Synthesis and Olfactory Evaluation of (4a*R**,8a*R**)-1,1,8a-Trimethyldecahydronaphthalen-4a-ol: A *cis*-Decalol Intersection Structure of (–)-Patchoulol and (5*R**,6*S**)-1,1,6-Trimethylspiro[4.5]decan-6-ol

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Dedicated with best wishes to Professor Werner Tochtermann on the occasion of his 75th birthday

Abstract: Superposition analysis of (–)-patchoulol (**1**) and the spirocyclic patchouli odorant (5*R**,6*S**)-1,1,6-trimethylspiro[4.5]decan-6-ol (**3**) suggested the intersection structure (4a*S**,8a*S**)-1,1,8a-trimethyldecahydronaphthalen-4a-ol (**4**) as potential patchouli odorant. The synthesis commenced with the Robinson annulation of mesityl oxide with 2-cyanocyclohexanone, accessible by intramolecular cyclization of pimelonitrile. Weitz–Scheffer epoxidation of the resulting Michael system with hydrogen peroxide in the presence of sodium hydroxide and subsequent Wharton rearrangement employing hydrazine hydrate and acetic acid furnished with complete *cis*-selectivity (4a*R**,8a*R**)-8a-hydroxy-5,5-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene-4a-carbonitrile (**14**), possibly due to neighboring group participation of the cyano function in the epoxidation step. Subsequent hydrogenation of the allylic double bond with palladium on carbon as catalyst, followed by reduction of the nitrile group with DIBAL-H afforded (4a*R**,8a*R**)-8a-(aminomethyl)-1,1-dimethyldecahydronaphthalen-4a-ol (**16**), which was deaminated with hydroxylamine-*O*-sulfonic acid to afford the target compound **4** that possesses an interesting woody odor with green-mossy, camphoraceous, and patchouli-type facets.

Key words: annulations, *cis*-decalins, epoxidations, neighboring group effects, odorants

With about one third of all fine fragrances containing patchouli oil [*Pogostemon cablin* (Blanco) Benth.] as important base-note ingredient, it is quite remarkable that no synthetic patchouli odorant has as yet been introduced to perfumery, especially since the price of this natural material fluctuates considerably and has been on an upward spiral for the last few years.[1] Despite some controversy,[2] its main constituent (35–40%), the sesquiterpene alcohol (–)-patchoulol (**1**), is primarily responsible for the typical well-balanced woody–earthy–camphoraceous odor profile of the essential oil, and **1** is even used in perfumery in isolated form, for example, under the name *Healingwood* (IFF).

While a sterically congested structure and a secondary or tertiary alcohol group were considered structurally important features of patchouli odorants,[3] it was recently demonstrated by the synthesis of the ketol **2** that the gem-dimethyl moiety of (–)-patchoulol (**1**) was no prerequisite for its characteristic odor.[4] The bridgehead methyl substituent of **1**, however, seems odor determining as its removal decreases the camphoraceous character, while rendering the overall odor impression mainly woody.[5]

In attempts to mimic the tricyclo[5.3.1.$0^{3,8}$]undecane sesquiterpene skeleton of **1**, alternative spirocyclic motifs have recently been designed,[6] in the course of which the intermediate **3** with an unusually characteristic patchouli note was discovered (odor threshold 5.0 ng/L air). The typical patchouli, woody odor profile of (5*R**,6*S**)-1,1,6-trimethylspiro[4.5]decan-6-ol (**3**, Figure 1) is all the more surprising since the geometry of the methyl carbinol function is inverted to what one would expect when the gem-dimethyl motifs of compounds **1** and **3** would be superimposed. So, the spiro[4.5]decan-6-ol **3** coins a different superposition motif.

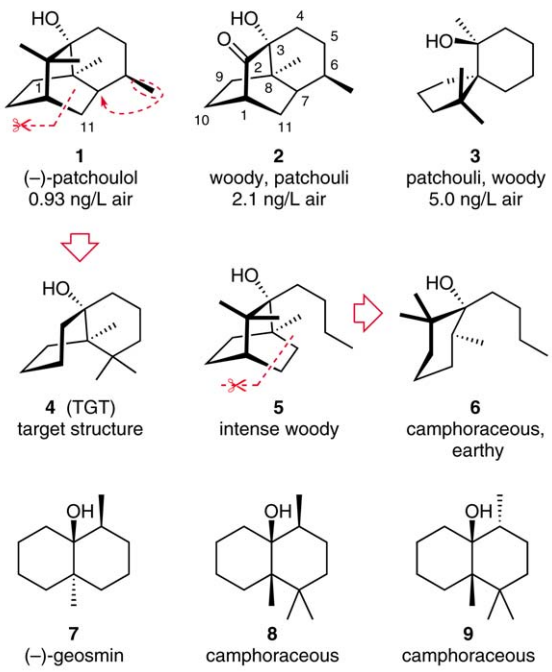

Figure 1 Patchouli odorants, decalin odorants, and the derivation of the *cis*-decalol intersection target structure **4**

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It was thus very tempting to explore this new motif by a biflexible superposition analysis, which was performed with the MOE 2007.09 software package,[7] and is delineated in Figure 2. Interestingly, only one of the methyl groups of the gem-dimethyl moiety of **1** is mapped by the cyclohexyl ring of **3**, but the gem-dimethyl moiety of **3** superimposes on the bridgehead methyl substituent of (–)-patchoulol (**1**), stressing its importance as hydrophobic element. The spiro[4.5]decan-6-ol **3**, in fact, intersects the natural lead **1** in such a way as to complete a *cis*-decalol system with the hydroxy function and the bridgehead methyl group of **1** on the bridgehead positions of the decalin ring, C-4a and C-8a, respectively. In fact, the framework of (–)-patchoulol (**1**) contains a *cis*-decalin system, which becomes most apparent if one dissects the C-1–C-11 bond as indicated in Figure 1. This *cis*-decalin intersection structure indeed embraces the perimeter of the (–)-patchoulol (**1**) molecule. Dissecting the bond C-1–C-11 would result in a methyl group at position C-1 in the 4a-decalol. Thus, looking at the superposition analysis in Figure 2, it seems the cyclopentyl ring of **3** hints at extending this to a geminal 1,1-dimethyl group, which would eliminate a stereocenter.

