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A General Enantioselective Approach to Jasmonoid Fragrances: Synthesis of (+)-(1*R*,2*S*)-Methyl Dihydrojasmonate and (+)-(1*R*,2*S*)-Magnolione

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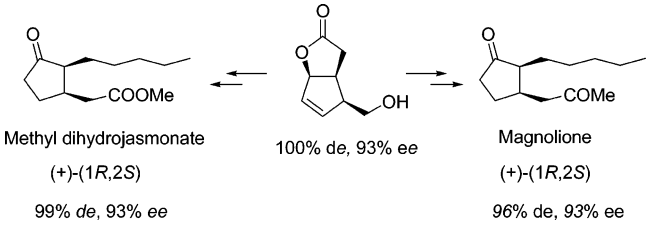

Methyl dihydrojasmonate **1** and magnolione **3** are of both academic and industrial interest. In this paper, we describe a flexible, high-yielding route to diastereomerically pure (+)-*cis*-(1*R*,2*S*)-methyl dihydrojasmonate **1** and the first synthesis of (+)-*cis*-(1*R*,2*S*)-magnolione **3**, both with enantiomeric excesses up to 93%. The two syntheses diverged from the same advanced intermediate **5**, readily available from the enantioenriched hydroxymethyl δ-lactone (−)-(3a*S*,4*S*,-6a*R*)-**6**. The olfactory properties of (1*R*,2*S*)-**1** and (1*R*,2*S*)-**3** are reported.

Methyl dihydrojasmonate is largely used in the perfume industry owing to its pleasant olfactory properties. It was first synthesized during the structure elucidation of methyl jasmonate in 1962,[1] before its discovery as a biologically interesting compound.[2] Since the early 1970s, Firmenich has commercialized the racemic, near-equilibrium mixture of the *cis* (**1**) and *trans* (**2**) stereoisomers (Figure 1) under the trade name of Hedione ((±)-**1** + (±)-**2**, ca. 10:90).[3]

In fact, Hedione is endowed with a transparent, floral-jasmine warm note with lemon scent characters, and for these reasons, it is now a greatly appreciated ingredient of high-selling perfumes, toilette, and laundry products.[4] As to the olfactory properties of individual stereoisomers,[5] *cis*-methyl dihydrojasmonates **1** are about 70 times more powerful than the *trans* isomers **2**, and the scent of the

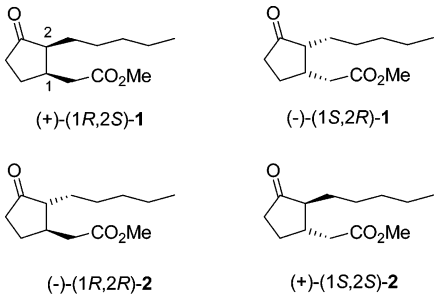

FIGURE 1. Stereoisomers of methyl dihydrojasmonate.

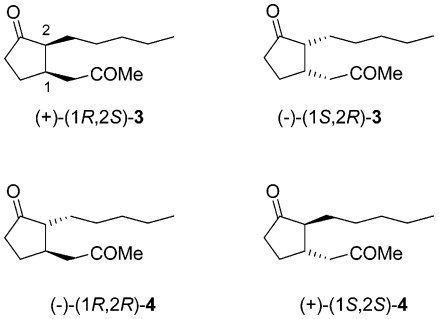

FIGURE 2. Stereoisomers of magnolione.

cis-isomers is almost exclusively due to the (+)-(1*R*,2*S*)-enantiomer, while (−)-(1*S*,2*R*)-**1** is much weaker and more earthy than floral in smell.[4c] (+)-(1*R*,2S)-**1** exhibited an odor threshold concentration of only 0.028 ng/L of air, whereas the value for the corresponding *trans*-isomer was determined to be 1.85 ng/L of air.[6]

These factors have made the diastereo- and enantioselective synthesis of (+)-(1*R*,2*S*)-**1** a long-sought synthetic goal (Figure 2).[4c] Enantiomerically enriched (ca. 90% ee) (+)-(1*R*,2*S*)-methyl dihydrojasmonate was recently obtained at Firmenich by a high-pressure catalytic asymmetric hydrogenation of the corresponding 1,2-dehydro derivative and introduced to perfumery as Paradisone.[7] An alternative approach to (+)-**1** (92% pure; 100% ee; 96% de), involving a Lewis acid promoted stereocontrolled rearrangement of an epoxide to cyclopentanone, was also developed at Firmenich.[8]

The structurally and organoleptically related diketone magnolione was first synthesized as a mixture of the four stereoisomers **3** and **4** in 1963, in a study of the structure−odor relationship of methyl jasmonates.[9] However, the synthesized material was contaminated by an unpleasant garlicky note and thus not suitable to be used in perfumery. Another synthetic route to magnolione was later patented by Givaudan, but it was neither enantio-

(1) For a comprehensive early review, see: Demole, E. In *Fragrance Chemistry*; Theimer, E. T., Ed.; Academic Press: New York, 1982; p 349.

