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Total Synthesis and Olfactory Evaluation of (1*R**,3*S**,6*S**,7*S**,8*S**)-3-Hydroxy-6,8-dimethyltricyclo[5.3.1.0^{3,8}]undecan-2-one: A New Synthetic Route to the Patchoulol Skeleton

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Dedicated with best wishes to Dr. Charles Fehr on the occasion of his 60th birthday

Keywords: Fused-ring systems / Olfactory properties / Patchouli / Prins reaction / Structure–activity relationships

The superposition analysis of (–)-patchoulol (**1**), the odorous principle of patchouli oil, with the recently discovered high-impact spirocyclic patchouli odorant (+)-(1*S*,4*R*,5*R*,9*S*)-1-hydroxy-1,4,7,7,9-pentamethylspiro[4.5]decan-2-one (**2**) resulted in the question as to whether a patchoulol derivative in which the *gem*-dimethyl group is replaced by a carbonyl function would be a powerful patchouli odorant. The total synthesis of the racemic superstructure (1*R**,3*S**,6*S**,7*S**,8*S**)-3-hydroxy-6,8-dimethyltricyclo[5.3.1.0^{3,8}]undecan-2-one (**3**) was accomplished in 13 steps from the inexpensive commercial odorant Cyclal C (**7**) with a total yield of 7 %. Conversion of **7** to the corresponding enamine **8** and subsequent copper-catalyzed oxidative degradation afforded 2,4-dimethylcyclohex-3-enone (**6**), which was subjected to a Robinson annulation with 1,4-dimethoxybutan-2-one (**9**). The carbonyl function of the resulting annulation product **10** was removed by LAH reduction, acylation with Ac_2O, and dissolving metal reduction. The deoxygenated methyl enol ether **12** thus obtained was then cleaved by mild hydrolysis with oxalic acid, and the resulting 2,9-dimethyl-Δ^1-octalin-5-one (**5**) was hydroxymethylenated by Claisen ester condensation with ethyl formate to provide the *cis*-configured (2Z)-2,3,4,4a,8,8a-hexahydro-2-(hydroxymethylene)-4a,6-dimethylnaphthalen-1(7*H*)-one (**4**). In a novel intramolecular Prins reaction with an equimolar amount of *p*-toluenesulfonic acid monohydrate, the ideally preformed precursor **4** cyclized to (1*R**,2*R**,3*S**,7*R**,8*S**)-2-hydroxy-4,8-dimethyltricyclo[5.3.1.0^{3,8}]undec-4-en-11-one (**13**), comprising the complete carbon framework of the target compound **3**. A Barton–McCombie deoxygenation of the corresponding *O*-phenoxythiocarbonyl derivative, followed by oxidation of the lithium enolate of the resulting ketone **14** with the molybdenum peroxide reagent MoO_5–pyridine–DMPU, and the face-selective hydrogenation of the obtained (1*R**,3*S**,7*S**,8*S**)-3-hydroxy-6,8-dimethyltricyclo[5.3.1.0^{3,8}]-undec-5-en-2-one (**15**) concluded the synthesis of the target molecule **3**, which was accompanied by its odorless C-6 epimer *epi*-**3** in the ratio 84:16. Both the target structure **3** and its unsaturated precursor **15** possessed pronounced patchouli odors, albeit slightly weaker in threshold than (–)-patchoulol (**1**). This proved the superposition analysis of the templates **1** and **2** to be correct and provided novel insight into the structural requirements of patchouli odorants. As **3** was an intermediate in a total synthesis of *rac*-**1**, the synthesis also constitutes a new formal total synthesis of racemic patchoulol (*rac*-**1**).

"*Kudra doused him with enough patchouli to stampede a herd of elephants. His eyes flew open like the hatch covers of an exploding ship, and he commenced to sniff at his extremities, as if he were wildly in love with himself.*"

Tom Robbins, '*Jitterbug Perfume*'[1]

Introduction

Patchouli, the name of which was borrowed from the Tamil *'patch ilai'* for *'green leaf'*, became popular in Europe in the early 19th century with the fashion of cashmere shawls that accompanied the tiny bodices that revealed the necklines of elegant ladies. To protect the fine cashmere wool on its long voyage to Europe, the precious folds of cloth were layered with leaves of patchouli, which was the most effective moth repellant then known. Its woody-balsamic scent with its well-balanced herbaceous, earthy, camphoraceous, and floral facets soon turned out to be as much a draw for buyers as the colorful cashmere itself, and thus patchouli rose from a bug repellant to a popular perfumery raw material. The recently released perfume "Bornéo 1834"

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(Les Salons du Palais Royal Shiseido, 2005) by Christopher Sheldrake and Serge Lutens tells this story with the extreme content of 57% (!) decolorized patchouli oil juxtaposed to about 8% of Iso E Super® and Vertofix® each and 1% of *Cyperus scariosus* oil, and then skillfully contrasted with a bitter-sweet, nutty chocolate accord around the 2,3,5-trimethylpyrazine-containing base Chocovan as well as with the incense-like smelling opoponax resinoid and myrrh extract: Early in 1834, Paris went literally crazy for the patchouli-scented fabrics imported via Borneo, Java, and Sumatra, while the resulting crisis of the local textile industry in Lyon culminated in April in an uprising of the weavers with some three hundred victims.

Nowadays, well over 1200 tons of patchouli oil is produced *per annum* by steam distillation of the dried and fermented leaves of *Pogostemon cablin* (Blanco) Benth. (syn. *Pogostemon patchouli* Pellet). The 40–90-cm tall scrub is cultivated not only in Indonesia, Malaysia, and the Philippines, but also in India, China, Madagascar, the Seychelles, the West Indies, Brazil, and Uruguay. With a content of 35–40%, the sesquiterpene alcohol (–)-patchoulol (**1**, Figure 1) is the main component of the essential oil and contributes markedly to its characteristic odor. Several total syntheses of racemic and enantiopure **1** have been reported,[2–10] but not surprisingly, no route to this complex tricyclic structure proved commercially feasible. Due to its low price of around $40–50/kg, no other synthetic odorant has thus far been able to compete with patchouli oil.

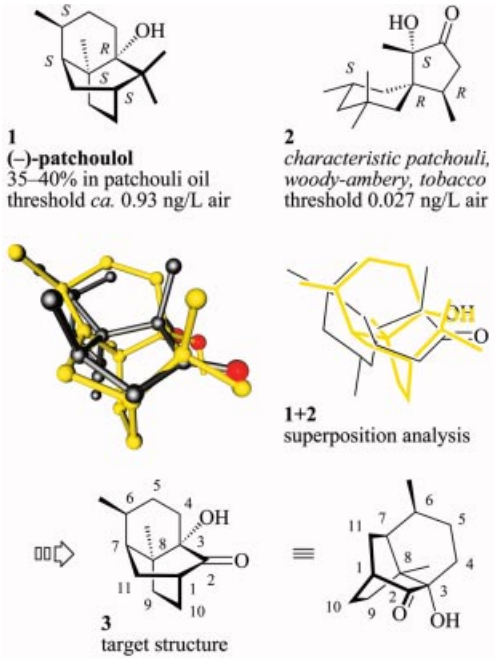
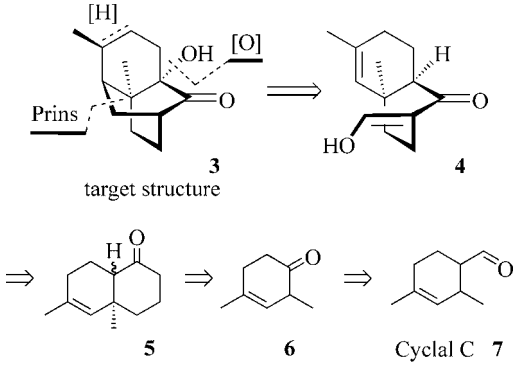


Figure 1. (–)-Patchoulol (**1**), the high-impact spirocyclic α-ketol **2**, and the target compound **3** that was derived by superposition analysis of the former two.

Recently, however, we discovered a very powerful patchouli odorant of structure **2**[11] which possesses an odor threshold of 0.027 ng/L air, over 30 times lower than that of **1** (0.93 ng/L air). Except for the fruity, the sweet and the floral family, no intense bifunctional odorants with a proton-donor–proton-acceptor unit within a 3-Å distance[12] were known, and thus the ketol motive of **2** was a striking exception for a patchouli odorant. It was therefore tempting to superimpose the spirocyclic hydroxyketone **2** on the tricyclic alcohol **1**, the odorous principle of patchouli oil.[11] As shown in Figure 1, the two structures match best when the *gem*-dimethyl-substituted carbon atom of (–)-patchoulol (**1**) lies over the carbonyl carbon atom of **2**. This raises the question as to whether a patchoulol derivative in which the *gem*-dimethyl group is replaced by a carbonyl function would smell patchouli-like, and how intensely it would do so. If the superstructure **3** reflects the true geometry in which the patchouli odorants **1** and **2** are bound to the receptor(s), it actually could even be more potent than (–)-patchoulol (**1**).

