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Synthesis of a Spirocyclic Seco Structure of the Principal Vetiver Odorant Khusimone

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Dedicated to Professor Scott E. Denmark on the occasion of his 60th birthday

Keywords: Fragrances / Natural products / Spiro compounds / Structure–activity relationships

The three-dimensional structure of tricyclic compounds with a zero-bridge to one bridgehead atom is determined by the underlying spirocyclic framework. (–)-Khusimone (**1**), the principal odorant of vetiver oil (content up to 2%), is such a tricyclic norsesquiterpene, and dissection of the 7,8-bond between the methylene and the *gem*-dimethyl unit of **1** results in a spirocycle extending over an almost identical molecular volume and shape. Given that the "vetiver rule" postulates that one α-branched carbonyl osmophore in a certain spatial distance to a bulky moiety is responsible for the odor of vetiver, a 7,8-seco structure of **1** could prove or disprove these structural requirements. Therefore, (4*R**,5*R**)-7-isopropyl-4-vinylspiro[4.4]nonan-1-one [(4*R**,5*R**)-**2**] was synthesized in a 10-step synthetic sequence commencing with Steglich esterification of allyl alcohol (**15**) and isovaleric acid (**14**). Ireland–Claisen rearrangement of the formed allyl isovalerate (**16**) with subsequent lithium aluminum hydride reduction of resulting γ,δ-unsaturated acid **18**, Appel bromination of corresponding alcohol **19**, and ozonolysis provided 4-bromo-3-isopropylbutanal (**23**) in 19% overall yield as a building block for the projected spiroannulation reactions. Although attempts on cyclopentanone (**7**) failed, cyclopent-2-en-1-one, via its TMS-trapped lithium 3-vinylcyclopent-1-enolate **12**, turned out to be a successful starting material. Evans' variant of the Mukaiyama aldol reaction with 1-trimethylsiloxy-3-vinylcyclopent-1-ene (**12**) in the presence of $BF_3{\cdot}OEt_2$, followed by palladium-catalyzed conjugate tin hydride reduction of resulting enone **28** provided 2-(4′-bromo-3′-isopropylbutyl)-3-vinylcyclopentanone (**29**) in 50% overall yield as the anlation precursor. LDA-mediated 5-*exo*-*tet* cyclization of **29** concluded the synthesis of the racemic 7,8-seco-/6-epi-7,8-secokhusimone mixture (4*R**,5*R**)-**2**, which possessed a floral, rosy, green, geranium-like odor with a threshold of 42.0 ng L^{-1} air, which is 10 times less intense than that of (–)-khusimone (**1**). Most importantly, seco structure (4*R**,5*R**)-**2** did not display any woody nor any vetiver character, which proves the postulated vetiver rule wrong.

"*Me, my thoughts are flower strewn*
Ocean storm, bayberry moon
I have got to leave to find my way [...]
I have got to find the river,
Bergamot and vetiver
Run through my head and fall away"
R.E.M., *'Find The River'*[1]

Introduction

The concept of the Chypre fragrance family, which originated from the classical 'Chypre' of Coty (1917) and comprises perfumes such as 'Aromatics Elixir' (Clinique, 1972), 'Polo' (Ralph Lauren, 1978), 'Chance' (Chanel, 2002), and '2 Man' (Comme des Garçons, 2004), is based on the contrast between a fresh citrus accord and a mossy-woody foundation.[2] Whereas patchouli oil is more typical for the woody part of a Chypre fragrance, vetiver often contributes markedly to their characteristic dry base note. The preferred citrus component of Chypre fragrances is bergamot, and so we find bergamot and vetiver in most of the many fragrances that bear the 'vetiver' designation in their name.[3] The harmony of 'bergamot and vetiver', however, is also employed in totally unrelated olfactory families, such as in floral-aldehydic fragrances around 'Chanel N°5'.[4] Roughly about one third of all fragrances on the market feature the 'bergamot–vetiver' complex. Although the important odor vectors of bergamot oil, linalyl acetate (22–36%),[5] linalool (3–16%),[5] and limonene (30–45%)[5] are today inexpensive commodities, no synthetic vetiver odorant is commercially available. There is not even a consensus about which constituents contribute to its distinct and characteristic suave and sweet woody-earthy odor with green,

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grapefruit, and rhubarb-type facets.[6] The norsesquiterpene (–)-khusimone [12-norziza-6(13)-en-2-one, **1**, Figure 1], which constitutes only up to 2% of the essential oil,[7] is the only component that is agreed to possess a typical vetiver odor and, thus, is the only concrete lead structure.[6] Yet, by synthesis of novel spiro[4.5]decan-2-ones, together with the vetiver constituents khusimone (**1**), eremophiladienal, and 1,7-cyclogerma-1(10),4-dienal,[8] a vetiver rule could be postulated,[2,3] according to which a vetiver odorant should bear one α-branched carbonyl osmophore in a distance of 5.0 ± 0.5 Å to a bulky group, while possessing an overall dimension of 13–16 carbon atoms (Figure 1).

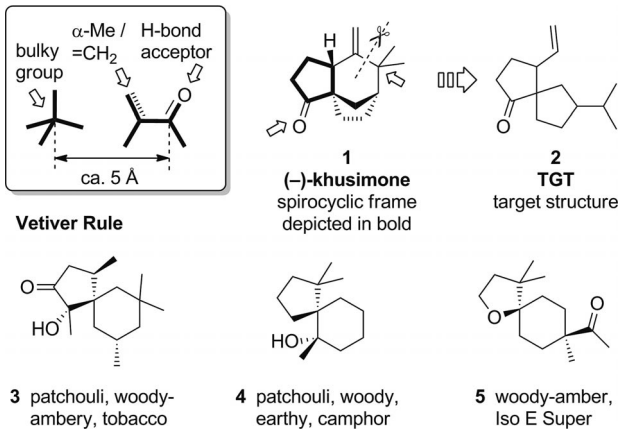
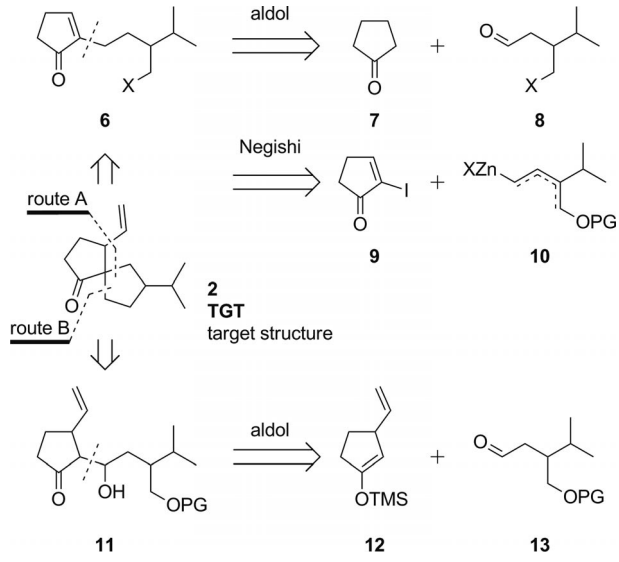


Figure 1. The vetiver rule applied to the design of spirocyclic core structure **2** from the natural lead (–)-khusimone (**1**) and related spirocyclic odorants **3**–**5** with patchouli and woody-ambery odor characteristics.

Any tricyclic skeleton with a zero-bridge to one bridgehead atom by definition contains a spirocyclic ring system.[2] It is this spirocyclic frame, highlighted in the structure of (–)-khusimone (**1**) in Figure 1, that determines the molecular shape of such tricyclic compounds. The woody odorants of nature are almost exclusively tricyclic sesquiterpenoids, and it is therefore not surprising that many synthetic spirocycles possess potent woody odors. Spirocyclic ketol **3**[9] and its ring-inverted methyl carbinol derivative **4**[10] for instance are closely reminiscent in odor to the tricyclic sesquiterpene (–)-patchoulol, the odorous principal of patchouli oil. Spirocyclic ketol **3** possesses an odor threshold that is more than 30 times lower than that of (–)-patchoulol.[3] In the family of woody-ambery odorants, *para*-linked acetyl-1-oxaspiro[4.5]decane **5** resembles Iso E Super closely in odor,[11] but it is much more water soluble and bioavailable.

Given that the synthesis of zizaanes poses some synthetic challenges and is industrially unfeasible,[12] and because (–)-khusimone (**1**), with an odor threshold of 4.7 ng L^{-1} air, is not very intense, similar spirocyclic structures might exhibit improved olfactory properties. Therefore, it seemed highly interesting to challenge the vetiver rule in the design of a new spirocyclic odorant devised by dissecting the bond between the methylene and the *gem*-dimethyl unit of **1** (Figure 1). As the spiro[4.4]nonyl core conformationally constrains the tricyclo[6.2.1.$0^{1,5}$]undecyl framework of the zizaanes, this scission should preserve the overall molecular shape, while simplifying its synthetic access.

Our retrosynthetic analysis of target structure **2** is delineated in Scheme 1. A concluding 1,4-conjugate addition of a vinyl Gilman reagent to enone **6** would proceed via an enolate intermediate, which could enable the concomitant closure of the spirocyclic ring in the presence of a suitable leaving group X (Scheme 1, route A). Enones **6** could be prepared by simple aldol condensation of cyclopentanone (**7**) with suitably substituted aldehyde **8** with subsequent isomerization[13] of the resulting exocyclic double bond into the endocyclic position. Pd-catalyzed Negishi cross-coupling[14] of 2-iodocyclopen-2-en-1-one (**9**)[15] with a suitably protected vinylic, allylic, or homoallylic organozinc reagent of type **10** (PG = protecting group) would avoid such an isomerization but would necessitate a very tricky and selective hydrogenation of the side-chain double bond.



