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Musk or violet? Design, synthesis and odor of *seco*-derivates of a musky carotol lead

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Dedicated with best wishes to Professor Georg Fráter on the occasion of his 65th birthday

Abstract—By a six-step synthetic route consisting of a Li_2MnCl_4-catalyzed coupling of branched alkyl magnesium chlorides with isovaleryl and 3,3-dimethylbutanoyl chloride, Grignard reaction of the product with ethynyl magnesium bromide, dehydration and transformation into a Grignard reagent, subsequent reaction with acetaldehyde, (*E*)-selective hydrogenation of the alkynol triple bond with lithium aluminum hydride, and finally pyridinium chlorochromate oxidation, four sterically highly demanding target structures were synthesized diastereoselectively. These four molecular targets were designed as *seco*-structures to a musky carotol lead, and their olfactory profiles that merge violet like with musky notes to different extents, provide interesting insight into structure–odor correlation.

1. Introduction

In the course of work for his master thesis on carotol derivatives in the late 1960s in the laboratory of Professor Janusz Kulesza in Lodz, Józef Kula discovered an interesting new musk odorant. Ozonolysis of carotol with subsequent intramolecular aldol condensation and dehydration of the resulting intermediate dihydroxy ketone afforded a product mixture imparting a pleasant musky scent.[1,2] They believed this scent to originate from its main compound to which they assigned structure **1** and named 'mageritone' (Fig. 1).[1] Over 30 years later however, Józef Kula, having become a professor at the University of Lodz, revisited this chemistry with his group and found mageritone **1** to have only a weak and uncharacteristic smell.[2,3] The actual cause of the musk odor of that mageritone-containing product mixture was the isomeric dienone **2**, which was present at a concentration of less than 5%. The odor and structure of this tetrahydroindene **2** was proven by a directed partial synthesis with isomerization of the double bond catalyzed by Pd/C in refluxing cyclohexene.[3] It was characterized as emanating a dry musky odor with a threshold of around 1 ng/L air.[2]

Already in the early 1960s, Kazimir Sestanj[4] discovered that the *seco*-structure **3**, in which the two carbon atoms C-2 and C-3 were cut out of the β-ionone ring,[5] retained all important odor characteristics of β-ionone. He reported two synthetic routes to **3**, the first one of which commenced with a Reformatsky reaction of ethyl 2-bromo-3-methylbutanoate with triethyl *ortho*-formiate, followed by Grignard reaction with methyl magnesium iodide, hydrolysis, and aldol condensation of the intermediate aldehyde with acetone.[4] The second approach started from 3-isopropyl-4-methylpent-1-yn-3-ol that was transformed into its acetate by reaction with ketene, which was then rearranged by silver-catalyzed Saucy–Marbet reaction[6] to the corresponding aldehyde. Grignard reaction with acetylene magnesium bromide and Rupe rearrangement of the resulting 5-isopropyl-6-methylhept-4-en-1-yn-3-ol at 50 °C in formic acid concluded his second synthesis of **3**.

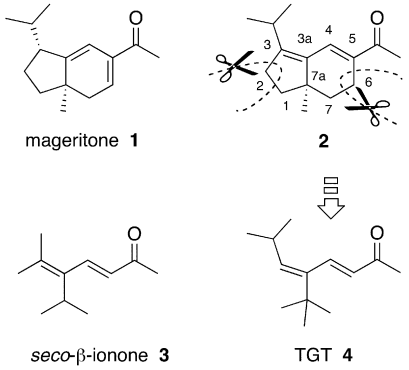

Figure 1. Mageritone (**1**), the *seco*-β-ionone of Sestanj (**3**), and the first target structure **4**, devised as a *seco*-structure to the musk odorant **2**.

Keywords: Alkynols; Carotol; Chemoselective hydrogenation; Ionone odorants; Odor–structure correlation; *seco*-Derivatives.
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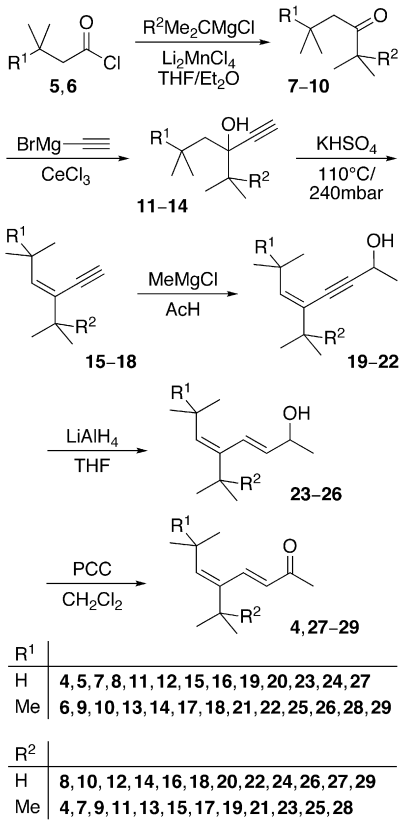
With the structural features and the odor characteristics of Sestanj's *seco*-β-ionone **3** in mind, the question arises as to what would be the odor of a *seco*-structure of the carotol derivative **2**, in which C-2 and C-6 were cut out from the 2,6,7,7a-tetrahydro-1*H*-inden-5-yl system. This target compound **4** (Fig. 1) should sterically mimic the musk odorant **2**, but would at the same time structurally resemble the truncated ionone **3**: Would the target molecule **4** thus smell musky or violet like? Or better still, can one construct in this way an odorant that would combine aspects of both primary odor notes? And finally, how would the exchange of a *tert*-butyl by an isopropyl group and vice versa or, in other words, how would the bulkiness of the substituents affect the odor character and intensity? In the following, these questions are addressed with the synthesis of **4** as well as of three additional derivatives **27–29** (Scheme 1), in which *tert*-butyl and isopropyl groups are permuted.



R^1	
H	**4,5,7,8,11,12,15,16,19,20,23,24,27**
Me	**6,9,10,13,14,17,18,21,22,25,26,28,29**

R^2	
H	**8,10,12,14,16,18,20,22,24,26,27,29**
Me	**4,7,9,11,13,15,17,19,21,23,25,28**

Scheme 1. Synthesis of the target structures **4** and **27–29** from isovaleryl and *tert*-butylacetyl chloride.

2. Results and discussion

Due to the severe steric hindrance of the *tert*-butyl and isopropyl groups, the synthesis of target compound **4** turned out to be far more difficult than anticipated. Attempts to introduce the *tert*-butyl group by reacting the Wittig–Horner reagent of Lee and Wiemer[7] with isopropyl methyl ketone failed utterly, and the aldol condensation of the lithium enolate of ethyl 3,3-dimethylbutanoate with isopropyl methyl ketone also proved unsuccessful. Even all attempts to prepare aldol adducts by treatment of ethyl 2-acetyl-3,3-dimethylbutanoate with isopropyl lithium, and ethyl 2-*tert*-butyl-4-methyl-3-oxopentanoate with methyl lithium were to no avail. Thus, we finally decided to employ acetylene chemistry, just as Sestanj[4] had with his symmetric system. We decided, however, against a Rupe rearrangement in the final step, as yields are often low and Sestanj[4] did not report one for this step. Most importantly, however, we wanted to control the geometry of both double bonds of the target structure **4** and its derivatives **27–29** throughout the entire synthetic sequence.