Surprisingly, this target structure **3** had already been prepared by Yamada et al.[6] as an intermediate in the total synthesis of (±)-patchoulol and (±)-seychellene via the base-catalyzed cyclization of a cyclohexenone derivative. However, no odor description had been reported for **3**, so it was very exciting to examine if simply no attention had been paid to the olfactory properties or if the compound was odorless after all. Since Yamada et al.[6] had introduced the ketol function of **3** by selective α-hydroxylation of the corresponding lithium enolate with the molybdenum peroxide reagent (MoO_5–pyridine–HMPA, MoOPH),[13] it seemed reasonable to introduce the hydroxy function at the end of the synthetic sequence in the same way. For the construction of the tricyclic homoisotwistane skeleton, we wanted, however, to explore a new route via an intramolecular Prins reaction. This approach should afford the correct stereochemistry at C-4 by a simple hydrogenation. As delineated in Scheme 1, the Prins retron reveals the hydroxymethylene ketone **4** as the synthetic precursor, which was expected to epimerize readily at the bridgehead carbon atoms under acidic reaction conditions and react out of this *cis*/*trans*-equilibrium. The hydroxymethylene moiety can be introduced by a classical Claisen ester condensation with ethyl formate, which gives 3,4,4a,7,8,8a-hexahydro-4a,6-dimethylnaphthalen-1(2*H*)-one (**5**). This octalinone **5** could be synthesized from 2,4-dimethylcyclohex-3-enone (**6**) by a Robinson annulation with a methoxymethyl vinyl ketone

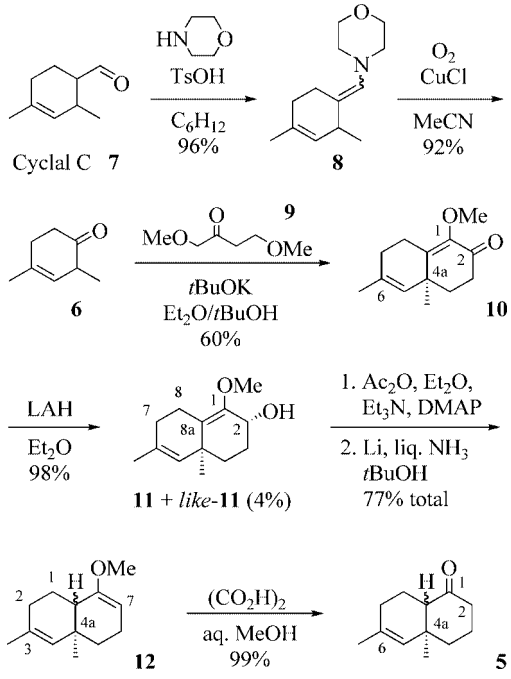


Scheme 1. Retrosynthetic analysis of the target superstructure **3**.

synthon according to the methodology of Wenkert et al.,[14] followed by reductive removal of the carbonyl function formed, for instance by Wolff–Kishner reduction. The required deconjugated cyclohexenone **6** is not yet known in the literature, but should be easy to obtain on a multigram scale without isomerization from the inexpensive commercial odorant Cyclal C (**7**, ca. $30/kg) by copper-catalyzed oxygenation of its enamine according to the protocol of van Rheenen.[15]

Results and Discussion

Following the synthetic plan sketched out above, Cyclal C (**7**) was first converted into its enamine **8** by standard reaction with morpholine in refluxing cyclohexane in the presence of catalytic amounts of *p*-toluenesulfonic acid monohydrate with azeotropic removal of the formed water in a Dean–Stark trap (Scheme 2). The morpholine enamine **8** was thus obtained in 96% yield by distillation in vacuo. While aldehyde enamines such as **8** are stable towards molecular oxygen at ambient temperature, they readily react with oxygen in the presence of catalytic amounts of copper(I) chloride under oxidative cleavage of the enamine double bond.[15] The process hence results in an amine *N*-carbaldehyde and the corresponding carbonyl compound without the formyl group. The copper-catalyzed oxidative degradation of the morpholine enamine **8** in acetonitrile at 30±2 °C went smoothly and furnished the required building block 2,4-dimethylcyclohex-3-enone (**6**) after distillation in an excellent 92% yield. The deconjugated cyclohexenone **6** proved astonishingly stable towards isomerization, even upon prolonged storage.



Scheme 2. Synthesis of the central intermediate 3,4,4a,7,8,8a-hexahydro-4a,6-dimethylnaphthalen-1(2*H*)-one (**5**).

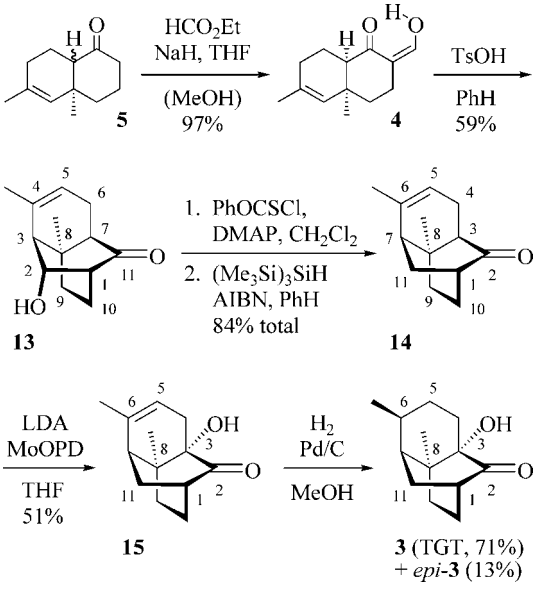
In the next step, this cyclohex-3-enone **6** was subjected to a Robinson annulation with 1,4-dimethoxybutan-2-one (**9**), which was introduced by Wenkert et al.[14] as a synthetic equivalent of 1-methoxybut-3-en-2-one. The convenient annulation reagent **9** was prepared according to the protocol of Hennion and Kupiecki[16] from but-2-yne-1,4-diol in 79% total yield by alkylation of the alcoholate with dimethyl sulfate and hydration of the resulting butynediol dimethyl ether with catalytic amounts of red mercury(II) oxide and sulfuric acid in aqueous methanol. Condensation of this reagent **9** with 2,4-dimethylcyclohex-3-enone (**6**) was conducted between –10 °C and –5 °C by employing catalytic amounts of potassium *tert*-butoxide as base in *tert*-butanol/diethyl ether. The annulation product **10** was obtained after purification by chromatography in 60% yield as crystalline material. Besides the main product **10**, the conjugated 2,4-dimethylcyclohex-2-enone was obtained in 28% yield, formed by isomerization of the starting material **6**.

Next, the carbonyl function of **10** had to be removed, but since all attempts to attain this by a Wolff–Kishner reduction failed utterly, a stepwise pathway was taken. First, the keto enol ether **10** was transformed to the corresponding hydroxy enol ether **11** by standard lithium aluminum hydride reduction in an almost quantitative yield. The *unlike*-configuration of the hydroxy enol ether **11** (**11**:*like*-**11**, 96:4, GC) is the consequence of the 4a-methyl group on the α-face of **10**, which is situated right in the Bürgi–Dunitz trajectory of the carbonyl function, thus forcing the hydride nucleophile to approach from the opposite side. This relative stereochemistry was deduced from the strong nuclear Overhauser effect between 2-H_{ax} and 4-H_{ax}, the latter hydrogen atom of which is in *trans-diaxial* relation to 4a-Me, as a distinct crosspeak in the COSY-DQF spectrum shows.

The hydroxy group of **11** was then transformed into the corresponding acetate by reaction with acetic anhydride and triethylamine in the presence of 4-dimethylaminopyridine as acylation catalyst. The acetate intermediate was subsequently subjected to the dissolving metal reduction of Barton et al.,[17] employing *tert*-butanol and lithium metal in liquid ammonia.[18] After these two steps and purification by silica-gel filtration and Kugelrohr distillation, the deoxygenated methyl enol ether **12** was obtained in 77% yield, while 18% of the hydroxy enol ether substrate **11** was recovered, which corresponds to a 94% yield based on recovered starting material. Evidenced by pronounced crosspeaks between 4a-Me and 8a-H as well as between 4a-Me and 6-H_b in the NOESY spectrum, the *cis*/*trans* ratio of **12** was determined as 73:27. The deoxygenated enol ether **12** was then cleaved by mild hydrolysis in aqueous methanol in the presence of catalytic amounts of oxalic acid to provide the central octalinone intermediate **5** in 99% yield with the *cis*/*trans* ratio 89:11, again confirmed by the crosspeaks 8-H_b×4a-Me and 8a-H×4a-Me, respectively, in the NOESY experiment. The 2,9-dimethyl-Δ^1-octalin-5-one (**5**), which possessed a pleasant woody, green-earthy, sweet, fruity-grapefruit odor with slightly minty aspects, had been prepared by W. S. Johnson et al.[19] by a different route on a milligram scale, but our new route opened up an easy-to-perform multigram access to isomerically pure **5**. As far as

reported, the spectroscopic data were identical to those in the literature.[19]

The hydroxymethylene moiety was constructed in the next step by a standard Claisen ester condensation[20] of the octalinone **5** with ethyl formate between 0 °C and room temperature in THF, employing sodium hydride as base and a catalytic amount of methanol. The crystalline product **4** was obtained by chromatography and crystallization, and it was found to now exist exclusively in *cis*-configuration (Scheme 3). This is due to the strong intramolecular hydrogen bridge, which causes 1,3-diaxial interactions between 4a-Me_{ax} and 3-H_{ax} and 8-H_{ax} in the more strained *trans*-isomer. Density-functional calculations on the B3LYP level with the 6-31G* basis set indicated the *cis*-isomer **4** to be favored by 8.12 kJ/mol (1.94 kcal/mol) over the *trans*-isomer, which explains why the *trans*-isomer was no longer detectable in the NMR spectrum. Thus, the intramolecular hydrogen bridge between the hydroxymethylene moiety and the carbonyl group ideally preformed the *cis*-geometry required for the central Prins reaction to take place.