(2) (a) Bauer, K.; Grabe, D.; Surburg, H. *Common Fragrance and Flavour Materials*, Wiley-VCH: Weinheim, 2001; p 94. (b) Reference 7 cited in ref 7a.

(3) Firmenich, A.; Firmenich, R.; Firmenich, G.; Firmenich, R. E. GB Patent 907431, 1962.

(4) (a) Ohloff, G. *Scent and Fragrances*; Springer, Berlin, 1994; pp 151−154. (b) Fráter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* **1998**, *54*, 7633. (c) Kraft, P.; Bajgrowicz, J. A.; Denis, C.; Fráter, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 2980.

(5) (a) Rautenstrauch, V.;. Riedhauser, J.-J (Firmenich SA) WO 9600206, 1996; *Chem. Abstr.* **1996**, *124*, 232126c. (b) Werkhoff, P.; Krammer, G.; Brennecke, S.; Roloff, M.; Bertram, H.-J. *Food Rev. Intern.* **2002**, *18*, 103.

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(7) (a) Dobbs, D. A.; Vanhessche, K. P. M.; Brazi, E.; Rautenstrauch, V.; Lenoir, J. Y.; Genêt, J.-P.; Wiles, J.; Bergens, S. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1992. (b) Genêt, J.-P. *Acc. Chem. Res.* **2003**, *36*, 908.

(8) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 569.

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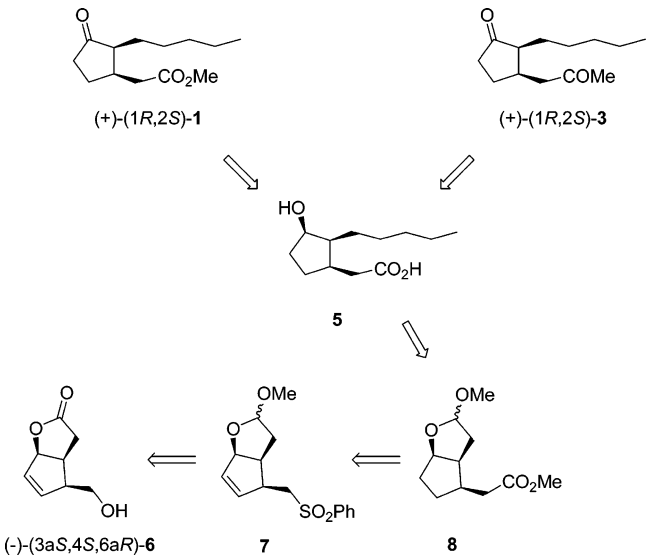
SCHEME 1. Retrosynthetic Analysis of (+)-(1*R*,2*S*)-1 and (+)-(1*R*,2*S*)-3



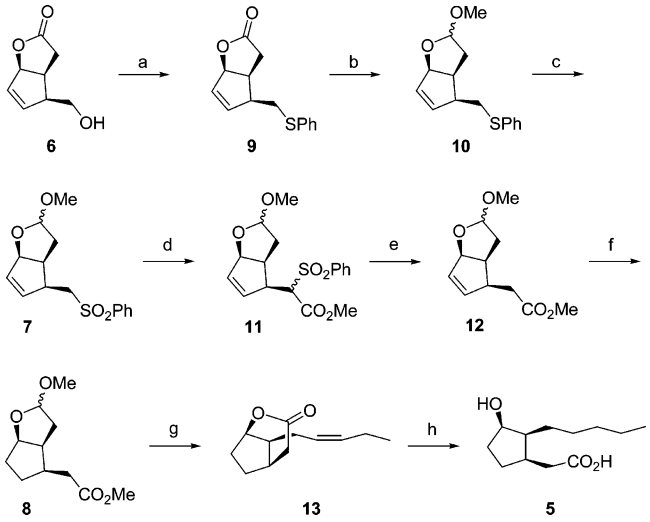
nor diastereoselective.[10] The obtained magnolione exhibited, however, a soft, delicate magnolia fragrance, with an increased odor strength, a better stability, and a more floral note than methyl dihydrojasmonate.[4c]

The so-called garlicky-free magnolione is now a precious ingredient in several perfumes and odorant compositions.[4c] The first synthesis of both enantiomers of *trans*-magnolione **4** was achieved by Rosini and collaborators very recently, allowing the authors to establish the absolute configuration of these two stereoisomers;[11] the highest enantiomeric excess was, however, only 76%, impairing the odor tests.