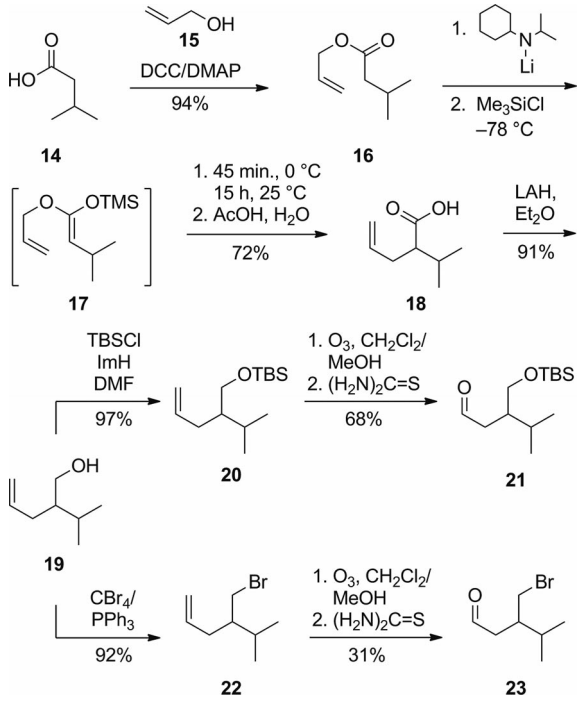
Scheme 1. Retrosynthetic analysis of target structure **2**.

Inspired by Noyori's three-component prostaglandin synthesis,[17] introduction of an auxiliary hydroxy function into target structure **2** would, however, allow the directed aldol reaction of protected hydroxy aldehyde **13** with trapped enolate **12** from the conjugate addition of a vinyl Gilman reagent to cyclopentenone. Albeit less elegant, this seems synthetically more sound, as there is a very good chance that the desired 5-*exo*-*tet* cyclization would energetically win over the 7-*exo*-*tet* alternative, after reductive removal of the hydroxy function of **11** and exchange of the protecting group for a leaving group (Scheme 1, route B). These two additional synthetic operations, however, seem a bit cumbersome at first sight.

Results and Discussion

Both routes A and B require 3-substituted 1,4-bifunctional building blocks **8** and **13**, which could be accessible by oxidative degradation of γ,δ-unsaturated carbonyl com-

pounds, that is, Claisen rearrangement products. The Ireland–Claisen modification is particularly appealing and led to allyl isovalerate (**16**) as an easily accessible starting material. As illustrated in Scheme 2, allyl ester **16** was prepared by Steglich esterification[18] of 3-methylbutanoic acid (isovaleric acid, **14**) and prop-2-en-1-ol (allyl alcohol, **15**) in anhydrous diethyl ether. After silica gel flash chromatography, **16**, possessing a fruity-green odor reminiscent of pineapples, was isolated in 94% yield. For the subsequent Ireland–Claisen rearrangement, we followed a procedure previously used in the synthesis of a constitutional nerol isomer.[19] Allyl ester **16** was deprotonated with lithium cyclohexylisopropylamine (LICA) in THF at –78 °C, the corresponding lithium enolate was trapped with trimethylsilyl chloride, and the resulting silyl ester enolate **17** was stirred at 0 °C for 45 min, and then overnight at room temperature. Mild hydrolysis afforded 2-isopropylpent-4-enoic acid (**18**) in 72% yield after chromatographic isolation. Standard lithium aluminum hydride (LAH) reduction of γ,δ-unsaturated acid **18** in ether provided corresponding alcohol **19** in 91% yield, without any need for further purification.



Scheme 2. Synthesis of building blocks **21** and **23** by Ireland–Claisen rearrangement of allyl isovalerate (**16**) to 2-isopropylpent-4-enoic acid (**18**) and subsequent functionalization of corresponding alcohol **19**.

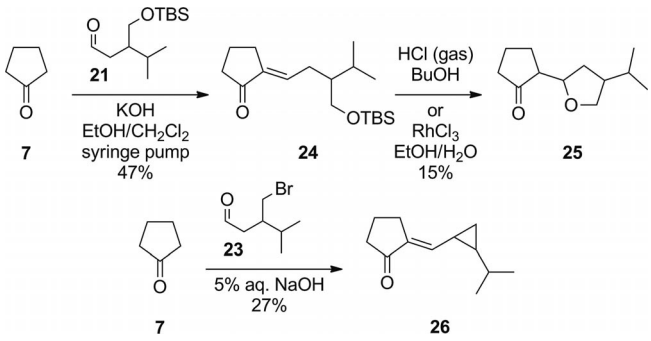
En route to building block **13** (PG = TBS), the hydroxy function of **19** was then protected as a *tert*-butyldimethylsilyl (TBS) ether by reaction with TBSCl in DMF at room temperature, and **19** was isolated by flash chromatography in 97% yield. Ozonolysis of **19** with reductive workup by employing thiourea then afforded TBS-protected γ-hydroxy aldehyde **21** in 68% yield.

Building block **8** (X = Br) for the aldol reaction with cyclopentanone (**7**) was prepared by standard Appel bromination[20] of alk-4-enol **19** with tetrabromomethane and triphenylphosphane in dichloromethane at room temperature for 1 d. After chromatographic purification, resulting 5-bromo-4-isopropylpent-1-ene (**22**) was isolated in 92% yield. Ozonolysis of **22** with reductive workup by employing thiourea then provided γ-bromo aldehyde **23** in moderate 31% yield.

Following the supposedly shorter retrosynthetic route A, siloxy aldehyde **21** was slowly added with the use of a syringe pump to a solution of cyclopentanone (**7**) and potassium hydroxide in ethanol, in analogy to a procedure by Sarpong and co-workers.[21] After standard workup and chromatographic purification, corresponding aldol condensation product **24** was obtained in 47% yield. The acid-catalyzed kinetic isomerization of an exocyclic cyclopentenone double bond into the endocyclic position is the key step in the commercial synthesis of Hedione,[3] that is, the isomerization of 2-pentylidenecyclopentanone into 2-pentylcyclopent-2-enone.[13] Treatment of **24** with hydrochloric acid in butanol, however, led to 4-isopropyltetrahydrofuran-2-yl system **25** by deprotection and cyclization. The same result was obtained when rhodium trichloride in ethanol[22] was employed in the isomerization reaction of 3-isopropylbutylidene cyclopentanone **24**, although that reaction was expected to proceed under much milder conditions. Instead of varying the protecting group of aldehyde building block **21**, we believed bromo aldehyde **23** could be employed directly in the aldol condensation reaction with **7** by employing 5% aqueous NaOH as the base.[16] Yet, not so surprisingly, the corresponding bromo-substituted aldol adduct reacted further, and following elimination of hydrogen bromide, cyclopropylmethylene derivative **26** was formed.

Therefore, we switched to the alternative retrosynthetic strategy B, starting from cyclopent-2-en-1-one (**27**), as delineated in Scheme 4. Conjugate 1,4-addition of the vinyl Gilman reagent, prepared in situ by transmetalation of the vinyl Grignard reagent with *tert*-butyllithium and copper iodide to enone **27**, provided the lithium 3-vinylcyclopent-1-enolate, which was trapped by trimethylsilyl chloride according to a procedure of Snider and Yang[23] to afford **12** in 60% yield after Kugelrohr distillation. The 3-vinylcyclopent-1-enolate was released by reaction of **12** with butyllithium. Subsequent reaction of this enolate with aldehyde **21** in the presence of zinc(II) chloride led, however, with elimination of the hydroxy function, to a complex mixture of exo/endocyclic and unconjugated double bond isomers. To prevent the elimination of the hydroxy function from the aldol adduct, the reaction was then conducted under Mukaiyama conditions.[24] Trapped 1-trimethylsiloxy-3-vinylcyclopent-1-ene (**12**) was thus added to a solution of aldehyde **21** in dichloromethane in the presence of titanium(IV) chloride at –78 °C. Although the Mukaiyama aldol reaction itself went smoothly, the formation of hydrochloric acid from titanium(IV) chloride upon quenching, even when employing aqueous buffer systems, led to deprotec-

tion and cyclization to form the diastereomeric 3-vinyl-substituted analogs of **25** (Scheme 3).



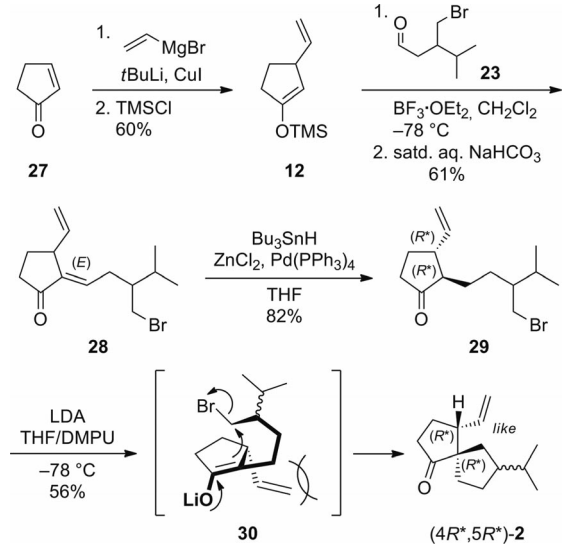
Scheme 3. Synthetic attempts towards target structure **2** according to retrosynthetic analysis route A.

If this elimination of the hydroxy function from the aldol adduct could not be restrained, and if the aldol hydroxy group subsequently could not be removed reductively, for instance through Barton–McCombie deoxygenation[25,26] of the corresponding *O*-phenoxythiocarbonyl derivative, a 2-tetrahydrofuran-2′-ylcyclopentanone derivative threatened to be the dead end of route B as well. Therefore, a Mukaiyama-type aldol reaction with a Lewis acid that would not form a strong Brønsted acid upon hydrolysis was in demand, and the $BF_3{\cdot}OEt_2$-catalyzed variant of Evans et al.[27] seemed to be the method of choice; yet, even these conditions led to the aldol condensation product rather than the expected β-hydroxy ketone.