Scheme 3. Hydroxymethylenation, Prins-type cyclization, and concluding functional group transformations that lead to the tricyclic target structure **3**.

Immersing a stirred mixture of **4** with an equimolar amount of *p*-toluenesulfonic acid monohydrate in benzene for a quarter of an hour in a hot oil bath at 85 °C, effected the crucial Prins reaction, and after chromatographic purification, the epimeric homoisotwistaneketol mixture **13**/2-*epi*-**13** (ratio ca. 4:1) was isolated in 74% yield as a colorless solid. Crystallization from Et_2O/hexane furnished the main stereoisomer **13** in pure form in 59% yield. The relative configuration of C-2 was proposed on the basis of a prominent crosspeak between 2-H and 4-Me in the NOESY spectrum, the high-field shift of 2-H at δ = 3.69 ppm shielded by the double bonds, and the diminishingly small coupling constant between 2-H and 3-H, which indicated a dihedral angle of φ = 85°–105° in a vicinal Karplus correlation. This configuration was confirmed by an X-ray crystal structure (Figure 2), which indeed revealed a dihedral angle φ = –104.3° between the hydrogen bonds of C-2 and C-3. As was expected for ketols with an AH/B distance above 3 Å,[12] both isomers **13** and 2-*epi*-**13** were devoid of any odor (distance OH/O = 4.84 Å in the X-ray crystal structure of **13**). After removal of the C-2 hydroxy function, however, an odor should be detectable.

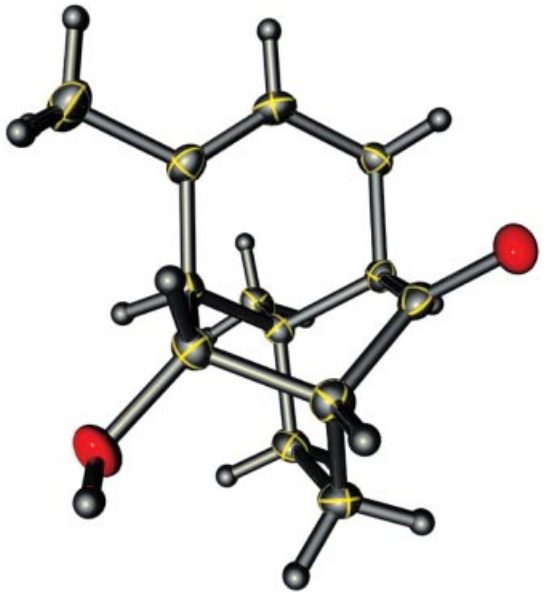


Figure 2. X-ray crystal structure of (±)-(1*R**,2*R**,3*S**,7*R**,8*S**)-2-hydroxy-4,8-dimethyltricyclo[5.3.1.$0^{3,8}$]undec-4-en-11-one (**13**) with thermal ellipsoids at the 50% probability level.

To study the odor of the Δ^5-unsaturated ketol **15** as well, and to make use of the haptophilicity of the hydroxy group of **15** to direct the hydrogen from the same face upon hydrogenation, it was decided first to deoxygenate the secondary alcohol of **13**. A reliable method that works under neutral conditions and is well compatible with a variety of functional groups including carbonyl functions and double bonds is the Barton–McCombie reaction.[21] It takes advantage of the radicophilic nature of the thiocarbonyl group, especially in *O*-phenoxythiocarbonyl derivatives of alcohols as introduced by Robins et al.,[22] but suffers the drawback of relying on tributylstannane as reducing agent, which leads to the formation of toxic and smelly tin-containing byproducts. Roberts et al.,[23] and Schummer and Höfle,[24] however, demonstrated that this disadvantage can be avoided by employing organosilanes as radical-based reducing agents[25] in the Barton–McCombie reaction. For the deoxygenation of compound **13**, the procedure of Schummer and Höfle[24] was followed, which uses tris(trimethylsilyl)-silane (TTMSS) as reagent. The β-ketol **13** was first acylated at room temp. with phenoxythiocarbonyl chloride in dichloromethane to furnish, through catalysis by DMAP, the corresponding crystalline *O*-phenylcarbonothioate in 96% yield after work-up and chromatographic purification. This was then reduced with TTMSS in refluxing benzene in the presence of AIBN [2,2′-azobis(2-methylpropionitrile)]

as radical initiator. To facilitate the separation, the tris(trimethylsilyl)silanol formed and the other silanol byproducts were converted into the corresponding fluorosilanes by titration with a tetrabutylammonium fluoride (TBAF) solution in THF after the usual work-up procedure. By subsequent flash chromatography, the unsaturated tricyclic ketone **14** was isolated in 88% yield, which results in a total yield of 84% for the deoxygenation of the secondary alcohol **13**. Indeed, ketone **14** proved not to be odorless, but instead emanated a fresh, minty-camphoraceous and eucalyptol-like smell with a slight woody inflexion which was, however, devoid of any earthy tonality or any resemblance to (–)-patchoulol (**1**).

As the molybdenum peroxide reagent (MoO_5–pyridine–HMPA, MoOPH),[13] should only attack the lithium enolate but not other double bonds,[26] the introduction of the C-3 hydroxy group was next on the agenda. In accordance with the results of Yamada et al.,[6] the enolization of ketone **14** was expected to be completely C-3 regioselective. Applying the guidelines that Köbrich[27] established for the application of Bredt's rule, the $\Delta^{1,2}$-system should correspond to an $S = 6$ [**2**,2,2] Bredt-forbidden olefin, while the $\Delta^{2,3}$-enol should not be a Bredt alkene, as its ring strain would be in the order of an $S = 7$ [**3**,3,1] bicycle. In agreement with this were density-functional calculations on the B3LYP level with the 6-31G* basis set, which favored the $\Delta^{2,3}$-enol system by as much as 159 kJ/mol (38.0 kcal/mol). For the oxidation of the lithium enolate of **14**, however, we wanted to avoid the toxicity of the complexed hexamethylphosphoramide (HMPA) and thus switched to oxodiperoxymolybdenum(pyridine)-1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (MoO_5–pyridine–DMPU, MoOPD),[28] which in some cases was reported to give even superior yields. It was prepared by the procedure of Vedejs and Larsen,[26] but by replacing the carcinogenic HMPA with DMPU. Work-up and purification followed the paper of Anderson and Smith,[28] where also the analytical data reported for MoOPD were in agreement with our own. The lithium enolate of **14** was prepared at –78 °C with lithium diisopropylamide (LDA) in THF, and the MoO_5–pyridine–DMPU was added at –30 °C to it in one dash. Usual work-up and purification by silica-gel FC furnished the unsaturated odoriferous ketol **15** in 51% yield, while 9% of the starting material **14** was recovered. Much to our delight, the unsaturated **15** with the double bond in the same position as in (+)-*nor*-patchoulenol,[11] already possessed a refined, typical, and powerful patchouli scent.

To complete the synthesis of our target superstructure **3**, all that was missing was the diastereoselective hydrogenation of the C-5(6) double bond of ketol **15**. In analogy to the total syntheses of *rac*-patchoulol (*rac*-**1**) by Magee, Stork, and Fludzinski[9] and especially of the enantioselective syntheses of the Valerianananoids A–C by Srikrishna and Satyanarayana,[29] which feature analogous diastereoselective hydrogenations of 3-hydroxytricyclo[5.3.1.$0^{3,8}$]undec-5-ene systems, it was expected that Pd on charcoal in methanol would give optimal selectivity. Hemiketal formation by reaction of the carbonyl group with methanol was expected to block the face of the carbonyl group, while the haptophilicity[30] of the 3-hydroxy function should make it bind to the catalyst surface and thus direct the delivery of the hydrogen from this side of the molecule. The reduction of the unsaturated ketol **15** under these conditions in a hydrogen atmosphere at ambient pressure was indeed diastereoselective in this way, but unfortunately not completely. It provided the odoriferous target molecule **3** together with its odorless C-6 epimer *epi*-**3** with unaltered OH/H unit in 84% yield after chromatographic purification in the ratio 84:16, which corresponds to a 71% yield of the target compound **3** and 13% of its C-6 epimer *epi*-**3**. Changing the solvent to 2-propanol to increase the shielding of the carbonyl side upon hemiketalization brought no improvement in yield or selectivity. However, for olfactory characterization, it was interesting to have obtained the odorless epimer *epi*-**3** as well. The correct relative stereochemistry of the target structure **3** was unambiguously established by prominent crosspeaks between 6-H and 8-Me as well as between 11-H_a and 6-Me in the NOESY experiment. From our target molecule **3**, the synthesis of which was accomplished in a total of 13 steps from Cyclal C (**7**) with 7% yield and 9% yield based on recovered starting material, it is 5 additional steps in the synthesis of Yamada et al.[6] to *rac*-patchoulol (*rac*-**1**). These 5 steps transformed the ketol **3** in a total of 12% based on reacted material to *rac*-**1**, the racemate of the odorous principle of patchouli oil. So, our new route to the ketol **3** constitutes as well a new formal total synthesis of racemic patchoulol *rac*-**1**; yet, above all we were of course interested in the olfactory properties of our target molecule **3**, and Yamada et al.[6] indeed had completely missed its pronounced patchouli character.