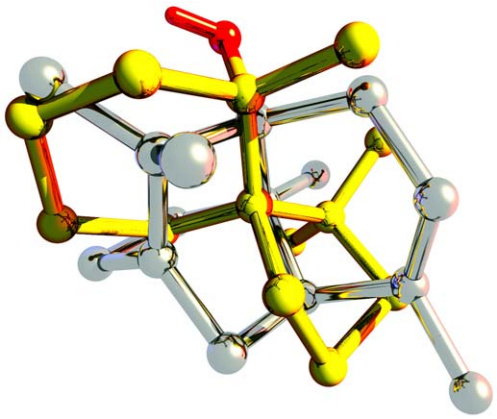


Figure 2 Biflexible superposition analysis of (–)-patchoulol (**1**, depicted in silver) on the patchouli-smelling (5*R**,6*S**)-1,1,6-trimethylspiro[4.5]decan-6-ol (**3**, displayed in gold) with the MOE 2007.09 software package[7]

Not taking the spiro[4.5]decan-6-ol **3** into account, one can derive the resulting target structure **4** imaginarily also from (–)-patchoulol (**1**) alone, by transposing one methyl group from C-6 to C-7, dissecting the C-1–C-11 bond, and abstracting the gem-dimethyl moiety. These severe structural simplifications, however, can preserve the patchouli odor characteristics of the natural lead **1** only if the binding motif on the olfactory receptor corresponds to the superposition analysis in Figure 2, so it puts these structural features to the test.

So far, *seco*-structures of (–)-patchoulol (**1**) did not display the typical patchouli odor characteristics. On dissecting the C-6–C-7 bond of **1**, Spreitzer observed that the patchouli odor was lost, and **5** only smelled intensely woody.[8] Dissection of the C-1–C-11 and C-7–C-8 bonds leads to the substituted cyclohexanol **6**, which Weyerstahl and co-workers synthesized and reported to smell camphoraceous and earthy, with woody and patchouli aspects being absent.[9]

This makes the synthesis of compound **4** even more exciting. Besides, bridgehead decalols are interesting target structures in itself since the *trans*-configured (–)-geosmin (**7**), which emanates the typical earthy odor of freshly ploughed soil, is one of the most intense odorants known to date, with an odor threshold of 0.002 ng/L air.[10] Its *cis*-configured stereoisomers display odors reminiscent of cedarwood and camphor set against the earthy background of the *trans*-isomer.[11] The *cis*-decalin derivatives **8** and **9**, mentioned in connection with the triaxial rule of ambergris odorants[12] and devised as *cis*-decalin superstructures of geosmin and dihydroambrinol (2,5,5-trimethyldecahydronaphthalen-2-ol), were reported to exhibit camphoraceous odors only.[12]

However, the synthesis of **8** and **9**, 4-methyl homologues of our target structure **4**, has never been published. The steric crowd around the three quaternary carbon atoms C-1, C-4a, and C-8a in **4** actually does represent a synthetic challenge, though the geminal 1,1-dimethyl moiety could come in handy for the *cis*-selective introduction of the hydroxy function as it should hinder a nucleophilic attack from the α-face of a 1,1,8a-trimethyldecalin system. The introduction of the gem-dimethyl moiety was envisaged in the construction of the core decalin ring system by Robinson annulation.

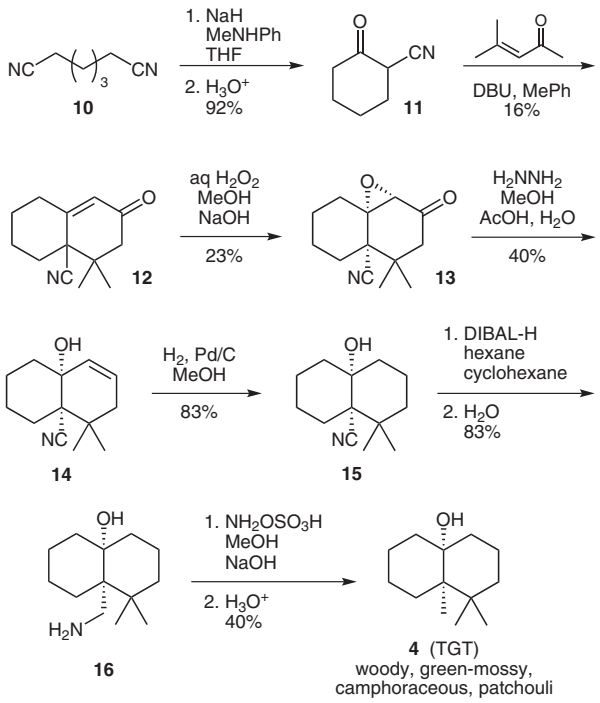
However, the reactivity of 4-methylpent-3-en-2-one as hindered Michael acceptor system was an issue, and it seemed sensible to enhance the carbanion character of the Michael partner by an auxiliary α-cyano function. Liu and co-workers[13] have recently employed such α-cyano ketones in an elegant modification of the Robinson annulation to furnish α,α-disubstituted β,γ-unsaturated cyclohexanone systems by reductive removal of the cyano function in a subsequent alkylation step. In the construction of our target compound **4**, the auxiliary cyano function could, however, even be reduced to the required bridgehead 8a-methyl group in the concluding steps of the projected synthesis. Furthermore, it was tempting to study if this cyano function could be utilized as participating neighboring group in the *syn*-delivery of an oxygen nucleophile on the adjacent bridgehead position.

