The Smelling Principle of Vetiver Oil, Unveiled by Chemical Synthesis

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300–400 t
vetiver oil produced per annum

> 150
sesquiterpenoid constituents known to date

... but odorous principle is still disputed.

1 t → 2–3 kg
of roots
of essential oil

US$ 350–500
cost per kg

36% of all fine fragrances

Vetiver grass (Chrysopogon zizanioides)
Abstract: Vetiver oil, produced on a multiton-scale from the roots of vetiver grass, is one of the finest and most popular perfumery materials, appearing in over a third of all fragrances. It is a complex mixture of hundreds of molecules and the specific odorant, responsible for its characteristic suave and sweet transparent, woody-ambery smell, has remained a mystery until today. Herein, we prove by an eleven-step chemical synthesis, employing a novel asymmetric organocatalytic Mukaiyama–Michael addition, that (+)-2-epi-ziza-6(13)-en-3-one is the active smelling principle of vetiver oil. Its olfactory evaluation reveals a remarkable odor threshold of 29 picograms per liter air, responsible for the special sensuous aura it lends to perfumes and the quasi-pheromone-like effect it has on perfumers and consumers alike.

From “Chanel No5” (1921) by Ernest Beaux and “Vetiver de Guerlain” (1959) by Jean-Paul Guerlain to the extreme dose of 90% in the rebellious “Turtle Vetiver” (LesNez, 2019) by Isabelle Doyen, vetiver oil is omnipresent in perfumery.[5-6] No other fragrance material appears more often in the name of a perfume: fragrantica.com currently lists 2267 masculine, 1976 feminine, and 2302 unisex perfumes centered on this, in the truest sense, essential oil. It is a chameleon in applications and can, for instance, be used to make a classic cologne more feminine, and 2302 unisex perfumes centered on this, in 0.2–0.3% yield by hydrodistillation of the dried roots of vetiver grass, is one of the finest and most popular perfumery materials, appearing in over a third of all fragrances. It is a complex mixture of hundreds of molecules and the specific odorant, responsible for its characteristic suave and sweet transparent, woody-ambery smell, has remained a mystery until today. Herein, we prove by an eleven-step chemical synthesis, employing a novel asymmetric organocatalytic Mukaiyama–Michael addition, that (+)-2-epi-ziza-6(13)-en-3-one is the active smelling principle of vetiver oil. Its olfactory evaluation reveals a remarkable odor threshold of 29 picograms per liter air, responsible for the special sensuous aura it lends to perfumes and the quasi-pheromone-like effect it has on perfumers and consumers alike.

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state-of-the-art analytical techniques (Figure 2), the pure substances are required to reach a definitive conclusion about their olfactory importance. As for GC olfactometry, any effort to physically isolate the key odorant from the complex matrix even by preparative GC is prone to contaminations.

In light of these considerations, it became apparent that only a stereoselective chemical total synthesis could provide clarity. We therefore embarked upon the development of an enantioselective and diastereoselective route toward 2-epi-ziza-6(13)-en-3-one (10). In our synthesis design, the emphasis was placed on developing a route that would establish the correct (R)-configuration at C-8 early on, which is common to all the zizaenone natural products. The synthesis should be more flexible concerning the additional stereogenic centers, potentially enabling access to different zizaenone diastereomers for olfactory evaluation.

As delineated in Figure 3, for the key step in the construction of the unique carbon skeleton of 2-epi-ziza-6(13)-en-3-one (10), we designed an intramolecular Pauson–Khand cyclization of 1-ethylidene-3-(2-methyl-3-methylene-
pent-4-yn-2-yl)cyclopentane (20), which should afford the tricyclic ziza-6(13)-en-3-one 21. Seeking to realize this synthetic blueprint, an enantioselective Mukaiyama–Michael reaction of 2-cyclopentenone 12 with the readily accessible and commercially available silyl ketene acetal (SKA) of methyl isobutyrate appeared to be ideally suited to assemble enantiopure cyclopentane 15, which in turn appeared to be a convenient precursor of the Pauson–Khand substrate 20.

