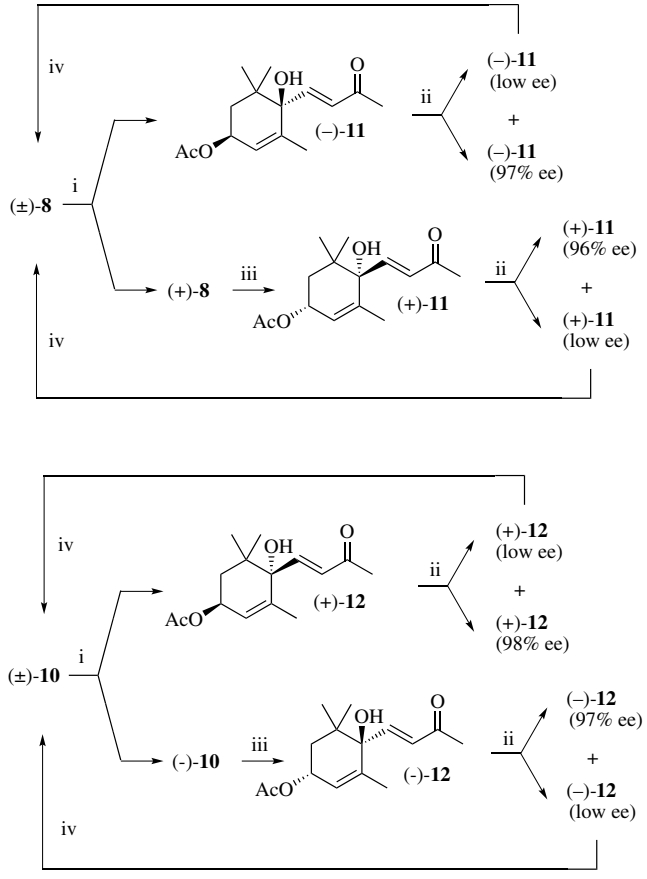
Diol	Enzyme	Conversion (%)	ee (%) and absolute configuration[a]	E[b]
8	PPL	3	9 (3*S*,6*R*)	1.2
	CRL	42	3 (3*S*,6*R*)	1.1
	Lipase PS	50	60 (3*S*,6*R*)	7.2
10	PPL	15	3 (3*S*,6*S*)	1.1
	CRL	30	8 (3*R*,6*R*)	1.2
	Lipase PS	13	36 (3*S*,6*S*)	2.3

[a] The ee and absolute configuration were determined on the isolated 3-acetoxy-derivative **11** and **12** according with Section 2.3.
[b] $E = \ln[1 - c \times (1 + ee_p)]/\ln[1 - c \times (1 - ee_p)]$.

All the lipases tested, regioselectively catalyzed the acetylation of the secondary alcohol function. Transformation of *cis*-diol **8** afforded (3*S*,6*R*)-3-acetoxy-derivative with an enantioselectivity that ranged from very low for PPL and CRL to moderate for lipase PS. Similarly, PPL and lipase PS mediated the conversion of *trans*-diol **10** in the (3*S*,6*S*)-3-acetoxy-derivative with very low and modest enantioselectivity, respectively. Conversely, CRL catalyzed the acetylation of the same diol with opposite enantioselectivity

showing a preference for the (3*R*)-configuration and thus affording the (3*R*,6*R*)-3-acetoxy-derivative. Also in the latter case, the enantioselectivity was very low. Overall, the enantiomeric ratio did not exceed the value of 1.2 for PPL and CRL whereas values of 7.2 and 2.3 were seen when lipase PS catalyzed the acetylation of **8** and **10**, respectively. Even though by the employment of the latter enzyme, an efficient resolution process of **8** and **10** was not easily achieved. Providentially, we observed that both *cis*- and *trans*-3-acetoxy-derivatives were nice crystalline compounds and for an ee inferior to 60–70%, racemic crystals were much less soluble than enantiomeric enriched ones. The combined application of the enzyme-mediated acetylation and of fractional crystallization was a successful path to enantiopure 3-acetoxy-derivatives.

Taking advantage of the aforementioned results, we devised a large-scale method for the resolution of the title compounds. Following Scheme 2, diols **8** and **10** were submitted to lipase PS-mediated acetylation to afford acetates (−)-**11** and (+)-**12**, respectively, and unreacted diols (+)-**8** and (−)-**10**, respectively. After chromatographic separation, the latter diols were converted into the corresponding acetates (+)-**11** and (−)-**12**, respectively, by treatment with pyridine and acetic anhydride. The enantiomeric purity of the four acetates obtained was increased by crystallization from hexane/ethyl acetate. The crystals obtained showed