Subjecting acrylonitrile to the conditions of a Weitz–Scheffer epoxidation[14] does in fact not provide the corresponding epoxynitrile, but gylcidamide, via rearrangement of the intermediate peroxyacrylimidic acid.[15] Thus, in favor of the Michael system, the hydroperoxide anion preferentially attacks the cyano carbon atom, which is more positively charged than the β-carbon atom of the α,β-unsaturated carbonyl group. A cyano function might therefore very well exert a *syn*-selective neighboring-group effect on the nucleophilic attack of the hydroperoxide anion on a Michael acceptor via a reversibly formed peroxycarboximidic acid species, though, to the best of

our knowledge, this has not yet been described. Neighboring group participation in the Weitz–Scheffer epoxidation by intramolecular *syn*-delivery of the hydroperoxide anion had only been reported for oxo[16] and hydroxy groups.[17]

In the projected synthesis of the target compound **4**, the cyano function should be utilized (a) as activating auxiliary to enable a Robinson annulation with 4-methylpent-3-en-2-one, (b) as neighboring group for the *syn*-selective introduction of the oxygen functionality, and finally (c) as precursor for the 8a-methyl group.

The elaborated seven-step synthesis of the target compound **4** is delineated in Scheme 1. Thorpe–Ziegler condensation[18] of pimelonitrile (**10**) employing sodium *N*-methylanilide, generated in situ from sodium hydride and *N*-methylaniline,[13b] provided the starting α-cyanocyclohexanone (**11**) in 92% yield after quenching with water and concentrated hydrochloric acid, standard workup, and chromatographic purification.



Scheme 1 Synthesis of the *cis*-configured target compound **4** from pimelonitrile by Robinson annulation, Weitz–Scheffer epoxidation, Wharton olefination with subsequent hydrogenation, nitrile reduction, and concluding deamination

Robinson annulation of 2-oxocyclohexanecarbonitrile (**11**) with 4-methylpent-3-en-2-one and stoichiometric amounts of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base in refluxing toluene afforded, after repeated flash chromatography, the desired annulation product **12**, albeit in a rather disappointing yield (16%), which was accounted to the steric demand of the Michael acceptor. Nota bene, ethyl 2-oxocyclohexanecarboxylate does not react at all with 4-methylpent-3-en-2-one under these reaction conditions, illustrating the importance of the nitrile function.

The stage was now set for the crucial Weitz–Scheffer epoxidation[14] of the cyano enone **12** employing the standard conditions, that is, 30% aqueous hydrogen peroxide in methanol with aqueous sodium hydroxide. The yield of the reaction was only moderate (23%), but the reaction provided exclusively one single diastereomer, and much to our satisfaction, the single-crystal X-ray diffraction analysis (Figure 3a) indeed established the configuration of the 4,4-dimethyl-2-oxooctahydro-4a*H*-naphtho[1,8a-*b*]oxirene-4a-carbonitrile (**13**) obtained to be (1*R**,4a*S**,8a*R**), that is, *cis* with respect to the bridgehead atoms. Though the steric hindrance of the axial 5-methyl group in **12** might also favor the nucleophilic attack of the hydroperoxide anion on the enone from the opposite face, this complete selectivity could additionally involve the participation of the cyano function. Weitz–Scheffer epoxidation of differently substituted methyl octalones only furnished mixtures of α- and β-epoxides in ratios of 46:54 and 22:78, respectively.[19] Thus, neighboring group participation of the cyano function with intramolecular *syn*-delivery of the hydroperoxide anion seems to be a likely reason for the exclusive formation of the (1*R**,4a*S**,8a*R**)-configured epoxide **13**. The nucleophilic attack of the hydroperoxide anion might be guided by the cyano group in a *syn*-directive manner as visualized in the proposed transition state **TS** in Figure 4.

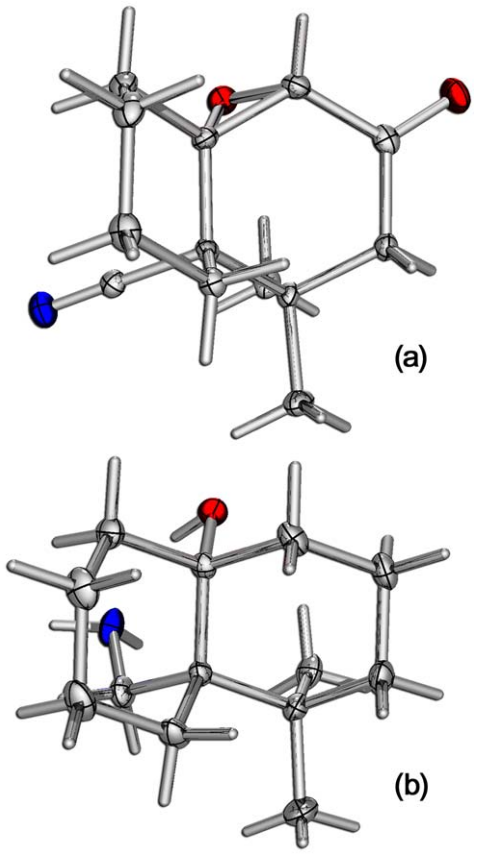


Figure 3 Molecular structures of **13** (a) and **16** (b) in the crystal with thermal ellipsoids at the 50% probability level

