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Synthesis of the enantiomeric forms of α- and γ-damascone starting from commercial racemic α-ionone

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Abstract—A straightforward synthesis of both enantiomers of α- and γ-damascone is described. The title compounds were prepared by a divergent pathway starting from the enantiomeric forms of (6*RS*,7*SR*,9*RS*)-7-hydroxy-7,8-dihydro-α-ionol and of (6*RS*,7*SR*,9*RS*)-7-hydroxy-7,8-dihydro-γ-ionol. These building blocks were obtained from racemic α-ionone in four and five steps, respectively. The 7-hydroxy group was introduced by regio- and diastereoselective epoxidation of the conjugated double bond followed by reductive opening of the oxirane ring. The hydroxy-ketone obtained was reduced diastereoselectively to *trans*-α-diol that could be converted to the *trans*-γ-diol by photochemical isomerization. Both diols were then resolved by lipase-mediated acetylation.

1. Introduction

The norterpenoid ketones α- and γ-damascone are relevant chiral flavors which possess a typical fruity–flowery rose scent.[1] α-Damascone was first synthesized in 1970[2] and can be found in black tea,[3] where it occurs as its (*S*)-(−)-enantiomer, and as trace component in tobacco[4] and different essential oils.[5] More recently, γ-damascone has been recognized as an original fragrance material,[6] which can favorably complement the above-mentioned α-isomer (Fig. 1).

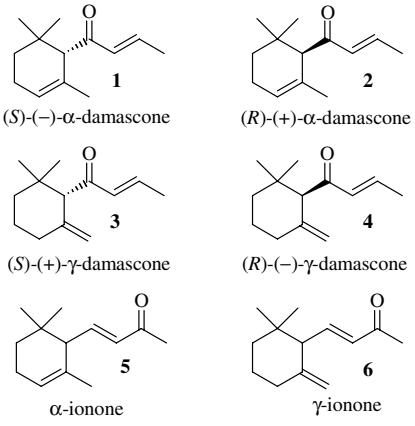

Figure 1.

Olfactory evaluation of these isomers shows that the regio-isomeric and enantiomeric composition greatly affected their fragrance properties,[7] either in terms of features or as odor thresholds. For example, (*S*)-(−)-α-damascone is the more powerful enantiomer.[8] (odor threshold = 1.5 ppb) and was described as floral, reminiscent of rose petals also having a winy character. Otherwise, the (*R*)-(+)-α-isomer is weaker (odor threshold = 100 ppb) with a cork and green apple off-note. In the same way, the (*S*)-(+)-γ-damascone showed superior organoleptic properties rather than those of the (*R*)-(−)-isomer.[6] These noteworthy results exhibit a behavior similar to that of the α- and γ-ionone isomers, where (*S*)-enantiomers are again the most pleasant and powerful compounds.[9]

In spite of these astounding differences among the isomeric series, damascones and ionone share the same difficult accessibility by chemical synthesis, particularly in their enantiomerically pure forms. In this context, many enantioselective pathways to damascones have been developed (Scheme 1). Early studies on the conversion of α-ionone **5** and γ-ionone **6** into α- and γ-damascones,[2,10] respectively needed the scarcely available enantioenriched

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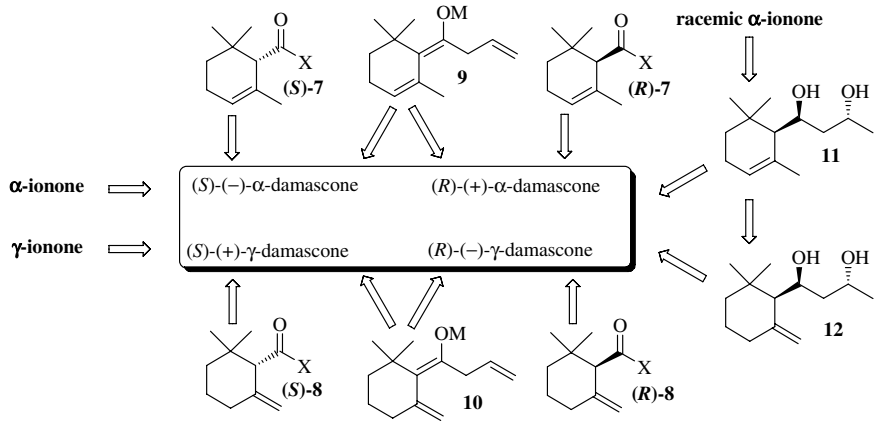


Scheme 1. Retrosynthetic approaches to damascone isomers.

ionone isomers[11] and led only to the preparation of (*R*)-(+)-**2** in modest ee.[2,10b] A more general approach is based on the employment of enantioenriched (*S*)- and (*R*)-cyclocitral derivatives **7** and **8**. In 1973, Yamada et al.[12] achieved an asymmetric synthesis of **2** via (*R*)-α-cyclocitral, obtained in poor ee by cyclization of a chiral enamine of citral.

Later, Mori et al.[13] prepared almost enantiopure **1** from (*S*)-**7** (X = H). The latter aldehyde was synthesized starting from a chiral precursor, obtained in turn by enantioselective enzyme-mediated resolution. Moreover, the enantiomers of α- and γ-cyclocitral, and therefore the damascones **1**–**4** were prepared by Vidari et al.[14] by a multistep enantioselective synthesis that involved the cyclization of enantioenriched epoxyderivatives. Two different approaches based on the enantioselective protonation of enolates were developed by Fehr et al.[15] Thioesters (*S*)- and (*R*)-**7** and (*S*)- and (*R*)-**8** (X = SPh) were obtained[6] in high ee (99% and 96%, respectively) and employed in the synthesis of compounds **1**–**4**. In addition, a more direct path to the latter ketones has been accomplished by the enantioselective protonation of enolates of type **9** and **10**[15] to afford damascone isomers in high and moderate ee (98% and 75%, respectively). Even with the above-mentioned number of studies, all the latter approaches are difficult to apply industrially and damascone is still commercialized as a racemic flavor.