To ensure the (3*E*)-configuration of the double bond in conjugation with the carbonyl group in the target structures **4** and **27–29**, the partial reduction of 2-alkynols[8] with lithium aluminum hydride was envisaged, followed by subsequent oxidation of the resulting allylic alcohols. This partial hydrogenation was discovered by Chanley and Sobotka in 1949,[8a] and it proceeds in a completely *trans*-selective manner as was rationalized by mechanistic studies.[9] More recently, this method had also been employed in a muscone synthesis of Thies and Daruwala[10] by siloxy-Cope ring expansion. The oct-5-en-3-yn-2-ols required as substrates for the partial hydrogenation with lithium aluminum hydride were projected to be prepared following the route recently reported by us in the synthesis of *seco*-theaspiranes.[11] The entire synthetic sequence is delineated in Scheme 1, and starts from isovaleryl (**5**) and *tert*-butylacetyl chloride (**6**), respectively, which are both commercially available.

In the synthesis of our first and principal target molecule **4**, isovaleryl chloride (**5**) was coupled with *tert*-butyl magnesium chloride applying the manganese-catalyzed acylation reaction developed by Cahiez and Laboue.[12] In the presence of the soluble ate complex Li_2MnCl_4, prepared by mixing manganese(II) chloride with 2 equiv of lithium chloride at room temperature,[13] 2,2,5-trimethylhexan-3-one (**7**) was obtained in 53% yield after 4.5 h of reaction at 0 °C and room temperature, standard workup, and purification by distillation in vacuo.

The construction of the but-3-yn-2-ol side chain was next on the agenda, and to avoid protecting groups to selectively eliminate one hydroxy group only, it was decided to carry this out stepwise by a procedure developed by us in the synthesis of *seco*-theaspiranes:[11] Instead of employing the Grignard reagent prepared from but-3-yn-2-ol and 2 equiv of ethyl magnesium bromide, ketone **7** was to be reacted with acetylene magnesium bromide, then transformed to a Grignard reagent itself and reacted with acetaldehyde. The intermediary tertiary carbinol **11** could then be dehydrated without any selectivity issue. In addition, we had observed[11] that the reaction with acetylene magnesium bromide was far less prone to sterical hindrance than the analogous one with the Grignard reagent of but-3-yn-2-ol. Thus, we were rather astonished to find that the sterically crowded ketone **7** did not react with acetylene magnesium bromide at room temperature or in refluxing THF. However, in the presence of stoichiometric amounts of cerium chloride as introduced for sterically hindered ketones by Imamoto et al.,[14] the Grignard reaction with ethynyl magnesium bromide went smoothly, even at room temperature albeit not exothermic. After quenching with aqueous ammonium chloride, extraction and chromatographic purification furnished the desired *tert*-butyl ethynyl carbinol **11** in excellent 68% yield.

Tertiary alcohols could dehydrate following an E1 or E2 mechanism, and only the latter leads to a well-defined double-bond geometry. As the bulky *tert*-butyl and the isopropyl groups tend to adopt *anti*-periplanar conformations with respect to one another, an *anti*-selective E2 dehydration should provide the desired *Z*-configured enyne product **15**, and these reactive conformations should also favor an E2 mechanism over the E1 alternative. A quick conformational search (MMFF/PM3) indicated the first conformer of **11** to lead to *E*-geometry by *anti*-selective E2 elimination to be disfavored by 2.47 kcal/mol, so we were confident of a good selectivity. Heating the *tert*-butyl ethynyl carbinol **11** in a Kugelrohr apparatus to 110 °C/240 mbar in the presence of potassium hydrogen sulfate with trapping of the evaporating product in a cold trap at −78 °C indeed provided exclusively the desired *Z*-configured product **15** as was established by a NOESY experiment on the first target structure **4** (vide infra). Therefore, no special *anti*-selective dehydration reagents, such as Martin's sulfurane,[15] were required.

The isomerically pure (*Z*)-3-*tert*-butyl-5-methylhex-3-en-1-yne (**15**) thus obtained in 54% yield after flash chromatography was then transformed into the corresponding Grignard reagent by reaction with methyl magnesium chloride. Addition of acetaldehyde, refluxing the resulting reaction mixture overnight, quenching with aqueous ammonium chloride, and the usual workup with chromatographic purification furnished the first alk-5-en-3-yn-2-ol intermediate **19** in 85% yield. The stage was thus set for the crucial (*E*)-selective partial reduction of the triple bond according to the method of Chanley and Sobotka.[8] Carrying out this reaction proved as easy as analogous hydride reductions of ketones, and (*Z*)-5-*tert*-butyl-7-methyloct-5-en-3-yn-2-ol (**19**) was simply added dropwise into a stirred suspension of 1 equiv of lithium aluminum hydride in THF. After heating to reflux for 3 h, the reaction was quenched with water and aqueous sodium hydroxide. The standard workup procedure then afforded alka-3,5-dien-2-ol **23** in an excellent 80% yield as one single diastereoisomer, which was deduced from the assignment of the target structure **4** to be also (3*E*,5*E*)-configured.

All that was missing for the completion of the first target molecule **4** was the oxidation of the allylic hydroxy function to a carbonyl group, for which a full panoply of oxidation reagents is available, including activated manganese dioxide, first employed by Ball et al.[16] for the oxidation of vitamin A, also a polyunsaturated allylic alcohol. Yet manganese dioxide oxidations are generally slow, and we decided to employ pyridinium chlorochromate on Celite®,[17] instead, which we found most versatile and convenient to use.[11,17b] And once more this reagent system worked very well, and the corresponding ketone **4** was obtained as a colorless odoriferous liquid in 73% yield after simply filtering off the insoluble materials and chromatography of the resulting residue on silica gel. Strong and distinct crosspeaks between 6-H and the protons of the *tert*-butyl group, as well as between 4-H and all seven protons of the isopropyl moiety in the ^{1}H–^{1}H NOESY experiment unequivocally proved the intended (3*E*,5*E*)-configuration of our first target structure **4**. Most gratifyingly, however, the scent of ketodienone **4** also met our high expectations in that it combined characteristics of violet and musk odorants, two independent families of primary odorants with no known olfactory overlap. The intense woody-musky odor of the first target structure **4** was reminiscent of the violet-woody odor of β-ionone as much as of the woody-musky odor of Cashmeran® [6,7-dihydro-1,1,2,3,3-pentamethyl-4(5*H*)-indanone],[2,18] with fruity facets in the direction of raspberries. Impressive was also the odor threshold of 0.66 ng/L air that was measured by us for the new odorant **4**. Hence, it is only slightly weaker than the best benchmarks of both the musk,[2] ionone,[19] and irone[20] family, and better than many commercial odorants.

Incited by the interesting olfactory properties of the ketodienone **4** as well as by the short synthetic route to these sterically crowded structures, it was desired to study the scope of the synthetic sequence and the importance of the bulky groups on the odor characteristics. The *tert*-butyl and isopropyl groups should therefore be systematically permuted, which amounted to the synthesis of the three additional structures **27**–**29**.

Employing the manganese-catalyzed acylation detailed above, isovaleryl (**5**) and 3,3-dimethylbutanoyl chloride (**6**) were coupled with isopropyl (for **8** and **10**, respectively) and *tert*-butyl magnesium chloride (in case of **9**), and the corresponding methylhexan-3-ones **8**–**10** were obtained in 51–52% yield. These were all submitted in the next step to the cerium chloride-mediated Grignard reaction with ethynyl magnesium bromide at room temperature, which yielded after workup and chromatographic purification the acetylene alcohols **12**–**14** in 71–76% yield. Dehydration of these alcohols **12**–**14** with potassium hydrogen sulfate at 110 °C/240 mbar followed in all cases an *anti*-selective E2 mechanism as was proven by NOESY experiments on the final products **27**–**29**, and the hex-3-en-1-ynes **16**–**18** were isolated in 37–52% yield after chromatography. Transfer Grignard reaction with methyl magnesium chloride, followed by reaction of the resulting Grignard reagent with acetaldehyde, then provided in 76–83% yield the sterically demanding alkynols **20**–**22**. The subsequent partial reduction of these oct-5-en-3-yn-2-ols **20**–**22** with lithium aluminum hydride went smoothly, and the exclusively (3*E*)-configured products **24**–**26** were isolated in excellent 80–83% yield. The synthesis of the three additional target structures was completed with the pyridinium chlorochromomate oxidation of the allylic alcohols **24**–**26** that provided the highly methyl-substituted octa-3,5-dien-2-ones **27**–**29** in 70–75% yield as colorless odoriferous liquids. In all cases, the geometry of both double bonds was unambiguously determined by distinct NOE crosspeaks between the hydrogen atoms of the methyl groups and 4-H and 6-H, respectively (see Section 4 for details).