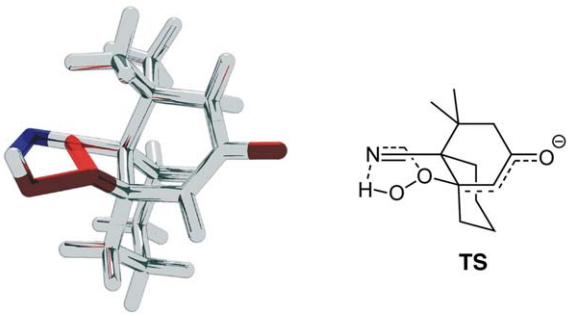


Figure 4 Possible transition state **TS** accounting for the observed exclusive *syn*-delivery of the hydroperoxide anion in the reaction **12** →**13**

Preserving the generated stereochemical information at the bridgehead positions, now the epoxide was to be opened and the carbonyl group to be removed. For this purpose, the Wharton oxygen transposition[20] with subsequent hydrogenation of the resulting allylic alcohol seemed to be the method of choice. Accordingly, the α,β-epoxy ketone **13** was reductively rearranged with hydrazine hydrate in methanol at ambient temperature in the presence of acetic acid to afford the corresponding (4a*R**,8a*R**)-configured allylic alcohol **14** in 40% yield. Subsequent hydrogenation of this Δ^7-octalol **14** in methanol in the presence of catalytic amounts of palladium on carbon furnished the (4a*R**,8a*R**)-configured (4a*R**,8a*R**)-8a-hydroxy-4,4-dimethyldecahydronaphthalene-4a-carbonitrile (**15**) in 83% yield.

All that was missing now to complete the synthesis of the target compound **4**, was the reduction of the auxiliary cyano function of the nitrile **15** to a methyl group. Though this could in principle have been accomplished together with the reduction of the allylic double bond in **14**, even the separate reduction of the nitrile function turned out to be more difficult than anticipated, probably because of the severe steric crowd around the three quaternary carbon centers 4, 4a, and 8a in **15**. So a two-step detour, consisting of hydride reduction and subsequent deamination, had to be taken. In the hydride reduction of the cyano function of **15**, lithium aluminum hydride (LAH) performed surprisingly badly. However, excess diisobutylaluminum hydride (DIBAL-H) in refluxing cyclohexane worked out fine, and the 8a-aminomethyl-4a-decalol was obtained in 83% yield. Since DIBAL-H possesses only one hydride per molecule, one can speculate that after reaction with the hydroxy function of **15**, with release of one molar equivalent of H_2, an intramolecular chelate ring is formed, incorporating the cyano function and thereby activating it towards intermolecular reduction by a second equivalent of DIBAL-H. The retention of the *cis*-configuration of the decalin skeleton of **16** and its overall structure could be established by NMR experiments in conjunction with a single crystal X-ray diffraction analysis (Figure 3b).

The reductive deamination of the amino alcohol **16** was all that remained to conclude the synthesis of the target compound **4**. One of the most reliable selective and mild reagents for the reductive deamination of primary amines that is compatible with a wide variety of functional groups including hydroxy functions, is hydroxylamine-*O*-sulfonic acid (HOS) as introduced by Doldouras and Kollonitsch.[21] This hydrodeamination is thought to proceed via N-amination of the amine to the corresponding hydrazine under alkaline conditions. Nitrene, also formed from HOS under these conditions, then oxidizes the alkyl hydrazine to the corresponding metastable alkyldiazene (diimide), which decomposes to the alkane under extrusion of dinitrogen.[21] Accordingly, to control the evolution of dinitrogen, a solution of the primary amine **16** in methanol was treated repeatedly with aqueous sodium hydroxide and HOS, and the mixture was refluxed for 15 minutes after each complete addition. After neutralization with 2 M hydrochloric acid, diethyl ether extraction, chromatographic purification, and bulb-to-bulb distillation, the target compound **4** was obtained in 40% as a colorless, odoriferous solid. The identities and chemical purities of **4** and compounds **12**–**16** were established by C,H,N elemental analyses and NMR experiments, and the olfactory purity of the target compound **4** was additionally assured by GC–olfactometry.

The olfactory evaluation of the target compound **4** by expert perfumers was both, gratifying and disappointing. Gratifying, since the main odor character of **4** was neither predominantly earthy, such as that of (–)-geosmin (**7**), nor predominantly camphoraceous, such as that of the related *cis*-decalols **8** and **9** (Figure 1). Instead, the main odor character of **4** was woody, green-mossy. However, camphoraceous aspects were also present as a side note, as was a patchouli tonality. Disappointingly, however, this patchouli note was not the dominant theme, as had been hoped for, and the odor threshold of 13.1 ng/L air was inferior to that of the lead structure **3** (5.0 ng/L air), though GC–olfactometry on a chiral stationary phase revealed only one enantiomer of **4** to be responsible for the odor impression of the racemate, while the other enantiomer was odorless. Thus, the smelling enantiomer should possess half the odor threshold of the racemate (6.6 ng/L air). Unfortunately, the steric crowd around the hydroxy function of **4** prevented the esterification with (–)-camphanoyl chloride as chiral resolving agent, and the olfactory properties of the racemate were not interesting enough to venture into an enantioselective approach, such as a Juliá–Colonna epoxidation of the enone **12**.