We decided to embark upon the stereoselective synthesis of *cis*-(1*R*,2*S*)-**3**, which, notwithstanding lack of experimental evidence, we presumed to exhibit superior olfactory properties than the other stereoisomers due to the close structural analogy with methyl dihydrojasmonate (1*R*,2*S*)-**1**.

A recurrent synthetic challenge in the construction of 1,2-disubstituted cyclopentanone derivatives of this kind is the installation of the two *cis*-oriented side chains, which are prone to undergo a ready acid- and base-catalyzed epimerization to the thermodynamically more stable *trans*-configuration. According to our strategy (Scheme 1), which significantly differs from previous syntheses, we envisaged to deliver both compounds **1** and **3** from the same advanced intermediate **5**. A likely starting material for the hydroxy acid **5** was the enantioenriched hydroxymethyl δ-lactone (−)-(3a*S*,4*S*,6a*R*)-**6**, which was available on a multigram scale[12] and already contained two differently functionalized 1,2-*cis*-oriented alkyl substituents; furthermore, to minimize epimerization, we considered it advantageous to delay unveiling of the stereochemically fragile cyclopentanone moiety until the final step.

SCHEME 2 [a]



[a] Key: (a) $(PhS)_2$, *n*-Bu_3P, THF, 0 °C, 92%; (b) DIBAL-H, DCM, −78 °C, followed by MeOH, PTSA, −20 °C, 94%; (c) $(NH_4)_2MoO_4$, H_2O_2, MeOH, rt, 98%; (d) *n*BuLi, THF, −78 °C, followed by ClC(O)OMe, −50 °C; (e) Mg, MeOH, rt, 85% overall; (f) H_2, 5% Rh on Al_2O_3, MeOH, rt, 99.5%; (g) (i) 0.3 N HCl, THF/H_2O, rt, 87%, (ii) propyltriphenylphosphonium bromide, KHMDS, PhMe, rt, 95%; (h) (i) H_2, 5% Rh on Al_2O_3, EtOAc, 99%, (ii) 2N KOH, MeOH/H_2O, rt, followed by 1 N HCl to pH = 7, 100%.

Conversion of lactone **6** into acid **5** seemed to be feasible through homologation of the homoallylic alcohol, followed by a standard Wittig reaction[13] to install the side chain at C-2. On the other hand, **5** appeared to be the immediate precursor of methyl dihydrojasmonate **1**, while the same acid was envisaged to afford the acetyl group of (1*R*,2*S*)-**3** by alkylation with methyllithium.

At first, one-carbon homologation of the hydroxymethyl group of **6** was tried by nucleophilic substitution of the corresponding iodide either with a cyanide or an 1,3-dithiane anion; however, we met with no success, owing to a considerable formation of elimination products. We then decided to reverse the reactivity of **6** by preparing the corresponding protected sulfone **7** which was expected to open the way to the carbomethoxy derivative **8**, an advanced precursor of acid **5** (Scheme 1).

According to this plan, protected sulfide **10**, the direct precursor of sulfone **7**, was readily prepared by a three-step sequence following the reaction conditions depicted in Scheme 2. Thus, lactone **6** was first treated with diphenyl disulfide in the presence of tributylphosphine to give the corresponding sulfide **9** in 92% yield.[14] Reduction of the lactone moiety with DIBAL-H afforded the corresponding lactol in 99% yield, which was immediately protected as methyl acetal **10** (MeOH, PTSA, −20 °C, 95%). The synthesis proceeded with the chemoselective oxidation of sulfide **10** to sulfone **7**, which was carried out with hydrogen peroxide in the presence of a catalytic amount of $(NH_4)_2MoO_4$ in methanol (Scheme

