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A Simple and Efficient Highly Enantioselective Synthesis of α-Ionone and α-Damascone

Marcella Bovolenta, Francesca Castronovo, Alessandro Vadalà, Giuseppe Zanoni, and Giovanni Vidari*

Dipartimento di Chimica Organica, Università di Pavia, Via Taramelli 10, 27100 Pavia, Italy

vidari@unipv.it

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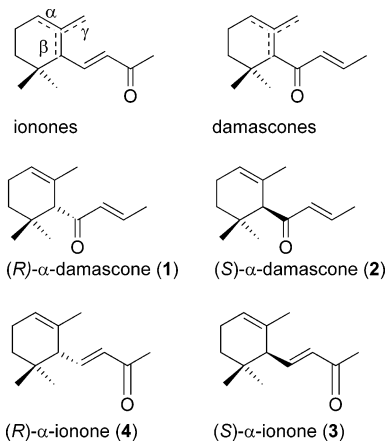
Abstract: An efficient highly enantioselective (ee ≥99%) synthesis of α-ionone and α-damascone is described. Both enantiomers of title compounds were synthesized through two straightforward pathways diverging from enantiopure (*R*)- or (*S*)-α-cyclogeraniol. These versatile building blocks were obtained by regioselective $ZrCl_4$-promoted biomimetic cyclization of (6*S*)- or (6*R*)-(*Z*)-6,7-epoxygeraniol, respectively, followed by deoxygenation of the so formed secondary alcohol. The chiral information was encoded by a highly regioselecive Sharpless asymmetric dihydroxylation of inexpensive geranyl acetate.

Ionones and damascones are established among the most highly valued fragrance constituents as a result of their distinctive fine violet and rose scents.[1,2] Besides their use in the perfumery industry, ionones and damascones are also appreciated synthetic building blocks.[3,4] Both of these C_{13} norterpenoids exist in nature as three distinct regioisomers, which differ in the position of the double bond, and are called the α-, β-, and γ-isomers.



Olfactory evaluation shows that the regioisomeric purity and the absolute stereochemistry of these isomers dramatically determines the fragrance properties, sometimes with amazingly pronounced differences between the notes and the odor thresholds even of the two enantiomers. Furthermore, the endocyclic double bond confers particularly characteristic nuances to the fragrance that can favorably complement the use of other widely used compounds from the same family.

For example, whereas β-damascone is floral-woody, somewhat tobacco-like, α-damascone smells floral-fruity, green, apple-like with a harsh camphoraceous cork-note. This cork-stopper off-note is due to (*R*)-(+)-α-damascone **1**, whereas the (S)-(−)-isomer **2** is linear, clean, and more intense, besides possessing a pleasant wine-like nuance.[3] As to α-ionone, relative sensitivities for the enantiomers were found to diverge widely for different flavorists;[5−8] however, according to recent results collected by Fuganti et al. on almost enantiopure samples, both stereoisomers show similar odor description, (*S*)-(−)-α-ionone **3** being slightly more powerful than the (*R*)-antipode **4**.[9] The odor of (*S*)-(−)-α-ionone is described as floral, woody, with an additional honey aspect.[9] Early enantioselective approaches to α-damascone by Yamada[10] and Ohloff[11] delivered the (*R*)-(+)-enantiomer **1** in poor to modest ee's of 17.5% and 66%, respectively. Later, thanks to an efficient method for the enantioselective protonation of enolates,[12] coupled with a fractional crystallization, Fehr and Galindo achieved both α-damascone enantiomers in a very high ee (>98%).[12−15] Despite its elegance, this approach requires, however, very demanding reaction conditions and is therefore of difficult industrial applicability. From (*R*)- and (*S*)-α-damascone, Fehr then developed a four-step entry to the corresponding α-ionone enantiomers (ee >98%) through an ingenious enone transposition.[8] Highly enantioselective enzyme-based synthesis of useful precursors of damascones and ionones have been published recently. They are exemplified by the preparation of (*S*)-α-damascone **2** (ee ca. 100%) by Mori,[16] as well as of (*R*)-α-ionone **4** (85% ee) by Pfander[17]

* To whom correspondence should be addressed. Tel: +39 0382507322. Fax: +39 0382507323.