Nevertheless, in contrast to the patchoulol partial structures **5** and **6** (Figure 1), the target compound **4** is clearly reminiscent of patchouli oil, even if that is not its main character. This demonstrates that decalin systems could indeed be interesting patchouli odorants and that the superposition analysis in Figure 2 might reveal some insight into the binding geometry of patchouli odorants on the relevant olfactory receptor(s). Only very recently, 4-ethyl-8,8a-dimethyldecahydronaphthalen-1-ol, prepared as isomeric mixture by Diels–Alder reaction of 4-ethyl-2-methylcyclohex-2-en-1-one with penta-1,3-diene, hydrogenation, and subsequent LAH reduction, was disclosed as woody patchouli odorant with camphoraceous aspects.[22]

In conclusion, besides the olfactory aspects, this paper presents an interesting strategy for the construction of sterically demanding *cis*-decalin systems, for making use of neighboring-group effects in directing selectivity, and for employing cyano functions as versatile auxiliary groups. The underlying methodology should thus be of broader applicability in synthetic chemistry.

All reactions involving chemicals sensitive to H_2O and/or O_2 were carried out under a dry argon atmosphere. The organic solvents used were dried and purified according to standard procedures and stored under dry N_2. Starting materials, reagents, and solvents were purchased from Aldrich or Acros and were used without further purification (except for 4-methylpent-3-en-2-one, which was obtained from Merck). Bulb-to-bulb distillations were performed with a Büchi B-580 apparatus, analytical TLC on silica gel (TLC aluminum sheets, silica gel $60F_{254}$, Merck, 105554) with 5% phosphomolybdic acid in EtOH as visualization reagent. Melting points were determined with a Büchi Melting Point B-540 apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded at 23 °C on a Bruker DRX-300 (^1H, 300.1 MHz; ^{13}C, 75.5 MHz) or Bruker Avance 500 NMR spectrometer (^1H, 500.1 MHz; ^{13}C, 125.8 MHz) using $CDCl_3$ as the solvent. The 2D ^{13}C,^{13}C INADEQUATE experiment of **4** was recorded on a Bruker DMX-600 NMR spectrometer using a ^1H,^{13}C cryo probe. Chemical shifts (ppm) were determined relative to internal $CHCl_3$ (^1H, δ = 7.24; $CDCl_3$) or $CDCl_3$ (^{13}C, δ = 77.0; $CDCl_3$). Analysis and assignment of the ^1H NMR data were supported by ^1H,^1H COSY, ^{13}C,^1H HMQC, and ^{13}C,^1H HMBC experiments. Assignment of the ^{13}C NMR data was supported by ^{13}C,^1H HMQC, ^{13}C,^1H HMBC, INADEQUATE, and DEPT-135 experiments. The GC/EI-MS studies were performed on a Thermo MS-8060 gas chromatograph [Phenomenex Zebron ZB-1 capillary column; length, 15 m; i.d. 0.32 mm; flow rate, 0.73 mL min^{-1}, injector, split 36.6 mL min^{-1}, split ratio 1:25, 220 °C; carrier gas, He; temperature program, 80 °C (2 min) with 20 °C min^{-1}] and a Thermo TRIO 1000 mass spectrometer (EI-MS, 70 eV). Elemental analyses were performed on a VarioMicro of Elementar Analysensysteme GmbH. For the X-ray diffraction experiments, suitable single crystals were mounted in inert oil (perfluoropolyalkyl ether, ABCR) on a glass fiber and then transferred to the cold N_2 gas stream of the diffractometer [BrukerNonius KAPPA-APEX II, with Göbel mirror, Mo K_α radiation (λ = 0.71073 Å)]. The structures were solved by direct methods.[23] All non-hydrogen atoms were refined anisotropically.[24] A riding model was employed in the refinement of the H atoms.

Olfactory evaluations were performed by expert perfumers with a 10% solution of the sample substance in EtOH and 10% solution of the sample substance in dipropylene glycol (DPG) on smelling blotters. 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 concentration was halved. The last concentration detected at the correct retention time is the individual odor threshold. The reported threshold value represents the geometrical mean of the individual odor thresholds of the different panelists.

5,5-Dimethyl-7-oxo-1,2,3,4,4a,5,6,7-octahydronaphthalene-4a-carbonitrile (12)

1,8-Diazabicyclo[5.4.0]undec-7-ene (9.00 g, 59.1 mmol) was added at r.t. to a stirred solution of 2-oxocyclohexanecarbonitrile (**11**; 5.00 g, 40.6 mmol), prepared according to ref. 14b, and 4-methylpent-3-en-2-one (10.2 g, 104 mmol) in toluene (60 mL). The reaction mixture was heated under reflux for 20 h, and subsequently allowed to cool to r.t., followed by the addition of 2 M aq HCl (60 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (2 × 50 mL). The organic extracts were combined, washed with aq sat. $NaHCO_3$ (50 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting residue purified by column chromatography on silica gel (50 × 3 cm diameter, silica gel 35–70 μm, 180 g, hexane–EtOAc, 3:2). The relevant fractions (GC) were combined, and the solvent was removed under reduced pressure to afford compound **12**; yield: 1.32 g (16%); colorless solid; mp 117 °C, R_f = 0.6 (hexane–EtOAc, 3:2).

^1H NMR (300.1 MHz, $CDCl_3$): δ = 1.05 [s, 3 H, 5-$(CH_3)_a$)], 1.27 [s, 3 H, 5-$(CH_3)_b$], 1.38 (m_c, 1 H, H-2_a), 1.62 (m_c, 1 H, H-4_a), 1.80–1.99 (m, 2 H, H_2-3), 1.98 (m_c, 1 H, H-2_b), 2.18 (m_c, 1 H, H-4_b), 2.24 (d, *J* = 16.0 Hz, 1 H, H-6_a), 2.51 (m_c, 1 H, H-1_a), 2.59 (m_c, 1 H, H-1_b), 2.53 (d, *J* = 16.0 Hz, 1 H, H-6_b), 5.91 (d, *J* = 2.0 Hz, 1 H, H-8).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 22.9 [1-$(CH_3)_a$)], 23.1 (CH_2, C-3), 25.8 [5-$(CH_3)_b$)], 26.8 (CH_2, C-2), 31.6 (CH_2, C-4), 33.7 (CH_2, C-1), 37.9 (C_q, C-5), 48.4 (C_q, C-4a), 49.6 (CH_2, C-6), 119.6 (CN), 125.7 (CH, C-8), 157.1 (C_q, C-8a), 196.8 (C_q, C-7).