3. Olfactory evaluation and conclusions

Interestingly, the odor of the octa-3,5-dien-2-one target structures **4** and **27**–**29** critically depends on the steric bulk of the substituents. The smallest representative **27** with a diisopropyl substituted Δ^5 double bond was the weakest odorant of the series, with an odor threshold as high as 251 ng/L air (Fig. 2). Its odor does not resemble musks or ionones; instead it emanates a vague woody-fruity odor

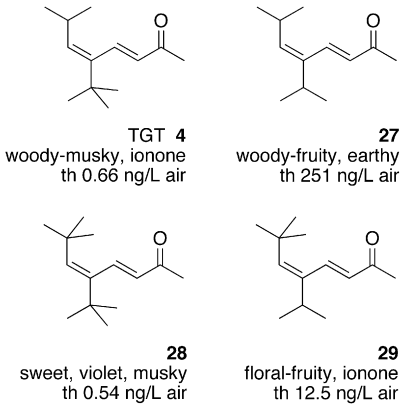


Figure 2. Comparison of the target structures **4** and **27**–**29** concerning the odor character and threshold.

with earthy and rooty nuances. Replacement of the 5-isopropyl group by a *tert*-butyl substituent gives the original target structure **4**, with its well-balanced woody-musky Cashmeran® and typical violet-raspberry β-ionone characters. And this striking shift in the odor character from **27**→**4** coincides with an almost 400-fold intensity gain in odor threshold. Upon replacement of the second isopropyl group of compound **4** by a *tert*-butyl moiety the good odor threshold of 0.66 ng/L air even improved further slightly to 0.54 ng/L air, measured for the di-*tert*-butyl derivative **28**. Both the musk and the violet notes of the original target structure **4** were retained in odorant **28**. In comparison, the violet note of **28** was described as sweeter but less fruity as that of **4**, devoid of a pronounced raspberry tonality, while the musky side of **28** had also a woody character as in Cashmeran®, but different from **4** exhibited also slightly camphoraceous and agrestic facets. If the 5-*tert*-butyl moiety of this musk odorant **28** is replaced by an isopropyl group, the musk character disappears completely, while the fruity, raspberry side reappears. So, target structure **29** can be considered entirely an ionone odorant. Its floral-fruity odor of violets and raspberries resembles those of α-irone and β-ionone; yet, with 12.5 ng/L air, the *seco*-structure **29** is about 100 times weaker than β-ionone (0.12 ng/L air)[19] in terms of odor threshold.

These data impressively demonstrate the importance of hydrophobic volumes on both odor character and intensity, and show how one can fine-tune olfactory properties with only slight structural changes. With perhaps the exception of **27**, our design concept of new *seco*-structures devised from the carotol musk odorant **2** and the truncated β-ionone structure **3** worked out well. In terms of overall olfactory performance, the original target structure **4**, however, remained the best, which highlights once again the significance of the shape similarity in odorant design.

The synthetic hurdle in the preparation of these highly branched systems was tackled by simple and industrially applicable Grignard reactions from the ketones **7**–**10**, which are themselves easily accessible by Li_2MnCl_4-catalyzed Grignard reactions on the acid chlorides **5** and **6**. The chemoselective hydrogenation of **19**–**22** employing lithium aluminum hydride was however crucial for the success of this efficient strategy, which opens up a general and stereodefined access to numerous polyene systems.

4. Experimental

4.1. General methods

All reactions were performed under nitrogen atmosphere, unless otherwise stated. Starting materials, reagents, and solvents were purchased from SAFC, Acros or Alfa Aesar, and used without further purification. Anhyd cerium(III) chloride was prepared by heating the heptahydrate for 3 h at 140 °C/0.2 mbar. Merck silica gel 60 (particle size 0.040–0.063 mm) was used for flash chromatography. Analytical TLC was performed on precoated Merck silica gel 60 F_{254} plates on glass, and the products were visualized with phosphomolybdic acid. Attenuated-total-reflection IR spectra were recorded on a Bruker VECTOR 22 with Harrick SplitPea micro ATR unit. ^{1}H and ^{13}C NMR spectra were measured either with a Bruker AVANCE DPX-400 or an AVANCE 500 TCI spectrometer. ^{13}C multiplicities were determined using DEPT pulse sequences. Mass spectra were recorded with a Finnigan MAT 95 or on a HP Chemstation 6890 GC/5973 with mass sensitive detector. The Mikroanalytisches Laboratorium Ilse Beetz in 96301 Kronach, Germany, performed the elemental analyses. The odor thresholds are geometrical means of individual thresholds that were determined by GC-olfactometry injecting different dilutions of sample substance into a gas chromatograph in descending order of concentration until the panelists failed to detect an odor at the correct retention time.

4.2. Preparation of compounds 4 and 7–29

4.2.1. 2,2,5-Trimethylhexan-3-one (7). Between 0 and 2 °C, a *tert*-butyl magnesium chloride soln in Et_2O (2 M, 500 mL, 1.00 mol) was added within 3 h to a stirred mixture of isovaleryl chloride (**5**, 121 g, 1.00 mol) and Li_2MnCl_4 soln in THF (0.5 M, 60 mL, prepared according to Ref. 13) in THF (1 L). The resulting reaction mixture was stirred for additional 30 min at 0 °C, and then for 1 h at room temperature. Water (700 mL) was added dropwise with stirring, and the aqueous layer was extracted with Et_2O (2×500 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator at 42 °C/100 mbar. The resulting residue was purified by distillation in a 10-cm Vigreux assembly to afford the title compound **7** at 46–48 °C/6 mbar. Yield 53% (75.4 g); colorless liquid; IR (neat, cm^{-1}) 1704 (ν C=O), 1467 (δ_{as} CH_3), 1365 (δ_s CH_3); ^{1}H NMR ($CDCl_3$, ppm) δ 0.89 (d, J=7.0 Hz, 6H, 5-Me_2), 1.12 (s, 9H, 2-Me_3), 2.16 (sept, J=7.0 Hz, 1H, 5-H), 2.35 (d, J=7.0 Hz, 2H, 4-H_2); ^{13}C NMR ($CDCl_3$, ppm) δ 22.5 (q, 5-Me_2), 23.9 (d, C-5), 26.2 (q, 2-Me_3), 44.0 (s, C-2), 45.4 (t, C-4), 215.3 (s, C-3); MS (EI, %) *m*/*z* 142 (6) [M^+], 85 (38) [$M^+-C_4H_9$], 57 (100) [$C_4H_9^+$], 43 (8) [$C_3H_7^+$].