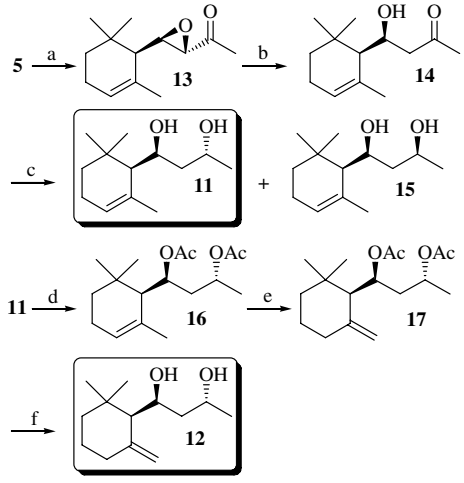
2. Results and discussion

2.1. Preparation of racemic diols 11 and 12

As part of a program of the synthesis of enantioenriched norterpenoid odorants, we achieved the preparation of the enantiomers of ionone[11] and irone[16] isomers through enantioselective lipase-mediated resolution of the related ionols and irols. In order to extend the latter procedure to damascone synthesis, we performed some preliminary experiments on the damascol isomers. The most common lipases were tested and none of them are able to mediate he esterification. This behavior is probably due to the steric crowding around position 7 (carotenoid numbering).

Since the acetylation of the hydroxy functionality at the 9-position of the ionone framework is catalyzed by different types of lipases, we envisaged that diols of type **11** and **12** could be ideal substrates for enzymic resolution. Afterwards, the latter compounds are easily convertible in their corresponding damascone isomers. Herein, we reported the accomplishment of this original approach to enantioenriched compounds **1**–**4**.

According to Scheme 2 diols, **11** and **12** can be prepared straightforwardly from inexpensive racemic α-ionone. The 7-hydroxy group was introduced diastereoselectively in two steps. Epoxidation of the conjugated double bond of **5** by means of H_2O_2/NaOH occurs with complete regio- and diastereoselectivity [2] to afford ketone **13** in good yield. The following reductive opening of the oxirane ring is a demanding synthetic transformation. Indeed the presence of a reducible ketonic functionality and the intrinsic insta-



Scheme 2. Preparation of racemic diols **11** and **12**. Reagents and conditions: (a) H_2O_2/H_2O, MeOH, NaOH, 4 °C, 81% (after recrystallization from hexane); (b) Al/Hg, THF/EtOH/H_2O, 0 °C→rt, 87% (after recrystallization from hexane); (c) $Me_4NHB(OAc)_3$, MeCN/$MeCO_2H$, 97% (87% of isolated **11**); (d) Ac_2O, Py; (e) high-pressure Hg lamps light, *i*PrOH/xylene; (f) KOH, MeOH, recrystallization from hexane; 64% from **11**.

bility of the β-hydroxy-ketone system could give rise to different regioisomers and/or side products. Only one example of this type of reaction was previously performed on compound **13** using lithium naphthalenide as a reducing agent.[17] Our attempts to reproduce the latter procedure furnished hydroxy-ketone **14** in modest yields (39%), even when carefully controlling the experimental conditions.

We found that aluminum amalgam[18] was the optimal reagent for this transformation. Indeed, the reduction of **13** dissolved in THF–H_2O–ethanol at 0 °C smoothly afforded crystalline hydroxy derivative **14** in good yield (87%).

Moreover, the product was diastereoisomerically pure and the selective reduction of the ketone functionality could then afford diol **11** or **15** stereoselectively. A preliminary lipase-mediated acetylation experiment was performed on a mixture of **11** and **15** (6:4) obtained by $NaBH_4$ reduction of **14**. We observed that only diol **11** was transformed, therefore demonstrating that the latter compound should be used in the resolution procedure. In the synthesis of this target, **14** was submitted to the diastereoselective reducing procedure developed by Evans et al.[19]

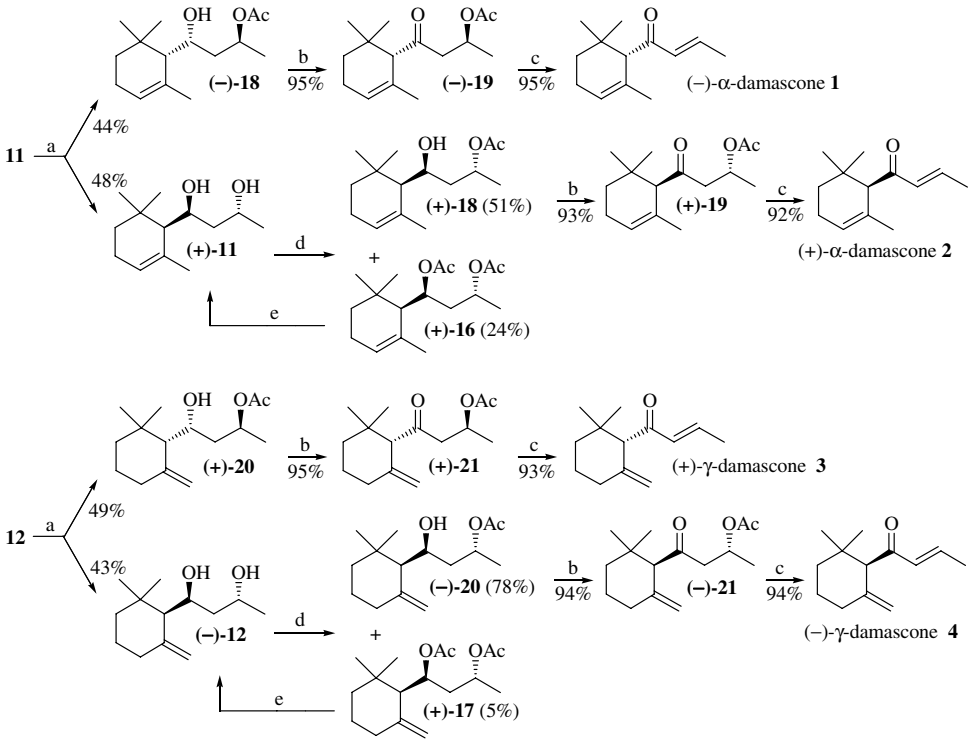
Accordingly, tetramethylammonium triacetoxyborohydride quantitatively converted the latter hydroxy-ketone into diols **11** and **15** with good selectivity (*anti*:*syn* = 93:7). Moreover, the purity of the devised compound **11** could be increased to 99% de by chromatography or crystallization from hexane. Our second target, diol **12**, was prepared following a photochemical double bond isomerization protocol previously employed in ionone and dehydroionone α–γ conversion.[20]

As a result of the latter studies diacetate **16** was irradiated, with high-pressure Hg lamps using xylene as activator. The reaction was interrupted until the α isomer became less than 5% of the mixture; then saponification, chromatographic purification and crystallization afforded diol **12** in satisfactory yield (64%) and in the isomerically pure form (98% chemical purity, 99% de).