GC/EI-MS: t_R = 7.15 min; *m*/*z* (%) = 203 (15, [M^+]), 147 (100).

Anal. Calcd for $C_{13}H_{17}NO$ (203.3): C, 76.81; H, 8.43; N, 6.89. Found: C, 76.53; H, 8.40; N, 6.92.

(1*R**,4a*S**,8a*R**)-4,4-Dimethyl-2-oxooctahydro-4a*H*-naphtho[1,8a-*b*]oxirene-4a-carbonitrile (13)

At 0 °C, 30% aq H_2O_2 (*d* = 1.11 g/mL, 12.0 mL, 106 mmol) was added in a single portion to a stirred solution of **12** (7.00 g, 34.4 mmol) in MeOH (120 mL), followed by the addition of 2 M aq NaOH (14 mL), also in a single portion. The reaction mixture was stirred at 0 °C for 90 min, prior to the addition of aq sat. $Na_2S_2O_3$ (100 mL). The aqueous layer was separated and washed with Et_2O (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to a volume of about 70 mL. The resulting suspension was filtered and the colorless solid washed with Et_2O (2 × 15 mL) to furnish compound **13**; yield: 1.70 g (23%); colorless solid; mp 170 °C.

^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.06 [s, 3 H, 4-$(CH_3)_a$], 1.37 (m_c, 1 H, H-8_a), 1.45 (m_c, 1 H, H-7_a), 1.45 [s, 3 H, 4-$(CH_3)_b$)], 1.50 (m_c, 1 H, H-5_a), 1.79–1.94 (m, 2 H, H_2-6), 2.00 (m_c, 1 H, H-7_b), 2.17 (dd, *J* = 18.0, 0.5 Hz, 1 H, H-3_a), 2.22 (m_c, 1 H, H-5_b), 2.30 (m_c, 1 H, H-8_b), 2.45 (d, *J* = 18.0 Hz, 1 H, H-3_b), 3.06 (s, 1 H, H-1).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.2 (CH_2, C-6), 24.1 (CH_2, C-7), 27.2 [4-$(CH_3)_a$)], 29.1 [4-$(CH_3)_b$)], 31.2 (CH_2, C-5), 32.1 (CH_2, C-8), 36.4 (C_q, C-4), 47.42 (CH_2, C-3), 47.43 (C_q, C-4a), 59.4 (CH, C-1), 66.9 (C_q, C-8a), 119.5 (CN), 202.7 (C_q, C-2).

GC/EI-MS: t_R = 7.22 min; *m*/*z* (%) = 219 (5, [M^+]), 83 (100).

Anal. Calcd for $C_{13}H_{17}NO_2$ (219.3): C, 71.21; H, 7.81; N, 6.39. Found: C, 70.99; H, 8.01; N, 6.16.

Crystal Structure Analysis[25]

A single crystal of the dimensions 0.3 × 0.05 × 0.05 mm was obtained from a solution of **13** (150 mg) in Et_2O–EtOAc (2:1, 7.5 mL) by slow evaporation of the solvent mixture; $C_{13}H_{17}NO_2$, *M*r = 219.28, analysis at 100 (2) K, trigonal, space group $P3_2$ (no. 145), *a* = 12.6998(5) Å, *b* = 12.6998(5) Å, *c* = 6.0414(4) Å, *V* = 843.894(7) $Å^3$, *Z* = 3, ρ_{calcd} = 1.294 mg/cm^3, μ = 0.087 mm^{-1}, *F*(000) 354, 2θ range 2.70–57.46°, 7813 collected reflections, 2861 unique reflections (R_{int} = 0.0510), refinement full-matrix least-squares methods on F^2 for all unique reflections, 1 restraint, 150 parameters, *S* = 1.034, R_1 = 0.0431 [$I > 2\sigma(I)$], wR_2 (all data) = 0.1057, max/min electron density +0.306/–0.1086 e $Å^{-3}$.

(4a*R,8a*R**)-8a-Hydroxy-5,5-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene-4a-carbonitrile (14)**

At 0 °C, 80% aq hydrazine hydrate (d = 1.03 g/mL, 1.50 mL, 24.7 mmol) was added dropwise with stirring within 30 min to a solution of **13** (1.60 g, 7.30 mmol) in MeOH (250 mL). After complete addition, the reaction mixture was allowed to warm to r. t., and glacial AcOH (84.0 mg 1.40 mmol) was added in a single portion. The mixture was stirred for 1 h at r.t. and then added in a single portion to a stirred mixture consisting of CH_2Cl_2 (500 mL) and H_2O (100 mL). Stirring was continued for 10 min at 20 °C, prior to the separation of the organic layer, drying (Na_2SO_4), and removal of the solvent under reduced pressure. The resulting oily residue was purified by column chromatography on silica gel (50 × 3 cm diameter, silica gel 35–70 µm, 180 g, hexane–EtOAc, 2:1). The relevant fractions (GC) were combined, and the solvent was removed under reduced pressure to furnish compound **14**; yield: 600 mg (40%); colorless solid; mp 131–132 °C; R_f = 0.7 (hexane–EtOAc, 2:1).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.12 (m_c, 1 H, H-2_a), 1.13 [s, 3 H, 5-$(CH_3)_a$)], 1.30 (ddd, J = 13.5, 13.5, 4.0 Hz, 1 H, H-4_a), 1.36 [s, 3 H, 5-$(CH_3)_b$], 1.55 (ddddd, J = 13.5, 13.5, 13.5, 3.5, 3.5 Hz, 1 H, H-3_a), 1.63–1.71 (m, 2 H, H-3_b, H-2_b), 1.73 (ddd, J = 13.5, 13.5, 3.5 Hz, 1 H, H-1_a), 1.82 (m_c, 1 H, H-1_b), 1.98 (dd, J = 3.5, 2.5 Hz, 2 H, H_2-6), 2.05 (m_c, 1 H, H-4_b), 5.47 (dt, J = 10.0, 2.0 Hz, 1 H, H-7), 5.80 (dt, J = 10.0, 4.0 Hz, 1 H, H-8), OH resonance not detected.