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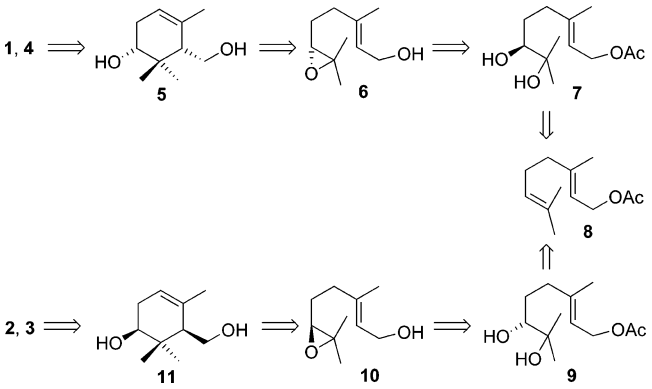
SCHEME 1. Retrosynthetic Analysis of Damascones 1, 2 and Ionones 3, 4

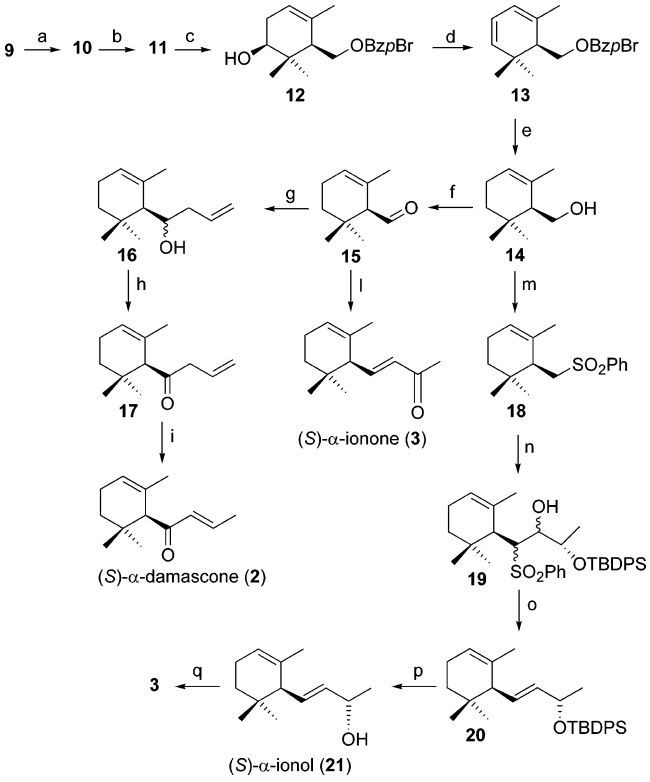


and of **4** (98% ee) and (*S*)-α-ionone **3** (97% ee) by Fuganti et al.[18,19] These achievements, though still quite laborious, compare favorably with the original preparation of α-ionone enantiomers based on a classical resolution through multiple tedious fractional crystallization of (−)-menthyl hydrazone derivatives.[20]

As shown in Scheme 1, our original access to compounds **1**, **4** and **2**, **3** is through the use of diols **5** and **11**, respectively, which we envisaged to obtain in high optical purities by biomimetic cyclization of the corresponding epoxygeraniol antipodes **6** and **10**, respectively. Actually, each of these valuable chiral oxirane intermediates is readily available by selective mesylation of diols **7** and **9**, respectively, followed by exposure to a base (Scheme 2).[21,22] On the other hand, the two diols are smoothly derived from inexpensive (*E*)-geranyl acetate **8** simply by switching the chiral auxiliary used in two separate Sharpless asymmetric dihydroxylation (AD) reactions.[22] The same cheap monoterpene ester **8** would thus furnish 10 of the 13 carbons of the final products **1**−**4**. The synthesis of each enantiomeric pair **1**, **4** and **2**, **3** would then proceed from the same intermediates **5** and **11**, respectively, on the basis of a diverging strategy conceived to install the two isomeric enone appendages. For the sake of conciseness, herein we describe only the synthesis of the enantiomers (*S*)-(−)-α-damascone **2** and (*S*)-(−)-α-ionone **3**, by using diol **9**[21,22] as chiral building block. The opposite series of antipodes was obtained starting from diol **7**[22] via the same synthetic pathway.