2.2. Lipase-mediated resolution of diols 11 and 12. Preparation of damascone isomers 1–4

Scheme 3 summarizes the enzyme-mediated resolution of the latter diols and their conversion into damascones **1**–**4**. As verified before with racemic diol **11**, lipases also catalyzed the acetylation of diol **12**. Lipase PS (*Pseudomonas cepacia*) was the enzyme of choice for the resolution procedure since diastereoisomerically pure diols were used and, on the basis of our previous experience, the latter lipase gives the best results in terms of enantioselectivity.

Accordingly, both diols **11** and **12** were submitted to kinetic acetylation procedure using vinyl acetate as acyl donor and *t*-BuOMe as the solvent. The reactions were performed at rt and then interrupted at about 50% conversion. For both substrates we observed complete regioselectivity as indicated by the exclusive formation of 9-acetoxy-derivatives **18** and **20**.



Scheme 3. Resolution of diols **11** and **12** and synthesis of enantioenriched α- and γ-damascone. Reagents and conditions: (a) lipase PS, *t*-BuOMe, vinyl acetate, column chromatography; (b) Dess–Martin periodinane, CH_2Cl_2, rt; (c) DBU, CH_2Cl_2, rt; (d) Ac_2O, Py, CH_2Cl_2, rt, column chromatography; (e) KOH, MeOH.

Concerning the enantioselectivity of the processes, the results were again very good. Diol **11** gave monoacetate (−)-**18** in 99% ee and diol (+)-**11** in 94% ee whereas diol **12** afforded monoacetate (+)-**20** in 99% ee and diol (−)-**12** in 98% ee. Hence, all the stereoisomers of damascone were accessible by simple chemical transformations. Oxidation of monoacetate (−)-**18** with the Dess–Martin periodinane reagent[21] gave almost quantitatively (95% yield), acetoxy-ketone (−)-**19** that underwent the elimination reaction smoothly by DBU treatment in CH_2Cl_2 solution at rt.

(−)-(*S*)−α-Damascone **1** was obtained in good yield (95%) and without a decrease of enantiomeric excess as judged from the comparison of the measured specific rotation value, $[\alpha]_D^{20} = -520.5$ (*c* 2, $CHCl_3$), with that reported in the lit.[13] $[\alpha]_D^{23} = -514$ (*c* 4, $CHCl_3$) for (−)-**1** with 100% ee. Afterwards, (+)-α-damascone **2** was prepared from diol (+)-**11** by chemical acetylation. Treatment of the latter compound with a slight excess of acetic anhydride in pyridine gave separable monoacetate (+)-**18** (51%), diacetate (+)-**16** (24%) and the unreacted starting material. The overall efficiency of the process could be increased for recovering further diol (+)-**11** by treatment of diacetate (+)-**16** with KOH in methanol. Application of the oxidation–elimination protocol described above for the compound (+)-**18** afforded (+)-(*R*)-α-damascone **2**, whose ee was quantifiable from the measured specific rotation value $\{[\alpha]_D^{20} = +489.7$ (*c* 2, $CHCl_3)\}$ as higher then 94%, in perfect accordance with the ee of the starting diol.

The preparation of γ-damascone enantiomers **3** and **4** was performed starting from monoacetate (+)-**20** and diol (−)-**12**, respectively. The synthetic path, the behavior of the reactions and the yields were the same of those described above for α-isomers **1** and **2**. For the sake of brevity we underlined only one difference found during the chemical acetylation of (−)-**12**. In this case, (−)-**20** was obtained with better regioselectivity (78% yield). According to Scheme 2, (*S*)-(+)-γ-damascone **3** and (*R*)-(−)-γ-damascone **4** were obtained from acetoxy-ketone (+)- and (−)-**21** in 93% and 94% yields, respectively.

The enantiomeric purities were reasonably similar to the starting compounds (+)-**20** and (−)-**12** as of 99% and 98% ee as judged from the comparison of the measured specific rotation value, $[\alpha]_D^{20} = +272.3$ (*c* 2, $CHCl_3$) and $[\alpha]_D^{20} = -270.5$ (*c* 2, $CHCl_3$), respectively with those reported in the lit[6] $[\alpha]_D^{20} = +259$ for (+)-**3** of 96% ee and $[\alpha]_D^{20} = -267$ (*c* 0.02, $CHCl_3$) for (−)-**4** of 98% ee.

3. Conclusions

Several results have been achieved. We have reported a new chemio-enzymatic approach to all the isomeric forms of the norterpenoid flavor damascone. Our synthetic pathway is divergent, compact, and operationally simple and does not require demanding reaction conditions or reagents. The starting material is a racemic α-ionone that is inexpensive and commercially available. The procedure described gives access to the title compounds in high regio- and enantiomeric purity and compares favorably to the previously reported syntheses.