Olfactory Properties and Conclusion

(–)-Patchoulol (**1**) possesses a typical woody–balsamic odor with herbaceous, earthy, camphoraceous, and floral facets that make a dominant contribution to the overall odor of the essential oil,[31] which of course is more complex, narcotic and medicinal, because of the presence of numerous other odoriferous constituents, amongst them patchouli pyridine[32] and epiguaipyridine,[32] which make patchouli oil blend so well with roast, nut, and chocolate notes. For (–)-patchoulol (**1**) an odor threshold of 0.93 ng/L air was determined,[11] while the characteristic patchouli-like smelling spirocyclic ketol **2** with woody-ambery, tobacco-like facets was much stronger with a threshold of 0.027 ng/L air. While *epi*-**3** is odorless, both the target compound **3** as well as its unsaturated precursor **15** share the typical patchouli note of the templates **1** and **2**, which demonstrates that the superposition analysis in Figure 1 is correct and relevant, as ketols are generally odorless, especially those with a molecular weight in the sesquiterpenoid range. (1*R**,3*S**,7*S**,8*S**)-3-Hydroxy-6,8-dimethyltricyclo[5.3.1.$0^{3,8}$]-undec-5-en-2-one (**15**) was described by our perfumers to be more natural and distinct in its patchouli character and to emanate a powerful and pronounced patchouli odor with

a fresh, camphoraceous tonality, and warm, woody, slightly earthy facets, while the saturated, (1*R**,3*S**,6*S**,7*S**,8*S**)-configured 3-hydroxy-6,8-dimethyltricyclo[5.3.1.$0^{3,8}$]undecan-2-one (**3**) possesses a woody–patchouli-like note with an agrestic tonality and slightly fruity-lactonic aspects; an animalic side became more apparent in the dry-down. Whereas **15** became more agrestic after 4 h, both were linear in smell overall. On blotter, **15** was more powerful than **3**, and this was also reflected in the lower odor threshold of 1.4 ng/L air for the unsaturated ketol **15** as compared to 2.1 ng/L air for the saturated ketol **3**. Both **3** and **15** are actually weaker than the natural lead structure (–)-patchoulol (**1**; 0.93 ng/L air), so the additional carbonyl group did not improve the binding to the receptor (distance OH/O around 2.6 Å). Yet, as all are more or less in the same range, the polar carbonyl function of compounds **3** and **15** could indeed replace the hydrophobic *gem*-dimethyl group of **1** without much effect on the odor character and intensity – a very surprising finding which indicates that the superposition **1** + **2** in Figure 1 most probably reflects the real binding situation of the ligand on the patchouli receptor(s).

So, even though we did not discover a superior patchouli odorant in the superstructures **3** and **15**, we gained additional insight in the structure–odor requirements of the patchouli receptor(s). The total synthesis of the target molecules **3** and **15** commenced with the copper-catalyzed oxidative degradation of the formyl group of the inexpensive commercial product Cyclal C (**7**) to afford, via its enamine **8**, the building block **6** for the construction of octalinone **5** by Robinson annulation with subsequent simple functional group manipulations. A classical Claisen ester condensation on octalinone **5** then provided the nicely preformed *cis*-configured substrate **4** for the central Prins cyclization. The tricyclic Prins product **13** comprised the complete carbon framework of the target compound **3**, to which it was transformed by Barton–McCombie deoxygenation, MoOPD oxidation of the lithium enolate, and face-selective hydrogenation. As the target molecule **3** constitutes an intermediate in the *rac*-patchoulol synthesis of Yamada et al.,[6] the presented sequence is also a new formal total synthesis of *rac*-patchoulol (*rac*-**1**).

Experimental Section

IR: Bruker VECTOR 22/Harrick SplitPea micro ATR, Si; frequencies in order of decreasing intensity. NMR: Bruker AVANCE DPX-400, Bruker AVANCE 500 (TCI), Bruker AVANCE 600, TMS int. (δ = 0 ppm). MS: Finnigan MAT 95 (EI: 70 eV), HP Chemstation 6890 GC/5973 Mass Sensitive Detector. FC: Merck Kieselgel 60 (40–63 μm). TLC: Merck Kieselgel 60 F_{254} (particle size 5–20 μm, layer thickness 250 μm on glass, 5 cm × 10 cm); visualization reagent: phosphomolybdic acid spray and plunge solution (Fluka 02553). Melting points: Büchi Melting Point B545 (uncorrected). Elemental analyses: Mikroanalytisches Laboratorium Ilse Beetz, 96301 Kronach, Germany. X-ray: Hoffmann-La Roche, CH-4070 Basel, Switzerland; Stoe IPDS I diffractometer (Image Plate Diffraction System); SHELX-97. Unless otherwise stated, all reactions were performed under nitrogen with reagents and solvents (*puriss.* or *purum*) from Fluka, used without further purification. Cyclal C (**7**) is a product of Givaudan, and the commercial grade was used. The annulation reagent 1,4-dimethoxybutan-2-one (**9**) was synthesized from but-2-yne-1,4-diol according to the procedure of Hennion and Kupiecki.[16] The molybdenum peroxide reagent (MoO_5–pyridine–DMPU, MoOPD) was freshly prepared by following the literature procedure of Vedejs and Larsen,[26] but replacing HMPA with DMPU according to Anderson and Smith.[28] In this latter paper, the work-up, purification, and analytical data for MoOPD are detailed.[28]

The odor thresholds are determined by GC-olfactometry: Different dilutions of the sample substance are injected into a gas chromatograph in descending order of concentration until the panelist fails to detect the respective substance at the sniffing port. The panelist smells in blind and presses a button on perceiving an odor. If the recorded time matches the retention time, the sample is further diluted. The last concentration detected at the correct retention time is the individual odor threshold. The reported threshold values are the geometrical means of the individual odor thresholds of the different panelists.

CCDC 287802 (**13**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(±)-(*E*/*Z*)-4-[(2′′,4′′-Dimethylcyclohex-3′′-enylidene)methyl]-morpholine (8): Morpholine (209 g, 2.40 mol) was carefully added to a stirred solution of Cyclal C (**7**, Givaudan, 276 g, 2.00 mol) in cyclohexane (500 mL). Then, *p*-toluenesulfonic acid monohydrate (250 mg, 1.32 mmol) was added, and the resulting reaction mixture was refluxed in a Dean–Stark apparatus. After 20 h, when water (55 mL, theor. 36 mL) had been collected in the trap, the reaction was stopped, and the solvent with the excess morpholine was removed under reduced pressure. The resulting residue was purified by fractional distillation in a Vigreux assembly to furnish, at 80 °C/0.05 mbar, the enamine **8** (398 g, 96%) as a colorless oil with the (*E*)/(*Z*)-ratio 53:47. IR (ATR): $\tilde{\nu}$ = 1115 (s, ν_{as}C–N), 863/837 (s, ν_sC–N), 1449 (m, δCH_2), 1359 (m, δCH_3), 1667 (w, νC=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.06/1.07 (2d, J = 7.0 Hz, 3 H, 2′′-Me), 1.63/1.64 (2 br. s, 3 H, 4′′-Me), 1.96–2.02 (m, 2 H, 5′′-,6′′-H_{ax}), 2.23–2.29 (m, 1 H, 5′′-H_{eq}), 2.53–2.68 (m, 5 H, 3-,5-H_2, 6′′-H_{eq}), 3.71/3.37 (2t, J = 4.0 Hz, 4 H, 2-,6-H_2), 5.27 (d, J = 1.5 Hz, 1 H, 3′′-H), 5.30 (qd, J = 7.0, 1.5 Hz, 1 H, 2′′-H), 5.44 (s, 1 H, 1′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.6/22.3 (2q, 2′′-Me), 22.0/26.4 (2t, C-6′′), 23.4/23.5 (2q, 4′′-Me), 31.2/35.6 (2d, C-2′′), 31.5/32.5 (2t, C-5′′), 53.5/53.7 (2t, C-3,-5), 66.8/66.8 (2t, C-2,-6), 126.6/127.1 (2d, C-3′′), 132.6/132.8 (2d, C-1′), 132.7/132.9/133.2/133.5 (4s, C-1′′, -4′′) ppm. MS (EI): *m*/*z* (%) = 207 (14) [M^+], 192 (100) [$M^+ - CH_3$], 134 (9) [$C_9H_{12}N^+$], 121 (11) [$C_9H_{13}^+$], 105 (35) [$C_8H_9^+$], 91 (23) [$C_7H_7^+$], 86 (17) [$C_4H_8ON^+$], 79 (15) [$C_6H_7^+$].

(±)-2,4-Dimethylcyclohex-3-enone (6): CuCl (4.95 g, 50.0 mmol) was added to a solution of the enamine **8** (207 g, 1.00 mol) in MeCN (800 mL). Using a gas stirrer, i.e. a mechanical stirrer that allows a reactant gas to be dispersed via the propelled stirrer blades, O_2 was then bubbled through the reaction mixture, with occasional cooling of the flask in an ice/water bath to adjust the temp. at 28–32 °C. Reaction control by GC indicated the complete consumption of the starting material after 1 h. The gas flow was thus stopped, and the reaction mixture was poured into half-saturated aq. $NaHCO_3$ solution. The product was extracted with pentane (3×), and the combined organic extracts dried (Na_2SO_4) and concentrated in a rotary evaporator under reduced pressure. The resulting yellowish residue was distilled in a Vigreux assembly em-

ploying a water aspirator as vacuum source to provide, at 60–62 °C/25 mbar, the β,γ-unsaturated ketone **6** (114 g, 92%) as a colorless liquid. IR (ATR): $\tilde{\nu}$ = 1714 (s, νC=O), 1443 (m, δCH_2), 1191 (m, ν_{as}C–C–C), 1343 (m, δCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.13 (d, J = 7.0 Hz, 3 H, 2-Me), 1.76 (ddd, J = 2.5, 1.0, 1.0 Hz, 3 H, 4-Me), 2.38–2.57 (m, 4 H, 5-,6-H_2), 2.88 (m_c, 1 H, 2-H), 5.33 (dq, J = 6.0, 1.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 16.7 (q, 2-Me), 22.7 (q, 4-Me), 31.0 (t, C-5), 37.1 (t, C-6), 42.7 (d, C-2), 125.3 (d, C-3), 133.7 (s, C-4), 212.8 (s, C-1) ppm. MS (EI): m/z (%) = 124 (49) [M^+], 109 (1) [$M^+ - CH_3$], 82 (72) [$M^+ - C_2H_2O$], 67 (100) [$M^+ - C_2H_2O - CH_3$], 53 (14) [$C_4H_5^+$], 39 (17) [$C_3H_3^+$].