Surprisingly, however, despite intense recent research on asymmetric, catalytic Mukaiyama–Michael-type addition reactions, examples with 2-cyclopentenone as electrophile are extremely rare, and the suggested substrate combination has even been entirely unprecedented.[14]

Based on the concept of asymmetric counteranion-directed silyllium Lewis acid catalysis (Si-ACDC), previously developed in our laboratory,[15] we suspected that our imidodiphosphorimidate (IDPi) catalyst class could enable the desired transformation.[16] Indeed, after some design and experimentation, which will be published separately, we could establish a method to access the desired substituted cyclopentenone 15. Thus, upon treating 0.1 mol % of imidodiphosphorimidate (IDPi) catalyst 14 with 2-cyclopentenone and silyl ketene acetal 13, the desired (R)-configured silyl enol ether 15 was obtained on a multigram scale in 95 % yield with an excellent enantiomeric ratio of 98:2. Protodesilylation with trifluoroacetic acid and Wittig reaction with ethyltriphenylphosphonium bromide provided the olefin 17 in 83 % yield, with an E/Z ratio of 1:1.7.[17] This material was directly converted into the corresponding methyl ketone 18 in 83 % yield on a multigram scale by adding trimethylsilyl methyl lithium, followed by protodesilylation.[18] Subsequent addition of ethynyl magnesium bromide, under conditions established by Knochel et al. to counteract steric hindrance and reactivity issues, led to the corresponding isolated alcohol in 81 % yield.[19] The dehydration of this intermediate turned out to be more challenging than expected and could only be realized by utilizing the mild and efficient Burgess reagent,[20] providing the desired product 20, the precursor of the central Pauson–Khand reaction, in 70 % yield. As expected, the sterically highly demanding intramolecular Pauson–Khand [2+2+1] cycloaddition became a critical bottleneck of our synthetic sequence. Several well-established Pauson–Khand protocols failed to furnish even traces of the desired product 21.[21] After surveying various options, a stepwise strategy was chosen in which the 18-electron dicobaltatetrahedrane complex was first prepared and isolated by reacting alkyne 20 with dicobalt octacarbonyl. Its subsequent cyclization was promoted by tert-butyl(methyl)sulfide in refluxing benzene to afford the
desired product 21 and its separable C-2-epimer 27 (cf. Supp. Info.) in 25% yield. While the overall yield of this transformation remained unsatisfactory, despite our best efforts, the powerful Pauson–Khand cyclization established the entire carbon skeleton of the natural product, inducing all three rings, and the critical quaternary stereogenic center in its correct configuration.

With enone 21 in hand, we felt in a very good position to accomplish the last challenge of our synthesis, consisting of the selective reduction of the cyclopentenone double bond. Even though this transformation seemed simple, it turned out to be the most difficult one of the entire sequence. Under various reduction conditions (e.g. Stryker/C₂9s Reagent,[22] SmI₂,[23] Hantzsch ester, [24] Wilkinson/C₂9s reagent,[25] etc., see Supp. Info.), rather than the desired 1,4-reduction product, only products from the corresponding 1,6-reduction of the exocyclic double bond were obtained. Accordingly, an indirect method had to be developed. Indeed, by first epoxidizing the much more reactive exocyclic olefin with freshly prepared dimethyldioxirane (DMDO), epoxide 22 was smoothly obtained in 75% yield (dr 9:1 at C-6).[26] The constitution and stereochemistry of this product were confirmed by X-ray crystallography. Subsequent hydrogenation of the enone double bond in the presence of Pd/C proceeded readily, along with a hydrogenative ring-opening of the epoxide to provide alcohol 23 in 64% yield (dr 2:1, at C-5). We attributed the moderate diastereofacial differentiation of this conjugate reduction to the negligible steric effect of the equatorial methylene group of the epoxide at C-13. The subsequent dehydration of primary alcohol 23 was realized via a Grieco elimination,[27] resulting in three diastereoisomers in 65% total yield with a diastereomeric ratio of 2.9:1:0.1 in favor of target 10. The obtained traces of product 25 presumably result from the isomerization of the minor isomer 24 under the basic elimination conditions.