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 and used without further purification. Yields are reported for spectroscopically pure isolated compounds. All the photoisomerization experiments were carried out using a Rayonet photochemical reactor equipped with twelve 8-W high-pressure Hg lamps. Lipase PS from *P. cepacia* (*Amano Pharmaceuticals Co.*, Japan, 30 U mg^{-1} was employed in this work. TLC: *Merk* silica gel *60* F_{254} plates. Column chromatography (CC): silica gel. Gas chromatographic (GC) analyses: *HP-6890* gas chromatograph; determined on a *HP-5* column (30 m × 0.32 mm; *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); t_R (min): **13** (17.07), **14** (16.86), **11** (18.27), **15** (18.02), **12** (19.44), **16** (20.19), **17** (20.55), **18** (19.26), **19** (19.54), **20** (19.03), **21** (18.87), **1** (14.42), **3** (13.70). Chiral GC analyses: DANI-HT-86.10 gas chromatograph; enantiomer excesses determined on a CHIRASIL DEX CB-Column (25 m × 0.25 mm; *Chrompack*) with the following temp. program 80 °C–1 °C/min–95 °C (1 min)–0.3 °C/min–105 °C–25 °C/min–180 °C; t_R (min) of the corresponding acetates: (−)-**18** (40.52), (+)-**11** (46.17), (+)-**20** (45.19), (−)-**12** (45.77). Optical rotations: *Jasco-DIP-181* digital polarimeter. ^1H and ^{13}C NMR spectra: $CDCl_3$ solutions. at rt; *Bruker-AC-400* spectrometer; chemical shifts in parts per million rel to internal $SiMe_4$ (= 0 ppm), *J* values in Hertz. Mass spectra were measured on a *Finnigan-Mat TSQ 70* spectrometer; *m*/*z* (rel.%). IR spectra were recorded on a *Perkin–Elmer 2000 FT-IR* spectrometer; films; *v* in cm^{-1}. Melting points were measured on a Reichert apparatus, equipped with a Reichert microscope, and are uncorrected. Microanalyses were determined on an analyzer *1106* from *Carlo Erba*.

4.2. Synthesis of racemic (6*RS*,7*SR*,9*RS*)-7-hydroxy-7,8-dihydro-α-ionol and of (6*RS*,7*SR*,9*RS*)-7-hydroxy-7,8-dihydro-γ-ionol

4.2.1. (6*RS*,7*RS*,8*SR*)-7,8-Epoxy-α-dihydroionone 13. H_2O_2 (30% in water, 110 ml, 1.08 mol) and 6 M NaOH aq (25 ml, 150 mmol) were successively added dropwise to a cooled (0 °C) and stirred solution of α-ionone **5** (50 g, 260 mmol) in methanol (300 ml). The resulting mixture was stirred for 6 days at 4 °C and then further H_2O_2 (50 ml) and methanol (30 ml) were added each day. The reaction was then quenched with water (300 ml) and extracted with ether. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue (55 g) was submitted to chromatography (eluting from hexane to hexane/Et_2O 8:2) and the obtained **13** (52 g) was further purified by crystallization from hexane to afford pure (6*RS*,7*RS*,8*SR*)-7,8-epoxy-α-dihydroionone **13** (44 g, 81% yield, 99% chemical purity, up to 99% de (GC)) as colorless

crystals: mp 38–39 °C (lit.[2] mp 38 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (br s, 1H), 3.29 (d, $J = 2$ Hz, 1H), 2.91 (dd, $J = 2$, 8.6 Hz, 1H), 2.07–1.99 (m, 2H), 2.06 (s, 3H), 1.72–1.69 (m, 3H), 1.53 (dt, $J = 8.2$, 13.4 Hz, 1H), 1.40 (d, $J = 8.6$ Hz, 1H), 1.29 (dt, $J = 4.8$, 13.4 Hz, 1H), 1.10 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz) δ 205.7, 130.3, 124.5, 59.1, 58.5, 52.4, 32.6, 31.7, 27.2, 26.9, 24.3, 23.5, 22.9. IR ($CHCl_3$, cm^{-1}) 1711, 1365, 1246, 881, 846. MS (EI) m/z (rel intensity) 208 (M^+, 1), 193 (2), 175 (8), 165 (40), 147 (42), 135 (48), 123 (35), 109 (99), 95 (88), 81 (100), 67 (22), 55 (23). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.90; H, 9.70.

4.2.2. (6*RS*,7*SR*)-7-Hydroxy-α-dihydroionone 14. An aluminum amalgam (freshly prepared from 25 g of aluminum foil) was added portionwise to a stirred solution of epoxide **13** (12 g, 57.7 mmol), THF (90 ml), water (30 ml), and ethanol (30 ml) at 0 °C. The reaction was allowed to proceed for 2 h at 0 °C. Cooling was then removed and the stirring prolonged until no more starting material was detected by TLC analysis (1 h). The mixture was diluted with ether (250 ml), filtered, and the filtrate then washed with ether (100 ml). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was submitted to chromatography (eluting from hexane to hexane/Et_2O 7:3) and the obtained **14** (11.5 g) was further purified by crystallization from hexane to afford pure (6*RS*,7*SR*)-7-hydroxy-α-dihydroionone **14** (10.6 g, 87% yield, 98% chemical purity, up to 99% de (GC)) as colorless crystals: mp 67–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (br s, 1H), 4.34 (dq, $J = 3$, 9.6 Hz, 1H), 2.94 (d, $J = 3$ Hz, 1H), 2.56 (ddd, $J = 3$, 9.6, 17.8 Hz, 2H), 2.17 (s, 3H), 2.05–1.95 (m, 2H), 1.80–1.75 (m, 4H), 1.41–1.30 (m, 1H), 1.22–1.13 (m, 1H), 1.02 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz) δ 210.3, 133.3, 122.7, 68.1, 54.5, 48.5, 32.1, 31.4, 30.8, 28.5, 28.2, 25.6, 22.9. IR (Nujul, cm^{-1}) 3435, 1709, 1167, 1063, 815. MS (EI) m/z (rel intensity) 192 (M^+-H_2O, 2), 177 (1), 152 (3), 136 (2), 134 (2), 123 (15), 121 (14), 109 (38), 93 (21), 91 (22), 87 (34), 81 (43), 67 (18), 55 (12), 43 (100). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.30; H, 10.55.

