Recent Results in the Search for New Molecules with Ambergris Odor[1])

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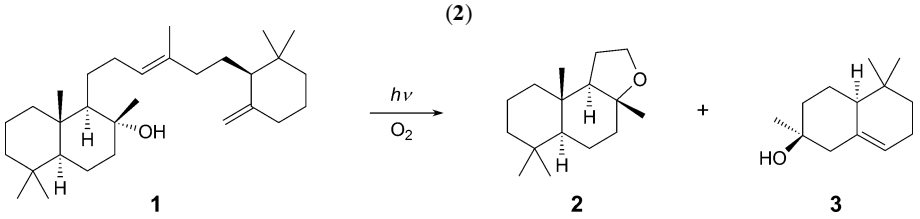
The synthesis of new odorant molecules is still a challenging task for the fragrance chemist, because now as ever it is difficult to predict the odor properties of small organic molecules. Therefore, certain tools, such as, *e.g.*, lead-structure optimization of existing odorants, are helpful techniques. In this article, we describe the synthesis and the odor properties of a new molecule derived by the so-called '*seco*' lead-structure optimization of the ambergris compound *Ambroxide®*. Based on these results, more representatives with similar structures have been synthesized and evaluated for their olfactory properties.

Introduction. – The odor of ambergris is one of the most desired in perfumery. The discovery of the ambergris odor goes back to the very early history. In ancient times, grey lumps had been found at the beaches of the oceans. Solutions of these grey lumps in alcohol tincture exhibit a sweet, earthy odor. Because of this nice odor, the lumps (also called *ambra*) had been described as the '*gold of the sea*'. In antiquity, this material became a desirable commodity and a commercial product. In the 10th century, the Arabs in Spain used this raw material for fine perfumery. In the 18th century, whale fishermen were successful to clarify the mystery of the origin of the grey lumps: it is a metabolic product of the gut of diseased sperm whales. In more recent times, the ambra lumps were as valuable as gold. Scarcity of the resource and the animal origin has motivated the fragrance chemist to look for alternative approaches towards this odorant.

In 1820, *Caventou* and *Pelletier* were the first to identify the triterpene ambrein (**1**) as an important part of ambra lumps [1]. The structure of **1** was first described by *Lederer* in 1946. He also postulated that **1** acts as a precursor, which is cleaved by a photolytic singlet O_2 reaction, leading to the tricyclic molecule **2** and the bicyclic alcohol α-ambrinol (**3**; *Scheme 1*) [2].

Scheme 1. *Photolytic Cleavage of Ambrein* (**1**) *by Singlet* O_2 *Reaction to Ambrinol* (**3**) *and* Ambroxide® (**2**)



1 **2** **3**

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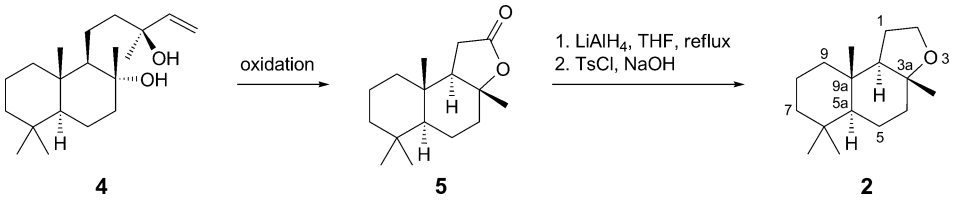
Scheme 2. *Industrial Synthesis of* Ambroxide® (**2**) *Starting from Sclareol* (**4**)



4 **5** **2**

In 1977, *Ohloff* determined the absolute configuration of **2** [3]. As it became obvious that **2** is the sensorially valuable compound behind the ambergris odor, an industrial synthesis has been developed and established in the mid 20th century by *Stoll*, making this molecule available from a non-animal source and an indispensable ingredient in modern perfumery [4]. Several companies are producing this material under trade names like such as *Ambroxan*®, *Ambrox*®, or *Ambroxide*®. Starting material of the industrial process is sclareolide (**5**), which is readily available from sclareol (**4**), a natural product obtained by steam distillation of clary sage oil (*Scheme 2*).