However, it seemed possible that the mild reaction conditions of the Evans' variant of the Mukaiyama aldol reaction would tolerate a bromine substituent, and thus, building block **23** was directly subjected to an aldol reaction with 1-trimethylsiloxy-3-vinylcyclopent-1-ene (**12**). Indeed, dropwise addition of $BF_3{\cdot}OEt_2$ to a solution of **12** and **23** in freshly distilled dichloromethane furnished (4′-bromo-3′-isopropylbutylidene)-3-vinylcyclopentanone (**28**) as a diastereomeric mixture in 61% yield after chromatographic purification. As was deduced from the strong nuclear Overhauser effect between 3-H and 2′-H in the ^1H–^1H NOESY spectrum, both diastereoisomers were unequivocally [2(1′)*E*]-configured.

The problem of the reductive removal of the aldol hydroxy group of **11** thus shifted to that of the selective reduction of the (*E*)-configured conjugated double bond of **28**. For this synthetic operation, a number of practical methods are available, for instance, Stryker's method[28] with copper(I) hydride cluster $[(PPh_3)CuH]_6$, which we had used earlier in the synthesis of linear musks,[29] or the catacholborane procedure of Evans and Fu,[30] which we had recently applied in the synthesis of orris odorants.[31] As neither Stryker's method[28] nor catacholborane[30] furnished any reduction product **29**, and because there was precedence on a related system,[32] the palladium-catalyzed tin hydride reduction of Keinan and Gleize[33] was selected for the conjugate reduction of enone **28** to bromo ketone **29**. This reduction proceeds through palladium-catalyzed hydrostannylation in the presence of an activating Lewis acid, in this case, zinc(II) chloride. The stereochemical outcome of this reduction[34] is determined by the tendency of 2,3-disubstituted cyclopentene-derived enols to afford the thermodynamically favored *trans* product following protonation.[35] Thus, conjugate palladium-catalyzed tin hydride reduction of enone **28** in the presence of zinc(II) chloride after 2 h afforded 2,3-*trans*-configured cyclopentanone **29** in 82% yield after chromatography on potassium carbonate/silica (10% w/w) to remove all organotin impurities to levels below 15 ppm.[36] Attempts to improve the yield by forcing the reaction conditions, for instance by increasing the amount of $[Pd(PPh_3)_4]$, led to reduction of the vinyl moiety as well, the resulting product of which proved difficult to separate by chromatography.

With 3-vinyl-substituted bromo ketone **29** in hand, the stage was now set for the final cyclization of lithium enolate **30** to target structure **2**. As the C-2 stereocenter of **29** was flattened in enolate intermediate **30**, the relative *trans* stereochemistry of **29** was irrelevant. However, as indicated in suggested transition state **30** in Scheme 4, we hoped that the vinyl moiety would sterically shield the *Si* face, which would thus lead to *anti* selectivity of the nucleophilic substitution on the *Re* face of the cyclopentenolate ring. Indeed, treatment of bromo ketone **29** with freshly prepared lithium diisopropylamine (LDA) at –78 °C in THF/DMPU (5:1) nicely afforded only one single pair of diastereoisomers in 56% yield, the like-configured (4*R**,5*R**)-7-isopropyl-4-vinylspiro[4.4]nonan-1-one [(4*R**,5*R**)-**2**], isomeric only in the configuration of the 7-isopropyl group. The stereochemistry of the (4*R**,5*R**,7*R**)-diastereomer of **2** was tentatively assigned by nuclear Overhauser effects between 4-H_{ax} and 6-H_b, as well as between 6-H_b and 2′′-H and between 6-H_a and 1′′-Me in the ^1H–^1H NOESY spectrum. The relative (4*R**,5*R**) configuration was unequivocally proven by



Scheme 4. Concluding steps in the synthesis of (4*R**,5*R**)-configured target structure **2** from cyclopent-2-en-1-one (**27**) by retrosynthetic route B.

the distinct and characteristic NOE cross-peak between 4-H_{ax} and 6-H_b in both diastereoisomers. Together with chemical shift correlations and mechanistic considerations, the other diastereomer was tentatively assigned a (4*R**,5*R**,7*S**) configuration. To our great disappointment, the diastereoisomers of (4*R**,5*R**)-**2** proved inseparable by all chromatographic means, including preparative GC. Chiral stationary GC phases were also employed, but only the enantiomers of (4*R**,5*R**)-**2** were separable, whereas the 7-diastereoisomers co-eluted.

The relative (4*R**,5*R**) stereochemistry, however, nicely matched that of natural (–)-khusimone (**1**), as can also be seen in the superposition analyses of compounds **1** and (4*R*,5*R*,7*R*)-**2** in Figure 2 with the MOE 2011.10 software.[37] Thus, we successfully concluded the synthesis of our target molecule in only 10 steps from isovaleric acid (**14**) and allyl alcohol (**15**). Although we could not separate the C-7 diastereomers, the correct relative (4*R**,5*R**) stereochemistry still allows meaningful insights, especially if synthesized racemic 7,8-seco-/6-epi-7,8-secokhusimone mixture (4*R**,5*R**)-**2** displays no woody-vetiver character, which is the case.

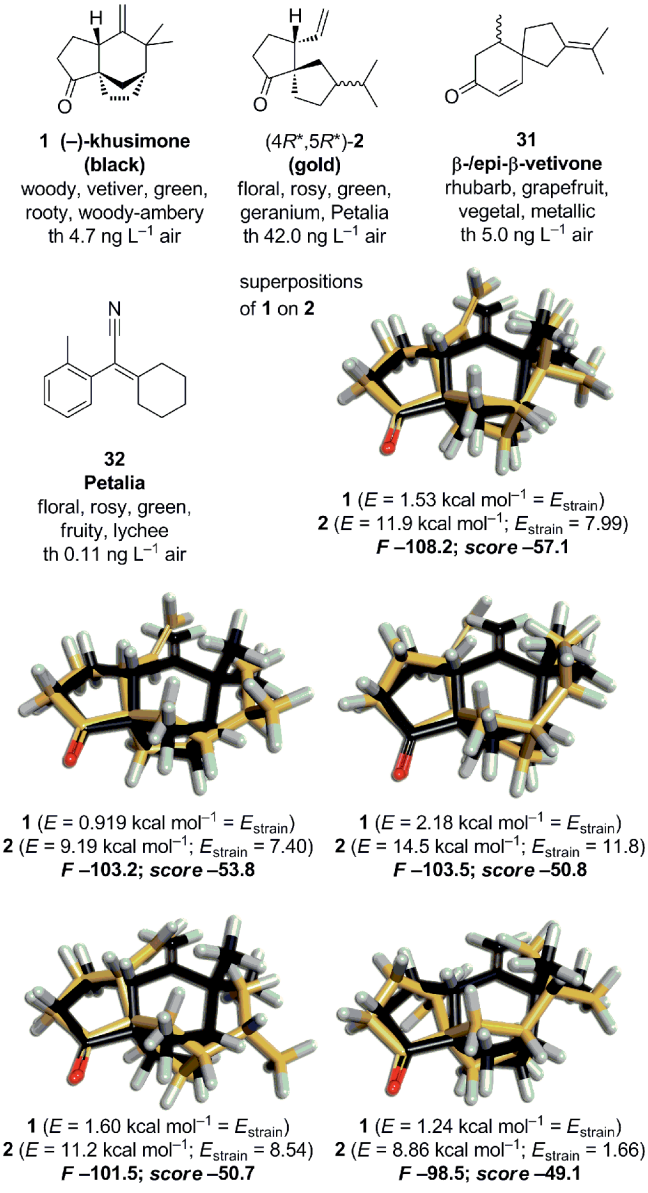


Figure 2. Olfactory properties of (–)-khusimone (**1**, black), target compound (4*R**,5*R**)-**2** (gold), β-/epi-β-vetivone (**31**), and Petalia (**32**, silver) in comparison, as well as superposition analyses of natural template **1** on (4*R*,5*R*,7*R*)-**2** in biflexible alignment mode with CCG's Molecular Operating Environment MOE2011.10,[37] within a conformational space of 15 kcal mol^{-1}. *E* potential energy above the global minimum-energy conformer (MMFF94x); E_{strain} strain energy component; *F* feature overlap describing the configurational similarity as negative value of the probability-density overlap function, with lower values indicating greater similarity; *score* grand alignment score of the probability-density overlap, and the average strain energy of the molecules in alignment, with lower values indicating better alignments.

Olfactory Properties, Superposition Analyses, and Conclusions

Whereas (–)-khusimone (**1**) with an odor threshold of 4.7 ng L^{-1} air indeed possesses a typical woody, vetiver-type note with green-rooty, woody-ambery facets accompanied by a slight grapefruit nuance, β-/epi-β-vetivone (**31**) with a spiro[4.5]dec-6-en-8-one skeleton is clearly reminiscent of grapefruit and rhubarb, with a vegetal, metallic connotation but without much woody character. β-/epi-β-Vetivone (**31**) recalls the citrusy aspects of decatone [6-isopropyloctahydronaphthalen-2(1*H*)-one] and possesses an odor threshold of 5.0 ng L^{-1} air, so it is comparable in odor strength to (–)-khusimone (**1**). β-Vetivone makes up 4–10% of vetiver oils, but contributes to the less-desired grapefruit aspects of the essential oil rather than to its elegant woody note.

The synthesized racemic 7,8-seco-/6-epi-7,8-secokhusimone mixture (4*R**,5*R**)-**2** has an odor threshold of 42.0 ng L^{-1} air, which is almost 10 times less intense than that of both (–)-khusimone (**1**) and β-/epi-β-vetivone (**31**), and to our great disappointment shares neither of their odor characteristics. Instead it has a floral, rosy, green, geranium-type odor in the direction of Petalia [**32**, 2-cyclohexylidene-2-(*o*-tolyl)acetonitrile] and Magnolan (2,4-dimethyl-4,4a,5,9b-tetrahydroindeno[1,2-*d*][1,3]dioxine) with some slightly fatty-metallic facets (Figure 2). So it is devoid of any woody-vetiver character, and it does not smell like anything in a woody direction. GC-Olfactometry analysis with a chiral Hydrodex β-6TBDM [heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin] phase indicated that the odor of the (4*R**,5*R**)-**2** mixture was mainly a result of the more intense first eluting diastereomeric peak of enantiomers with a floral, rosy, green, powdery odor, whereas the second diastereomeric pair of enantiomers was weaker, floral-herbaceous, slightly celery-like, and somewhat reminiscent of *cis*-jasmone.