4.2.3. (6*RS*,7*SR*,9*RS*)-7-Hydroxy-α-dihydroionol 11. Tetramethylammonium triacetoxyborohydride (15 g, 57 mmol) was stirred at rt for 30 min in anhydrous acetonitrile (20 ml) and acetic acid (20 ml). The solution obtained was cooled to −20 °C and hydroxyketone **14** (3 g, 14.3 mmol) in anhydrous acetonitrile (10 ml) added dropwise. The reaction was stirred at −10 °C until no more starting material was detected by TLC analysis (15 h), then quenched with 1 M aqueous sodium potassium tartrate (80 ml). The mixture was diluted with CH_2Cl_2 (150 ml) and the aqueous layer extracted again with CH_2Cl_2 (2×100 ml). The combined organic phases were washed with satd $NaHCO_3$ (50 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The GC analysis of the residue (2.95 g) indicated a 93:7 ratio of isomeric diols. The mixture was separated by chromatography (eluting from hexane/AcOEt 9:1 to hexane/AcOEt 1:1). The first-eluted fractions afforded diol **15** contaminated with diol **11** as a colorless oil (0.25 g, 20% de (GC)). The last-eluted fractions gave pure diol **11** (2.65 g, 87% yield, 97% chemical purity, 99% de (GC)) as a colorless oil that crystallized on standing: mp 63–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (br s, 1H), 4.27 (dt, $J = 2.4$, 10.8 Hz, 1H), 4.13–4.04 (m, 1H), 2.80 (br s, 1H), 2.70 (br s, 1H), 2.01–1.90 (m, 2H), 1.78–1.75 (m, 3H), 1.73–1.62 (m, 2H), 1.47–1.35 (m, 2H), 1.22 (d, $J = 6.4$ Hz, 3H), 1.16–1.07 (m, 1H), 1.01 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz) δ 133.3, 122.5, 69.1, 65.9, 56.0, 42.3, 32.2, 31.5, 28.6, 28.6, 25.6, 23.1, 22.8. IR (Nujul, cm^{-1}) 3372, 1378, 1363, 1131, 1063, 818. MS (EI) m/z (rel intensity) 194 (M^+-H_2O, 3), 179 (1), 161 (2), 153 (1), 135 (2), 124 (38), 109 (100), 93 (8), 89 (11), 81 (15), 71 (11), 68 (16), 55 (4). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.40; H, 11.45.

4.2.4. (6*RS*,7*SR*,9*RS*)-7-Hydroxy-γ-dihydroionol 12. A sample of diol **11** (1.4 g, 6.6 mmol) was dissolved in pyridine (15 ml) and acetic anhydride (15 ml) and set aside at rt until the complete formation of diacetate **16** (24 h). The reaction was concentrated under reduced pressure and the residue dissolved in a mixture of isopropanol (80 ml) and xylene (20 ml). The resulting solution was poured in a quartz vessel under a static atmosphere of nitrogen and irradiated with twelve 8-W high-pressure Hg lamps. The reaction was monitored by NMR analysis and the irradiation interrupted until compound **16** became less than 5% of the mixture (6 days). The solution was then concentrated under reduced pressure to afford an oil that was treated with a solution of KOH (2 g, 35.6 mmol) in methanol (30 cm^3), stirring at rt until no more starting acetate was detected by TLC analysis. The mixture was diluted with water (80 cm^3) and extracted with diethyl ether (3×100 cm^3). The combined organic phases were washed with 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 afford **12** (1.04 g, 90% de) that was further purified by crystallization from hexane to give diol **12** as a single isomer (0.9 g, 64% yield, 98% chemical purity, 99% de); mp 98–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (t, $J = 2.1$ Hz, 1H), 4.64 (s, 1H), 4.27–4.10 (m, 2H), 2.29 (br s, 2H), 2.12 (dm, $J = 13.3$ Hz, 1H), 1.95 (d, $J = 8.0$ Hz, 1H), 1.83–1.70 (m, 1H), 1.65–1.43 (m, 5H), 1.31–1.19 (m, 1H), 1.21 (d, $J = 6.4$ Hz, 3H), 1.11 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz) δ 148.2, 111.9, 67.6, 65.3, 60.5, 43.1, 35.2, 34.5, 32.8, 29.7, 28.5, 23.5, 23.1. IR (nujol, cm^{-1}) 3291, 1646, 1377, 1135, 1058, 1031, 889, 867, 829. MS (EI) m/z (rel intensity) 194 (M^+-H_2O, 1), 179 (2), 161 (3), 153 (2), 150 (2), 135 (4), 124 (21), 109 (100), 95 (6), 93 (5), 89 (7), 81 (14), 69 (13), 55 (5). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.40; H, 11.40.

4.3. Lipase-mediated resolution of racemic substrates

4.3.1. Resolution of (6*RS*,7*SR*,9*RS*)-7-hydroxy-α-dihydroionol 11. A mixture of (±)-**11** (2.2 g, 10.4 mmol), lipase PS (2 g), vinyl acetate (15 ml), and *t*-BuOMe (50 ml) was stirred at rt for 6 days. After filtration and evaporation of the filtrate, the residue was chromatographed (hexane/AcOEt 8:2). The first-eluted fractions afforded (−)-(6*S*,7*R*,9*S*)-7-hydroxy-α-dihydroionol acetate **18** as a colorless

oil (1.17 g, mmol; 44%; 98% chemical purity, 99% de (GC), ee 99% (chiral GC)); $[\alpha]_D^{20} = -122.8$ (*c* 2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.45 (br s, 1H), 5.22–5.10 (m, 1H), 3.91–3.79 (m, 1H), 2.56 (br s, 1H), 2.05 (s, 3H), 2.03–1.95 (m, 2H), 1.80–1.75 (m, 3H), 1.63–1.53 (m, 2H), 1.49–1.39 (m, 1H), 1.26 (d, $J = 6.4$ Hz, 3H), 1.19–1.10 (m, 1H), 0.99 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz) δ 171.5, 133.2, 122.5, 69.0, 68.1, 55.2, 42.0, 32.0, 31.5, 28.5, 28.5, 25.5, 22.8, 21.1, 20.8. IR (film, cm^{-1}) 3505, 1736, 1374, 1247, 1138, 1055, 1037, 1019, 957. MS (EI) *m*/*z* (rel intensity) 236 (M^+-H_2O, 2), 194 (3), 176 (4), 150 (6), 131 (57), 123 (26), 109 (68), 93 (12), 81 (20), 71 (100), 61 (44), 55 (6). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.95; H, 10.25. The last-eluted fractions gave (+)-(6*R*,7*S*,9*R*)-7-hydroxy-α-dihydroionol **11** as a colorless oil that crystallized on standing (1.05 g, mmol; 48%; 98% chemical purity, 99% de (GC), ee 94% (chiral GC)); mp 62–63 °C; $[\alpha]_D^{20} = +160.5$ (*c* 2, $CHCl_3$). IR, ^1H NMR, MS: in accordance with that of (±)-(6*RS*,7*SR*,9*RS*)-7-hydroxy-α-dihydroionol **11**.