^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 22.9 (CH_2, C-3), 23.1 (CH_2, C-2), 27.3 [5-$(CH_3)_a$)], 28.3 [5-$(CH_3)_b$)], 29.8 (CH_2, C-4), 25.5 (C_q, C-5), 36.5 (CH_2, C-6), 40.5 (CH_2, C-1), 51.6 (C_q, C-4a), 70.9 (C_q, C-8a), 121.3 (CN), 128.8 (CH, C-7), 129.4 (CH, C-8).

GC/EI-MS: t_R = 6.75 min; m/z (%) = 205 (30, [M$^+$]), 69 (100).

Anal. Calcd for $C_{13}H_{19}NO$ (205.3): C, 76.06; H, 9.33; N, 6.82. Found: C, 76.00; H, 9.33; N, 7.00.

(4a*R,8a*R**)-8a-Hydroxy-4,4-dimethyldecahydronaphthalene-4a-carbonitrile (15)**

At r.t., Pd/C (250 mg, 10 wt%, 235 µmol of Pd) was added in a single portion to a stirred solution of **14** (900 mg, 4.38 mmol) in MeOH (30 mL). The suspension was then stirred under an atmosphere of H_2 for 24 h. The precipitate was filtered off and washed with MeOH (2 × 10 mL). The filtrate was combined with the washings, and the resulting solution was dried (Na_2SO_4) and concentrated under reduced pressure to afford compound **15**; yield: 750 mg (83%); colorless solid; mp 122 °C.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.96 [s, 3 H, 4-$(CH_3)_a$)], 1.30–1.41 (m, 2 H, H_2-3), 1.35 (m_c, 1 H, H-7_a), 1.35 (m_c, 1 H, H-1_a), 1.43 (m_c, 1 H, H-2_a), 1.44 [s, 3 H, 4-$(CH_3)_b$)], 1.58 (m_c, 1 H, H-5_a), 1.60 (m_c, 1 H, H-6_a), 1.62 (m_c, 1 H, H-8_a), 1.64 (m_c, 1 H, H-7_b), 1.72 (m_c, 1 H, H-6_b), 1.73 (m_c, 1 H, H-8_b), 1.78 (m_c, 1 H, H-1_b), 1.89 (m_c, 1 H, H-2_b), 1.91 (m_c, 1 H, H-5_b), OH resonance not detected.

^{13}C NMR (125.5 MHz, $CDCl_3$): δ = 17.2 (CH_2, C-2), 23.0 (CH_2, C-7), 23.2 (CH_2, C-6), 27.5 [4-$(CH_3)_a$)], 28.9 [4-$(CH_3)_b$)], 29.2 (CH_2, C-5), 30.9 (CH_2, C-1), 34.2 (CH_2, C-3), 36.5 (C_q, C-4), 40.8 (CH_2, C-8), 52.3 (C_q, C-4a), 73.0 (C_q, C-8a), 121.8 (CN).

GC/EI-MS: t_R = 6.86; m/z (%) = 189 (25, [M$^+$ – H_2O]), 41 (100).

Anal. Calcd for $C_{13}H_{21}NO$ (207.3): C, 75.32; H, 10.21; N, 6.76. Found: C, 74.92; H, 9.95; N, 6.73.

(4a*R,8a*R**)-8a-(Aminomethyl)-1,1-dimethyldecahydronaphthalen-4a-ol (16)**

At r.t., a 1.1 M solution of DIBAL-H (20.0 mL, 22.0 mmol) in cyclohexane was added in a single portion to a stirred solution of **15** (260 mg, 1.25 mmol) in hexane (5 mL). The reaction mixture was heated under reflux for 16 h and then cooled to 0 °C. Subsequently, MeOH (5 mL) was added dropwise with stirring within 10 min, followed by the addition of brine (5 mL). The precipitate was filtered off and washed successively with H_2O (4 × 10 mL) and Et_2O (4 × 10 mL). The filtrate was combined with the washings, the organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 25 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting oily residue was purified by bulb-to-bulb distillation (150 °C/0.50 mbar) to afford compound **16** as a highly viscous liquid, which crystallized within 24 h at 20 °C; yield: 220 mg (83%); colorless solid; mp 53 °C.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.74 [s, 3 H, 1-$(CH_3)_a$)], 1.07 (m_c, 1 H, H-8_a), 1.08 (m_c, 1 H, H-2_a), 1.10 (m_c, 1 H, H-4_a), 1.30 (m_c, 1 H, H-3_a), 1.34–1.47 (m, 2 H, H_2-7), 1.38 (m_c, 1 H, H-5_a), 1.38 [s, 3 H, 1-$(CH_3)_b$], 1.43 (m_c, 1 H, H-6_a), 1.51 (m_c, 1 H, H-8_b), 1.51 (m_c, 1 H, H-6_b), 1.54 (m_c, 1 H, H-2_b), 1.75 (m_c, 1 H, H-5_b), 1.90 (ddd, J = 13.5, 13.5, 3.5 Hz, 1 H, H-4_b), 1.97 (m_c, 1 H, H-3_b), 3.06 and 3.26 (AB system, $^2J_{AB}$ = 15.0 Hz, 2 H, CH_AH_BNH$_2$), OH resonance not detected.