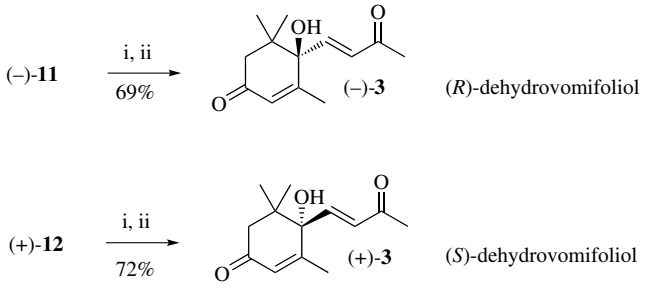
Scheme 2. Preparation of the enantiomeric forms of acetates **11** and **12** by a chemoenzymatic resolution procedure. Reagents and conditions: (i) lipase PS, *t*-BuOMe, vinyl acetate, column chromatography; (ii) fractional crystallization procedure; (iii) Ac_2O, Py; (iv) KOH, MeOH.

very low ee values. Thus, the liquid phases were submitted again to the crystallization process, which was repeated using the mother liquors till the crystals showed a specific rotation value superior of that measured for the liquid. At this point a further crystallization of the solid afforded enantiomerically pure acetate whose optical rotation value did not increase by recrystallization. All the crystal crops showing low ee were collected and then converted again into the starting diols **8** and **10** by means of treatment with methanolic KOH. Although a number of simple chemical manipulations are necessary, the recycling of compounds with low ee increase the significance of the method and overall the process gives access to the enantiomeric forms of acetate **11** and **12** in high ee.

2.3. Determination of the absolute configuration of acetates (−)-11 and (+)-12; synthesis of dehydrovomifoliol

The absolute configuration of the enantiomeric forms of **11** and **12** was unknown. Therefore, we decided to assign these data by chemical correlation. Since we were unable to accurately determine the ee of the above-mentioned compounds by GC or HPLC analysis, we converted these acetates in (−)- and (+)-enantiomers of dehydrovomifoliol **3** of known absolute configuration, which display high and easily measurable specific rotation values.[16a,b,17]

Following Scheme 3, enantiomerically pure (−)-**11** and (+)-**12** were treated with methanolic KOH and the diols obtained were oxidized with MnO_2 in CH_2Cl_2 to afford (−)-(*R*) and (+)-(*S*) dehydrovomifoliol **3**, respectively. Judging from the comparison of the measured specific rotation value, $[\alpha]_D^{20} = -219.5$ (*c* 0.5, CH_2Cl_2) and $[\alpha]_D^{20} = +222$ (*c* 0.5, CH_2Cl_2), with that reported in the lit.[16b] $[\alpha]_D^{20} = -219$ (*c* 0.4, CH_2Cl_2) for (−)-**3** of ee >95%, we assigned the absolute configurations of (−)-**11** and (+)-**12**, as (3*S*,6*R*) and (3*S*,6*S*), respectively. Concerning the enantiomeric purity of the latter two compounds we assert that both show an ee >95%. This assumption has been confirmed by chiral GC analysis of dehydrotheaspirones (−)-**5** and (+)-**5** (see Section 2.4).



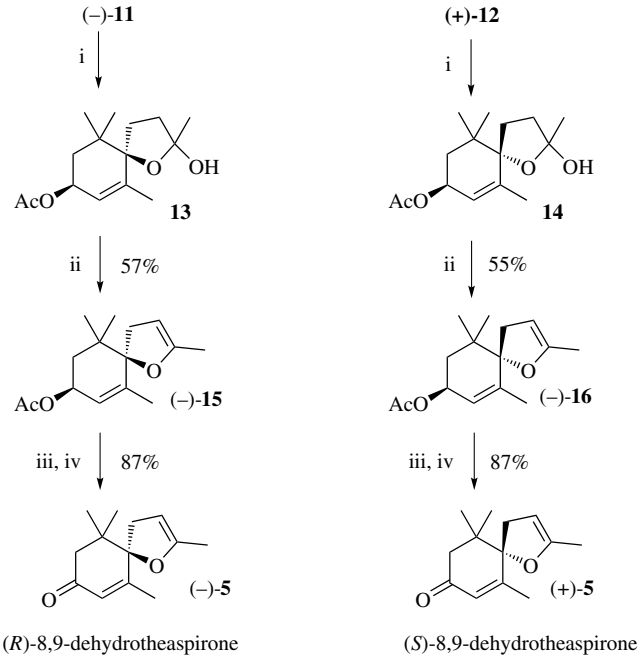
Scheme 3. Chemical correlation of acetates **11** and **12** with dehydrovomifoliol **3**. Reagents and conditions: (i) KOH, MeOH; (ii) MnO_2, CH_2Cl_2, rt.

2.4. Synthesis of the enantiomeric forms of 8,9-dehydrotheaspirone 5

As mentioned in Section 1, enantioenriched 3,6-dihydroxy-α-ionone derivatives are important synthetic intermediates. Since we are involved in a research program devoted to the

preparation of enantiopure odorants, we decided to exploit the use of compounds **11** and **12** for the synthesis of flavors of type **4** and **5**. Herein, we report the transformation of the enantioenriched acetates (−)-**11** and (+)-**12** in the 8,9-dehydrotheaspirone enantiomers (−)-**5** and (+)-**5**, respectively.