(±)-4,4a,7,8-Tetrahydro-1-methoxy-4a,6-dimethylnaphthalen-2(3*H*)-one (10): A solution of **9** (13.2 g, 100 mmol) in Et_2O (140 mL) was added between –10 °C and –5 °C dropwise over a period of 3.5 h to a stirred solution of **6** (12.4 g, 100 mmol) and *t*BuOK (2.80 g, 25.0 mmol) in Et_2O/*t*BuOH (10:1, 110 mL) immersed in an ice/EtOH cooling bath. Upon completed addition, the cooling bath was removed, and the reaction mixture was warmed to room temp. Stirring was continued for further 2 d at ambient temp., before the brownish reaction mixture was transferred into a separating funnel by rinsing the reaction flask with Et_2O followed by saturated aq. NH_4Cl. The organic layer was separated and washed with brine prior to drying (Na_2SO_4) and evaporation of the solvent in a rotary evaporator. The resulting yellow residue was purified by silica-gel FC (pentane/Et_2O, 5:1, R_f = 0.25) followed by distillation in a Kugelrohr apparatus at 130–140 °C/0.1 mbar to afford the annulation product **10** (12.4 g, 60%) as a colorless semi-crystalline solid, m.p. ca. 30 °C. IR (ATR): $\tilde{\nu}$ = 1674 (s, νC=O), 1095/1073 (s, νC–O), 1620 (m, νC=C), 1446 (m, δCH_2), 1346 (m, δCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.26 (s, 3 H, 4a-Me), 1.69 (d, J = 1.5 Hz, 3 H, 6-Me), 1.72 (ddd, J = 13.5, 5.0, 3.0 Hz, 1 H, 4-H_{eq}), 1.86 (ddd, J = 13.5, 13.5, 5.0 Hz, 1 H, 4-H_{ax}), 2.07–2.17 (m, 3 H, 7-H_2, 8-H_b), 2.46 (ddd, J = 18.0, 5.0, 3.0 Hz, 1 H, 3-H_{eq}), 2.61 (ddd, J = 18.0, 13.5, 5.0 Hz, 1 H, 3-H_{ax}), 3.06 (ddd, J = 14.0, 10.5, 8.0 Hz, 1 H, 8-H_a), 3.62 (s, 3 H, OMe), 5.12 (q, J = 1.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.6 (t, C-8), 22.9 (q, 6-Me), 24.8 (q, 4a-Me), 31.1 (t, C-3), 34.4 (t, C-7), 35.2 (t, C-4), 37.0 (s, C-4a), 60.4 (q, OMe), 130.3 (d, C-5), 132.0 (s, C-6), 146.5 (s, C-8a), 153.0 (s, C-1), 194.2 (s, C-2) ppm. MS (EI): m/z (%) = 206 (153) [M^+], 191 (100) [$M^+ - CH_3$], 175 (2) [$M^+ - CH_3O$], 163 (67) [$M^+ - C_2H_3O$], 147 (17) [$M^+ - CH_3O - CO$], 131 (13) [$C_{10}H_{11}^+$], 105 (26) [$C_8H_9^+$], 91 (35) [$C_7H_7^+$], 31 (1) [CH_3O^+]. $C_{13}H_{18}O_2$ (206.28): calcd. C 75.69, H 8.80; found C 75.67, H 8.87.

(±)-(2*R,4a*S**)-2,3,4,4a,7,8-Hexahydro-1-methoxy-4a,6-dimethylnaphthalen-2-ol (11):** At –15 °C (ice/EtOH bath), a solution of **10** (20.6 g, 100 mmol) in Et_2O (180 mL) was added dropwise over a period of 2.5 h to a stirred suspension of $LiAlH_4$ (1.90 g, 50 mmol) in Et_2O (200 mL). At this temp., the reaction was quenched with water (2.0 mL), aq. NaOH (15%, 2.0 mL), and again water (6.0 mL) in turn, and after 30 min of stirring at room temp., the insoluble material was filtered off by suction and carefully washed with Et_2O. The combined filtrates were concentrated in a rotary evaporator to furnish a colorless viscous oil (21.1 g), which was further purified by Kugelrohr distillation to provide, at 160 °C/0.025 mbar, the methoxy alcohol **11** (20.4 g, 98%) in almost isomerically pure form (**11**/*like*-**11**, 96:4, GC). Upon standing, colorless crystals formed, m.p. 51 °C. IR (ATR): $\tilde{\nu}$ = 1062/1016 (s, νC–O), 1113/1144/1238 (s, νC–O–C), 3300 (br. m, νO–H), 1667 (m, νC=C), 1440 (m, δCH_2). ^1H NMR ($CDCl_3$): δ = 1.14 (s, 3 H, 4a-Me), 1.40 (ddd, J = 13.5, 13.5, 3.0 Hz, 1 H, 4-H_{ax}), 1.47 (ddd, J = 13.5, 4.0, 4.0 Hz, 1 H, 4-H_{eq}), 1.63 (d, J = 1.0 Hz, 3 H, 6-Me), 1.74 (dddd, J = 16.5, 13.5, 9.0, 4.0 Hz, 1 H, 3-H_{ax}), 1.92–2.12 (m, 4 H, 3-H_{eq}, 7-H_2, 8-H_b), 2.43 (s, 1 H, O–H), 2.79 (dd, J = 8.0, 2.0 Hz, 1 H, 8-H_a), 3.58 (s, 3 H, OMe), 4.38 (dd, J = 9.0, 7.0 Hz, 1 H, 2-H_{ax}), 5.09 (br. s, 1 H, 5-H) ppm. ^1H, ^1H NOESY (C_6D_6): 2-H_{ax} × 4-H_{ax}. ^1H, ^1H COSY-DQF (C_6D_6): 4-H_{ax} × 4a-Me (^4J *trans-diaxial*). ^{13}C NMR ($CDCl_3$): δ = 20.3 (t, C-8), 23.2 (q, 6-Me), 26.5 (q, 4a-Me), 27.6 (t, C-3), 32.2 (t, C-7), 34.3 (t, C-4), 36.1 (s, C-4a), 59.0 (d, C-2), 65.3 (q, O-Me), 127.9 (s, C-8a), 131.1 (s, C-6), 132.0 (d, C-5), 147.5 (s, C-1) ppm. MS (EI): m/z (%) = 208 (7) [M^+], 193 (100) [$M^+ - CH_3$], 190 (12) [$M^+ - H_2O$], 175 (52) [$M^+ - CH_3 - H_2O$], 161 (76) [$M^+ - CH_3 - CH_3OH$], 143 (36) [$M^+ - CH_3 - H_2O - CH_3OH$], 133 (29) [$C_{10}H_{13}^+$], 128 (23) [$C_8H_{16}O^+$], 119 (33) [$C_9H_{11}^+$], 105 (42) [$C_8H_9^+$], 91 (52) [$C_7H_7^+$], 45 (4) [$C_2H_5O^+$], 31 (2) [$CH_3O^+$]. $C_{13}H_{20}O_2$ (208.30): calcd. C 74.96, H 9.68; found C 74.99, H 9.62.