4.2.2. 3-*tert*-Butyl-5-methylhex-1-yn-3-ol (11). In one dash, a soln of **7** (48.4 g, 340 mmol) in THF (400 mL) was added at 0 °C to anhyd cerium(III) chloride (83.3 g, 340 mmol), and the suspension was stirred at room temperature for 5 h. The resulting viscous slurry was added at ambient temperature dropwise with stirring over a period of 30 min to a soln of ethynyl magnesium bromide in THF (0.5 M, 1020 mL, 510 mmol), upon which no temperature rise was observed. The reaction mixture was stirred at room temperature overnight, quenched with satd aq NH_4Cl (800 mL) and

extracted with Et_2O (3×400 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography on silica gel furnished the title compound **11**. Yield 68% (38.9 g); yellowish oil; R_f 0.30 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 3489 (ν O–H), 3308 (ν C≡C–H), 1467 (δ_{as} CH_3), 1366 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 1.02 (s, 9H, 1′-Me_3), 1.02–1.04 (2d, J=7.0 Hz, 6H, 5-Me_2), 1.42 (dd, J=14.0 and 7.5 Hz, 1H, 4-H_a), 1.58 (dd, J=14.0 and 5.0 Hz, 1H, 4-H_b), 1.83 (br s, 1H, OH), 2.07 (dseptd, J=7.5, 7.0 and 5.0 Hz, 1H, 5-H), 2.45 (s, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 24.1/24.7 (2q, 5-Me_2), 24.9 (q, 1′-Me_3), 25.5 (d, C-5), 38.8 (s, C-1′), 43.4 (t, C-4), 73.6 (d, C-1), 77.1 (s, C-3), 85.9 (s, C-2); MS (EI, %) m/z 153 (4) [M^+-CH_3], 111 (70) [$M^+-C_4H_9$], 70 (49) [$C_5H_{10}^+$], 57 (93) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$].

4.2.3. (*Z*)-3-*tert*-Butyl-5-methylhex-3-en-1-yne (15). In a Kugelrohr apparatus, the alkynol **11** (34.2 g, 203 mmol) was heated to 110 °C/240 mbar in the presence of $KHSO_4$ (5.53 g, 40.6 mmol) for 3 h, with the evaporating product mixture being trapped in a bulb cooled to −78 °C. This crude product was purified by flash chromatography on silica gel to provide the title compound **15**. Yield 54% (16.5 g); colorless liquid; R_f 0.57 (pentane/Et_2O 99:1); IR (neat, cm^{-1}) 3312 (ν C≡C–H), 1461 (δ_{as} CH_3), 1362 (δ_s CH_3), 955 (δ C≡C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.98 (d, J=7.0 Hz, 6H, 5-Me_2), 1.08 (s, 9H, 1′-Me_3), 2.87 (dsept, J=9.5 and 7.0 Hz, 1H, 5-H), 3.11 (s, 1H, 1-H), 5.57 (d, J=9.5 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 22.4 (q, 5-Me_2), 29.1 (q, 1′-Me_3), 29.8 (d, C-5), 34.9 (s, C-1′), 81.4 (s, C-2), 81.8 (d, C-1), 129.7 (s, C-3), 142.3 (d, C-4); MS (EI, %) m/z 150 (20) [M^+], 107 (36) [M^+-CH_3], 93 (42) [$M^+-C_4H_9$], 57 (100) [$C_4H_9^+$], 43 (16) [$C_3H_7^+$].

4.2.4. (*Z*)-5-*tert*-Butyl-7-methyloct-5-en-3-yn-2-ol (19). At room temperature, a soln of **15** (790 mg, 5.26 mmol) in THF (15 mL) was added dropwise to a stirred methyl magnesium chloride soln in THF (3 M, 2.10 mL, 6.30 mmol), and the resulting reaction mixture was refluxed for 2 h. A soln of acetaldehyde (278 mg, 6.31 mmol) in THF (6 mL) was then added within 5 min, and the reaction mixture was again heated to reflux overnight. The reaction mixture was allowed to cool to room temperature, quenched with satd aq NH_4Cl (100 mL), and extracted with Et_2O (3×150 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated on a rotary evaporator. The resulting residue was purified by flash chromatography on silica gel to furnish the title compound **19**. Yield 85% (868 mg); colorless oil; R_f 0.13 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3354 (ν O–H), 1460 (δ_{as} CH_3), 1361 (δ_s CH_3), 1073 (ν C–O), 861 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.97 (d, J=6.5 Hz, 6H, 7-Me_2), 1.08 (s, 9H, 1′-Me_3), 1.51 (d, J=6.5 Hz, 3H, 1-H_3), 2.07 (br s, 1H, OH), 2.80 (dsept, J=9.5 and 6.5 Hz, 1H, 7-H), 4.71 (q, J=6.5 Hz, 1H, 2-H), 5.49 (d, J=9.5 Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$, ppm) δ 22.5 (q, 7-Me_2), 24.6 (q, C-1), 29.2 (q, 1′-Me_3), 29.8 (d, C-7), 35.0 (s, C-1′), 59.8 (d, C-2), 81.7 (s, C-3), 95.9 (s, C-4), 129.9 (s, C-5), 140.9 (d, C-6); MS (EI, %) m/z 194 (14) [M^+], 179 (3) [M^+-CH_3], 123 (36) [$M^+-C_4H_7O$], 93 (42) [$C_7H_9^+$], 57 (100) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$].

4.2.5. (3*E*,5*E*)-5-*tert*-Butyl-7-methylocta-3,5-dien-2-ol (23). To a stirred suspension of lithium aluminum hydride (139 mg, 3.65 mmol) in THF (2.0 mL), a soln of **19** (716 mg, 3.68 mmol) in THF (15 mL) was added dropwise at room temperature, and the reaction mixture was refluxed for 3 h. At 2–4 °C water (0.15 mL) was added dropwise, followed by 15% aq NaOH (0.15 mL) and again water (0.45 mL). After stirring for a further 30 min at room temperature, the formed precipitate was filtered off by suction with the aid of a sintered funnel and washed with Et_2O (20 mL). The combined filtrates were evaporated under reduced pressure and the resulting residue was purified by flash chromatography on silica gel to provide the title compound **23**. Yield 80% (579 mg); colorless oil; R_f 0.11 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3331 (ν O–H), 1461 (δ_{as} CH_3), 1360 (δ_s CH_3), 1060 (ν C–O), 969 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.92 (d, J=6.5 Hz, 6H, 7-Me_2), 1.02 (s, 9H, 1′-Me_3), 1.31 (d, J=6.5 Hz, 3H, 1-H_3), 1.58 (d, J=1.0 Hz, 1H, OH), 2.58 (dsept, J=9.5 and 6.5 Hz, 1H, 7-H), 4.37 (quintd, J=6.5 and 1.0 Hz, 1H, 2-H), 5.09 (d, J=9.5 Hz, 1H, 6-H), 5.53 (dd, J=16.0 and 6.5 Hz, 1H, 3-H), 6.06 (d, J=16.0 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 23.5 (q, C-1), 23.6/23.7 (2q, 7-Me_2), 27.7 (d, C-7), 29.6 (q, 1′-Me_3), 35.1 (s, C-1′), 69.2 (d, C-2), 128.6 (d, C-6), 131.2 (d, C-3), 136.9 (s, C-4), 143.5 (s, C-5); MS (EI, %) m/z 196 (5) [M^+], 181 (3) [M^+-CH_3], 139 (16) [$M^+-C_4H_9$], 123 (24) [$M^+-C_4H_9O$], 57 (100) [$C_4H_9^+$], 43 (88) [$C_3H_7^+$].