Following Scheme 4, regioselective hydrogenation of (−)-**11** and (+)-**12** using Ni Raney as a catalyst afforded hemiacetals **13** and **14**, respectively; each of them were obtained as an inseparable mixture of diastereoisomers. The latter compounds were not characterized and were used in the next step. Thus, dehydratation of **13** and **14** with $POCl_3$ and Et_3N afforded compounds (−)-**15** and (−)-**16**, respectively. The removal of the acetyl protecting group by the reaction with methanolic KOH and the following oxidation of the obtained allyl alcohols by MnO_2 treatment, afforded dehydrotheaspirone isomers (−)-**5** and (+)-**5**, respectively. The enantiomeric excesses of the latter compounds were easily measured by chiral GC analysis as 97% and 98%, respectively. These values also indicate the ee of the starting materials (−)-**11** and (+)-**12** and the ee of the synthesized (−)-(*R*) and (+)-(*S*) dehydrovomifoliol **3**. All these data (absolute configuration and enantiomeric purity) are in good agreement with those described above (see Section 2.3) and those reported by other authors.[15c,16b]



Scheme 4. Preparation of the enantiomeric forms of 8,9-dehydrotheaspirone **5** starting from acetates **11** and **12**. Reagents and conditions: (i) H_2, AcOEt, Ni Raney cat.; (ii) $POCl_3$, Et_3N, 0 °C; (iii) KOH, MeOH; (iv) MnO_2, CH_2Cl_2, rt.

2.5. Olfactory evaluation of the enantiomeric forms of dehydrotheaspirone 5

The enantiomerically enriched forms of 8,9-dehydrotheaspirone were evaluated by qualified perfumers (Givaudan Schweiz AG, Fragrance Research). The following results were obtained:

(−)-(*R*)-**5**: woody, dry, cedarwood odor with a green, earthy, tobacco and olibanum inflection and floral-fruity nuances. Odor threshold (5 panellists): 13.7 ng/L air.

(+)-(*S*)-**5**: floral, woody-ambery, powdery, reminiscent of Cetonal with natural fruity, orris-like facets. Odor threshold (5 panellists): 9.8 ng/L air.

3. Conclusions

A number of results have been achieved. We have reported a new chemoenzymatic approach to all isomeric forms of the 3-acetoxy-6-hydroxy-α-ionone. Our synthetic pathways consist of the preparation of the diastereoisomerically pure racemic 3,6-dihydroxy-α-ionone isomers and then in their resolution by means of the combination of the lipase-mediated enantioselective acetylation and of the fractional crystallization of the acetates obtained. The proposed process is operationally simple, does not require demanding reaction conditions or reagents, and the starting material is the inexpensive 3,4-dehydro-β-ionone. The chiral building blocks obtained were used for the synthesis of the enantiomeric forms of the natural norterpenoid dehydrovomifoliol **3** and 8,9-dehydrotheaspirone **5**. Finally, the odor properties of the latter compound were evaluated by professional perfumers.

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. Lipase from *Porcine pancreas* (PPL) type II, Sigma, 147 units/mg; lipase from *Candida rugosa* (CRL) type VII, Sigma, 1150 units/mg and Lipase from *Pseudomonas cepacia* (PS), Amano Pharmaceuticals Co., Japan, 30 units/mg were employed in this work. TLC: Merk Silica Gel $60F_{254}$ 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 film thickness; Hewlett Packard) with the following temperature 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 (**3**) 22.2, t_R (**5**) 18.0, t_R (**7**) 21.6, t_R (**8**) 24.8, t_R (**10**) 22.4, t_R (**11**) 23.4, t_R (**12**) 23.2, t_R (**15**) 19.9, t_R (**16**) 19.5; mass spectra: *m*/*z* (rel %). Chiral GC analyses: DANI-HT-86.10 gas chromatograph; enantiomeric excesses determined on a CHIRASIL DEX CB-Column with the following temperature program 80 °C (0 min)–2 °C/min–100 °C (0 min)–1 °C/min–110 °C (0 min)–25 °C/min–180 °C (2 min); t_R given in min: t_R((+)-**5**) 16.8, t_R((−)-**5**) 15.3. Optical rotations: Jasco-DIP-181 digital polarimeter. ^1H and ^{13}C Spectra: $CDCl_3$ soln 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 Hz. IR spectra were recorded on a Perkin–Elmer 2000 FT-IR spectrometer; films; *v* in cm^{-1}. Melting points were measured on a Reic-

hert apparatus, equipped with a Reichert microscope, and are uncorrected. Microanalyses were determined on an analyzer 1106 from Carlo Erba.