(±)-*cis*/*trans* –1,2,4a,5,6,8a-Hexahydro-8-methoxy-3,4a-dimethylnaphthalene (12): At room temp., Ac_2O (12.3 g, 120 mmol) was added dropwise with stirring to a solution of the methoxy alcohol **11** (23.1 g, 111 mmol), Et_3N (12.1 g, 120 mmol), and 4-dimethylaminopyridine (0.61 g, 4.99 mmol) in Et_2O (200 mL), upon which the reaction mixture warmed to 30 °C. Stirring was continued at ambient temp. for 2 h, prior to pouring the reaction mixture onto crushed ice. The product was extracted with pentane (3×), and the combined organic extracts were washed with half-saturated brine, dried ($MgSO_4$), and concentrated under reduced pressure. Filtration of the resulting residue over silica gel (100 g, pentane/Et_2O, 4:1) gave, after evaporation of the solvent in a rotary evaporator and Kugelrohr distillation at 140 °C/0.05 mbar, the acetate of **11** (27.7 g, 99%) as a colorless oil. A solution of this acetate (27.5 g, 110 mmol) and *t*BuOH (8.15 g, 110 mmol) in Et_2O (100 mL) was then added at –78 °C dropwise over a period of 30 min to a stirred dark-blue solution of Li (2.30 mg, 331 mmol) in liq. NH_3 (800 mL), prepared in advance by condensing NH_3 in the reaction flask at –78 °C (dry ice/Me_2CO cooling bath), adding Li wire in pieces of ca. 0.3 cm, and stirring the resulting mixture for 1 h at this temp. After stirring for 2 h at –78 °C, the cooling bath was removed, and the reaction mixture was allowed, with further stirring, to warm to –40 °C within about 1 h. At this temp., solid NH_4Cl was carefully added in small portions until the solution became colorless. The NH_3 was allowed to evaporate overnight, the resulting residue was transferred into a separating funnel with Et_2O and water, and the organic layer was separated. The aqueous layer was extracted with Et_2O/pentane (1:1, 3×), and the combined organic extracts were washed with brine to neutrality. Drying of the organic solution (Na_2SO_4), and evaporation of the solvent in a rotary evaporator afforded a residue (22.0 g) that was separated by filtration through silica gel (120 g, pentane/Et_2O, 4:1) with subsequent Kugelrohr distillation to provide, at 80–90 °C/0.04 mbar, the methyl enol ether **12** (16.4 g, 78%, *cis*/*trans* ratio 73:27) as a colorless liquid, and at 120 °C/0.04 mbar, the starting material **11** (4.17 g, 18%; total yield of **12** from **11** based on recovered starting material: 94%). Analytical data of the main *cis*-isomer: IR (ATR): $\tilde{\nu}$ = 1138/1075/1212/1032 (s, νC–O–C), 841 (s, δC=C–H oop), 1448 (m, δCH_2), 1353 (m, δCH_3), 1682/1666 (m, νC=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.96 (s, 3 H, 4a-Me), 1.24 (ddd, J = 13.0, 5.0, 5.0 Hz, 1 H, 5-H_b), 1.43 (ddd, J = 13.0, 7.5, 7.5 Hz, 1 H, 5-H_a), 1.54 (m_c, 1 H, 1-H_b), 1.64 (d, J = 1.5 Hz, 3 H, 3-Me), 1.78–1.90 (m, 2 H, 2-H_2), 1.83 (m_c, 1 H, 8a-H), 1.91 (m_c, 1 H, 1-H_a), 1.96–2.02 (m, 2 H, 6-H_2), 3.50 (s, 3 H, O–Me), 4.56 (t, J = 4.0 Hz, 1 H, 7-H), 5.03 (tq, J = 1.5, 1.5 Hz, 1 H, 4-H) ppm. ^1H, ^1H NOESY ($CDCl_3$): 4a-Me × 8a-H, 4a-Me × 6-H_b. ^{13}C NMR ($CDCl_3$): δ = 20.8 (t, C-6), 23.7 (q, 3-Me), 24.9 (t, C-1), 26.3 (q, 4a-Me), 29.2 (t, C-2), 32.2 (t, C-5), 34.4 (s, C-4a), 43.3 (d, C-8a), 54.0 (q, O–Me), 92.2 (d, C-7), 131.0 (d, C-4), 132.5 (s, C-3), 157.1 (s, C-8) ppm. MS (EI): m/z (%) = 192 (4) [M^+], 177 (100) [$M^+ - CH_3$], 145 (10) [$M^+ - CH_3 -$

CH_3OH], 119 (5) [$C_9H_{11}^+$], 105 (11) [$C_8H_9^+$], 91 (15) [$C_7H_7^+$], 79 (5) [$C_6H_7^+$]. $C_{13}H_{20}O$ (192.30): calcd. C 81.20, H 10.48; found C 81.22, H 10.50.

(±)-*cis*/*trans*-3,4,4a,7,8,8a-Hexahydro-4a,6-dimethylnaphthalen-1(2*H*)-one (5): Anhydrous oxalic acid (480 mg, 5.33 mmol) was added in one dash at room temp. to a vigorously stirred solution of the methyl enol ether **12** (4.81 g, 25.0 mmol) in a solvent mixture of MeOH (40 mL) and water (14 mL). Within 10 min of stirring, the milky-white emulsion became a clear colorless solution. Vigorous stirring was continued for a further 60 min, prior to pouring the reaction mixture into pentane/water (1:1, 100 mL). The organic layer was separated, the aqueous one extracted with pentane (4×), and the combined organic extracts were washed with brine to which saturated aq. $NaHCO_3$ (1 mL) was added for neutralization. After drying ($MgSO_4$) and evaporation of the solvent under reduced pressure in a rotary evaporator, the crude product (4.50 g) was obtained, which was purified by distillation in a Kugelrohr apparatus to furnish, at 110 °C/0.25 mbar, the octalinone **5** (4.44 g, 99%, *cis*/*trans* ratio 89:11) as a colorless odoriferous liquid. Analytical data of the main *cis*-isomer: IR (ATR): $\tilde{\nu}$ = 1702 (s, νC=O), 1446/1427 (m, δCH_2), 831/813 (m, δC=C–H oop), 1345 (w, δCH_3) cm^{-1}. ^1H NMR (C_6D_6): δ = 0.91 (s, 3 H, 4a-Me), 1.23 (m_c, 1 H, 4-H_b), 1.36–1.42 (m, 3 H, 3-H_2, 4-H_a), 1.47 (s, 3 H, 6-Me), 1.53 (m_c, 1 H, 8-H_b), 1.62 (m_c, 1 H, 7-H_b), 1.84 (t, J = 5.0 Hz, 1 H, 8a-H), 1.87 (m_c, 1 H, 2-H_b), 2.10–2.21 (m, 3 H, 2-,7-,8-H_a), 4.90 (q, J = 1.5 Hz, 1 H, 5-H) ppm. ^1H, ^1H NOESY (C_6D_6): 3-H_a × 4a-Me, 3-H_b × 4a-Me, 8-H_b × 4a-Me, 8a-H × 4a-Me. ^{13}C NMR ($CDCl_3$): δ = 20.6 (t, C-8), 21.9 (t, C-3), 23.5 (q, 6-Me), 27.5 (t, C-7), 29.0 (q, 4a-Me), 37.0 (t, C-4), 38.5 (s, C-4a), 40.3 (t, C-2), 54.2 (d, C-8a), 129.5 (d, C-5), 133.8 (s, C-6), 213.2 (s, C-1) ppm. MS (EI): *m*/*z* (%) = 178 (57) [M^+], 163 (43) [$M^+ - CH_3$], 145 (100) [$M^+ - CH_3 - H_2O$], 135 (29) [$M^+ - CH_3CO$], 119 (14) [$C_9H_{11}^+$], 107 (40) [$C_8H_{11}^+$], 91 (44) [$C_7H_7^+$], 77 (25) [$C_6H_5^+$], 55 (24) [$C_4H_7^+$], 41 (18) [$C_3H_5^+$]. $C_{12}H_{18}O$ (178.27): calcd. C 80.85, H 10.18; found C 80.74, H 10.13. Odor: woody, green-earthy, sweet, fruity-grapefruit with slightly minty aspects.

(±)-*cis*-(2*Z*)-2,3,4,4a,8,8a-Hexahydro-2-(hydroxymethylene)-4a,6-dimethylnaphthalen-1(7*H*)-one (4): At 0 °C, a solution of the octalinone **5** (8.91 g, 50.0 mmol) and HCO_2Et (4.44 g, 59.9 mmol) in anhydrous THF (50 mL) was added dropwise with stirring to a suspension of NaH (1.56 g, 65.0 mmol) in dry THF (150 mL). MeOH (1.0 mL) was added, and stirring was continued at 0 °C for 1 h and then overnight at room temp., prior to transferring the pink heterogeneous reaction mixture into a separating funnel with Et_2O followed by rinsing with saturated aq. NH_4Cl. By addition of aq. HCl (2 N) with vigorous shaking of the separating funnel, the mixture was acidified (pH 4). The aqueous layer was separated and extracted with Et_2O (2×), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in a rotary evaporator. Purification of the resulting yellowish-brown residue (10.7 g) by silica-gel FC (pentane/Et_2O, 20:1, R_f = 0.40) and subsequent Kugelrohr distillation of the combined product fractions (10.0 g) furnished, at 100–110 °C/0.04 mbar, the *cis*-configured hydroxymethylene ketone **4** (9.96 g, 97%) as colorless crystals, m.p. 66–67 °C. IR (ATR): $\tilde{\nu}$ = 1584 (s, νC=C–OH enol), 1159 (s, νHC–OH), 894/873/849/828 (s, δC=C–H oop), 1316 (s, δC–O–H), 1372 (s, δCH_3), 993 (s, δC=C–H oop conj. C=O), 1615 (s, νC=O intramol. H bond), 1444 (m, δCH_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.02 (s, 3 H, 4a-Me), 1.41 (dt, J = 13.5, 6.0 Hz, 1 H, 4-H_b), 1.58 (dt, J = 13.5, 6.0 Hz, 1 H, 4-H_a), 1.64 (s, 3 H, 6-Me), 1.87 (m_c, 2 H, 7-H_2), 1.96 (m_c, 2 H, 8-H_2), 2.17 (dd, J = 7.0, 4.5 Hz, 1 H, 8a-H), 2.25 (t, J = 6.0 Hz, 2 H 3-H_2), 5.03 (tq, J = 1.5, 1.5 Hz, 1 H, 5-H), 8.77 (s, 1 H, 1′-H), 14.6 (s, 1 H, O–H) ppm. ^1H, ^1H NOESY ($CDCl_3$): 5-H × 4a-Me, 5-H × 6-Me, 8a-H × 4a-Me, 1′-H × 3-H. ^{13}C NMR ($CDCl_3$): δ = 20.1 (t, C-3), 23.0 (t, C-8), 23.6 (q, 6-Me), 27.6 (q, 4a-Me), 27.9 (t, C-7), 33.6 (t, C-4), 33.7 (s, C-4a), 45.5 (d, C-8a), 107.9 (s, C-2), 129.1 (d, C-5), 133.8 (s, C-6), 184.7 (s, C-1), 189.7 (d, C-1′) ppm. MS (EI): *m*/*z* (%) = 206 (98) [M^+], 191 (100) [$M^+ - CH_3$], 188 (4) [$M^+ - H_2O$], 177 (11) [M^+ – CHO], 173 (27) [$M^+ - CH_3 - H_2O$], 163 (75) [$M^+ - C_2H_3O$], 145 (70) [$M^+ - C_2H_3O - H_2O$], 107 (72) [$C_8H_{11}^+$], 91 (77) [$C_7H_7^+$], 77 (50) [$C_6H_5^+$], 55 (52) [$C_4H_7^+$], 41 (41) [$C_3H_5^+$], 29 (13) [CHO^+]. $C_{13}H_{18}O_2$ (206.28): calcd. C 75.69, H 8.80; found C 75.71, H 8.75.