In the generation of computational structure–activity models, it is generally assumed that a receptor can induce a fit of an agonist within a conformational space of 20 kcal mol^{-1}.[38] Restricting the conformational space even

more conservatively to about 15 kcal mol^{-1} above the global energy minima, Figure 2 details the five best superposition alignments for **1** and (4*R*,5*R*,7*R*)-**2**, as calculated with the MOE 2011.10 software package.[37] Unsurprisingly, (–)-khusimone (**1**) remains rather rigid in these biflexible alignments, and a maximum of 2.18 kcal mol^{-1} is induced in the superposition scored at –50.8, all of which is in the form of strain energy. It thus seems to be a valid template for the receptor binding site of vetiver odorants.

Seco structure (4*R*,5*R*,7*R*)-**2** is far more flexible and populates, for instance, a conformer that is 14.5 kcal mol^{-1} above the global energy minimum in the superposition scored at –50.8. Generally, only 70–80% of the total energy of the delineated conformers of **2** is transformed into strain energy, and the vinyl moiety avoids some steric interactions by rotating out. The bulky *gem*-dimethyl group of (–)-khusimone (**1**) and the (7*R*)-isopropyl moiety of **2**, however, generally overlap well, despite the puckering of the spirocyclic cyclopentyl ring, and because both carbonyl osmophores are α-branched, the vetiver rule should have been served adequately.

The good superposition of **1** on **2** depicted in Figure 2 is, of course, only valid for the (4*R*,5*R*,7*R*)-enantiomer of **2**, so the floral rosy-green, geranium odor of (4*R**,5*R**)-**2** could very well originate mainly from another isomer. Because the correct (4*R*,5*R*,7*R*)-enantiomer of **2** is also contained in the mixture, and no vetiver character was observed at all, these results still disprove the vetiver rule,[2] at least in its genuine wording. This is also in agreement with the rather high threshold of (4*R**,5*R**)-**2**, which indicates a less specific fit to the olfactory receptor(s).

In the superposition analyses in Figure 2, the 4-vinyl moiety is somewhat displaced from its original position in (–)-khusimone (**1**). It is therefore possible that the precise relative orientation of this double bond as constrained by the tricyclic skeleton of **1** is of utmost importance for the characteristic odor of vetiver. In any case, the structural requirements are certainly more complex than suggested by the vetiver rule in Figure 1,[2] and further derivatives of (–)-**1** and probably also (4*R**,5*R**)-**2** are required to gain the necessary insight into the structural requirements for a targeted design of new vetiver odorants.

The presented 10-step synthetic sequence to (4*R**,5*R**)-**2** consisting of Steglich esterification of allyl alcohol (**15**) and isovaleric acid (**14**), Ireland–Claisen rearrangement of formed allyl isovalerate (**16**), LAH reduction of the resulting γ,δ-unsaturated acid, Appel bromination, ozonolysis, Evans' variant of the Mukaiyama aldol reaction with trapped 1-trimethylsiloxy-3-vinylcyclopent-1-ene (**12**), palladium-catalyzed conjugate tin hydride reduction of intermediate enone **28**, and LDA-mediated 5-*exo*-*tet* cyclization to the [4.4]-spirocyclic target compound allows further structural modifications of the target structure rather easily. A C-7 stereocenter could be introduced into these spiro-[4.4]nonan-1-ones by asymmetric allylation of chiral imide enolates according to Evans et al.,[39] which after LAH reduction of the resulting oxazolidinones should afford the enantiomers of **19** or related alk-4-enols for the construction of further analogs of our target compound **2**.

Besides the synthesis of new vetiver odorants, the presented sequence will also be of general synthetic value for the spiroannulation of cyclic and open-chain ketones.

Experimental Section

General Methods: IR spectra were recorded with a Bruker VECTOR 22/Harrick SplitPea micro ATR, Si. NMR spectra were recorded with a Bruker Avance DPX-400, Bruker Avance 500 (TCI), or Bruker Avance 600 spectrometer with tetramethylsilane as an internal standard (δ = 0 ppm). MS was performed with an HP Chemstation 6890 GC/5973 Mass Sensitive Detector. HRMS was performed with a Finnigan MAT 95 (EI: 70 eV). Flash chromatography was performed with Merck Kieselgel 60 (40–63 μm). TLC was carried out with Merck Kieselgel 60 F_{254} (particle size 5–20 μm, layer thickness 250 μm on glass, 5 cm × 10 cm), and phosphomolybdic acid spray and plunge solution (Fluka 02553) was used for visualization. Unless otherwise stated, all reactions were performed under an atmosphere of N_2 with reagents and solvents (puriss. or purum) from SAFC, which were used without further purification.

The odor thresholds were determined by GC-Olfactometry: Different dilutions of the sample substance were injected into a gas chromatograph in descending order of concentration until the panelist failed to detect the respective substance at the sniffing port. The panelist smelled in blind and pressed a button on perceiving an odor. If the recorded time matched the retention time, the sample was further diluted. The last concentration detected at the correct retention time was the individual odor threshold. The reported threshold values are the geometrical mean values of the individual odor thresholds of the different panelists.

Allyl-3-methyl Butanoate (16): Isovaleric acid (**14**; 10.2 g, 100 mmol), prop-2-en-1-ol (**15**; 5.81 g, 100 mmol), and 4-dimethylaminopyridine (DMAP; 1.22 g, 10.0 mmol) were dissolved in Et_2O (100 mL). At 0 °C, a solution of 1,3-dicyclohexylcarbodiimide (DCC, 22.7 g, 110 mmol) in Et_2O (50.0 mL) was added, and the mixture was stirred at room temperature overnight prior to filtration of the insoluble material and concentration of the filtrate under reduced pressure. The resulting residue was purified by silica gel flash chromatography (FC; pentane/Et_2O = 96:4, R_f = 0.4) to provide **16** (13.3 g, 94%). IR (neat): $\tilde{\nu}$ = 3087 (w, ν=CH_2), 1735 (s, νC=O), 1649 (w, νC=C), 1170 (s, νCO–O), 991 (δCH=CH_2) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, J = 7.0 Hz, 6 H, 3-Me_2), 2.12 (ddq, J = 13.5, 8.0, 7.0 Hz, 1 H, 3-H), 2.22 (d, J = 7.0 Hz, 2 H, 2-H_2), 4.57 (dt, J = 5.5, 1.0 Hz, 2 H, 1′-H_2), 5.23 (dq, J = 10.5, 1.0 Hz, 1 H, 3′-H_E), 5.31 (dq, J = 17.5, 1.0 Hz, 1 H, 3′-H_Z), 5.92 (ddt, J = 17.5, 10.5, 5.5 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3 (2 q, 3-Me_2), 25.7 (d, C-3), 43.3 (t, C-2), 64.8 (t, C-1′), 118.0 (t, C-3′), 132.3 (d, C-2′), 172.7 (s, C-1) ppm. MS (EI, 70 eV): *m*/*z* (%) = 142 (1) $[M]^+$, 100 (11) $[M - C_3H_6]^+$, 85 (70) $[M - C_4H_9]^+$, 57 (100) $[C_4H_9]^+$, 41 (75) $[C_3H_5]^+$, 29 (11) $[CHO]^+$.

2-Isopropylpent-4-enoic Acid (18): At 0 °C under a N_2 atmosphere, *N*-isopropylcyclohexylamine (15.4 mL, 92.0 mmol) was added to a stirred solution of *n*BuLi (1.6 M in hexane, 57.5 mL, 92.0 mmol). The solvent was evaporated at room temperature with a vacuum line, and the yellowish residue was taken up in anhydrous THF (120 mL). At –78 °C, a solution of 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one (DMPU; 5.50 mL, 46.2 mmol) and allyl-3-methyl butanoate (16, 10.7 g, 75.2 mmol) in THF (30 mL) was

added dropwise with stirring over a period of 30 min, prior to the dropwise addition of Me_3SiCl (22.0 mL, 175 mmol) at the same temperature. After stirring at 0 °C for 45 min, and then overnight at room temperature, the reaction was carefully quenched at –20 °C by slow addition of acetic acid (15.0 mL, 0.26 mol), followed by the dropwise addition of water (85 mL). The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the resulting residue (pentane/Et_2O = 19:1, R_f = 0.20) afforded **18** (7.70 g, 72%). IR (neat): $\tilde{\nu}$ = 2963 (br. m, νCOO–H), 1702 (s, νC=O), 1643 (w, νC=C), 1468/1439 (w, δCH_2, CH_3), 1390/1372 (w, δCH_3), 914 (s, $\delta CH{=}CH_2$) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.97/0.99 (2 d, J = 7.0 Hz, 6 H, 1′-Me, 3′-Me), 1.92 (oct., J = 7.0 Hz, 1 H, 2′-H), 2.24 (ddd, J = 10.0, 7.0, 4.5 Hz, 1 H, 2-H), 2.31 (ddddt, J = 14.0, 10.0, 7.0, 4.5, 1.0 Hz, 1 H, 3-H_b), 2.32 (ddddt, J = 14.0, 10.0, 7.0, 4.5, 1.0 Hz, 1 H, 3-H_a) 5.02 (dquint., J = 10.0, 1.0 Hz, 1 H, 5-H_E), 5.08 (dq, J = 17.0, 1.0 Hz, 1 H, 5-H_z), 5.78 (ddt, J = 17.0, 10.0, 7.0 Hz, 1 H, 4-H), 11.65 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 (2 q, C-1′, C-3′), 29.9 (d, C-2′), 33.5 (t, C-3), 52.2 (d, C-2), 116.6 (t, C-5), 135.5 (d, C-4), 181.5 (s, C-1) ppm. MS (EI, 70 eV): m/z (%) = 142 (1) $[M]^+$, 127 (1) $[M - CH_3]^+$, 99 (100) $[M - C_3H_7]^+$, 81 (20) $[C_6H_9]^+$, 71 (12) $[C_4H_7O]^+$, 55 (49) $[C_4H_7]^+$, 43 (50) $[C_3H_7]^+$, 41 (44) $[C_3H_5]^+$, 39 (27) $[C_3H_3]^+$, 27 (13) $[C_2H_3]^+$.