4.2.6. (3*E*,5*E*)-5-*tert*-Butyl-7-methylocta-3,5-dien-2-one (4). At room temperature, pyridinium chlorochromate (795 mg, 3.68 mmol) was added portionwise to a suspension of dienol **23** (481 mg, 2.45 mmol) and Celite® (5.00 g) in CH_2Cl_2 (25 mL). After stirring for 5 h at ambient temperature, the reaction mixture was diluted with Et_2O (15 mL), the insoluble materials filtered off over a pad of Celite® and washed with Et_2O (10 mL). The combined filtrates were evaporated on a rotary evaporator, and the resulting residue was purified by chromatography on silica gel to furnish the target compound **4**. Yield 73% (348 mg); colorless odoriferous liquid; odor description: very pleasant woody-musky odor reminiscent of β-ionone and Cashmeran® with fruity facets in the direction of raspberries; odor threshold: 0.66 ng/L air; R_f 0.10 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 1696 (ν C=O conj), 1463 (δ_{as} CH_3), 1360 (δ_s CH_3), 1247 (ν_{as} C=C–C=O), 980 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.95 (d, J=6.5 Hz, 6H, 7-Me_2), 1.08 (s, 9H, 1′-Me_3), 2.31 (s, 3H, 1-H_3), 2.59 (dsept, J=10.0 and 6.5 Hz, 1H, 7-H), 5.33 (d, J=10.0 Hz, 1H, 6-H), 6.11 (d, J=16.5 Hz, 1H, 3-H), 7.22 (d, J=16.5 Hz, 1H, 4-H); ^1H–^1H NOESY ($CDCl_3$) 1′-Me_3×6-H, 7-Me_2×4-H, 7-H×4-H; ^{13}C NMR ($CDCl_3$, ppm) δ 23.4 (q, 7-Me_2), 27.2 (q, C-1), 27.9 (d, C-7), 29.7 (q, 1′-Me_3), 35.4 (s, C-1′), 131.8 (d, C-6), 135.5 (d, C-3), 142.2 (s, C-5), 142.7 (d, C-4), 198.5 (s, C-2); MS (EI, %) m/z 194 (3) [M^+], 151 (100) [$M-C_2H_3O^+$], 123 (26) [$M-C_4H_7O^+$], 57 (74) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$]. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.38; H, 11.46.

4.2.7. 2,5-Dimethylhexan-3-one (8). As described for the preparation of **7**, from isopropyl magnesium chloride soln in Et_2O (2 M, 500 mL, 1.00 mol), isovaleryl chloride (**5**, 121 g, 1.00 mol) and Li_2MnCl_4 soln in THF (0.5 M, 60 mL), the title compound **8** was obtained after standard workup and purification by distillation in a 10-cm Vigreux assembly at 45–47 °C/8 mbar. Yield 52% (66.7 g); colorless

liquid; IR (neat, cm^{-1}) 1708 (ν C=O), 1466 (δ_{as} CH_3), 1365 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.90 (d, J=7.0 Hz, 6H, 5-Me_2), 1.08 (d, J=7.0 Hz, 6H, 2-Me_2), 2.16 (sept, J=7.0 Hz, 1H, 5-H), 2.32 (d, J=7.0 Hz, 2H, 4-H_2), 2.57 (sept, J=7.0 Hz, 1H, 2-H); ^{13}C NMR ($CDCl_3$, ppm) δ 18.1 (q, 2-Me_2), 22.5 (q, 5-Me_2), 24.2 (d, C-5), 41.0 (d, C-2), 49.4 (t, C-4), 215.1 (s, C-3); MS (EI, %) m/z 128 (12) [M^+], 85 (41) [$M^+-C_3H_7$], 57 (100) [$M^+-C_4H_7O$], 43 (39) [$C_3H_7^+$].

4.2.8. 3-Isopropyl-5-methylhex-1-yn-3-ol (12). As described for the preparation of **11**, from **8** (19.2 g, 150 mmol) and anhyd cerium(III) chloride (37.0 g, 150 mmol) in THF (200 mL), and a soln of ethynyl magnesium bromide in THF (0.5 M, 450 mL, 225 mmol), the title compound **12** was obtained after standard workup and purification by chromatography on silica gel. Yield 71% (16.5 g); colorless oil; R_f 0.31 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 3467 (ν O–H), 3309 (ν C≡C–H), 1468 (δ_{as} CH_3), 1368 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 1.00 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.02 (d, J=6.5 Hz, 6H, 5-Me_2), 1.48 (dd, J=14.0 and 6.5 Hz, 1H, 4-H_a), 1.62 (dd, J=14.0 and 6.0 Hz, 1H, 4-H_b), 1.81 (sept, J=7.0 Hz, 2H, 1′-H, 1-H), 1.89 (br s, 1H, OH), 2.02 (sept, J=6.5 Hz, 1H, 5-H), 2.44 (s, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 16.8–17.7 (2q, 1′-Me_2), 24.2–24.3 (2q, 5-Me_2), 24.8 (d, C-5), 38.3 (d, C-1′), 47.1 (t, C-4), 73.1 (d, C-1), 74.4 (s, C-3), 86.0 (s, C-2); MS (EI, %) m/z 139 (2) [M^+-CH_3], 111 (62) [$M^+-C_3H_7$], 97 (32) [$M^+-C_4H_9$], 43 (100) [$C_3H_7^+$].

4.2.9. (*Z*)-3-Isopropyl-5-methylhex-3-en-1-yne (16). As described for the preparation of **15**, from **12** (6.63 g, 43.0 mol) and $KHSO_4$ (1.17 g, 8.60 mmol), the title compound **16** was obtained after standard workup and purification by chromatography on silica gel. Yield 52% (3.05 g); colorless liquid; R_f 0.58 (pentane/Et_2O 99:1); IR (neat, cm^{-1}) 3312 (ν C≡C–H), 1465 (δ_{as} CH_3), 1362 (δ_s CH_3), 923 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.98 (d, J=6.5 Hz, 6H, 5-Me_2), 1.07 (d, J=7.0 Hz, 6H, 1′-Me_2), 2.32 (sept, J=7.0 Hz, 1H, 1′-H), 2.83 (dsept, J=9.5 and 6.5 Hz, 1H, 5-H), 3.07 (s, 1H, 1-H), 5.56 (d, J=9.5 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.6 (q, 1′-Me_2), 22.3 (q, 5-Me_2), 29.6 (d, C-5), 34.8 (d, C-1′), 81.0 (s, C-2), 81.4 (d, C-1), 126.3 (s, C-3), 144.0 (d, C-4); MS (EI, %) m/z 136 (25) [M^+], 121 (29) [M^+-CH_3], 93 (100) [$M^+-C_3H_7$], 79 (100) [$C_6H_8^+$], 43 (17) [$C_3H_7^+$].

4.2.10. (*Z*)-5-Isopropyl-7-methyloct-5-en-3-yn-2-ol (20). As described for the preparation of **19**, from **16** (1.50 g, 11.0 mol), methyl magnesium chloride soln in THF (3 M, 4.40 mL, 13.2 mmol) and acetaldehyde (582 mg, 13.2 mmol) in THF (30 mL), the title compound **20** was obtained after standard workup and purification by chromatography on silica gel. Yield 83% (1.65 g); colorless oil; R_f 0.14 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3317 (ν O–H), 1464 (δ_{as} CH_3), 1361 (δ_s CH_3), 1070 (ν C–O), 854 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.97 (d, J=6.5 Hz, 6H, 5-Me_2), 1.05 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.50 (d, J=6.5 Hz, 3H, 1-H_3), 2.00 (br s, 1H, OH), 2.30 (sept, J=7.0 Hz, 1H, 1′-H), 2.77 (dsept, J=9.5 and 6.5 Hz, 1H, 5-H), 4.70 (q, J=6.5 Hz, 1H, 2-H), 5.48 (d, J=9.5 Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.7 (q, 1′-Me_2), 22.4 (q, 5-Me_2), 24.6 (q, C-1), 29.5 (d, C-7), 34.9 (s, C-1′), 58.9 (d, C-2), 81.3 (s, C-3), 95.6 (s, C-4), 126.6 (s, C-5), 142.7 (d, C-6); MS (EI, %) m/z 180 (13) [M^+], 165 (4) [M^+-CH_3], 137 (26) [$M^+-C_3H_7$], 95 (24) [$M^+-C_6H_{12}$], 43 (100) [$C_3H_7^+$].