(±)-(1*R,2*R**,3*S**,7*R**,8*S**)-2-Hydroxy-4,8-dimethyltricyclo-[5.3.1.0^{3,8}]undec-4-en-11-one (13):** A stirred mixture of **4** (4.12 g, 20.0 mmol) and *p*-toluenesulfonic acid monohydrate (3.80 g, 20.0 mmol) in benzene (40.0 mL) was immersed in an oil bath preheated at 85 °C. After a reaction time of 15 min, the flask was removed from the heating bath, and the product mixture was cooled down to room temp., upon which a reddish semi-crystalline material was formed. Without further work-up, this material was loaded on top of an FC column and the product eluted (pentane/Et_2O, 2:1, R_f = 0.13) to provide **13**/2-*epi*-**13** (ca. 4:1, 3.07 g, 74%) as a colorless and odorless solid. Crystallization (Et_2O/hexane) at low temp. afforded the isomerically pure title compound **13** (2.45 g, 59%) as colorless and odorless crystals, m.p. 80–81 °C. IR (ATR): $\tilde{\nu}$ = 1696 (s, νC=O), 3421 (s, νO–H), 1296/1337 (m, δC–O–H), 1059 (m, νC–O), 1373 (m, δCH_3), 1434 (m, δH–C–H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.93 (s, 3 H, 8-Me), 1.51 (m_c, 1 H, 9-H_b), 1.53 (m_c, 1 H, 10-H_b), 1.69 (br. s, 1 H, 3-H), 1.71 (dd, J = 2.0, 2.0 Hz, 3 H, 4-Me), 1.76 (m_c, 1 H, 9-H_a), 1.91 (dt, J = 6.5, 2.0 Hz, 1 H, 7-H), 2.20 (m_c, 1 H, 6-H_b), 2.25 (m_c, 1 H, 10-H_a), 2.43 (m_c, 1 H, 6-H_a), 2.48 (td, J = 5.5, 4.0 Hz, 1 H, 1-H), 3.69 (d, J = 4.0 Hz, 1 H, 2-H), 5.21 (br. t, J = 2.5 Hz, 1 H, 5-H) ppm. ^1H, ^1H NOESY ($CDCl_3$): 2-H × 4-Me, 3-H × 4-Me, 3-H × 8-Me, 6-H × 8-Me, 7-H × 8-Me. ^{13}C NMR ($CDCl_3$): δ = 16.7 (t, C-10), 22.4 (q, 4-Me), 23.0 (q, 8-Me), 26.5 (t, C-6), 30.5 (t, C-9), 33.5 (s, C-8), 47.9 (d, C-7), 49.2 (d, C-1), 53.4 (d, C-3), 71.8 (d, C-2), 119.5 (d, C-5), 134.8 (s, C-4), 219.3 (s, C-11) ppm. MS (EI): *m*/*z* (%) = 206 (58) [M^+], 191 (28) [$M^+ - CH_3$], 188 (5) [$M^+ - H_2O$], 178 (11) [M^+ – CO], 173 (19) [$M^+ - CH_3 - H_2O$], 160 (76) [$M^+ - CO - H_2O$], 145 (85) [$C_{10}H_{25}^+$], 107 (100) [$C_8H_{11}^+$], 91 (92) [$C_7H_7^+$]. Crystal structure data and refinement: empirical formula $C_{13}H_{18}O_2$, molecular mass 206.27, crystal dimensions 0.5 × 0.4 × 0.07 mm, temperature 110 K, wavelength 0.71073 Å, orthorhombic crystal system, space group *Pbca*, unit cell dimensions a = 7.5226(15) Å, b = 13.876(3) Å, c = 21.808(4) Å, α = 90°, β = 90°, γ = 90°, V = 2276.3(8) Å^3, Z = 8, ρ = 1.204 Mg/m^3, μ(Mo-K_α) = 0.079 mm^{-1}, F(000) 896, θ range 3.08–25.98°, limiting indices $-8 \le h \le 9$, $-17 \le k \le 14$, $-26 \le l \le 26$, total reflections collected 12049, symmetry-independent reflections 2236, R_{int} = 0.0468, refinement full-matrix least-squares on F^2, data 2236, parameters 139, goodness-of-fit on F^2 1.071, final R indices [$I > 2\sigma(I)$], R_1 = 0.0436, wR_2 = 0.1131, R indices (all data) R_1 = 0.0494, wR_2 = 0.1171, $\Delta\rho$(max, min) = 0.412, –0.164 e·Å^{-3}. CCDC 287802. $C_{13}H_{18}O_2$ (206.28): calcd. C 75.69, H 8.80; found C 75.67, H 8.79.

(±)-(1*R,3*R**,7*S**,8*S**)-6,8-Dimethyltricyclo[5.3.1.0^{3,8}]undec-5-en-2-one (14):** At room temp., a solution of phenoxythiocarbonyl chloride (2.07 g, 12.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise with stirring to a solution of β-ketol **13** (2.06 g, 10.0 mmol) and 4-dimethylaminopyridine (2.44 g, 20.0 mmol) in CH_2Cl_2 (50 mL), upon which the temp. of the resulting yellow reaction mixture rose to 28 °C. Stirring was continued for 2 d at ambient temp., prior to pouring the reaction mixture in ice/water (1:1). The organic layer was separated, the aqueous one was extracted with CH_2Cl_2 (3×),

and the combined organic extracts were washed with ice/aq. HCl (1 N, 1:1) and brine. After filtration through a wad of cotton wool, the organic solution was concentrated in a rotary evaporator under reduced pressure. The resulting yellowish-brown residue (4.04 g) was purified by silica-gel FC (pentane/Et_2O, 10:1, R_f = 0.33) to furnish (±)-*O*-(1*R**,2*R**,3*S**,7*R**,8*S**)-4,8-dimethyl-11-oxotricyclo[5.3.1.$0^{3,8}$]undec-4-en-2-yl *O*-phenylcarbonothioate (3.29 g, 96%) as colorless crystals, m.p. 103.5–104.5 °C (Et_2O/hexane). This *O*-phenylcarbonothioate (2.40 g, 7.01 mmol) was then added to a solution of tris(trimethylsilyl)silane (2.09 g, 8.40 mmol) and 2,2′-azobis(2-methylpropionitrile) (230 mg, 1.40 mmol) in benzene (50 mL), and the resulting reaction mixture was refluxed with stirring for 90 min. After the reaction mixture had cooled down to room temp., it was diluted with Et_2O (50 mL) and washed in turn with aq. $NaHCO_3$ (5%, 2×), aq. HCl (0.5 N, 1×) and brine (2×). After drying ($MgSO_4$) and evaporation of the solvent in a rotary evaporator, the residue was dissolved in Et_2O/pentane (1:1, 50 mL), and a solution of tetrabutylammonium fluoride in THF (1 M) was added dropwise with stirring until TLC control (SiO_2, hexane/EtOAc, 10:1; phenol: R_f = 0.20, silanol: R_f = 0.35, **14**: R_f = 0.40) indicated complete conversion of the tris(trimethylsilyl)silanol formed. The solvent mixture was removed under reduced pressure, and the resulting residue purified by silica-gel FC (hexane/EtOAc, 20:1) to provide the unsaturated tricyclic ketone **14** (1.17 g, 88%) as a colorless liquid. IR (ATR): $\tilde{\nu}$ = 1715 (s, νC=O), 1435 (m, δC=C–CH_2), 866/774/837/819 (m, δC=C–H oop), 1375 (m, δCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.90 (s, 3 H, 8-Me), 1.54 (ddd, *J* = 13.5, 11.0, 3.0 Hz, 1 H, 9-H_b), 1.63 (d, *J* = 1.5 Hz, 3 H, 6-Me), 1.64–1.85 (m, 5 H, 9-H_a, 10-,11-H_2), 1.97 (dt, *J* = 6.5, 2.0 Hz, 1 H, H-3), 2.02 (ddd, *J* = 12.5, 10.5, 1.5 Hz, 1 H, H-7), 2.15 (dddq, *J* = 18.5, 4.5, 4.5, 1.5 Hz, 1 H, 4-H_b), 2.22 (ddd, *J* = 5.5, 3.5, 1.5 Hz, 1 H, 1-H), 2.61 (ddt, *J* = 18.5, 4.5, 2.0 Hz, 1 H, 4-H_a), 5.17 (tq, *J* = 3.5, 2.0 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.3 (q, 6-Me), 22.7 (q, 8-Me), 23.5 (t, C-11), 25.6 (t, C-10), 31.2/32.5 (2t, C-4,-9), 33.2 (s, C-8), 41.3/42.1 (2d, C-1,-3), 49.3 (d, C-7), 117.6 (d, C-5), 137.6 (s, C-6), 221.3 (s, C-2) ppm. MS (EI): *m*/*z* (%) = 190 (100) [M^+], 175 (24) [$M^+ - CH_3$], 172 (13) [$M^+ - H_2O$], 162 (7) [M^+ – CO], 157 (22) [$M^+ - CH_3 - H_2O$], 147 (20) [$C_{11}H_{15}^+$], 135 (66) [$C_{10}H_{15}^+$], 119 (27) [$C_9H_{11}^+$], 107 (72) [$C_8H_{11}^+$], 91 (80) [$C_7H_7^+$], 77 (37) [$C_6H_5^+$], 55 (24) [$C_4H_7^+$], 41 (23) [$C_3H_5^+$]. $C_{13}H_{18}O$ (190.28): calcd. C 82.06, H 9.53; found C 82.02, H 9.57. Odor: fresh, minty, camphoraceous, eucalyptol-like with a slight woody inflexion.