Due to its outstanding olfactory character, **2** has not only become an important part of the perfumer's shelf but has also been the object of numerous investigations on understanding and improvement of the molecular structure and the olfactophore model of ambergris odor. More particularly, one of the first serious structure–odor relationship (SOR) study has been carried out with odor materials preferred in this type of odor and naturally with these kind of structures: the '*triaxial rule of amber compounds*' postulated by *Ohloff* [5]. The main principle of this rule describes the position and the distances of the substituents at C(3a), C(5a), and C(9a) within the *trans*-decalin ring system of the *Ambroxide*® skeleton; for an ambergris odor sensation, it is essential that they all should have axial positions. Nowadays, there are numerous publications covering the synthesis of new ambergris molecules and the evaluation of their odors with respect to the '*triaxial rule*' and, despite some minor exceptions (see below), it has been recognized as the main rule of the ambergris olfactophore model. It is impossible to mention all investigations on structural modifications of **2** and related reports on SORs; a recent and good overview including references is given in [6]. Three examples should be exemplarily mentioned here: the contributions of *Ohloff et al.* [7], and of *Klein* and *Brunke* [8] on the influence of the geminal Me groups at C(6), both highlighting the 6-nor-derivative **6** with strong ambergris odor but slightly higher odor threshold than **2**; the synthesis of **7** by *Boden* and *Jones* [9] by varying the chain length of the axial substituent at C(3a), and the insertion of a C=C bond between C(5) and C(5a) in the tricyclic ring leading to **8** by *Snowden* and *Escher* [10] (*Fig. 1*).

In contrast to the 'triaxial rule', compound **8** (tradename *Superambrox*®) lacks a substituent at C(5a) but exhibits an outstanding powerful and strong '*ambery headnote, with much volume and fullness*' [11].

In our search for new structures with ambergris-like odor, we have been interested to synthesize molecules with variations of the tricyclic skeleton by using the 'seco principle'.

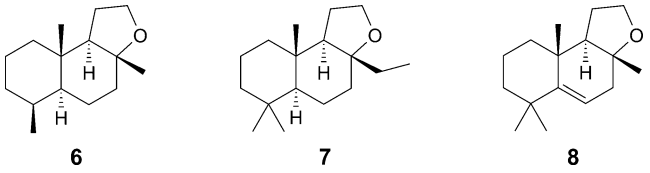


Fig. 1. *Selected molecules with* Ambroxide® *skeleton:* Norambroxide (**6**), Grisalva® (**7**), *and* Superambrox® (**8**)

Results and Discussion. – The 'seco principle' for targeted rational drug design has first been introduced by *Sestanj* in 1962 [12]. 'Cutting out' of two C-atoms from the β-ionone skeleton (**9**) leads to an acyclic fragment **10** (*Fig. 2*). The directed synthesis of such a fragment should lead to a molecule with a similar or preferably stronger effect. In [12], *Sestanj* reported that the target molecule had the same violet odor as β-ionon. Another example for a 'seco approach' to new fragrance molecules was described in a *Takasago* patent [13]. Cutting out two atoms from damascone (**11**) led to the acyclic molecule **12**. In this case, it was realized that the synthesis of **12** was impractical and did not necessarily lead to a molecule with a better performance. But at least, it has inspired *Kraft et al.* to design a similar molecule (tradename, *Pomarose*®) [14]. As **2** has a tricyclic structure, it offers theoretically several possibilities to create mono- or bicyclic ring systems by 'cutting out' some C-atoms. The already mentioned α-ambrinol (**3**) could be seen as an unsaturated 'seco-ambroxide' derived by cutting out atoms C(1), C(2), and the Me group at C(9a). In our project for new molecules with ambergris odor, we were interested to synthesize and to evaluate the odor of the seco derivative **13a**, derived from the *Ambroxide*® skeleton by cutting out three C-atoms (C(8), C(9), and the Me group at C(9a)). As **13a** does not contain a decalin skeleton, and only two