4.2.11. (3*E*,5*Z*)-5-Isopropyl-7-methylocta-3,5-dien-2-ol (24). As described for the preparation of **23**, from **20** (1.38 g, 7.66 mmol) and lithium aluminum hydride (291 mg, 7.66 mmol) in THF (25 mL), the title compound **24** was obtained after standard workup and purification by chromatography on silica gel. Yield 81% (1.13 g); colorless oil; R_f 0.13 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3328 (ν O–H), 1461 (δ_{as} CH_3), 1361 (δ_s CH_3), 1055 (ν C–O), 963 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 0.97 (d, J=6.5 Hz, 6H, 7-Me_2), 1.04 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.31 (d, J=6.5 Hz, 3H, 1-H_3), 1.73 (d, J=1.0 Hz, 1H, OH), 2.56 (sept, J=7.0 Hz, 1H, 1′-H), 2.73 (dsept, J=9.5 and 6.5 Hz, 1H, 7-H), 4.38 (quintd, J=6.5 and 1.0 Hz, 1H, 2-H), 5.16 (d, J=9.5 Hz, 1H, 6-H), 5.72 (dd, J=16.0 and 6.5 Hz, 1H, 3-H), 6.47 (d, J=16.0 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 22.4 (q, 1′-Me_2), 23.3 (q, 7-Me_2), 23.5 (q, C-1), 26.3 (d, C-7), 29.4 (d, C-1′), 69.6 (d, C-2), 126.0 (d, C-6), 132.2 (d, C-3), 134.6 (d, C-4), 139.2 (s, C-5); MS (EI, %) m/z 182 (3) [M^+], 164 (6) [M^+-H_2O], 137 (18) [$M^+-C_2H_5O$], 109 (41) [$M^+-C_4H_9O$], 43 (100) [$C_3H_7^+$].

4.2.12. (3*E*,5*Z*)-5-Isopropyl-7-methylocta-3,5-dien-2-one (27). As described for the preparation of **4**, from **24** (910 mg, 5.00 mmol), pyridinium chlorochromate (1.62 g, 7.51 mmol) and Celite® (10.0 g) in CH_2Cl_2 (50 mL), the title compound **27** was obtained after standard workup and purification by chromatography on silica gel. Yield 70% (631 mg); colorless odoriferous liquid; odor description: vague woody-fruity odor with earthy and rooty undertones; odor threshold: 251 ng/L air; R_f 0.13 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 1669 (ν C=O), 1463 (δ_{as} CH_3), 1358 (δ_s CH_3), 1253 (ν_{as} C=C–C=O), 971 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 1.00 (d, J=6.5 Hz, 6H, 7-Me_2), 1.07 (d, J=7.0 Hz, 6H, 1′-Me_2), 2.31 (s, 3H, 1-H_3), 2.62 (sept, J=7.0 Hz, 1H, 1′-H), 2.92 (dsept, J=9.5 and 6.5 Hz, 1H, 7-H), 5.60 (d, J=9.5 Hz, 1H, 6-H), 6.22 (d, J=16.0 Hz, 1H, 3-H), 7.56 (d, J=16.0 Hz, 1H, 4-H); ^1H–^1H NOESY (C_6D_6) 7-Me_2×6-H, 1′-Me_2×6-H, 7-Me_2×4-H, 7-H×4-H; ^{13}C NMR ($CDCl_3$, ppm) δ 22.3 (q, 1′-Me_2), 23.2 (q, 7-Me_2), 26.9 (q, C-1), 27.5 (d, C-1′), 28.9 (d, C-7), 126.2 (d, C-6), 139.0 (s, C-5), 139.6 (d, C-3), 143.4 (d, C-4), 198.9 (s, C-2); MS (EI, %) m/z 180 (2) [M^+], 165 (3) [M^+-CH_3], 137 (100) [$M^+-C_3H_7$], 109 (50) [$M^+-C_4H_7O$], 43 (76) [$C_3H_7^+$]. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.00; H, 11.10.

4.2.13. 2,2,5,5-Tetramethylhexan-3-one (9). As described for the preparation of **7**, from *tert*-butyl magnesium chloride soln in Et_2O (2 M, 500 mL, 1.00 mol), 3,3-dimethylbutanoyl chloride (**6**, 135 g, 1.00 mol) and Li_2MnCl_4 soln in THF (0.5 M, 60 mL), the title compound **9** was obtained after standard workup and purification by distillation in a 10-cm Vigreux assembly at 47–49 °C/3 mbar. Yield 52% (81.3 g); colorless liquid; IR (neat, cm^{-1}) 1707 (ν C=O), 1464 (δ_{as} CH_3), 1364 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 1.02 (s, 9H, 5-Me_3), 1.11 (s, 9H, 2-Me_3), 2.37 (s, 2H, 4-H_2); ^{13}C NMR ($CDCl_3$, ppm) δ 26.2 (q, 2-Me_3), 29.6 (q, 5-Me_3), 30.4 (s, C-5), 44.6 (s, C-2), 47.8 (t, C-4), 215.4 (s, C-3);

MS (EI, %) *m/z* 156 (4) [M^+], 99 (22) [$M^+-C_4H_9$], 57 (100) [$C_4H_9^+$].

4.2.14. 3-*tert*-Butyl-5,5-dimethylhex-1-yn-3-ol (13). As described for the preparation of **11**, from **9** (18.8 g, 120 mmol) and anhyd cerium(III) chloride (29.6 g, 120 mmol) in THF (200 mL), and a soln of ethynyl magnesium bromide in THF (0.5 M, 360 mL, 180 mmol), the title compound **13** was obtained after standard workup and purification by chromatography on silica gel. Yield 74% (16.2 g); colorless oil; R_f 0.28 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 3486 (ν O–H), 3308 (ν C≡C–H), 1466 (δ_{as} CH_3), 1365 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 1.02 (s, 9H, 1′-Me_3), 1.12 (s, 9H, 5-Me_3), 1.58 (d, J=14.5 Hz, 1H, 4-H_a), 1.62 (d, J=14.5 Hz, 1H, 4-H_b), 1.84 (br s, 1H, OH), 2.49 (s, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 24.9 (q, 1′-Me_3), 29.5 (s, C-5), 31.0 (q, 5-Me_3), 39.7 (s, C-1′), 46.7 (t, C-4), 74.7 (d, C-1), 75.6 (s, C-3), 86.8 (s, C-2); MS (EI, %) *m/z* 167 (2) [M^+-CH_3], 125 (6) [$M^+-C_4H_9$], 111 (26) [$M^+-C_5H_{11}$], 57 (100) [$C_4H_9^+$].

4.2.15. (*Z*)-3-*tert*-Butyl-5,5-dimethylhex-3-en-1-yne (17). As described for the preparation of **15**, from **13** (5.02 g, 2.75 mmol) and $KHSO_4$ (749 mg, 5.50 mmol), the title compound **17** was obtained after standard workup and purification by chromatography on silica gel. Yield 37% (1.68 g); colorless liquid; R_f 0.56 (pentane/Et_2O 99:1); IR (neat, cm^{-1}) 3311 (ν C≡C–H), 1462 (δ_{as} CH_3), 1361 (δ_s CH_3), 936 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 1.10 (s, 9H, 1′-Me_3), 1.19 (s, 9H, 5-Me_3), 3.24 (s, 1H, 1-H), 5.76 (s, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 29.2 (q, 1′-Me_3), 29.9 (q, 5-Me_3), 32.4 (s, C-5), 35.9 (s, C-1′), 81.9 (s, C-2), 85.0 (d, C-1), 129.5 (s, C-3), 144.7 (d, C-4); MS (EI, %) *m/z* 164 (26) [M^+], 149 (58) [M^+-CH_3], 107 (80) [$M^+-C_4H_9$], 57 (100) [$C_4H_9^+$].