4.2. Synthesis of racemic (3*RS*,6*SR*)-3,6-dihydroxy-α-ionone and of (3*SR*,6*SR*)-3,6-dihydroxy-α-ionone

4.2.1. (3*RS*,6*SR*)-3,6-Dihydroxy-α-ionone (±)-8. A solution of 3,4-dehydro-β-ionone **6** (25 g, 132 mmol) and Rose Bengal (0.3 g, 0.3 mmol) in methanol (600 mL) was irradiated with 12 8-W visible light lamps with continuous purging of dry oxygen until starting compound **6** was less than 5% of the mixture (2 days, GC analysis). The reaction was then flushed with nitrogen and a sample of the solution (10 mL) was concentrated in vacuo and purified by CC (hexane/Et_2O from 95:5 to 7:3) to allow the isolation of the stable peroxy-derivative **7**. ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, $J = 16.1$ Hz, 1H), 6.42 (d, $J = 16.1$ Hz, 1H), 6.32 (dq, $J = 6.2$, 1.7 Hz, 1H), 4.61–4.55 (m, 1H), 2.27 (s, 3H), 2.01 (dd, $J = 13.0$, 3.8 Hz, 1H), 1.87 (d, $J = 1.7$ Hz, 3H), 1.36 (dd, $J = 13.0$, 2.0 Hz, 1H), 1.13 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz) δ 196.6, 142.3, 138.8, 130.6, 124.7, 84.2, 72.4, 40.1, 35.1, 28.9, 27.9, 25.0, 19.4. IR (film, cm^{-1}) 1701, 1679, 1629, 1441, 1363, 1256, 986. GC–MS *m*/*z* (rel intensity) 222 (M^+, 10), 179 (54), 166 (9), 151 (4), 137 (11), 125 (50), 107 (22), 95 (100), 83 (24), 67 (15), 55 (20). The remaining solution was treated with thiourea (12 g, 158 mmol) stirring at room temperature for 12 h and then concentrated at reduced pressure. The residue obtained was chromatographed (hexane/Et_2O from 9:1 to 1:1) to afford starting **6** (1.1 g, 5.7 mmol) and *cis*-3,6-dihydroxy-α-ionone **8** (15.3 g, 68.3 mmol, 56% yield based on reacted **6**, 96% chemical purity (GC)) as a colorless oil that crystallized on standing: mp 71–73 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, $J = 16.4$ Hz, 1H), 6.47 (d, $J = 16.4$ Hz, 1H), 5.65 (s, 1H), 4.26 (br s, 1H), 2.63 (br s, 1H), 2.55 (s, 1H), 2.28 (s, 3H), 1.79 (dd, $J = 13.4$, 6.0 Hz, 1H), 1.71 (dd, $J = 13.4$, 8.0 Hz, 1H), 1.65 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz) δ 198.2, 148.0, 136.8, 130.3, 128.3, 77.2, 64.9, 41.9, 38.4, 27.9, 24.4, 24.2, 19.1. IR (film, cm^{-1}) 3364, 3317, 1683, 1459, 1250, 1022, 988. GC–MS *m*/*z* (rel intensity) 191 (<1), 164 (1), 155 (5), 137 (1), 121 (1), 111 (1), 105 (43), 104 (100), 91 (6), 85 (2), 79 (5), 77 (5), 71 (4). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.75; H, 9.00.

4.2.2. (3*SR*,6*SR*)-3,6-Dihydroxy-α-ionone (±)-10. A solution of 3,4-dehydro-β-ionone **6** (30 g, 158 mmol) in diethyl ether (250 mL) was treated with MCPBA (29.4 g, 170 mmol) stirring at 0 °C until no more starting compound **6** was detected by TLC analysis (3 h). The reaction was then treated with a 5% solution of $Na_2S_2O_5$ aq (100 mL) and stirred at rt for 2 h. Powdered $NaHCO_3$ (20 g, 238 mmol) was then added portionwise and the mixture was diluted with water (80 mL). The aqueous phase was separated and extracted with ether (2 × 100 mL). The organic layer was washed in turn with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography (hexane/Et_2O from 7:3 to 1:2) and the obtained oil was crystallized from hexane/ethyl acetate (1:1) to give pure *trans*-3,6-dihydroxy-α-ionone **10** (20.9 g, 59% yield, 98% chemical purity (GC)) as colorless crystals: mp 114–115 °C (lit.[20a] mp 116–117 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, $J = 15.8$ Hz, 1H), 6.34 (d, $J = 15.8$ Hz, 1H), 5.64–5.60 (m, 1H), 4.30 (br s, 1H), 2.28 (s, 3H), 1.91 (br s, 1H), 1.87 (ddd, $J = 13.4$, 6.5, 1.4 Hz, 1H), 1.79 (s, 1H), 1.67–1.57 (m, 1H), 1.63 (t, $J = 1.7$ Hz, 3H), 1.04 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz) δ 198.3, 148.6, 136.8, 129.4, 128.8, 78.9, 65.4, 44.0, 39.8, 27.8, 25.0, 22.4, 17.3. IR (Nujul, cm^{-1}) 3360, 3315, 1684, 1619, 1454, 1109, 990. GC–MS *m*/*z* (rel intensity) 224 (M^+, 1), 206 ($M^+ - H_2O$, 17), 191 (8), 164 (30), 150 (31), 135 (31), 125 (49), 111 (32), 108 (100), 97 (23), 91 (11), 77 (15), 71 (15), 55 (15). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.55; H, 9.03.