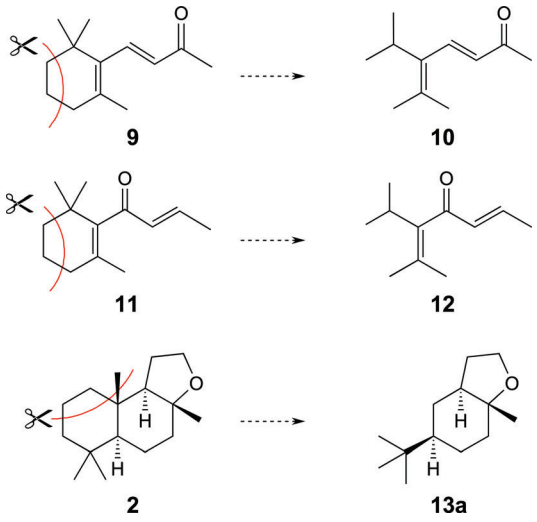


Fig. 2. *Seco derivatives of β-ionone, β-damascone, and ambroxide*

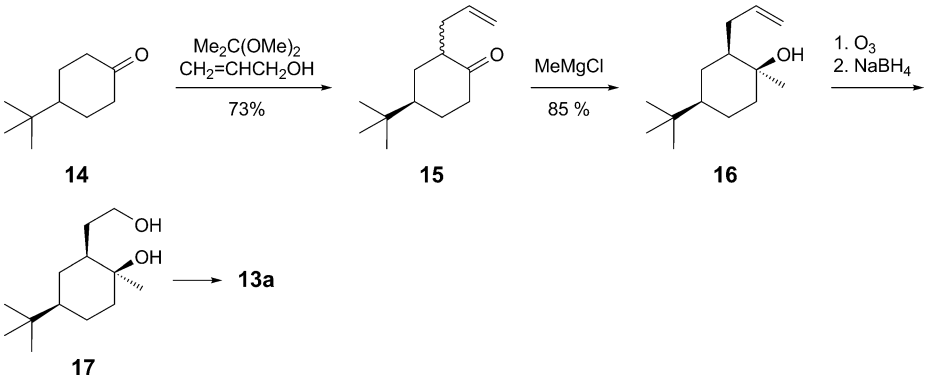
out of three axial substituents are present, we were interested to compare it with molecules relevant for the triaxial rule.

After analyzing several retrosynthetic pathways for seco-*Ambroxide* (***13a***), *we decided to carry out the synthesis by starting from the readily available 4-(tert-*butyl)cyclohexanone (**14**) and using a reaction sequence which is similar to that published by *Büchi* and *Wuest* in 1989 [15] as alternative pathway for the synthesis of racemic **2** (*Scheme 3*).

In the first step, **14** was to be converted into the α-allyl keton **15**. Several methods have been published in the literature for this type of transformation, *e.g.*, alkenylation of the corresponding pyrrolidine enamine with allyl bromide [16] or with allyl acetate by transition-metal catalysis [$Pd(Ph_3P)4$] [17], alkenylation using strong bases, *e.g.*, LiN^iPr_2 (LDA) and allyl bromide [18], or radical addition of (tributyl)(prop-2-enyl)tin to 4-(*tert*-butyl)-2-(phenylseleno)cyclohexanone [19]. In all investigated reactions, the *cis*/*trans* ratio of the alkenylated product has been one major issue (see also [20]): *cis*-selectivities have been favored by using the metal enolate pathway, whereas *trans*-selectivities have been favored by using the enamine or a radical pathway. However, an isomerization of the *trans*-isomer to the thermodynamically more stable *cis*-isomer could be easily afforded by treatment with EtONa [19]. Even the synthesis of the enantiomerically pure form of **15** has been published using the enamine pathway supported by L-proline esters as chiral auxiliary [21].

As our main interest has been to obtain an odor description for compound **13a**, we decided, for practical reasons, to use the *Claisen* rearrangement of the diallyl ketals of **14**. The detour *via* the dimethyl ketal was not necessary, but the yield towards the diallyl ketal was slightly higher in case of transketalization of dimethyl ketal with allylic alcohol than *via* a direct ketalization without purification. Thermal elimination of one allyl moiety led to an enol ether, which was readily converted *via Claisen* rearrangement to the α-allyl keton **15**. Using these conditions, **15** was obtained as a mixture of *cis*/*trans* isomers in a ratio of 3:1. The determination of the configuration was carried out by GC and ^{1}H-NMR analysis of the mixture according to the published data [19]. The *cis*-isomer content has been increased by stirring with MeONa according [19], and was used without further purification in the next step where an introduction of the Me

Scheme 3. *Retrosynthesis of Seco*-Ambroxide (**13**)



group *via Grignard* reaction with MeMgCl was achieved. The attack of the Me nucleophile at the C=O function proceeded predominantly to provide a *trans*-configuration of the Me group relative to the allyl moiety (more precisely, a 7:1 *trans*/*cis* ratio was observed). The yield of this transformation was 85%. The *Grignard* product **16** was then ozonized, followed by reductive workup, to provide diol **17** in 73% yield. No change in the isomeric ratios was observed. In the last step, diol **17** was cyclized. To achieve the desired configuration at C(7a), the orientation of the OH group had to be inverted. To achieve such an inversion, we used the same conditions as described in [15] with $MeNO_2$ as solvent and catalytic amounts of TsOH. Unfortunately, we were not able to achieve an inversion by this method, and we isolated **13** as a mixture of two isomers **13a**/**13b** in the same ratio, 1:7, as by using the 'classical' way with TsCl as cyclization reagent. Isomers **13a** and **13b** were separated by GC, and their structures were determined by ^{1}H-NMR spectroscopy according to the published data for **2** and its isomer (−)-3a-epiambroxide [22].