2-Isopropylpent-4-en-1-ol (19): At room temperature, lithium aluminum hydride (LAH; 1.50 g, 40.4 mmol) was dissolved in dry diethyl ether (160 mL). The solution was cooled down to 0 °C, and acid **18** (5.70 g, 40.4 mmol) dissolved in diethyl ether (40 mL) was carefully added dropwise. After stirring at this temperature for 15 min and then at room temperature for 2 h, the solution was carefully quenched by slow addition of a satd. aq. solution of NH_4Cl (80 mL). The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure to afford alcohol **19** (4.70 g, 91%), which was used in the next step without further purification. IR (neat): $\tilde{\nu}$ = 3332 (br. m, νO–H), 3076 (w, ν=CH_2), 1639 (m, νC=C), 1466/1440 (m, δCH_2, CH_3), 1386/1368 (m, δCH_3), 1040 (s, νCH_2–OH), 908 (s, $\delta CH{=}CH_2$) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91/0.92 (2 d, J = 7.0 Hz, 3 H, 1′-Me, 3′-Me), 1.42 (dddt, J = 8.0, 5.0, 5.0, 5.0 Hz, 1 H, 2-H),1.81 (sept.d, J = 7.0, 5.0 Hz, 1 H, 2′-H), 2.04 (tddt, J = 8.0, 8.0, 7.0, 1.5 Hz, 1 H, 3-H_b), 2.17 (tddt, J = 8.0, 7.5, 5.0, 1.5 Hz, 1 H, 3-H_a), 3.50 (dd, J = 11.0, 5.0 Hz, 1 H, 1-H_a), 3.61 (dd, J = 11.0, 5.0 Hz, 1 H, 1-H_b), 5.01 (ddt, J = 10.0, 3.0, 1.5 Hz, 1 H, 5-H_E), 5.06 (ddt, J = 17.0, 3.0, 1.5 Hz, 1 H, 5-H_z), 5.84 (dddd, J = 17.0, 10.0, 7.5, 7.0 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3/19.8 (2 q, C-1′, C-3′), 27.8 (d, C-2′), 32.9 (d, C-3), 46.4 (d, C-2), 63.6 (t, C-1), 115.7 (t, C-5), 138.0 (d, C-4) ppm. MS (EI, 70 eV): m/z (%) = 128 (1) $[M]^+$, 113 (1) $[M - CH_3]^+$, 110 (7) $[M - H_2O]^+$, 95 (77) $[C_7H_{11}]^+$, 86 (15) $[M - C_3H_6]^+$, 81 (19) $[C_6H_9]^+$, 69 (52) $[C_5H_9]^+$, 55 (94) $[C_4H_7]^+$, 45 (32) $[C_2H_5O]^+$, 41 (100) $[C_3H_5]^+$, 31 (13) $[CH_3O]^+$, 29 (16) $[C_2H_5]^+$. Odor description: powerful and pungent minty-camphoreous, with aspects of rotten wood and a meaty character.

1-(*tert*-Butyldimethylsiloxy)-2-isopropylpent-4-ene (20): At room temperature under a N_2 atmosphere, alcohol **19** (4.40 g, 34.3 mmol) and imidazole (7.00 g, 103 mmol) were dissolved in anhydrous DMF (5 mL), prior to the addition of *tert*-butyldimethylsilyl chloride (TBSCl; 7.70 g, 51.5 mmol). After stirring overnight, the solution was diluted with water (60 mL), and the aqueous layer was extracted with pentane. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the resulting product (pentane, R_f = 0.54) afforded **20** (8.07 g, 97%). IR (neat): $\tilde{\nu}$ = 3077 (w, ν=CH_2), 1640 (w, νC=C), 1471/1441 (m, δCH_2, CH_3), 1388/1362 (m, δCH_3), 1252 [m, ν$C(CH_3)_3$], 1083 (s, νSi–O–C), 833 (s, νSi–CH_3), 772 (s, δSi–CH_3) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6 H, $SiMe_2$), 0.86 (s, 9 H, CMe_3), 0.89/0.90 (2 d, J = 7.0 Hz, 3 H, 1′-Me, 3′-Me), 1.33 (dddt, J = 8.0, 5.0, 5.0, 5.0 Hz, 1 H, 2-H), 1.78 (sept.d, J = 7.0, 5.0 Hz, 1 H, 2′-H), 2.00 (dddt, J = 14.5, 8.0, 7.0, 1.5 Hz, 1 H, 3-H_b), 2.07 (dddt, J = 14.5, 7.0, 5.0, 1.5 Hz, 1 H, 3-H_a), 3.50 (dt, J = 10.0, 5.0 Hz, 2 H, 1-H_2), 4.93 (ddt, J = 10.0, 2.5, 1.5 Hz, 1 H, 5-H_E), 4.97 (ddt, J = 17.0, 2.5, 1.5 Hz, 1 H, 5-H_z), 5.75 (dddd, J = 17.0, 10.0, 7.0, 7.0 Hz, 1 H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 (q, $SiMe_2$), 18.2 (s, CMe_3), 19.4 (2 q, C-1′, C-3′), 25.9 (q, CMe_3), 27.6 (d, C-2′), 32.4 (t, C-3), 46.3 (d, C-2), 62.9 (t, C-1), 115.3 (t, C-5), 138.2 (d, C-4) ppm. MS (EI, 70 eV): m/z (%) = 242 (1) $[M]^+$, 185 (27) $[M - C_4H_9]^+$, 155 (13) $[M - C_6H_{15}]^+$, 129 (29) $[C_8H_{17}O]^+$, 101 (13) $[C_4H_9OSi]^+$, 89 (16) $[C_5H_{13}O]^+$, 75 (100) $[C_2H_7OSi]^+$, 59 (10) $[C_3H_7O]^+$, 41 (9) $[C_3H_5]^+$.

4-(*tert*-Butyldimethylsiloxy)-3-isopropylbutanal (21): At –78 °C under a N_2 atmosphere, ozone was bubbled through a solution of siloxy alkene **20** (5.23 g, 21.6 mmol) in MeOH (15 mL) and CH_2Cl_2 (60 mL) until a deep blue color persisted. Thiourea (2.46 g, 32.4 mmol) was then added, and the solution was warmed to room temperature and stirred at this temperature for 2 h prior to filtration through a pad of Celite. The filter cake was washed with water. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by silica gel FC (pentane/Et_2O = 95:5, R_f = 0.70) to provide **21** (3.58 g, 68%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 1726 (s, νC=O), 1471 (m, νCH_2, CH_3), 1252 [m, ν $C(CH_3)_3$], 1101 (s, νSi–O–C), 833 (s, νSi–CH_3), 774 (s, δSi–CH_3) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6 H, $SiMe_2$), 0.87 (s, 9 H, CMe_3), 0.88/0.90 (2 d, J = 7.0 Hz, 6 H, 1′-Me, 3′-Me), 1.76 (sept.d, J = 7.0, 5.0 Hz, 1 H, 1′-H), 2.04 (tdt, J = 8.0, 5.0, 5.0 Hz, 1 H, 3-H), 2.33 (ddd, J = 16.0, 5.0, 2.0 Hz, 1 H, 2-H_b), 2.38 (ddd, J = 16.0, 8.0, 5.0 Hz, 1 H, 2-H_a), 3.48 (dd, J = 10.0, 8.0 Hz, 1 H, 4-H_b), 3.65 (dd, J = 10.0, 5.0 Hz, 1 H, 4-H_a), 9.75 (dd, J = 3.0, 2.0 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.6 (q, $SiMe_2$), 18.2 (s, CMe_3), 19.3/20.1 (2 q, C-1′, C-3′), 25.8 (q, CMe_3), 28.5 (d, C-2′), 42.4 (d, C-3), 43.8 (t, C-2), 64.4 (t, C-4), 203.0 (d, C-1) ppm. MS (EI, 70 eV): m/z (%) = 244 (1) $[M]^+$, 229 (1) $[M - CH_3]^+$, 200 (1) $[M - C_2H_4O]^+$, 187 (20) $[M - C_4H_9]^+$, 169 (5) $[C_9H_{17}OSi]^+$, 157 (28) $[C_8H_{17}OSi]^+$, 143 (6) $[C_7H_{15}OSi]^+$, 131 (63) $[C_6H_{15}OSi]^+$, 115 (11) $[C_6H_{15}Si]^+$, 101 (34) $[C_6H_{13}O]^+$, 95 (50) $[C_7H_{11}]^+$, 75 (100) $[C_2H_7OSi]^+$, 59 (22) $[C_2H_7Si]^+$, 41 (16) $[C_3H_5]^+$.