4.3.2. Resolution of (6*RS*,7*SR*,9*RS*)-7-hydroxy-γ-dihydroionol 12. A mixture of (±)-**12** (1.2 g, 5.7 mmol), lipase PS (1 g), vinyl acetate (10 ml), and *t*-BuOMe (40 ml) was stirred at rt for 4 days. After filtration and evaporation of the filtrate, the residue was chromatographed (hexane/AcOEt 8:2). The first-eluted fractions afforded (+)-(6*S*,7*R*,9*S*)-7-hydroxy-γ-dihydroionol acetate **20** as a colorless oil that crystallized upon standing (0.71 g, mmol; 49%; 98% chemical purity, 99% de (GC), ee 99% (chiral GC)); mp 70–71 °C; $[\alpha]_D^{20} = +25.8$ (*c* 2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.22–5.13 (m, 1H), 4.78 (t, $J = 2.2$ Hz, 1H), 4.63 (s, 1H), 3.79–3.72 (m, 1H), 2.58 (d, $J = 5.2$ Hz, 1H), 2.13 (dm, $J = 13.4$ Hz, 1H), 2.08 (s, 3H), 1.87 (d, $J = 7.9$ Hz, 1H), 1.79–1.67 (m, 1H), 1.63–1.46 (m, 4H), 1.41 (ddd, $J = 2.4$, 10.8, 14.6 Hz, 1H), 1.29–1.21 (m, 1H), 1.25 (d, $J = 6.4$ Hz, 3H), 1.07 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz) δ 171.7, 148.0, 112.0, 68.6, 65.8, 60.1, 43.1, 35.4, 34.4, 32.9, 29.6, 28.4, 23.0, 21.2, 20.9. IR (film, cm^{-1}) 3492, 3063, 1720, 1645, 1440, 1373, 1276, 1218, 1132, 1055, 1020, 889, 808. MS (EI) *m*/*z* (rel intensity) 236 (M^+-H_2O, 1), 194 (M^+−AcOH, 2), 179 (5), 161 (7), 151 (6), 131 (59), 124 (13), 109 (100), 93 (13), 81 (20), 71 (84), 61 (33), 55 (9). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.70; H, 10.30. The last-eluted fractions gave (−)-(6*R*,7*S*,9*R*)-7-hydroxy-γ-dihydroionol **12** as a white crystals (0.52 g, 43%; 98% chemical purity, 99% de (GC), ee 98% (chiral GC)); mp 123–124 °C; $[\alpha]_D^{20} = -8.6$ (*c* 2, $CHCl_3$). IR, ^1H NMR, MS: in accordance with that of (±)-(6*RS*,7*SR*,9*RS*)-7-hydroxy-γ-dihydroionol **12**.

4.4. General procedure for regioselective acetylation of diols 11 and 12

Acetic anhydride (0.48 ml, 5.1 mmol) was added to a stirred solution of diol **11** or **12** (0.9 g, 4.2 mmol) in pyridine (5 ml) and CH_2Cl_2 (10 ml) at rt. After 24 h, water (0.1 ml) was added and the mixture concentrated under reduced pressure. The residue was purified by chromatography (eluting from hexane/AcOEt 9:1 to hexane/AcOEt 1:1).

4.4.1. Regioselective acetylation of diols 11. Acetylation of (+)-**11** (0.9 g, 4.2 mmol) according to general procedure gave three fractions. The first-eluted fraction afford diacetate (+)-**16** (0.3 g, 24%) as a colorless oil: $[\alpha]_D^{20} = +148.8$ (*c* 2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (br s, 1H), 5.32 (dm, $J = 9.4$ Hz, 1H), 4.95–4.86 (m, 1H), 2.08–1.96 (m, 1H), 2.01 (s, 3H), 2.01 (s, 3H), 1.81 (br s, 1H), 1.75–1.70 (m, 3H), 1.67–1.59 (m, 2H), 1.47–1.35 (m, 1H), 1.30–1.15 (m, 2H), 1.21 (d, $J = 6.4$ Hz, 3H), 1.11 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz) δ 170.6, 170.3, 131.8, 123.6, 71.0, 67.6, 52.4, 38.2, 31.9, 31.8, 28.7, 28.0, 25.1, 22.7, 21.3, 21.1, 20.6. IR (film, cm^{-1}) 1738, 1456, 1437, 1372, 1245, 1096, 1020, 957, 827. MS (EI) *m*/*z* (rel intensity) 237 (1), 236 (M^+−AcOH, 5), 193 (1), 176 (85), 172 (30), 161 (49), 147 (6), 131 (100), 123 (59), 113 (75), 105 (16), 93 (18), 81 (22), 71 (73), 61 (19), 55 (7). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 69.00; H, 9.55. The second eluted fractions afforded (+)-7-hydroxy-α-dihydroionol acetate **18** (0.55 g, 51%) as a colorless oil: $[\alpha]_D^{20} = +111.5$ (*c* 2, $CHCl_3$). ^1H NMR, MS: in accordance with that of (−)-7-hydroxy-α-dihydroionol acetate **18**. The last-eluted fraction afforded starting diol (+)-**11** (0.15 g, 17%).