4.3. General procedure for lipase-mediated resolution of racemic substrates (±)-8 and (±)-10

A mixture of the racemic diol (15 g, 67 mmol), lipase PS (15 g), vinyl acetate (50 mL), and *t*-BuOMe (180 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 by filtration of the enzyme and evaporation of the solvent at reduced pressure. The residue was purified by chromatography using hexane-diethyl ether as eluent to give the enantiomeric enriched (3*S*)-acetate and (3*R*)-diol. The latter compound was converted into the corresponding (3*R*)-acetate by treatment with pyridine (20 mL) and acetic anhydride (30 mL) and left at rt until no more starting diol was detected by TLC analysis (4 h) after which the solvents were removed at reduced pressure. The enantiomeric purity of both acetates was increased by crystallization from hexane/ethyl acetate (3:1). The recrystallization procedure was identical for all the acetates and the number of the steps depend upon the ee of the starting compounds. A general protocol is the following.

The crystals were filtered and washed with a minimum amount of cold solvent. The liquid was concentrated in vacuo and the specific rotation values were measured for both phases. Usually, for ee of the starting acetates inferior to 60–70%, racemic crystals were less soluble than the enantiomeric enriched ones. The corresponding solid crop showed specific rotation values inferior to those measured for the liquid. Thus the latter phase was submitted again to the crystallization process, which was repeated using the mother liquors until the crystals showed an optical rotation value superior to that measured for the liquid. At this point, a further crystallization of the solid afforded enantiomerically pure acetate whose specific rotation value does not increase by recrystallization.

4.3.1. Resolution of (3*RS*,6*SR*)-3,6-dihydroxy-α-ionone (±)-8. According to the general procedure, (±)-**8** was converted into acetate (−)-**11** and diol (+)-**8**. The latter compound was acetylated to give (+)-**11** and both esters were submitted to the fractional crystallization procedure to afford enantiopure (−)-**11** (3.6 g, 20% yield after 3 crystallizations) and (+)-**11** (2.8 g, 16% yield after 4 crystallizations) showing the following spectral data:

(3S,6R)-3-Acetoxy-6-hydroxy-α-ionone (−)-**11**: 98% chemical purity (GC), $[\alpha]_D^{20} = -198.8$ (*c* 1, $CHCl_3$), mp[†] 69–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, $J =$ 15.8 Hz, 1H), 6.43 (d, $J = 15.8$ Hz, 1H), 5.61 (s, 1H), 5.34–5.26 (m, 1H), 2.28 (s, 3H), 2.05 (s, 3H), 1.88 (dd, $J = 14.2$, 6.4 Hz, 1H), 1.78 (s, 1H), 1.75 (dd, $J = 14.2$, 6.1 Hz, 1H), 1.67 (t, $J = 1.5$ Hz, 3H), 1.02 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz) δ 197.6, 170.5, 147.0, 139.5, 130.2, 123.9, 77.6, 67.5, 38.4, 37.7, 28.1, 24.3, 23.8, 21.2, 18.7. IR (film, cm^{-1}) 3492, 1734, 1675, 1624, 1361, 1245, 1120, 1021, 991, 948. GC–MS *m/z* (rel intensity) 248 (M^+-H_2O, <1), 233 (2), 224 (5), 206 (33), 191 (32), 163 (82), 150 (74), 135 (42), 123 (95), 108 (100), 93 (22), 91 (22), 77 (21), 69 (14), 55 (20). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.80; H, 8.35.

(3R,6S)-3-Acetoxy-6-hydroxy-α-ionone (+)-**11**: 98% chemical purity (GC), $[\alpha]_D^{20} = -194.3$ (*c* 1, $CHCl_3$), mp 70–73 °C. IR, ^{1}H NMR, MS: in accordance with that of (−)-**11**.

4.3.2. Resolution of (3*SR*,6*SR*)-3,6-dihydroxy-α-ionone (±)-10. According to the general procedure, (±)-**10** was converted in the acetate (+)-**12** and diol (−)-**10**. The latter compound was acetylated to give (−)-**12** and both esters were submitted to the fractional crystallization procedure to afford enantiopure (+)-**12** (2.1 g, 12% yield after 3 crystallizations) and (−)-**12** (1.75 g, 10% yield after 4 crystallizations) showing the following spectral data:

(3S,6S)-3-Acetoxy-6-hydroxy-α-ionone (+)-**12**: 98% chemical purity (GC), mp[‡] 132–133 °C; $[\alpha]_D^{20} = +164$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, $J = 15.8$ Hz, 1H), 6.36 (d, $J = 15.8$ Hz, 1H), 5.57–5.52 (m, 1H), 5.41–5.32 (m, 1H), 2.29 (s, 3H), 2.06 (s, 3H), 1.90 (ddd, $J = 13.4$, 6.5, 1.4 Hz, 1H), 1.77 (s, 1H), 1.78–1.68 (m, 1H), 1.64 (t, $J = 1.5$ Hz, 3H), 1.08 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz) δ 198.0, 170.7, 148.0, 139.0, 129.6, 124.3, 78.6, 68.5, 39.7, 39.6, 27.9, 24.8, 22.3, 21.2, 17.5. IR (film, cm^{-1}) 3502, 1732, 1675, 1651, 1362, 1251, 1113, 1021, 973. GC–MS *m/z* (rel intensity) 248 (M^+-H_2O, <1), 233 (1), 224 (7), 206 (53), 191 (33), 163 (100), 150 (56), 135 (33), 121 (40), 108 (85), 93 (21), 91 (20), 77 (17), 69 (15), 55 (20). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.70; H, 8.35.