5-Bromo-4-isopropylpent-1-ene (22): Triphenylphosphane (24.0 g, 91.0 mmol) was added portionwise at room temperature to a solution of 2-isopropylpent-4-en-1-ol (**19**; 7.81 g, 60.9 mmol) and tetrabromomethane (30.3 g, 91 mmol) in CH_2Cl_2 (180 mL), and the resulting mixture was stirred overnight at ambient temperature. The solvent was removed under reduced pressure, and the residue was diluted with pentane/Et_2O (1:1, 400 mL) and filtered. The filter cake was washed with pentane/Et_2O (1:1, 400 mL), and the combined filtrates were concentrated under reduced pressure. Repeated silica gel FC (pentane, 100%, R_f = 0.86) of the resulting residue afforded **22** (10.7 g, 92%). IR (neat): $\tilde{\nu}$ = 3077 (w, ν=CH_2), 1835 (w, δ = CH_2 oop), 1639 (w, νC=C), 1463/1436 (m, δCH_2, CH_3), 1386/1369 (m, δCH_3), 992 (s, $\delta CH{=}CH_2$), 669 (s, δC–Br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92/0.93 (2 d, J = 7.0 Hz, 6 H, 1′-Me, 3′-Me), 1.50 (dddt, J = 8.0, 7.0, 5.0, 5.0 Hz, 1 H, 4-H), 1.84 (oct., J = 7.0 Hz, 1 H, 2′-H), 2.09 (dddt, J = 14.0, 8.0, 8.0, 1.0 Hz, 1 H, 3-H_b), 2.27 (dddt, J = 14.0, 6.5, 5.0, 1.5 Hz, 1 H, 3-H_a), 3.44 (dd, J = 10.0, 5.0 Hz, 1 H, 5-H_b), 3.47 (dd, J = 10.0, 5.0 Hz, 1 H, 5-H_a), 5.06 (ddt, J = 10.0, 2.0, 1.0 Hz, 1 H, 1-H_E), 5.10 (ddt, J =

17.0, 2.0, 1.5 Hz, 1 H, 1-H_Z), 5.73 (dddd, J = 17.0, 10.0, 8.0, 6.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3/19.9 (2 q, C-1′, C-3′), 28.9 (d, C-2′), 33.8 (t, C-3), 36.9 (t, C-5), 45.9 (d, C-4), 116.8 (t, C-1), 136.5 (d, C-2) ppm. MS (EI, 70 eV): *m/z* (%) = 191/189 (1) $[M]^+$, 150/148 (11) $[M - C_3H_5]^+$, 111 (3) $[M - Br]^+$, 95 (6) $[C_7H_{11}]^+$, 69 (100) $[C_5H_9]^+$, 55 (21) $[C_4H_7]^+$, 41 (47) $[C_3H_5]^+$, 27 (6) $[C_2H_3]^+$. Odor description: agrestic, terpenic odor with aspects of wet soil, and leathery facets recalling shoe wax.

4-Bromo-3-isopropylbutanal (23): At –78 °C under a N_2 atmosphere, ozone was bubbled through a solution of bromoalkene **22** (5.54 g, 29.0 mmol) in CH_2Cl_2 (100 mL) and MeOH (20 mL) until a deep blue color persisted. Thiourea (3.31 g, 43.5 mmol) was then added, and the solution was warmed to room temperature and stirred at this temperature for 2 h prior to filtration through a pad of Celite. The filter cake was washed with water. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by silica gel FC (pentane/Et_2O = 95:5, R_f = 0.35) to provide **23** (1.68 g, 30%) as a yellowish oil. IR (neat): $\tilde{\nu}$ = 1721 (s, νC=O), 1465/1438 (w, δCH_2, CH_3), 1388/1370 (m, δCH_3), 653 (w, δC–Br) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91/0.93 (2 d, J = 7.0 Hz, 6 H, 1′-Me, 3′-Me), 1.84 (oct., J = 7.0 Hz, 1 H, 2′-H), 2.17 (tddd, J = 7.0, 6.5, 5.5, 4.5 Hz, 1 H, 3-H), 2.55 (ddd, J = 17.5, 5.5, 1.5 Hz, 1 H, 2-H_b), 2.68 (ddd, J = 17.5, 7.0, 1.5 Hz, 1 H, 2-H_a), 3.44 (dd, J = 10.0, 6.5 Hz, 1 H, 4-H_b), 3.52 (dd, J = 10.0, 4.5 Hz, 1 H, 4-H_a), 9.81 (t, J = 1.5 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3/19.7 (2 q, C-1′, C-3′), 29.7 (d, C-2′), 36.9 (t, C-4), 40.6 (d, C-3), 44.7 (t, C-2), 201.2 (d, C-1) ppm. MS (EI, 70 eV): *m/z* (%) = 193/191 (1) $[M]^+$, 150/148 (11) $[M - C_2H_4O]^+$, 95 (26) $[C_7H_{11}]^+$, 69 (100) $[C_5H_9]^+$, 55 (12) $[C_3H_3O]^+$, 41 (54) $[C_3H_5]^+$, 29 (5) $[CHO]^+$.

[2(1′)*E*]-[4′-(*tert*-Butyldimethylsiloxy)-3′-isopropylbutylidene]cyclopentanone (24): At room temperature under a N_2 atmosphere, a solution of aldehyde **21** (1.0 g, 4.09 mmol) in EtOH (7.0 mL) was added by syringe pump over a period of 60 min to a solution of cyclopentanone (7, 340 mg, 4.09 mmol) and potassium hydroxide (230 mg, 4.09 mmol) in EtOH (7.0 mL) and CH_2Cl_2 (5.0 mL). The resulting mixture was stirred for 2 h at this temperature, quenched by addition of half-satd. aq. NH_4Cl solution (50 mL), and extracted with Et_2O (3× 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel FC (pentane/Et_2O = 9:1, R_f = 0.41) of the resulting residue afforded **24** (600 mg, 47%) as a yellowish oil. IR (neat): $\tilde{\nu}$ = 1721 (m, νC=O), 1649 (m, νC=C), 1471 (w, νCH_2, CH_3), 1251 [m, ν $C(CH_3)_3$], 1094 (s, νSi–O–C), 834 (s, νSi–CH_3), 773 (s, δSi–CH_3) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6 H, $SiMe_2$), 0.88 (s, 9 H, CMe_3), 0.89/0.90 (2 d, J = 7.0 Hz, 6 H, 1′′-Me, 3′′-Me), 1.50 (tddd, J = 7.5, 7.0, 6.0, 5.0 Hz, 1 H, 3′-H), 1.78 (sept.d, J = 6.5, 5.5 Hz, 1 H, 2′′-H), 1.88–1.97 (m, 2 H, 4-H_2), 2.12–2.17 (m, 2 H, 2′-H_2), 2.33 (t, J = 8.0 Hz, 2 H, 5-H_2), 2.60 (ttd, J = 10.0, 5.0, 3.0 Hz, 2 H, 3-H_2), 3.49 (dd, J = 10.0, 6.0 Hz, 1 H, 4′-H_b), 3.55 (dd, J = 10.0, 5.0 Hz, 1 H, 4′-H_a), 6.59 (tt, J = 7.5, 3.0 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.5 (2 q, $SiMe_2$), 18.2 (s, *C*Me_3), 19.7/19.8 (2 q, C-1′′, C-3′′), 19.9 (t, C-4), 25.9 (3 q, C*Me*$_3$), 26.8 (t, C-3), 28.0 (d, C-2′′), 28.4 (t, C-2′), 38.6 (t, C-5), 46.7 (d, C-3′), 63.2 (t, C-4′), 136.1 (d, C-1′), 137.6 (s, C-2), 206.9 (s, C-1) ppm. MS (EI, 70 eV): *m/z* (%) = 310 (1) $[M]^+$, 295 (1) $[M - CH_3]^+$, 253 (54) $[M - C_4H_9]^+$, 197 (20) $[C_{12}H_{21}O_2]^+$, 169 (41) $[C_9H_{17}OSi]^+$, 161 (20) $[C_{11}H_{13}O]^+$, 133 (13) $[C_9H_9O]^+$, 75 (100) $[C_2H_7OSi]^+$, 69 (11) $[C_5H_9]^+$, 55 (18) $[C_3H_3O]^+$, 41 (15) $[C_3H_5]^+$.

2-(4′-Isopropyltetrahydrofuran-2′-yl)cyclopentanone (25): At room temperature, a solution of $RhCl_3$ (6.7 mg, 0.03 mmol) in water (0.5 mL) was added to a solution of ketone **24** (210 mg, 0.677 mmol) in EtOH (6.0 mL). The resulting mixture was heated at reflux overnight and allowed to cool to room temperature prior to pouring into ice/water (1:1, 10 mL). The aqueous layer was extracted with Et_2O (3× 10 mL), and the combined organic extracts were washed with satd. aq. Na_2CO_3 and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by silica gel FC (pentane/Et_2O = 19:1, R_f = 0.89) to afford **25** (20 mg, 15%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 1737 (s, νC=O) cm^{-1}. ^{1}H NMR (600 MHz, C_6D_6): δ = 0.66 (m_c, 3 H, 3′′-H_3), 0.76 (m_c, 3 H, 1′′-H_3), 1.06 (q, J = 8.0 Hz, 1 H, 3′-H_b), 1.17 (m_c, 1 H, 2′′-H), 1.25 (m_c, 2 H, 4-H_2), 1.44 (m_c, 1 H, 4′-H), 1.74 (m_c, 2 H, 3-H_2), 1.87 (m_c, 1 H, 3′-H_a), 1.88 (m_c, 1 H, 2-H), 1.90 (m_c, 2 H, 5-H_2), 3.17 (t, J = 8.5 Hz, 1 H, 5′-H_b), 3.86 (t, J = 8.5 Hz, 1 H, 5′-H_a), 4.20 (m_c, 1 H, 2′-H) ppm. ^{13}C NMR (150 MHz, C_6D_6): δ = 21.0 (t, C-4), 21.5/21.6 (2 d, C-1′′, C-3′′), 25.0 (t, C-3), 32.3 (d, C-2′′), 36.3 (t, C-3′), 38.8 (t, C-5), 47.6 (d, C-4′), 52.9 (d, C-2), 72.4 (t, C-5′), 79.0 (d, C-2′), 216.4 (C-1) ppm. MS (EI, 70 eV): *m/z* (%) = 196 (5) $[M]^+$, 153 (5) $[M - C_3H_7]^+$, 113 (100) $[C_7H_{13}O]^+$, 95 (72) $[C_6H_7O]^+$, 83 (13) $[C_5H_7O]^+$, 69 (59) $[C_5H_9]^+$, 55 (37) $[C_4H_7]^+$, 43 (52) $[C_3H_7]^+$, 27 (12) $[C_2H_3]^+$. Odor description: woody, recalling Atlas cedarwood [*Cedrus atlantica* (Endl.) Manetti], and green-floral note with jasminic aspects, and a slight mushroom character.