4.4.2. Regioselective acetylation of 12. Acetylation of (−)-**12** (0.6 g, 2.8 mmol) according to the general procedure gave three fractions. The first-eluted fractions afforded (+)-diacetate **17** (45 mg, 5%) as a colorless oil: $[\alpha]_D^{20} = +5.8$ (*c* 2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (ddd, $J = 2.6$, 8.4, 10.2 Hz, 1H), 4.84 (t, $J = 2.0$ Hz, 1H), 4.83–4.73 (m, 1H), 4.68 (s, 1H), 2.17 (dm, $J = 13$ Hz, 1H), 2.10 (d, $J = 8.4$ Hz, 1H), 2.03 (s, 3H), 1.99 (s, 3H), 1.91–1.80 (m, 1H), 1.82 (ddd, $J = 2.6$, 10.2, 15.1 Hz, 1H), 1.66–1.46 (m, 4H), 1.31–1.17 (m, 1H), 1.18 (d, $J = 6.2$ Hz, 3H), 0.91 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz) δ 170.6, 170.4, 147.3, 112.7, 68.9, 66.8, 57.3, 40.0, 35.2, 32.6, 28.4, 28.1, 23.0, 21.4, 21.2, 20.6, 20.6. IR (film, cm^{-1}) 1741, 1647, 1451, 1372, 1244, 1144, 1091, 1021, 959, 894. MS (EI) *m*/*z* (rel intensity) 236 (M^+−AcOH, 4), 221 (2), 194 (12), 176 (56), 173 (53), 161 (67), 151 (22), 133 (78), 131 (100), 123 (21), 113 (89), 105 (25), 93 (33), 81 (25), 71 (69), 69 (33), 61 (21), 55 (14). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 70.00; H, 9.55. The second eluted fractions afforded (−)-7-hydroxy-γ-dihydroionol acetate **20** (0.56 g, 78%); mp 69–71 °C; $[\alpha]_D^{20} = -24.1$ (*c* 2, $CHCl_3$). ^1H NMR, MS: in accordance with that of (+)-7-hydroxy-γ-dihydroionol acetate **20**. The last-eluted fraction afforded starting diol (−)-**12** (75 mg, 12%).

4.5. General procedure for oxidation of stereoisomers of 7-hydroxy-α-dihydroionol acetate and 7-hydroxy-γ-dihydroionol acetate

Dess–Martin periodinane (1.45 g, 3.4 mmol) was added to a stirred solution of **18** or **20** (0.75 g, 2.9 mmol) in CH_2Cl_2 (40 ml) at rt. After 1 h the reaction was quenched by the addition of ether (100 ml), satd aq $NaHCO_3$ (50 ml), and satd aq $Na_2S_2O_3$ (50 ml). Stirring was continued until the clear phases were obtained (15 min). The aq layer was extracted with ether and the combined organic phases washed with brine, dried over Na_2SO_4, and concentrated under

reduced pressure. The residue was purified by chromatography (eluting with hexane/AcOEt 9:1).

4.5.1. (−)-(6*S*,9*S*)-7-Oxy-α-dihydroionol acetate 19. Oxidation of (−)-**18** (0.75 g, 2.9 mmol) according to the general procedure afforded (−)-(6*S*,9*S*)-7-oxy-α-dihydroionol acetate **19** (0.71 g, 95%) as a colorless oil. $[\alpha]_D^{20} = -378.4$ (*c* 2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (br s, 1H), 5.34–5.25 (m, 1H), 2.89 (dd, $J = 6.9$, 17.7 Hz, 1H), 2.72 (s, 1H), 2.62 (dd, $J = 5.9$, 17.7 Hz, 1H), 2.18–1.96 (m, 2H), 1.98 (s, 3H), 1.78–1.67 (m, 1H), 1.61–1.58 (m, 3H), 1.26 (d, $J = 6.4$ Hz, 3H), 1.21–1.13 (m, 1H), 0.93 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz) δ 210.0, 170.0, 129.8, 123.7, 66.9, 63.8, 50.8, 32.3, 30.7, 27.7, 27.7, 23.2, 22.5, 21.1, 19.8. IR (film, cm^{-1}) 1741, 1713, 1451, 1367, 1243, 1140, 1048, 1021, 958. MS (EI) *m*/*z* (rel intensity) 252 (M^+, 1), 193 (6), 192 (M^+−AcOH, 45), 177 (4), 149 (2), 135 (4), 123 (35), 107 (12), 91 (7), 81 (18), 69 (100), 55 (3). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.60.

4.5.2. (+)-(6*R*,9*R*)-7-Oxy-α-dihydroionol acetate (+)-19. Oxidation of (+)-**18** (0.4 g, 1.6 mmol) according to the general procedure afforded (+)-(6*R*,9*R*)-7-oxy-α-dihydroionol acetate (+)-**19** (0.37 g, 93%) as a colorless oil. $[\alpha]_D^{20} = +346.8$ (*c* = 2, $CHCl_3$). IR, ^{1}H NMR, MS: in accordance with that of (−)-(6*S*,9*S*)-7-oxy-α-dihydroionol **19**.

4.5.3. (+)-(6*S*,9*S*)-7-Oxy-γ-dihydroionol acetate 21. Oxidation of (+)-**20** (0.7 g, 2.8 mmol) according to general procedure afforded (+)-(6*S*,9*S*)-7-oxy-γ-dihydroionol acetate **21** (0.66 g, 95%) as a colorless oil. $[\alpha]_D^{20} = +287.4$ (*c* = 2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (sext, $J = 6.3$ Hz, 1H), 4.89 (s, 1H), 4.74 (s, 1H), 3.03 (s, 1H), 2.92 (dd, $J = 6.8$, 16.8 Hz, 1H), 2.49 (dd, $J = 6.2$, 16.8 Hz, 1H), 2.23–2.12 (m, 1H), 2.08 (dt, $J = 4.5$, 13.5 Hz, 1H), 2.02–1.92 (m, 1H), 1.97 (s, 3H), 1.68–1.58 (m, 1H), 1.55–1.41 (m, 1H), 1.25 (d, $J = 6.2$ Hz, 3H), 1.18 (dt, $J = 4.5$, 13.5 Hz, 1H), 0.95 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz) δ 207.1, 170.0, 144.5, 112.1, 66.8, 66.4, 49.6, 35.3, 35.0, 31.6, 27.6, 26.6, 22.9, 21.0, 19.8. IR (film, cm^{-1}) 1741, 1712, 1643, 1449, 1366, 1242, 1138, 1053, 1038, 959, 895. MS (EI) *m*/*z* (rel intensity) 252 (M^+, 1), 193 (6), 192 (M^+−AcOH, 40), 177 (12), 164 (2), 149 (6), 135 (14), 129 (13), 123 (22), 107 (13), 93 (8), 81 (16), 69 (100), 55 (6). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.60.