Scheme 2 summarizes our synthesis of **2** and **3**. The strategic common intermediate **11** was readily obtained by $ZrCl_4$-promoted cyclization of (*S*)-(−)-geraniol epoxide **10**. As already proven with racemic **10**, the reaction was remarkable as to positional control of the double bond in the product, yielding the monocyclic *endo*-olefin **11** in reproducible reasonable yields (50−55%).[23,24] The structure and stereochemistry of *cis*-diol **11**, resulting from a chairlike conformation of the cyclization transition state, were confirmed by comparison with literature data.[25] As to the ee of diol **11**, it could not be determined directly either by enantioselective HPLC or GC; we assumed it to be identical to that of diol **9**, namely, in the range of 88−94%,[26] since both the preparation of epoxide **10** and the subsequent highly concerted cyclization should occur with complete stereospecificity. The ee of diol **11** could, however, be increased by two successive recrystallizations to constant melting point from hexanes−Et_2O, and the so obtained excellent optical purity was proved by the ee observed for the subsequently produced alcohol **14** (vide

SCHEME 2 [a]



[a] Reagents and conditions: (a) (1) MsCl, Py, CH_2Cl_2, 22 °C; (2) K_2CO_3, MeOH, 0 °C, 80% overall; (b) $ZrCl_4$, CH_2Cl_2, 22 °C, 53% (48% after two recrystallizations to constant mp); (c) *p*-BrC_6H_4COCl, Et_3N, CH_2Cl_2, −40 °C, 84%; (d) (1) MsCl, Et_3N, CH_2Cl_2, 0 °C; (2) DBU, toluene, reflux, 72% overall; (e) (1) H_2, Rh/Al_2O_3, EtOAc, 22 °C; (2) NaOH, MeOH, 22 °C, 78% overall; (f) Dess−Martin periodinane,[31] CH_2Cl_2, 22 °C, 82%; (g) allylBu_3Sn, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 73%; (h) as (f), 88%; (i) DBU, CH_2Cl_2, 22 °C, 86%; (l) $(EtO)_2P(O)CH_2COCH_3$, $Ba(OH)_2{\cdot}8H_2O$, THF/H_2O 40:1, 22 °C, 57% at 13% conversion; (m) (1) PhSSPh, *n*Bu_3P, THF, 0 → 22 °C; (2) 30% H_2O_2, cat. $(NH_4)_2MoO_4$, MeOH, 0 → 22 °C, 71% overall; (n) *n*BuLi, THF, −78 °C, then add (*S*)-2-*tert*-butyldiphenylsilyloxypropanal,[37] THF, −78 °C; (o) 10% Na(Hg), MeOH, Na_2HPO_4, −40 → −20 °C; (p) Bu_4NF, THF, 0 → 22 °C, 71% from **18**; (q) as (f), 89%.

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(24) In addition to diol **11**, the product mixture contained 3−5% of the internal ether, 10−15% of chlorohydrins, and an intractable mixture of unidentified nonpolar compounds. Interestingly, the NMR spectra of chromatographically purified **11** revealed no regioisomeric olefins.
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infra). The latter was envisaged to be the immediate precursor of aldehyde **15**, which was the starting point from where we initially planned to reach the isomeric enones **2** and **3** by two separate routes. Conversion of **11** into **14** required selective deoxygenation of the secondary alcohol. This was readily executed in three uneventful steps. Selective protection of the primary alcohol of **11** as *p*-bromobenzoate **12** was followed by smooth dehydration of the secondary hydroxyl group to yield diene **13**, whose less substituted double bond was readily hydrogenated with complete regioselectivity.[27] Removal of the protective group afforded (*S*)-α-cyclogeraniol **14**,[16] $[\alpha]^{20}_D$ −109 (*c* 0.9, EtOH), ≥99% ee (GC). We preferred this lengthy but very clean procedure to different variants of the Barton-like radical deoxygenation reaction, which is the common protocol employed for the excision of hindered secondary alcohols structurally related to compound **11**.[28−30] Indeed, when the *O*-phenyl thionocarbonate or the imidazolyl thionoformate derivative of compound **12** was exposed to Bu_3SnH and catalytic AIBN, deoxygenation promptly occurred; however, the resulting product was contaminated by inseparable tin residues. Oxidation of (*S*)-α-cyclogeraniol **14** with the Dess−Martin periodinane reagent.[31] readily furnished the stereochemically labile aldehyde (*S*)-α-cyclocitral **15**, identical with the literature.[16b]