(3R,6R)-3-Acetoxy-6-hydroxy-α-ionone (−)-**12**: 98% chemical purity (GC), mp 129–130 °C; $[\alpha]_D^{20} = -162.6$ (*c* 1, $CHCl_3$). IR, ^{1}H NMR, MS: in accordance with that of (+)-**12**.

4.4. General procedure for conversion of 3-acetoxy-6-hydroxy-α-ionone isomers in the dehydrovomifoliol enantiomers

A sample of acetate **11** or **12** (400 mg, 1.5 mmol) was treated with a solution of KOH (1 g, 17.8 mmol) in methanol (10 mL) stirring at rt until no more starting acetate was detected by TLC analysis. The mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and treated with MnO_2 (1.5 g, 17.2 mmol) while stirring at rt for 4 h. The mixture was then filtered. The organic phase was concentrated under reduced pressure and the residue purified by chromatography (hexane/Et_2O from 9:1 to 2:1) to afford pure dehydrovomifoliol **3**.

4.4.1. (−)-Dehydrovomifoliol (−)-3. According to the general procedure (−)-**11** was converted into (6*R*)-3-oxy-6-hydroxy-α-ionone (−)-**3** (230 mg, 69%) as a colorless oil that crystallized on standing: 97% chemical purity (GC), mp 68–70 °C; $[\alpha]_D^{20} = -219.5$ (*c* 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, $J = 15.7$ Hz, 1H), 6.47 (d, $J = 15.7$ Hz, 1H), 5.97–5.94 (m, 1H), 2.49 (d, $J = 17.1$ Hz, 1H), 2.37 (s, 1H), 2.34 (dd, $J = 17.1$, 1.1 Hz, 1H), 2.30 (s, 3H), 1.89 (d, $J = 1.5$ Hz, 3H), 1.11 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz) δ 197.4, 197.0, 160.5, 145.1, 130.4, 127.7, 79.2, 49.6, 41.4, 28.2, 24.3, 22.9, 18.6. IR (film, cm^{-1}) 3438, 1698, 1651, 1629, 1266, 1076, 987. GC–MS *m/z* (rel intensity) 222 (M^+, 1), 204 (M^+-H_2O, 1), 189 (1), 180 (3), 166 (16), 149 (7), 124 (100), 109 (3), 95 (8), 77 (4), 69 (6), 55 (5). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.35; H, 8.15.

4.4.2. (+)-Dehydrovomifoliol (+)-3. According to the general procedure (+)-**12** was converted into (6*S*)-3-oxy-6-hydroxy-α-ionone (+)-**3** (240 mg, 72%) as a colorless oil that crystallized on standing: 96% chemical purity (GC), mp 68–69 °C; lit.[16a] 69–70 °C, $[\alpha]_D^{20} = +222$ (*c* 0.5, CH_2Cl_2). IR, ^{1}H NMR, MS: in accordance with that of (−)-**3**.

4.5. General procedure for conversion of 3-acetoxy-6-hydroxy-α-ionone isomers in the 8,9-dehydrotheaspirone enantiomers

A solution of acetates **11** or **12** (1 g, 3.8 mmol) in AcOEt (50 mL) was hydrogenated at atmospheric pressure using Ni Raney as a catalyst. After complete consumption of the starting materials (TLC monitoring, 1 h), the organic phases were filtered, and concentrated in vacuo. The residues were dissolved in triethylamine (10 mL) and cooled to 0 °C. $POCl_3$ (1 mL, 10.7 mmol) was added dropwise to the resulting solutions and the reactions were vigorously stirred for 30 min. The mixtures were then poured onto an ice cooled satd solution of $NaHCO_3$ (100 mL) and then extracted with diethyl ether (2 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residues were purified by chromatography (eluting with hexane/ether/triethylamine 94:5:1) to afford pure compounds **15** and **16**, respectively, as a colorless oil. The latter spiro derivatives were treated with a solution of KOH (1 g, 17.8 mmol) in methanol (10 mL) stirring at rt until no more starting acetates were detected by TLC analysis. The mixtures were diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated. The residues were dissolved in CH_2Cl_2 (20 mL) and treated with MnO_2 (2 g,

[†] For racemic **11** mp is 88–90 °C.
[‡] For racemic **12** mp is 118–119 °C.

23 mmol) stirring at rt for 2 h. The mixtures were then filtered, the organic phases concentrated under reduced pressure and the residues were purified by chromatography (hexane/Et_2O from 95:5 to 9:1) to afford pure dehydrotheaspirone **5** as a colorless oil that crystallized on standing.