[2(1′)*E*]-2-[(2′-Isopropylcyclopropyl)methylene]cyclopentanone (26): At 40 °C, a 5% aq. NaOH solution (100 mL, 125 mmol) was added dropwise to a solution of aldehyde **23** (240 mg, 1.24 mmol) and cyclopentanone (**7**, 150 mg, 1.86 mmol) in distilled water (200 mL). The resulting mixture was stirred for 1 h at 40 °C, allowed to cool down to room temperature, and extracted with Et_2O (3× 150 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography on silica gel (pentane/Et_2O = 19:1, R_f = 0.25) provided **26** (60.0 mg, 27%) as a yellowish oil. IR (neat): $\tilde{\nu}$ = 1712 (s, νC=O), 1633 (s, νC=C), 1464 (w, νCH_2, CH_3) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79–0.92 (m, 3 H, 2′′-H, 3′′-H_2), 0.97/0.98 (2 d, J = 7.5 Hz, 6 H, 1′′′-Me, 3′′′-Me), 1.04 (m_c, 1 H, 1′′-H), 1.26 (sept.d, J = 7.5, 5.0 Hz, 1 H, 2′′′-H), 1.90–2.01 (m, 2 H, 4-H_2), 2.32 (t, J = 8.0 Hz, 2 H, 5-H_2), 2.70 (tt, J = 7.0, 3.0 Hz, 2 H, 3-H_2), 6.01 (dt, J = 11.0, 2.5 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6 (t, C-3′′), 19.8 (d, C-1′′), 19.9 (t, C-4), 21.7/21.9 (2 d, C-1′′′, C-3′′′), 26.7 (t, C-3), 31.4 (d, C-2′′), 32.8 (d, C-2′′′), 38.4 (t, C-5), 134.2 (s, C-2), 141.4 (d, C-1′), 206.4 (s, C-1) ppm. MS (EI, 70 eV): *m/z* (%) = 178 (6) $[M]^+$, 121 (100) $[C_8H_9O]^+$, 107 (7) $[C_7H_7O]^+$, 69 (19) $[C_5H_9]^+$, 55 (10) $[C_4H_7]^+$, 41 (18) $[C_3H_5]^+$, 27 (4) $[C_2H_3]^+$. Odor description: fruity, butyric-sweaty, reminiscent of overripe pineapple and durian fruit.

1-Trimethylsiloxy-3-vinylcyclopent-1-ene (12): At –78 °C under a N_2 atmosphere, a solution of *t*BuLi (1.7 M in THF, 100 mL, 170 mmol) was added dropwise to a stirred solution of vinylmagnesium bromide (1 M in THF, 85 mL, 85 mmol), diluted by additional THF (150 mL). Stirring was continued at this temperature for 1 h, prior to rapid addition of CuI (8.10 g, 42.5 mmol). The resulting mixture was warmed to 0 °C over 10 min and then cooled back down to –78 °C prior to the dropwise addition of a solution of cyclopen-2-en-1-one (**27**; 3.46 g, 42.1 mmol) in THF (20 mL). After 45 min at the same temperature, a solution of chlorotrimethylsilane (1.0 M in THF, 6.46 g, 59.5 mmol) was added within 5 min, and the resulting mixture was warmed to 0 °C and stirred at this temperature for 1 h, prior to quenching with a half-satd. $NaHCO_3$ solution (50 mL). After filtration through a pad of Celite and extraction with pentane (2× 50 mL), the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Kugelrohr distillation of the resulting residue afforded **12** (4.60 g,

60%) as a colorless liquid. IR (neat): $\tilde{\nu}$ = 1640 (s, νC=C), 867 (s, νSi–CH_3) cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ = 0.14 (s, 9 H, $SiMe_3$), 1.39 (dddd, J = 13.0, 9.5, 7.0, 5.5 Hz, 1 H, 4-H_b), 1.84 (dtd, J = 13.0, 8.0, 4.5 Hz, 1 H, 4-H_a), 2.12 (dddt, J = 17.0, 8.0, 7.0, 2.0 Hz, 1 H, 5-H_b), 2.16 (dddt, J = 17.0, 9.5, 8.0, 2.0 Hz, 1 H, 5-H_a), 3.12 (ddddt, J = 7.0, 5.5, 4.5, 2.0, 1.0 Hz, 1 H, 3-H), 4.53 (q, J = 2.0 Hz, 1 H, 2-H), 4.78 (ddd, J = 10.0, 2.0, 1.0 Hz, 1 H, 2′-H_Z), 4.91 (ddd, J = 17.0, 2.0, 1.0 Hz, 1 H, 2′-H_E), 5.68 (ddd, J = 17.0, 10.0, 7.0 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = –0.32 (s, $SiMe_3$), 28.8 (t, C-4), 33.4 (t, C-5), 46.2 (d, C-3), 104.6 (d, C-2), 111.9 (t, C-2′), 143.8 (d, C-1′), 156.1 (s, C-1) ppm. MS (EI, 70 eV): m/z (%) = 182/181 (77) $[M]^+$, 167 (17) $[M – CH_3]^+$, 155 (22) $[M – C_2H_3]^+$, 151 (5) $[C_9H_{15}OSi – CH_3]^+$, 139 (3) $[C_8H_{15}OSi – CH_3]^+$, 111 (2) $[C_7H_{10}O]^+$, 75 (32) $[C_2H_7OSi]^+$, 73 (100) $[C_3H_9Si]^+$, 59 (5) $[C_3H_7O]^+$, 45 (15) $[C_2H_5O]^+$, 39 (4) $[C_3H_3]^+$, 27 (2) $[C_2H_3]^+$.

[2(1′)*E*]-(4′-Bromo-3′-isopropylbutylidene)-3-vinylcyclopentanone (28): At –78 °C under an Ar atmosphere, $BF_3{\cdot}OEt_2$ (2.21 g, 15.5 mmol) was added dropwise to a solution of silyl enolate **12** (4.20 g, 23.0 mmol) and bromo aldehyde **23** (3.00 g, 15.5 mmol) in freshly distilled CH_2Cl_2 (80 mL). The resulting mixture was stirred at the same temperature for 2 h and quenched by the dropwise addition of half-satd. $NaHCO_3$ solution (50 mL). The solution was then warmed up to room temperature, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Silica gel FC (pentane/Et_2O = 8:2, R_f = 0.12) of the resulting mixture afforded diastereoisomeric mixture **28** (2.70 g, 61%) as brownish oil. IR (neat): $\tilde{\nu}$ = 1719 (s, νC=O), 1645 (s, νC=C), 914 (s, δCH=CH_2), 648 (w, δC–Br) cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ = 0.63 [tt, J = 7.0, 3.0 Hz, 6 H, 3′-CH(CH_3)$_2$], 0.84/1.10 (m_c, 1 H, 3′-H), 1.36/1.58 (2 m_c, 2 H, 4′-H_2), 1.58 [m_c, 1 H, 3′-CH(CH_3)$_2$], 1.97/2.08 (2 m_c, 2 H, 5-H_2), 2.13 (m_c, 2 H, 2′-H_2), 2.98/3.10 (2 dd, J = 10.5/10.5, 7.0/5.0 Hz, 2 H, 4-H_2), 3.21/3.48 (m_c, 1 H, 3-H), 4.88 (m_c, 2 H, 2′′-H_2), 5.57 (ddd, J = 15.0, 10.0, 7.0 Hz, 1 H, 1′′-H), 6.62/6.69 (2 ddd, J = 9.5/8.0, 6.5/7.0, 2.0/2.5 Hz, 1 H, 1′-H) ppm. ^1H–^1H NOESY (C_6D_6): 3-H × 2′-H. ^{13}C NMR (100 MHz, C_6D_6): δ = 19.1/19.2 [2 q, CH(CH_3)$_2$-3′], 19.4/19.5 [2 q, CH(CH_3)$_2$-3′], 26.4/26.5 (2 t, C-2′), 29.0/29.4 (2 t, C-4′), 29.2/29.4 [2 d, CH(CH_3)$_2$-3′], 35.9 (t, C-5), 36.5/37.1 (2 t, C-4), 42.6/42.7 (2 d, C-3), 45.7/46.2 (2 d, C-3′), 114.2/114.4 (2 t, C-2′′), 135.4/135.5 (2 d, C-1′′), 139.5/139.7 (2 d, C-1′), 139.9/140.1 (2 s, C-2), 203.6/203.7 (2 s, C-1) ppm. MS (EI, 70 eV): m/z (%) = 284 (15) $[M]^+$, 241 (100) $[M – C_3H_7]^+$, 205 (32) $[M – Br]^+$, 191 (11) $[C_{14}H_{21}O – CH_2]^+$, 161 (30) $[C_{11}H_{14}BrO – HBr]^+$, 147 (19) $[C_{11}H_{13}O – CH_2]^+$, 135 (77) $[C_{11}H_{13}O – C_2H_3]^+$, 121 (44) $[C_3H_7Br]^+$, 79 (85) $[Br]^+$, 69 (43) $[C_5H_9]^+$, 55 (36) $[C_3H_3O]^+$, 41 (50) $[C_3H_5]^+$, 27 (11) $[C_2H_3]^+$. HRMS (EI): calcd. for $C_{14}H_{23}OBr$ $[M]^+$ 284.07758; found 284.07655. HRMS (EI): calcd. for $C_{14}H_{23}O^{81}Br$ $[M]^+$ 286.07553; found 286.07476.