(±)-(1*R,3*S**,7*S**,8*S**)-3-Hydroxy-6,8-dimethyltricyclo[5.3.1.$0^{3,8}$]-undec-5-en-2-one (15):** At –78 °C, a solution of the unsaturated tricyclic ketone **14** (950 mg, 4.99 mmol) in anhydrous THF (30 mL) was added dropwise with stirring within 30 min to a freshly prepared solution of lithium diisopropylamide in THF (0.95 M, 9.5 mL, 9.03 mmol). Stirring was continued at –78 °C for a further 30 min, prior to removal of the cooling bath. When the reaction mixture had reached –30 °C, the MoO_5–pyridine–DMPU complex (3.45 g, 9.00 mmol) was added in one dash with vigorous stirring. After further stirring of the resulting light-yellow solution for 90 min, between –30 °C and –20 °C, saturated aq. Na_2SO_3 (15 mL) was added, and the reaction mixture was warmed to room temp. prior to being transferred into a separating funnel with brine. This mixture was extracted with Et_2O (3×50 mL), and the combined organic extracts were washed with brine to neutrality, dried ($MgSO_4$), and concentrated in a rotary evaporator under reduced pressure. The resulting brownish viscous oil (1.53 g) was purified by silica-gel FC (pentane/Et_2O, 5:1) to furnish, besides recovered starting material **14** (88.0 mg, 9%, R_f = 0.50), the unsaturated odoriferous ketol **15** (526 mg, 51%, R_f = 0.20; yield based on recovered starting material: 56%) as colorless crystals, m.p. 112–113 °C (Et_2O/hexane). IR (ATR): $\tilde{\nu}$ = 1087 (s, νC–O), 1716 (s, νC=O), 3417 (s, νO–H), 839 (s, δC=C–H oop), 1444 (m, δCH_2), 1390 (m, δCH_3) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.94 (s, 3 H, 8-Me), 1.40 (m_c, 1 H, 9-H_b), 1.60 (ddd, *J* = 12.5, 5.0, 1.5 Hz, 1 H, 9-H_a), 1.64 (dt, *J* = 3.0, 1.5 Hz, 3 H, 6-Me), 1.85–1.99 (m, 5 H, 7-H, 10-,11-H_2), 2.01 (s, 1 H, O–H), 2.41 (dddd, *J* = 15.5, 6.0, 1.5, 1.0 Hz, 1 H, 4-H_b), 2.32 (ddd, *J* = 5.0, 3.0, 1.5 Hz, 1 H, 1-H), 2.41 (ddq, *J* = 15.5, 5.0, 1.5 Hz, 1 H, 4-H_a), 5.10 (tq, *J* = 4.0, 1.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.6 (q, 8-Me), 21.8 (q, 6-Me), 24.6 (t, C-11), 26.5 (t, C-10), 31.0 (t, C-9), 33.4 (t, C-4), 36.6 (s, C-8), 41.1 (d, C-1), 44.5 (d, C-7), 75.4 (s, C-3), 117.1 (d, C-5), 137.8 (s, C-6), 220.6 (s, C-2) ppm. MS (EI): *m*/*z* (%) = 206 (5) [M^+], 191 (1) [$M^+ - CH_3$], 188 (64) [$M^+ - H_2O$], 178 (24) [M^+ – CO], 173 (4) [$M^+ - H_2O - CH_3$], 160 (63) [$C_{12}H_{16}^+$], 145 (52) [$C_{11}H_{13}^+$], 135 (33) [$C_{10}H_{15}^+$], 121 (67) [$C_9H_{13}^+$], 97 (100) [$C_7H_{13}^+$], 91 (41) [$C_7H_7^+$], 77 (40) [$C_6H_5^+$], 55 (31) [$C_4H_7^+$], 41 (27) [$C_3H_5^+$]. $C_{13}H_{18}O_2$ (206.28): calcd. C 75.69, H 8.80; found C 75.72, H 8.71. Odor (10% DPG, blotter): Powerful and pronounced patchouli note, more natural and distinct than **3**, with a fresh, camphoraceous tonality and warm, woody, slightly earthy facets; +4 h, woody–patchouli-like, with a more evolved agrestic side; +24 h, woody–patchouli-like, with a natural earthiness, and now more agrestic than **3**. More powerful than **3** on blotter. Odor threshold: 1.4 ng/L air.

(±)-(1*R,3*S**,6*S**,7*S**,8*S**)-3-Hydroxy-6,8-dimethyltricyclo-[5.3.1.$0^{3,8}$]undecan-2-one (3):** Under nitrogen, Pd/C (10%, 50 mg, 0.048 mmol) was added to a stirred solution of the unsaturated ketol **15** (206 mg, 1.00 mmol) in dry MeOH (6 mL). The reaction flask was evacuated and flushed with H_2 three times, and the reaction mixture was then vigorously stirred at ambient temperature and pressure in hydrogen for 23 h. The catalyst was removed by filtration through a glass-fiber micro filter, rinsed with MeOH (2×6 mL), and the combined organic filtrates were concentrated under reduced pressure. The residue was taken up in Et_2O, and the resulting solution was filtered once again through a glass-fiber micro filter and evaporated in a rotary evaporator. A slightly brownish oil (215 mg), was thus obtained. It was further purified by silica-gel FC (pentane/Et_2O, 5:1, R_f = 0.14) to furnish the odoriferous target compound **3** together with its odorless C-6 epimer *epi*-**3** (**3**/*epi*-**3**, 84:16, 175 mg, 84%) as colorless crystals, m.p. 48–51 °C. Spectroscopic data for the main isomer **3**: IR (ATR): $\tilde{\nu}$ = 1711 (s, νC=O), 1101 (s, νC–O), 1460 (m, δCH_2), 3443 (br. m, νO–H), 1380 (w, δCH_3) cm^{-1}. ^1H NMR (C_6D_6): δ = 0.58 (d, *J* = 7.0 Hz, 3 H, 6-Me), 0.76 (ddd, *J* = 26.0, 14.0, 5.0 Hz, 1 H, 5-H_b), 0.97 (s, 3 H, 8-Me), 1.00 (ddd, *J* = 13.0, 13.0, 5.0 Hz, 1 H, 9-H_b), 1.07 (m_c, 1 H, 5-H_a), 1.17 (ddd, *J* = 14.5, 12.0, 2.5 Hz, 1 H, 11-H_b), 1.27 (m_c, 1 H, 11-H_a), 1.29 (m_c, 1 H, 7-H), 1.43 (ddt, *J* = 16.0, 11.5, 5.0 Hz, 1 H, 10-H_b), 1.57 (ddd, *J* = 17.5, 12.5, 5.0 Hz, 1 H, 4-H_b), 1.68–1.76 (m, 3 H, 4-H_a, 6-H, 10-H_a), 2.01 (ddd, *J* = 13.0, 11.5, 3.5 Hz, 1 H, 9-H_a), 2.19 (ddd, *J* = 6.0, 5.0, 2.5 Hz, 1 H, 1-H), 2.84 (s, 1 H, O–H) ppm. ^1H, ^1H NOESY (C_6D_6): 6-H×8-Me, 11-H_a×6-Me. ^{13}C NMR (C_6D_6): δ = 18.4 (q, 6-Me), 19.4 (q, 8-Me), 22.6 (t, C-11), 26.3 (t, C-10), 27.4 (t, C-5), 29.0 (t, C-9), 30.2 (d, C-6), 33.2 (t, C-4), 39.4 (s, C-8), 43.1 (d, C-1), 43.7 (d, C-7), 77.3 (s, C-3), 222.1 (s, C-2) ppm. MS (EI): *m*/*z* (%) = 208 (23) [M^+], 180 (22) [M^+ – CO], 165 (23) [$M^+ - CO - CH_3$], 147 (13) [$M^+ - CO - CH_3 - H_2O$], 138 (33) [$C_{10}H_{18}^+$], 125 (65) [$C_9H_{17}^+$], 109 (20) [$C_8H_{13}^+$], 98 (100) [$C_7H_{14}^+$], 83 (74) [$C_6H_{11}^+$], 67 (22) [$C_5H_7^+$], 55 (34) [$C_4H_7^+$], 41 (24) [$C_3H_5^+$]. $C_{13}H_{20}O_2$ (208.30): calcd. C 74.96, H 9.68; found C 75.00, H 9.70. Odor of **3** (10% DPG, blotter): Woody–patchouli-like, with an agrestic tonality and slightly metallic-fruity facets; +4 h, woody–patchouli-like, earthy, with slightly fruity-lactonic aspects, and an animalic side more pronounced as in **15**; +24 h,

woody, patchouli. Less powerful than **15** on blotter. Odor threshold of **3**: 2.1 ng/L air (*epi*-**3** is odorless).

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