4.5.1. (*R*)-8,9-Dehydrotheaspirone (−)-5. According to the general procedure, (−)-**11** afforded acetate (−)-**15** (0.54 g, 57% yield), which was transformed into (*R*)-dehydrotheaspirone (−)-**5** (0.39 g, 87% yield). The latter compounds showed the following analytical data:

(5R,8S)-2,6,10,10-Tetramethyl-1-oxa-spiro[4.5]deca-2,6-dien-8-yl acetate (−)-**15**: 99% chemical purity (GC), $[\alpha]_D^{20} = -17.4$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (s, 1H), 5.27–5.20 (m, 1H), 4.44–4.40 (m, 1H), 2.69 (dm, $J = 15.7$ Hz, 1H), 2.40 (dm, $J = 15.7$ Hz, 1H), 2.03 (s, 3H), 1.79–1.74 (m, 8H), 1.02 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz) δ 170.8, 154.7, 141.6, 121.1, 94.2, 90.1, 68.1, 38.4, 37.1, 35.0, 23.5, 22.5, 21.3, 17.9, 13.3. IR (film, cm^{-1}) 1737, 1683, 1380, 1246, 1189, 1016, 973, 951. GC–MS *m/z* (rel intensity) 251 (M^++1, 3), 250 (M^+, 23), 208 (2), 194 (37), 190 (36), 175 (100), 152 (48), 147 (37), 131 (29), 120 (64), 109 (36), 105 (51), 91 (23), 79 (12), 77 (13), 55 (7). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.80; H, 8.90.

(R)-8,9-Dehydrotheaspirone (−)-**5**: mp 80–82 °C; $[\alpha]_D^{20} = -34.2$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (br s, 1H), 4.52–4.48 (m, 1H), 3.02 (dm, $J = 15.7$ Hz, 1H), 2.46 (dm, $J = 15.7$ Hz, 1H), 2.41 (d, $J = 16.8$ Hz, 1H), 2.23 (d, $J = 16.8$ Hz, 1H), 1.97 (d, $J = 1.5$ Hz, 3H), 1.82–1.79 (m, 3H), 1.09 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz) δ 198.0, 164.7, 155.2, 123.9, 93.7, 90.7, 48.8, 40.6, 37.1, 22.8, 22.7, 18.2, 13.1. IR (film, cm^{-1}) 1675, 1628, 1382, 1262, 1188, 935. GC–MS *m/z* (rel intensity) 206 (M^+, 68), 191 (16), 173 (6), 163 (7), 150 (53), 136 (35), 121 (28), 108 (100), 93 (50), 91 (21), 79 (15), 77 (22), 53 (9). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.55; H, 8.82.

4.5.2. (*S*)-8,9-Dehydrotheaspirone (+)-5. According to the general procedure, (+)-**12** afforded acetate (−)-**16** (0.52 g, 55% yield), which was transformed into (*S*)-dehydrotheaspirone (+)-**5** (0.37 g, 87% yield). The latter compounds showed the following analytical data:

(5S,8S)-2,6,10,10-Tetramethyl-1-oxa-spiro[4.5]deca-2,6-dien-8-yl acetate (−)-**16**: $[\alpha]_D^{20} = -48.7$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38–5.30 (m, 1H), 5.27–5.23 (m, 1H), 4.45–4.40 (m, 1H), 2.78 (dm, $J = 15.7$ Hz, 1H), 2.44 (dm, $J = 15.7$ Hz, 1H), 2.03 (s, 3H), 1.83 (ddd, $J = 13.2$, 6.5, 1.4 Hz, 1H), 1.75–1.78 (m, 3H), 1.73 (t, $J = 1.5$ Hz, 3H), 1.57 (dd, $J = 13.2$, 9.1 Hz, 1H), 1.06 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz) δ 170.6, 155.1, 143.8, 119.4, 94.0, 90.8, 69.1, 39.3, 39.0, 38.7, 23.6, 22.2, 21.3, 17.1, 13.2. IR (film, cm^{-1}) 1735, 1713, 1376, 1256, 1101, 1053, 1011, 972, 936. GC–MS *m/z* (rel intensity) 251 (M^++1, 2), 250 (M^+, 17), 208 (2), 194 (31), 190 (32), 175 (100), 152 (42), 147 (38), 131 (36), 120 (73), 109 (35), 105 (58), 91 (24), 79 (13), 77 (14), 55 (8). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.85; H, 8.90.

(S)-8,9-Dehydrotheaspirone (+)-**5**: mp 79–81 °C; $[\alpha]_D^{20} = +35$ (*c* 1, $CHCl_3$). IR, ^{1}H NMR, MS: in accordance with that of (−)-**5**.

Acknowledgment

The authors would like to thank Dr. Philip Kraft (Givaudan Schweiz AG) for the odor evaluation of the dehydrotheaspirone enantiomers.