2-(4′-Bromo-3′-isopropylbutyl)-3-vinylcyclopentanone (29): At room temperature under an Ar atmosphere, a solution of $ZnCl_2$ (1 M in Et_2O, 0.30 g, 2.26 mmol) was added to a stirred solution of dienone **28** (290 mg, 1.02 mmol) in THF (5 mL) prior to the rapid addition of $Pd(PPh_3)_4$ (36.0 mg, 0.030 mmol). After stirring for 5 min at this temperature, Bu_3SnH (0.59 mL, 2.05 mmol, 97%) was added dropwise with stirring, and stirring was continued for 2 h, prior to the dropwise addition of water (5.0 mL). The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography on silica gel/K_2CO_3 (10% w/w, pentane/Et_2O = 19:1, R_f = 0.16) afforded bromo ketone **29** (240 mg, 82%) as a yellowish oil. IR (neat): $\tilde{\nu}$ = 1735 (s, νC=O), 1638 (w, νC=C), 912 (s, δCH=CH_2), 651 (w, δC–Br) cm^{-1}. ^1H NMR (600 MHz, C_6D_6): δ = 0.74/0.75/0.76/0.77 (4 d, J = 7.0 Hz, 6 H, 1′′′-,3′′′-Me), 1.05 (m_c, 1 H, 4-H_b), 1.16 (m_c, 1 H, 3′-H), 1.33 (m_c, 1 H, 2′-H_b), 1.35 (m_c, 1 H, 1′-H_b), 1.38 (m_c, 1 H, 2′-H_a), 1.40/1.42 (2 m_c, 1 H, 2-H), 1.46 (m_c, 1 H, 1′-H_a), 1.55 (m_c, 1 H, 4-H_a), 1.64/1.66 (2 m_c, 1 H, 5-H_b), 1.73/1.74 (2 m_c, 1 H, 2′′′-H), 1.94/1.98 (2 m_c, 1 H, 5-H_a), 1.99/2.01 (2 m_c, 1 H, 3-H), 3.18/3.22 (2 m_c, 2 H, 4′-H_2), 4.51/4.71 (2 m_c, 2 H, 2′′-H_2), 5.44/5.46 (2 m_c, 1 H, 1′′-H) ppm. ^{13}C NMR (150 MHz, C_6D_6): δ = 19.4/19.5/19.6/19.7 (4 q, C-1′′′,-3′′′), 25.3/25.8 (2 t, C-1′), 26.5/26.6 (2 t, C-4), 27.6/27.7 (2 t, C-2′), 29.4/29.5 (2 d, C-2′′′), 37.1/37.2 (2 t, C-4′), 37.3 (t, C-5), 46.5/46.6 (2 d, C-3), 47.1 (d, C-3′), 54.1/54.2 (2 d, C-2), 115.0/115.1 (2 t, C-2′′), 141.2/141.3 (2 d, C-1′′), 216.6/216.7 (2 s, C-1) ppm. MS (EI, 70 eV): m/z (%) = 259 (1) $[M – C_2H_3]^+$, 207 (5) $[M – Br]^+$, 189 (5) $[C_{14}H_{21}]^+$, 163 (2) $[C_{11}H_{16}O]^+$, 137 (3) $[C_9H_{13}O]^+$, 123 (3) $[C_8H_{11}O]^+$, 110 (100) $[C_7H_{10}O]^+$, 95 (13) $[C_6H_7O]^+$, 79 (8) $[Br]^+$, 67 (11) $[C_5H_7]^+$, 55 (11) $[C_4H_7]^+$, 41 (11) $[C_3H_5]^+$, 27 (2) $[C_2H_3]^+$. HRMS (EI): calcd. for $C_{14}H_{23}O^{79}Br$ $[M]^+$ 286.09323; found 286.09191. HRMS (EI): calcd. for $C_{14}H_{23}O^{81}Br$ $[M]^+$ 288.09118; found 288.09147.

(4*R,5*R**)-7-Isopropyl-4-vinylspiro[4.4]nonan-1-one [(4*R**,5*R**)-2]:** At –78 °C under an Ar atmosphere, a solution of *n*BuLi (2.7 M in heptane, 0.80 mL, 2.09 mmol) was added dropwise to a stirred solution of diisopropylamine (0.30 mL, 2.09 mmol) in THF/DMPU (5:1, 6.0 mL). The resulting mixture was warmed to 0 °C over 10 min and cooled back down to –78 °C prior to the dropwise addition of a solution of bromo ketone **29** (400 mg, 1.39 mmol) in THF (4.0 mL). The solution was stirred at the same temperature for 1 h, and then allowed to slowly warm up to room temperature over 4 h. The reaction mixture was then poured into water (50 mL), and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel FC of the resulting product (pentane/Et_2O = 19:1, R_f = 0.32) afforded (4*R**,5*R**)-**2** (160 mg, 56%) as a yellowish odoriferous liquid. IR (neat): $\tilde{\nu}$ = 1735 (s, νC=O), 1638 (w, νC=C), 914 (s, δCH=CH_2) cm^{-1}.

Tentative (4*R,5*R**,7*R**)-Diastereomer:** ^1H NMR (600 MHz, C_6D_6): δ = 0.86/0.89 (2 d, J = 7.0 Hz, 6 H, 1′′-Me, 3′′-Me), 0.97 (dd, J = 12.5, 11.0 Hz, 1 H, 6-H_b), 1.02 (ddd, J = 23.0, 11.0, 8.0 Hz, 1 H, 8-H_b), 1.28 (dsept., J = 8.0, 7.0 Hz, 1 H, 2′′-H), 1.31 (m_c, 1 H, 3-H_b), 1.38 (m_c,1 H, 9-H_b), 1.50 (m_c, 1 H, 9-H_a), 1.56 (m_c, 1 H, 3-H_a), 1.71–1.76 (m, 1 H, 8-H_a), 1.82 (m_c, 1 H, 2-H_b), 1.88 (m_c, 1 H, 7-H), 2.01 (m_c, 1 H, 2-H_a), 2.03 (m_c, 1 H, 6-H_a), 2.06 (m_c, 1 H, 4-H), 4.92 (ddd, J = 17.0, 2.5, 1.0 Hz, 1 H, 2′-H_E), 4.98 (ddd, J = 10.0, 2.5, 1.0 Hz, 1 H, 2′-H_Z), 5.58 (ddd, 17.0, 10.0, 7.0 Hz, 1 H, 1′-H) ppm. ^1H–^1H NOESY (C_6D_6): 4-H_{ax} × 6-H_b, 6-H_a × 1′′-Me, 6-H_b × 2′′-H. ^{13}C NMR (150 MHz, C_6D_6): δ = 21.7/21.8 (2 q, C-1′′, C-3′′), 25.4 (t, C-3), 30.4 (t, C-9), 31.8 (t, C-8), 33.8 (d, C-2′′), 35.3 (t, C-2), 39.7 (t, C-6), 48.0 (d, C-7), 51.5 (d, C-4), 58.8 (s, C-5), 116.3 (t, C-2′), 137.7 (d, C-1′), 220.0 (s, C-1) ppm.

Tentative (4*R,5*R**,7*S**)-Diastereomer:** ^1H NMR (600 MHz, C_6D_6): δ = 0.88/0.90 (2 d, J = 7.0 Hz, 6 H, 1′′-Me, 3′′-Me), 1.28 (m_c, 1 H, 3-H_b), 1.35 (m_c, 2 H, 9-H_2), 1.36 (m_c, 1 H, 8-H_b), 1.45 (m_c, 1 H, 7-H), 1.47 (m_c, 1 H, 6-H_b), 1.48 (m_c, 1 H, 2′′-H), 1.52 (m_c, 1 H, 3-H_a), 1.60 (m_c, 1 H, 8-H_a), 1.80 (m_c, 1 H, 6-H_a), 1.81 (m_c, 1 H, 2-H_b), 2.08 (m_c, 1 H, 2-H_a), 2.12 (m_c, 1 H, 4-H), 4.93 (ddd, J = 17.0, 2.5, 1.0 Hz, 1 H, 2′-H_E), 4.99 (ddd, J = 10.0, 2.5, 1.0 Hz, 1 H, 2′-H_Z), 5.62 (ddd, J = 17.0, 10.0, 7.0 Hz, 1 H, 1′-H) ppm. ^{13}C NMR (150 MHz, C_6D_6): δ = 21.8/21.9 (2 q, C-1′′′, C-3′′′), 24.6 (t, C-3), 30.0 (t, C-9), 30.7 (t, C-8), 33.7 (d, C-2′′′), 35.2 (t, C-2), 38.5 (t, C-6), 48.7 (d, C-7), 50.9 (d, C-4), 59.1 (s, C-5), 116.1 (t, C-2′), 138.0 (d, C-1′), 219.0 (s, C-1) ppm. MS (EI, 70 eV):

m/z (%) = 206 (32) $[M]^+$, 191 (18) $[M - CH_3]^+$, 163 (45) $[M - C_3H_7]^+$, 150 (21) $[C_{11}H_{18}]^+$, 135 (19) $[C_9H_{12}O]^+$, 123 (100) $[C_8H_{10}O]^+$, 109 (41) $[C_7H_9O]^+$, 91 (33) $[C_7H_7]^+$, 84 (30) $[C_6H_{12}]^+$, 67 (32) $[C_5H_7]^+$, 55 (20) $[C_4H_7]^+$, 41 (26) $[C_3H_5]^+$, 27 (6) $[C_2H_3]^+$. HRMS (EI): calcd. for $C_{14}H_{22}O$ $[M]^+$ 206.16707; found 206.16672. Odor description: floral, rosy, green, geranium-like, in the direction of Petalia [**32**, 2-cyclohexylidene-2-(*o*-tolyl)acetonitrile] and Magnolan (2,4-dimethyl-4,4a,5,9b-tetrahydroindeno[1,2-*d*][1,3]dioxine), with some slightly fatty-metallic facets. Odor threshold: 42.0 ng L^{-1} air.

Supporting Information (see footnote on the first page of this article): NMR spectra.

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