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 18.1 (CH_2, C-3), 21.5 (CH_2, C-7), 23.2 (CH_2, C-6), 27.2 [1-$(CH_3)_a$], 28.7 [1-$(CH_3)_b$], 28.9 (CH_2, C-8), 34.3 (CH_2, C-4), 37.8 (C_q, C-1), 38.7 (CH_2, C-2), 39.6 (CH_2, C-5), 42.2 (CH_2NH_2), 43.1 (C_q, C-8a), 76.2 (C_q, C-4a).

GC/EI-MS: t_R = 8.04 min; m/z (%) = 211 (2, [M$^+$]), 149 (100).

Anal. Calcd for $C_{13}H_{25}NO$ (211.3): C, 73.88; H, 11.92; N, 6.63. Found: C, 73.68; H, 11.86; N, 6.52.

Crystal Structure Analysis[25]

A single crystal of the dimensions 0.29 × 0.12 × 0.10 mm was obtained directly from the reaction mixture; $C_{13}H_{25}NO$, Mr = 211.34, analysis at 99(2) K, monoclinic, space group $P2_1/n$ (no. 14), a = 7.3270(2) Å, b = 8.2084(3) Å, c = 20.7399(6) Å, β = 98.347(2)°, V = 1234.15(7) Å^3, Z = 4, ρ_{calcd} = 1.137 mg/cm^3, μ = 0.070 mm^{-1}, F(000) 472, 2θ range 3.96–66.34°, 34782 collected reflections, 4695 unique reflections (R_{int} = 0.0431), refinement full-matrix least-squares methods on F^2 for all unique reflections, 158 parameters, S = 1.065, R_1 = 0.0459 [$I > 2\sigma(I)$], wR_2 (all data) = 0.1342, max/min electron density +0.465/–0.197 e Å^{-3}.

(4a*R,8a*R**)-1,1,8a-Trimethyldecahydronaphthalen-4a-ol (4)**

At 40 °C, 2.5 M aq NaOH (21.0 mL, 52.5 mmol) was added in a single portion to a stirred solution of **16** (550 mg, 2.60 mmol) in MeOH (22 mL), followed by the addition of hydroxylamine-*O*-sulfonic acid (550 mg, 4.86 mmol), also in a single portion. The resulting suspension was heated under reflux for 15 min and then allowed to cool to 40 °C. The last 3 steps were repeated 7 times, prior to final addition of 2 M aq HCl (50 mL). Et_2O (50 mL) was added, the organic layer separated, and the aqueous layer extracted with Et_2O (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), the solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (50 × 1.5 cm diameter, silica gel 15–40 µm, 50 g, hexane–EtOAc, 5:1). The relevant fractions (GC) were combined, the solvent was removed under reduced pressure, and the resulting residue was then purified by bulb-to-bulb distillation (60–80 °C/0.3 mbar) to afford compound **4**; yield: 205 mg (40%); colorless, odoriferous solid; mp 34 °C; R_f = 0.4 (hexane–EtOAc, 4:1).

Odor Description: woody odor with green-mossy, camphoraceous and patchouli-type facets; odor threshold: 13.1 ng/L air. The odor of the racemate is due entirely to the first eluting enantiomer on a chiral Hydrodex-β-6-TDBM (25 m × 0.25 mm) column as revealed by GC–olfactometry (60 kPa H_2, split 1:20, 150 °C isothermal), which accordingly possesses a threshold of 6.6 ng/L air.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.73 [s, 3 H, 1-$(CH_3)_a$], 0.96 [s, 3 H, 1-$(CH_3)_b$], 1.12 (m_c, 1 H, H-2_{eq}), 1.16 (s, 3 H, 8a-CH_3), 1.17 (m_c, 1 H, H-4_{eq}), 1.22 (m_c, 1 H, H-5_{eq}), 1.34 (m_c, 1 H, H-6_{eq}), 1.37 (m_c, 1 H, H-3_{eq}), 1.38 (m_c, 1 H, H-8_{ax}), 1.37–1.50 (m, 2 H, H_2-7),

1.54 (m_c, 1 H, H-6_{ax}) 1.56 (m_c, 1 H, H-8_{eq}), 1.51–1.61 (ddd, J = 13.0, 13.0, 4.0 Hz, 1 H, H-2_{ax}), 1.66 (ddd, J = 13.5, 13.5, 4.5 Hz, 1 H, H-5_{ax}), 1.83 (ddddd, J = 14.0, 14.0, 14.0, 3.5, 3.5 Hz, 1 H, H-3_{ax}), 2.03 (ddd, J = 14.0, 14.0, 4.5 Hz, 1 H, H-4_{ax}), OH resonance not detected.

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 13.4 (8a-CH_3), 18.1 (CH_2, C-6), 21.7 (CH_2, C-3), 23.7 (CH_2, C-7), 26.4 [1-$(CH_3)_a$], 27.3 [1-$(CH_3)_b$], 31.0 (CH_2, C-8), 33.9 (CH_2, C-4), 36.7 (C_q, C-1), 37.3 (CH_2, C-2), 39.2 (CH_2, C-5), 42.2 (C_q, C-8a), 74.9 (C_q, C-4a).

GC/EI-MS: t_R = 6.16 min; *m/z* (%) = 196 (5, [M^+]), 82 (100).

Anal. Calcd for $C_{13}H_{24}O$ (196.3): C, 79.53; H, 12.32. Found: C, 79.62; H, 12.67.

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(25) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-695876 (**13**) and CCDC-695877 (**16**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].