References

1. (a) Mayer, H. *Pure Appl. Chem.* **1979**, *51*, 535–564; (b) Pfander, H. *Pure Appl. Chem.* **1991**, *63*, 23–33.
2. (a) Brenna, E.; Fuganti, C.; Serra, S.; Kraft, P. *Eur. J. Org. Chem.* **2002**, 967–978; (b) Serra, S.; Fuganti, C.; Brenna, E. *Helv. Chim. Acta* **2006**, *89*, 1110–1122.
3. Brenna, E.; Fuganti, C.; Serra, S. *C.R. Chim.* **2003**, *6*, 529–546.
4. Serra, S.; Fuganti, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1573–1580.
5. Brenna, E.; Fuganti, C.; Serra, S. *Tetrahedron: Asymmetry* **2005**, *16*, 1699–1704.
6. (a) Diallo, B.; Vanhaelen, M. *Phytochemistry* **1987**, *26*, 1491–1492; (b) Achenbach, H.; Blümm, E.; Waibel, R. *Tetrahedron Lett.* **1989**, *30*, 3059–3060; (c) Tsushima, M.; Mune, E.; Maoka, T.; Matsuno, T. *J. Nat. Prod.* **2000**, *63*, 960–964; (d) Matsuno, T.; Tsushima, M.; Maoka, T. *J. Nat. Prod.* **2001**, *64*, 507–510; (e) DellaGreca, M.; Di Marino, C.; Zarrelli, A.; D'Abrosca, B. *J. Nat. Prod.* **2004**, *67*, 1492–1495.
7. Addicott, F. T. *Abscisic Acid*; Praeger: New York, 1983.
8. (a) Takasugi, M.; Anetai, M.; Katsui, N.; Masamune, T. *Chem. Lett.* **1973**, 245–248; (b) Achenbach, H.; Lottes, M.; Waibel, R.; Karikas, G. A.; Correa, M. D.; Gupta, M. P. *Phytochemistry* **1995**, *38*, 1537–1545; (c) D'Arcy, B. R.; Rintoul, G. B.; Rowland, C. Y.; Blackman, A. J. *J. Agric. Food Chem.* **1997**, *45*, 1834–1843; (d) Kai, H.; Baba, M.; Okuyama, T. *Chem. Pharm. Bull.* **2007**, *55*, 133–136.
9. Roberts, D. L.; Heckman, R. A.; Hege, B. P.; Bellin, S. A. *J. Org. Chem.* **1968**, *33*, 3566–3569.
10. Ohloff, G. *Scent and Fragrances: The Fascination of Fragrances and their Chemical Perspectives*; Springer: Berlin, 1994.
11. Fujimori, T.; Takagi, Y.; Kato, K. *Agric. Biol. Chem.* **1981**, *45*, 2925–2926.
12. Winterhalter, P.; Sefton, M. A.; Williams, P. J. *J. Agric. Food Chem.* **1990**, *38*, 1041–1048.
13. Knapp, H.; Weigand, C.; Gloser, J.; Winterhalter, P. *J. Agric. Food Chem.* **1997**, *45*, 1309–1313.
14. Surburg, H.; Güntert, M.; Harder, H. In *Bioactive Volatile Compounds from Plants*; Teranishi, R., Buttery, R. G., Sugisawa, H., Eds.; ACS Symposium Series 525; American Chemical Society: Washington, DC, 1993; pp 168–186.
15. (a) Koreeda, M.; Weiss, G.; Nakanishi, K. *J. Am. Chem. Soc.* **1973**, *95*, 239–240; (b) Kim, B. T.; Min, Y. K.; Asami, T.; Park, N. K.; Kwon, O. Y.; Cho, K. Y.; Yoshida, S. *Tetrahedron Lett.* **1997**, *38*, 1797–1800; (c) Hitomi, K.; Hideki, N.; Taro, K.; Masakazu, I. Japanese Patent, 2002, JP 2002069479 A.
16. (a) Acemoglu, M.; Uebelhart, P.; Rey, M.; Eugster, C. H. *Helv. Chim. Acta* **1988**, *71*, 931–956; (b) Meyers, A. I.; Sturgess, M. A. *Tetrahedron Lett.* **1989**, *30*, 1741–1744; (c) Smith, T. R.; Clark, A. J.; Clarkson, G. J.; Taylor, P. C.; Marsh, A. *Org. Biomol. Chem.* **2006**, *4*, 4186–4192.

17. Mori, K. *Tetrahedron* **1974**, *30*, 1065–1072.
18. Brenna, E.; Fuganti, C.; Serra, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1–42.
19. Abate, A.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Serra, S. *J. Mol. Catal. B: Enzym.* **2004**, *32*, 33–51.
20. (a) Kato, T.; Kondo, H.; Kitano, Y.; Hata, G.; Takagi, Y. *Chem. Lett.* **1980**, 757–760; (b) Kato, T.; Kondo, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1573–1574.
21. Strauss, C. R.; Dimitriadis, E.; Wilson, B.; Williams, P. J. *J. Agric. Food Chem.* **1986**, *34*, 145–149.