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2).[15] Under these conditions, the double bond was not affected by the oxidant, and the expected sulfone was obtained in a gratifying 98% yield. The lithium anion of sulfone **7** was then generated at −78 °C (*n*-BuLi, THF) and exposed to methyl chloroformate at −55 °C[16] to afford the corresponding methoxycarbonyl derivative **11** in an almost quantitative yield. Desulfonation of compound **11** with magnesium in MeOH delivered methyl ester **12** uneventfully in 85% overall yield.[17]

The double bond of cyclopentene **12** was hydrogenated in a quantitative yield, without affecting the allylic ether, by using rhodium on activated alumina in methanol under an atmosphere of H_2. Standard olefination of the masked aldehyde function released from acetal **8** (0.3 N HCl, THF−H_2O, rt, 87%) with the nonstabilized Wittig reagent generated from propyltriphenylphosphonium bromide and KHMDS in toluene smoothly led to the corresponding (*Z*)-olefin **13** in 95% isolated yield. The *Z*/*E* selectivity of this Wittig reaction, established by ^{1}H NMR and GC analysis, was 92:8, in agreement with literature precedents.[13,18]

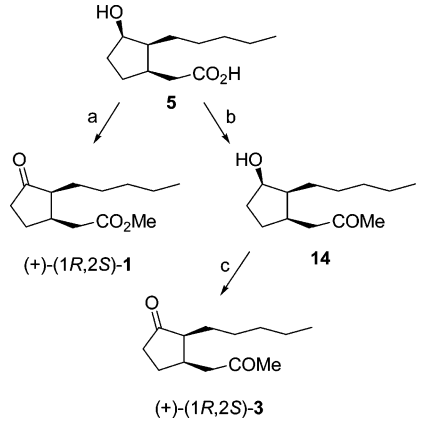
Rhodium-mediated hydrogenation of olefin **13**, followed by the δ-lactone ring opening with KOH in methanol, and careful neutralization with HCl afforded the key hydroxy acid **5** in an almost quantitative yield.

The synthesis of (+)-**1** was smoothly completed by subsequent esterification of **5**, followed by oxidation of the secondary alcohol with the Dess−Martin periodinane reagent[19] (DMP) to afford *cis*-(1*R*,2*S*)-methyl dihydrojasmonate **1**, $[\alpha]^{20}_D = +78$ (≥98% pure, ≥99% de, 93% ee by chiral HPLC), in 97% isolated yield (Scheme 3).

As anticipated, the same compound **5** allowed us to achieve the first synthesis of *cis*-(1*R*,2*S*)-magnolione **3**. Thus, exposure of acid **5** to MeLi and TMSCl,[20] followed by oxidation of the corresponding cyclopentanol **14** with DMP, readily delivered (+)-(1*R*,2*S*)-**3**, $[\alpha]^{20}_D = +44.3$ (≥97% pure, ≥96% de, 93% ee by chiral GC) in 95% isolated yield (Scheme 3).

The odor of (+)-(1*R*,2*S*)-**1** was found to be floral, jasminic, fresh, with some reminiscence of lemon peel, with a threshold value of 0.014 ng/L of air. The odor description for (+)-(1*R*,2*S*)-**3** was pronounced floral, jasminic, close to (+)-**1** but more floral, reminiscent of fresh magnolia blossoms; with a threshold value of 0.023 ng/L of air.[21]

SCHEME 3 [a]



[a] Key: (a) (i) CH_2N_2, 0 °C, 100%, (ii) DMP, DCM, rt, 97%; (b) MeLi, TMSCl, THF, 0 °C to rt, 85%; (c) DMP, DCM, rt, 95%.

In conclusion, the first synthesis of highly enantiomerically enriched (1*R*,2*S*)-magnolione [(+)-**3**] has been achieved in 50% overall yield from the known lactone **6**. The absolute configuration of the *cis*-magnolione enantiomers was thus assigned, and for the first time, the olfactory properties of enantioenriched magnolione have been determined. In addition, we have developed a concise and efficient synthesis of (1*R*,2*S*)-methyl dihydrojasmonate (+)-**1** with the highest diastereomeric excess reported to date. The same synthetic routes can be followed for the preparation of the enantiomers (−)-**1** and (−)-**3**, respectively, starting from the readily available hydroxymethyl δ-lactone (+)-(3a*R*,4*R*,6a*S*)-**6**.[12]

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Supporting Information Available: Experimental details are given for general procedures and for the preparation and spectral data of compounds **1**, **3**, **5**, acid **5** methyl ester, and **7**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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