4.5.4. (−)-(6*R*,9*R*)-7-Oxy-γ-dihydroionol acetate 21. Oxidation of (−)-**20** (0.45 g, 1.8 mmol) according to the general procedure afforded (−)-(6*R*,9*R*)-7-oxy-γ-dihydroionol acetate **21** (0.42 g, 94%) as a colorless oil. $[\alpha]_D^{20} = -287.2$ (*c* 2, $CHCl_3$). IR, ^{1}H NMR, MS: in accordance with that of (+)-(6*RS*,9*RS*)-7-oxy-γ-dihydroionol **21**.

4.6. General procedure for base-mediated elimination of 7-oxy-α-dihydroionol acetate and 7-oxy-γ-dihydroionol acetate

DBU (0.7 ml, 4.7 mmol) was added to a solution of acetate **19** or **21** (0.62 g, 2.5 mmol) in CH_2Cl_2 (40 ml) at rt. The mixture was stirred until no more starting acetate was detected by TLC analysis (3 h) then water (50 ml), ether (100 ml), and 5% aq HCl (30 ml) were added. The aq layer was extracted with ether (50 ml) and the combined organic phases were washed with aq $NaHCO_3$ (50 ml), water, and brine. The solution obtained was dried over Na_2SO_4 and concentrated by distillation of the solvent at atmospherical pressure. The residue was purified by chromatography (eluting with hexane/ether 95:5) and bulb-to-bulb distillation (bp 95–100 °C/0.1 mmHg).

4.6.1. (−)-α-Damascone 1. Base-mediated elimination of acetate (−)-**19** (0.62 g, 2.5 mmol) according to the general procedure afforded (−)-α-damascone **1** (0.45 g, 95% yield, 99% chemical purity (GC)) as a colorless oil that crystallized on cooling; mp 20–25 °C; $[\alpha]_D^{20} = -520.5$ (*c* 2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (dq, $J = 6.9$, 15.3 Hz, 1H), 6.31 (dq, $J = 1.7$, 15.3 Hz, 1H), 5.64–5.58 (m, 1H), 2.89 (s, 1H), 2.20–1.99 (m, 2H), 1.89 (dd, $J = 1.7$, 6.9 Hz, 3H), 1.71 (ddd, $J = 6.9$, 10.3, 13.3 Hz, 1H), 1.58–1.54 (m, 3H), 1.17 (ddd, $J = 2.6$, 5.8, 13.3 Hz, 1H), 0.95 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz) δ 202.0, 142.0, 132.2, 130.5, 123.4, 61.3, 32.3, 31.3, 27.9, 27.7, 23.2, 22.6, 18.1. IR (film, cm^{-1}) 1687, 1668, 1625, 1443, 1365, 1318, 1292, 1178, 1082, 972, 824. MS (EI) *m*/*z* (rel intensity) 193 (M^++1, 6), 192 (M^+, 47), 177 (7), 163 (1), 149 (3), 135 (8), 123 (36), 107 (9), 91 (10), 81 (30), 69 (100), 55 (4), 41 (15). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.30; H, 10.50.

4.6.2. (+)-α-Damascone 2. Base-mediated elimination of acetate (+)-**19** (0.3 g, 1.2 mmol) according to the general procedure afforded (+)-α-damascone **2** (0.21 g, 92% yield, 98% chemical purity (GC)) as a colorless oil. $[\alpha]_D^{20} = +489.7$ (*c* 2, $CHCl_3$). IR, ^{1}H NMR, MS: in accordance with that of (−)-α-damascone **1**.

4.6.3. (+)-γ-Damascone 3. Base-mediated elimination of acetate (+)-**21** (0.55 g, 2.2 mmol) according to general procedure afforded (+)-γ-damascone **3** (0.39 g, 93% yield, 98% chemical purity (GC)) as a colorless oil. $[\alpha]_D^{20} = +272.3$ (*c* 2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (dq, $J = 6.9$, 15.6 Hz, 1H), 6.16 (dq, $J = 1.8$, 15.6 Hz, 1H), 4.85 (t, $J = 1.8$ Hz, 1H), 4.69 (s, 1H), 3.21 (s, 1H), 2.32–2.23 (m, 1H), 2.09 (dt, $J = 4.7$, 13.4 Hz, 1H), 1.98 (ddd, $J = 4.4$, 11.3, 13.4 Hz, 1H), 1.86 (dd, $J = 1.8$, 6.9 Hz, 3H), 1.68–1.60 (m, 1H), 1.56–1.45 (m, 1H), 1.20 (dt, $J = 4.7$, 13.4 Hz, 1H), 0.95 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz) δ 199.2, 145.2, 141.3, 132.8, 111.7, 63.8, 35.8, 34.9, 31.9, 27.8, 26.6, 22.9, 17.9. IR (film, cm^{-1}) 3072, 1693, 1668, 1628, 1443, 1364, 1279, 1185, 1124, 1075, 967, 895. MS (EI) *m*/*z* (rel intensity) 193 (M^++1, 4), 192 (M^+, 26), 177 (10), 159 (3), 149 (9), 136 (9), 122 (16), 109 (12), 91 (7), 81 (16), 69 (100), 55 (5), 41 (20). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.35; H, 10.50.

4.6.4. (−)-γ-Damascone 4. Base-mediated elimination of acetate (−)-**21** (0.35 g, 1.4 mmol) according to general procedure afforded (−)-γ-damascone **4** (0.25 g, 94% yield, 99 % chemical purity) as a colorless oil. $[\alpha]_D^{20} = -270.5$ (*c* 2, $CHCl_3$). IR, ^{1}H NMR, MS: in accordance with that of (+)-γ-damascone **3**.

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