The olfactory properties and odor thresholds[28] of the four (1R)-configured ziza-6(13)-en-3-one stereoisomers are summarized in Figure 4. While the ziza-6(13)-en-3-one (9)
possesses a clean, fresh, transparent woody–ambery vetiver character with an odor threshold of 0.13 ng L\(^{-1}\)/C\(_0\) air. 2-\(\text{epi}\)-ziza-6(13)-en-3-one (10) featured a much more pronounced and typical vetiver character along with an accentuated dry and distinctly transparent woody–ambery note. This odor character is reminiscent of the popular perfumery material Iso E Super with a related transparent woody–ambery note in which arborone (26) is claimed to cause a quasi-pheromone-like attraction. This odor association was explained by a superposition analysis (75\% electronic, 25\% steric, Discovery Studio\(^{[31]}\)), a method preferentially used to evaluate the most substantial common three-dimensional substructure of a set of molecules that bind to the same receptor during drug or odorant discovery. As is depicted in the overlay analysis in Figure 4, 2-\(\text{epi}\)-ziza-6(13)-en-3-one (10) does superimpose surprisingly well on arborone (26, overlay similarity/26 = 0.87), which implies a substantial similarity of the smelling principles of vetiver oil and Iso E Super. As also evident from Figure 4, the odorless antipode \(\text{ent-10}\) does not superimpose that well, especially concerning the crucial hydrophobic gem-dimethyl group of 26.

Besides, comparing the naturally occurring ziza-6(13)-en-3-one (9) and 2-\(\text{epi}\)-ziza-6(13)-en-3-one (10), the synthetic diastereomers 2,5-di-\(\text{epi}\)-ziza-6(13)-en-3-one (24) and 5-\(\text{epi}\)-ziza-6(13)-en-3-one (25) also possess woody–ambery odors. However, neither 24, with more pronounced hesperidic rhubarb facets and a 1.3 ng L\(^{-1}\) threshold, nor 25, with a more cedarwood character and a 0.23 ng L\(^{-1}\) threshold in air, are stronger or more characteristic than the natural vetiver odor vector 10, and besides, are also not detectable in vetiver oil.

In conclusion, the described enantioselective total synthesis of 2-\(\text{epi}\)-ziza-6(13)-en-3-one (10) represents a successful departure from the traditional separation strategy to disclose a smelling principle. The eleven-step synthesis lays the foundation for an unprecedented enantioselective access to zizaenes. Threshold evaluation reveals the enantiopure ketone 10 to be the key contributor to the typical transparent woody–ambery vetiver note, being over 150 times more potent in odor threshold than khusimone (6), which was previously deemed the smelling principle of vetiver. Moreover, the excellent stereochemical superposition of 2-\(\text{epi}\)-ziza-6(13)-en-3-one (10) on arborone (26) could well explain the almost magic attraction that vetiver oil exerts on humans, and why this surprisingly resembles the irresistible pull of Iso E Super—an effect still not well-understood physiologically but now tangible on the molecular level.

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Conflict of interest

The authors declare the following competing financial interest(s): A patent, WO2017037141 (A1), has been filed by the MPI für Kohlenforschung covering the IDPi catalyst class and their applications in asymmetric synthesis. S.J., S.D., by the MPI für Kohlenforschung covering the IDPi catalyst class and their applications in asymmetric synthesis. S.J., S.D., and P.K. are employees of Givaudan S.A., a commercial producer of perfumes and fragrance ingredients.

Keywords: 2-epi-ziza-6(13)en-3-one · asymmetric Mukaiyama–Michael addition · enantioselective synthesis · smelling principle · vetiver oil

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