4.2.16. (*Z*)-5-*tert*-Butyl-7,7-dimethyloct-5-en-3-yn-2-ol (21). As described for the preparation of **19**, from **17** (1.43 g, 8.70 mol), methyl magnesium chloride soln in THF (3 M, 3.50 mL, 10.5 mmol) and acetaldehyde (463 mg, 10.5 mmol) in THF (25 mL), the title compound **21** was obtained after standard workup and purification by chromatography on silica gel. Yield 76% (1.38 g); colorless oil; R_f 0.12 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3320 (ν O–H), 1460 (δ_{as} CH_3), 1360 (δ_s CH_3), 1087 (ν C–O), 931 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 1.08 (s, 9H, 1′-Me_3), 1.17 (s, 9H, 7-Me_3), 1.50 (d, J=6.5 Hz, 3H, 1-H_3), 1.95 (br s, 1H, OH), 4.72 (q, J=6.5 Hz, 1H, 2-H), 5.69 (s, 1H, 6-H); ^{13}C NMR ($CDCl_3$, ppm) δ 24.2 (q, C-1), 29.3 (q, 1′-Me_3), 30.1 (q, 7-Me_3), 32.5 (s, C-7), 36.0 (s, C-1′), 59.0 (d, C-2), 82.6 (s, C-3), 98.3 (s, C-4), 129.7 (s, C-5), 143.3 (d, C-6); MS (EI, %) *m/z* 208 (16) [M^+], 193 (6) [M^+-CH_3], 165 (17) [$M^+-C_2H_5O$], 151 (18) [$M^+-C_4H_9$], 57 (78) [$C_4H_9^+$].

4.2.17. (3*E*,5*E*)-5-*tert*-Butyl-7,7-dimethylocta-3,5-dien-2-ol (25). As described for the preparation of **23**, from **21** (1.17 g, 5.62 mmol) and lithium aluminum hydride (213 mg, 5.62 mmol) in THF (25 mL), the title compound **25** was obtained after standard workup and purification by chromatography on silica gel. Yield 80% (947 mg); colorless oil; R_f 0.10 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3335 (ν O–H), 1460 (δ_{as} CH_3), 1359 (δ_s CH_3), 1057 (ν C–O), 973 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 1.00 (s, 9H, 1′-Me_3), 1.04 (s, 9H, 7-Me_3), 1.31 (d, J=6.5 Hz, 3H, 1-H_3), 1.63 (d, J=1.5 Hz, 1H, OH), 4.37 (quintd, J=6.5 and 1.5 Hz, 1H, 2-H), 5.27 (d, J=1.5 Hz, 1H, 6-H), 5.38 (dd, J=16.0 and 6.5 Hz, 1H, 3-H), 6.12 (dd, J=16.0 and 1.5 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 23.0 (q, C-1), 29.6 (q, 1′-Me_3), 31.7 (q, 7-Me_3), 32.6 (s, C-7), 36.2 (s, C-1′), 69.2 (d, C-2), 128.2 (d, C-6), 133.1 (d, C-3), 136.7 (d, C-4), 144.0 (s, C-5); MS (EI, %) *m/z* 210 (2) [M^+], 153 (6) [$M^+-C_4H_9$], 109 (58) [$M^+-C_6H_{13}O$], 57 (100) [$C_4H_9^+$].

4.2.18. (3*E*,5*E*)-5-*tert*-Butyl-7,7-dimethylocta-3,5-dien-2-one (28). As described for the preparation of **4**, from **25** (762 mg, 3.62 mmol), pyridinium chlorochromate (1.17 g, 5.43 mmol) and Celite® (5.0 g) in CH_2Cl_2 (40 mL), the title compound **28** was obtained after standard workup and purification by chromatography on silica gel. Yield 75% (567 mg); colorless odoriferous liquid; odor description: floral, sweet, violet, musky, with woody, slightly camphoraceous and agrestic facets; odor threshold: 0.54 ng/L air; R_f 0.10 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 1675 (ν C=O conj), 1462 (δ_{as} CH_3), 1359 (δ_s CH_3), 1249 (ν_{as} C=C–C=O), 983 (δ C=C–H); ^1H NMR ($CDCl_3$, ppm) δ 1.05 (s, 9H, 1′-Me_3), 1.06 (s, 9H, 7-Me_3), 2.30 (s, 3H, 1-H_3), 5.42 (d, J=1.5 Hz, 1H, 6-H), 6.02 (d, J=16.5 Hz, 1H, 3-H), 7.37 (dd, J=16.5 and 1.5 Hz, 1H, 4-H); ^1H–^1H NOESY (C_6D_6) 1′-Me_3×6-H, 7-Me_3×6-H, 7-Me_3×4-H; ^{13}C NMR ($CDCl_3$, ppm) δ 27.1 (q, C-1), 29.7 (q, 1′-Me_3), 31.6 (q, 7-Me_3), 32.8 (s, C-7), 36.4 (s, C-1′), 132.6 (d, C-6), 135.8 (d, C-3), 142.5 (s, C-5), 145.2 (d, C-4), 197.9 (s, C-2); MS (EI, %) *m/z* 193 (5) [M^+-CH_3], 165 (73) [$M^+-C_2H_3O$], 151 (38) [$M^+-C_4H_9$], 57 (100) [$C_4H_9^+$]. Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.75; H, 11.63.

4.2.19. 2,5-Dimethylhexan-3-one (10). As described for the preparation of **7**, from isopropyl magnesium chloride soln in Et_2O (2 M, 500 mL, 1.00 mol), 3,3-dimethylbutanoyl chloride (**6**, 135 g, 1.00 mol) and Li_2MnCl_4 soln in THF (0.5 M, 60 mL), the title compound **10** was obtained after standard workup and purification by distillation in a 10-cm Vigreux assembly at 46–48 °C/6 mbar. Yield 51% (72.6 g); colorless liquid; IR (neat, cm^{-1}) 1709 (ν C=O), 1465 (δ_{as} CH_3), 1364 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 1.01 (s, 9H, 5-Me_3), 1.05 (d, J=7.0 Hz, 6H, 2-Me_2), 2.34 (s, 2H, 4-H_2), 2.56 (sept, J=7.0 Hz, 1H, 2-H); ^{13}C NMR ($CDCl_3$, ppm) δ 17.9 (q, 2-Me_2), 29.6 (q, 5-Me_3), 30.8 (s, C-5), 42.0 (d, C-2), 52.6 (t, C-4), 214.4 (s, C-3); MS (EI, %) *m/z* 142 (10) [M^+], 99 (26) [$M^+-C_3H_7$], 71 (34) [$M^+-C_4H_7O$], 57 (100) [$C_4H_9^+$], 43 (39) [$C_3H_7^+$].

4.2.20. 3-Isopropyl-5,5-dimethylhex-1-yn-3-ol (14). As described for the preparation of **11**, from **10** (17.1 g, 120 mmol) and anhyd cerium(III) chloride (29.6 g, 120 mmol) in THF (180 mL), and a soln of ethynyl magnesium bromide in THF (0.5 M, 360 mL, 180 mmol), the title compound **14** was obtained after standard workup and purification by chromatography on silica gel. Yield 76% (15.4 g); colorless oil; R_f 0.30 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 3486 (ν O–H), 3308 (ν C≡C–H), 1468 (δ_{as} CH_3), 1365 (δ_s CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.96–1.01 (2d, J=7.0 Hz, 6H, 1′-Me_2), 1.11 (s, 9H, 5-Me_3), 1.52 (d, J=14.5 Hz, 1H, 4-H_b), 1.68 (d, J=14.5 Hz, 1H, 4-H_a),

1.78 (sept, J=7.0 Hz, 1H, 1′-H), 1.89 (br s, 1H, OH), 2.48 (s, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 16.7/17.7 (2q, 1′-Me_2), 31.1 (q, 5-Me_3), 31.2 (s, C-5), 40.1 (d, C-1′), 50.0 (t, C-4), 73.7 (s, C-3), 74.3 (d, C-1), 86.3 (s, C-2); MS (EI, %) *m/z* 153 (2) [M^+-CH_3], 125 (14) [$M^+-C_3H_7$], 97 (18) [$M^+-C_5H_{11}$], 57 (100) [$C_4H_9^+$], 43 (33) [$C_3H_7^+$].