The syntheses of (*S*)-α-damascone **2** and (*S*)-(−)-α-ionone **3** were completed by using aldehyde **15** as a common intermediate. Thus, $BF_3{\cdot}Et_2O$-promoted addition[30,32] of allyltributyltin to **15** smoothly afforded (*S*)-iso-α-damascol **16** in 73% yield, as a diastereomeric mixture (undetermined stereochemistry at the carbinol center) in a ratio of 9:1 (GC). Subsequent oxidation of alcohol **16** with the Dess−Martin periodinane reagent[31] gave ketone **17** in 88% yield, which on exposure to a hindered base (DBU) at room temperature underwent complete double bond isomerization, affording the crystalline conjugated ketone (*S*)-α-damascone **2**, $[\alpha]^{20}_D$ −482.6 (*c* 2.2, CH_2Cl_2), in 86% yield. The ee of synthetic (*S*)-**2** was estimated to be ≥99% by enantioselective HPLC analysis, confirming that no appreciable racemization occurred during the elongation of aldehyde **15**.

In the synthesis of our second target, (*S*)-(−)-α-ionone **3**, at first aldehyde **15** was submitted to the barium hydroxide promoted modification of the Horner−Wadsworth−Emmons (HWE) olefination reaction, according to the procedure previously reported by Monti.[33] Indeed, this has been suggested to be the method of choice for epimerizable, base-sensitive aldehydes.[34] The procedure applied to aldehyde **15** furnished (*S*)-(−)-α-ionone **3** very sluggishly, resulting in only 13% conversion after 17 h. Moreover, the optical purity of the product (95% ee) indicated a slight racemization due to the prolonged exposure to basic condition. Therefore, an unprecedented methodology for the construction of the enone moiety of α-ionone was investigated. Indeed, we anticipated that a highly stereoselective approach might be based upon a Julia−Lythgoe olefination,[35,36] in which the configurationally stable sulfone **18** and (*S*)-2-*tert*-butyldiphenylsilyloxypropanal[37] were the suitable starting compounds. Actually, the unique stereochemical features of the Julia−Lythgoe reaction not only would allow the absolute configuration of sulfone **18** to be preserved but also would give rise to the required stereodefined *E* double bond.[38] In the event, (*S*)-α-cyclogeraniol **14** was converted into the corresponding sulfide under Mitsunobu condition,[39] and the sulfide chemoselectively oxidized to sulfone **18** with H_2O_2 in the presence of a catalytic amount of $(NH_4)_2MoO_4$ in MeOH.[40] Under these conditions, the double bond was not affected by the oxidant and the expected product **18** was obtained in 71% yield. Subsequent condensation of sulfone **18** with the cited 2-hydroxypropanal derivative was carried out under our recently reported protocol,[41] which requires no Lewis acid activation, contrary to the original procedure developed by Wicha for the coupling of lithiated sulfones with protected hydroxy-aldehydes.[42] Thus, reaction of the lithium salt of **18** with the required aldehyde afforded the desired hydroxysulfone **19** as a mixture of stereoisomers, which were immediately exposed to 10% sodium amalgam to deliver the desired TBDPS protected (6S,9S)-(−)-α-ionol **20** in about 80% yield. Synthesis of enantiomerically pure (ee ≥99% by GC analysis) (*S*)-(−)-α-ionone **3**, $[\alpha]^{20}_D$ −414.7 (*c* 0.7, CH_2Cl_2), was completed uneventfully by hydroxyl group deprotection, followed by oxidation with the Dess−Martin periodinane reagent.[31]

In conclusion, the extremely valuable aroma constituents (*S*)-(−)-α-damascone **2** and (*S*)-(−)-α-ionone **3** have been obtained enantiomerically pure by following two simple synthetic pathways diverging from (*S*)-α-cyclogeraniol **14**, which was readily prepared from inexpensive geranyl acetate **8**. Of general interest in our approach are the $ZrCl_4$-promoted stereospecific and regioselective biomimetic cyclization of (*S*)-(−)-geraniol epoxide **10** to diol **11** and the installation of the enone moiety of compound **3** through a stereoselective Julia−Lythgoe olefination.

(27) When the primary hydroxyl group of diol **11** was protected as a nonaromatic ester, i.e., as a pivalate, hydrogenation of the diene moiety proceeded less cleanly and regioselectively, affording a mixture of dihydro- and tetrahydroderivatives. Presumably, the trisubstituted double bond of **13** was deactivated by π-stacking interaction with the benzoate group.

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Supporting Information Available: Experimental details for general procedures and for the preparation and spectral data of compounds **2**, **3**, **11**−**18**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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