4.2.21. (*Z*)-3-Isopropyl-5,5-dimethylhex-3-en-1-yne (18). As described for the preparation of **15**, from **14** (8.75 g, 52.0 mol) and $KHSO_4$ (1.42 g, 10.4 mmol), the title compound **18** was obtained after standard workup and purification by chromatography on silica gel. Yield 50% (3.91 g); colorless liquid; R_f 0.59 (pentane/Et_2O 99:1); IR (neat, cm^{-1}) 3311 (ν C≡C–H), 1461 (δ_{as} CH_3), 1362 (δ_s CH_3), 927 (δ C≡C–H); ^{1}H NMR ($CDCl_3$, ppm) δ 1.06 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.18 (s, 9H, 5-Me_3), 2.31 (sept, J=7.0 Hz, 1H, 1′-H), 3.19 (s, 1H, 1-H), 5.74 (s, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.7 (q, 1′-Me_2), 30.0 (q, 5-Me_3), 32.7 (s, C-5), 36.9 (d, C-1′), 81.3 (s, C-2), 84.2 (d, C-1), 126.0 (s, C-3), 146.6 (d, C-4); MS (EI, %) *m/z* 150 (30) [M^+], 135 (24) [M^+-CH_3], 107 (100) [$M^+-C_3H_7$], 33 (42) [$M^+-C_4H_9$], 57 (7) [$C_4H_9^+$], 43 (23) [$C_3H_7^+$].

4.2.22. (*Z*)-5-Isopropyl-7,7-dimethyloct-5-en-3-yn-2-ol (22). As described for the preparation of **19**, from **18** (2.11 g, 14.0 mol), methyl magnesium chloride soln in THF (3 M, 5.60 mL, 16.8 mmol) and acetaldehyde (741 mg, 16.8 mmol) in THF (40 mL), the title compound **22** was obtained after standard workup and purification by chromatography on silica gel. Yield 80% (2.18 g); colorless oil; R_f 0.13 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3317 (ν O–H), 1460 (δ_{as} CH_3), 1361 (δ_s CH_3), 1070 (ν C–O), 875 (δ C=C–H); ^{1}H NMR ($CDCl_3$, ppm) δ 1.04 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.16 (s, 9H, 7-Me_3), 1.50 (d, J=6.5 Hz, 3H, 1-H_3), 1.97 (br s, 1H, OH), 2.29 (sept, J=7.0 Hz, 1H, 1′-H), 4.70 (q, J=6.5 Hz, 1H, 2-H), 5.66 (s, 1H, 6-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.8 (q, 1′-Me_2), 24.2 (q, C-1), 30.1 (q, 5-Me_3), 32.8 (s, C-7), 36.8 (d, C-1′), 59.0 (d, C-2), 81.8 (s, C-3), 97.7 (s, C-4), 126.1 (s, C-5), 145.2 (d, C-6); MS (EI, %) *m/z* 194 (25) [M^+], 179 (4) [M^+-CH_3], 151 (43) [$M^+-C_3H_7$], 137 (17) [$M^+-C_4H_9$], 57 (15) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$].

4.2.23. (3*E*,5*Z*)-5-Isopropyl-7,7-dimethylocta-3,5-dien-2-ol (26). As described for the preparation of **23**, from **22** (1.91 g, 9.83 mmol) and lithium aluminum hydride (373 mg, 9.83 mmol) in THF (40 mL), the title compound **26** was obtained after standard workup and purification by chromatography on silica gel. Yield 83% (1.61 g); colorless oil; R_f 0.11 (pentane/Et_2O 95:5); IR (neat, cm^{-1}) 3330 (ν O–H), 1461 (δ_{as} CH_3), 1362 (δ_s CH_3), 1056 (ν C–O), 970 (δ C=C–H); ^{1}H NMR ($CDCl_3$, ppm) δ 1.03 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.13 (s, 9H, 7-Me_3), 1.51 (d, J=6.5 Hz, 3H, 1-H_3), 1.71 (d, J=1.0 Hz, 1H, OH), 2.55 (sept, J=7.0 Hz, 1H, 1′-H), 4.38 (quintd, J=6.5 and 1.0 Hz, 1H, 2-H), 5.34 (s, 1H, 6-H); 5.66 (dd, J=16.0 and 6.5 Hz, 1H, 3-H), 6.68 (d, J=16.0 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm) δ 22.6/22.7 (2q, 1′-Me_2), 23.4 (q, C-1), 31.0 (d, C-1′), 31.8 (q, 7-Me_3), 32.2 (s, C-7), 69.5 (d, C-2), 127.2 (d, C-6), 132.1 (d, C-3), 136.5 (d, C-4), 140.6 (s, C-5); MS (EI, %) *m/z* 196 (3) [M^+], 178 (5) [M^+-H_2O], 153 (6) [$M^+-C_3H_7$], 139 (3) [$M^+-C_4H_9$], 123 (21) [$M^+-C_4H_9O$], 57 (46) [$C_4H_9^+$], 43 (100) [$C_3H_7^+$].

4.2.24. (3*E*,5*Z*)-5-Isopropyl-7,7-dimethylocta-3,5-dien-2-one (29). As described for the preparation of **4**, from **26** (1.32 g, 6.72 mmol), pyridinium chlorochromate (2.17 g, 10.0 mmol) and Celite® (10.0 g) in CH_2Cl_2 (70 mL), the title compound **29** was obtained after standard workup and purification by chromatography on silica gel. Yield 71% (928 mg); colorless odoriferous liquid; odor description: floral-fruity, violet, raspberries, reminiscent to α-irone and β-ionone; odor threshold: 12.5 ng/L air; R_f 0.11 (pentane/Et_2O 98:2); IR (neat, cm^{-1}) 1669 (ν C=O conj), 1460 (δ_{as} CH_3), 1360 (δ_s CH_3), 1254 (ν_{as} C=C–C=O), 976 (δ C=C–H); ^{1}H NMR ($CDCl_3$, ppm) δ 1.05 (d, J=7.0 Hz, 6H, 1′-Me_2), 1.22 (s, 9H, 7-Me_3), 2.31 (s, 3H, 1-H_3), 2.60 (sept, J=7.0 Hz, 1H, 1′-H), 5.77 (s, 1H, 6-H), 6.16 (d, J=16.5 Hz, 1H, 3-H), 7.82 (d, J=16.5 Hz, 1H, 4-H); ^{1}H–^{1}H NOESY ($CDCl_3$) 7-Me_3×4-H, 1′-Me_2×6-H; ^{13}C NMR ($CDCl_3$, ppm) δ 22.6 (d, 1′-Me_2), 27.2 (q, C-1), 30.0 (d, C-1′), 32.0 (q, 7-Me_3), 33.1 (s, C-7), 126.1 (d, C-6), 140.2 (s, C-5), 141.0 (d, C-3), 145.3 (d, C-4), 198.9 (s, C-2); MS (EI, %) *m/z* 194 (2) [M^+], 179 (4) [M^+-CH_3], 151 (100) [$M^+-C_2H_3O$], 137 (19) [$M^+-C_4H_9$], 57 (12) [$C_4H_9^+$], 43 (74) [$C_3H_7^+$]. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.34; H, 11.41.

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