The odors of the two isomers differ significantly. The odor of seco-ambroxide **13a** was described as strong ambergris, balsamic and erogenic, whereas stereoisomer **13b** was found much weaker, more woody, and greasy-like (*Fig. 3*).

As **13a** exhibits a strong ambergris odor, the odor strength of this molecule was compared with that of **2** on a qualitative and time-dependent basis. Panelists were asked to compare the strength of both molecules on blotters on a scale from 1 to 9. At the beginning, panelists rated **13a** stronger than **2**. This impression disappeared after 3 h, at which time **2** became stronger. After 24 h on the blotter, there was no dry-down odor impression at all for **13a**, whereas **2** gave nearly the same strong odor impression as at the beginning (*Fig. 4*). This result implies that **13a** could be preferably more useful in a perfume for the creation of an ambergris top note rather than for the substantive part of the fond as is the case for **2**.

For a discussion on SORs, it is difficult to correlate these findings with the '*triaxial rule*', as this rule was clearly confined to a *trans*-decalin system. However, as **13a** exhibits a strong ambergris odor, we carried out modeling studies [23] to determine the superposition of **13a** on **2** (*Fig. 5*).

Not surprisingly, apart of the three omitted C-atoms, **13a** and **2** showed a very good superposition. To the best of our knowledge, the odor of a '9a-norambroxide' has not yet been described. It would be of interest to compare this molecule with **13a** to examine if an alkyl substituent at C(9a) in **2** is necessary to generate an ambergris odor sensation or not. Our results, taken together with the odor impression of α-ambrinol

13a **13b**

strong ambergris, balsamic erogenic

weak, woody, greasy

Fig. 3. *Odor descriptions of* **13a** *and* **13b**

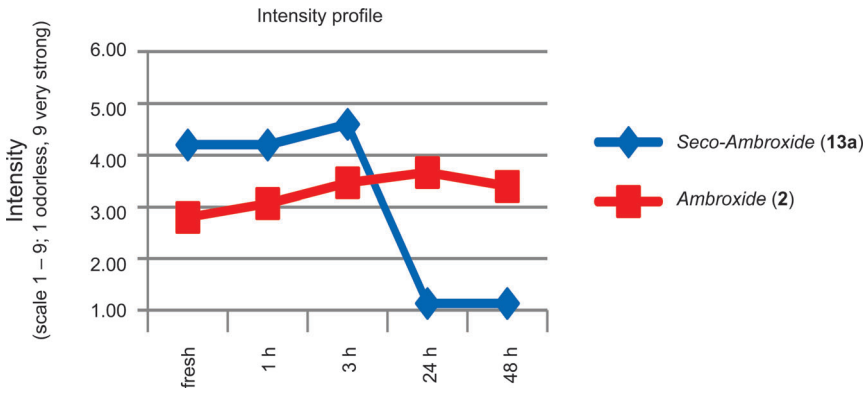


Fig. 4. *Intensity profile* **13a** vs. **2**

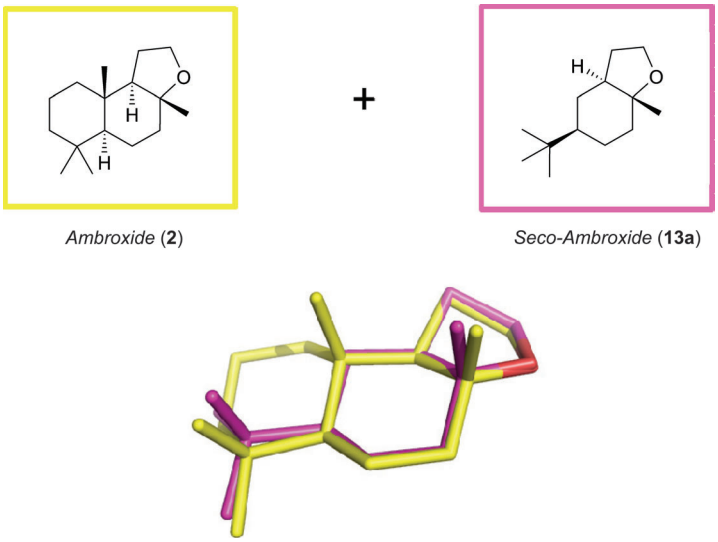
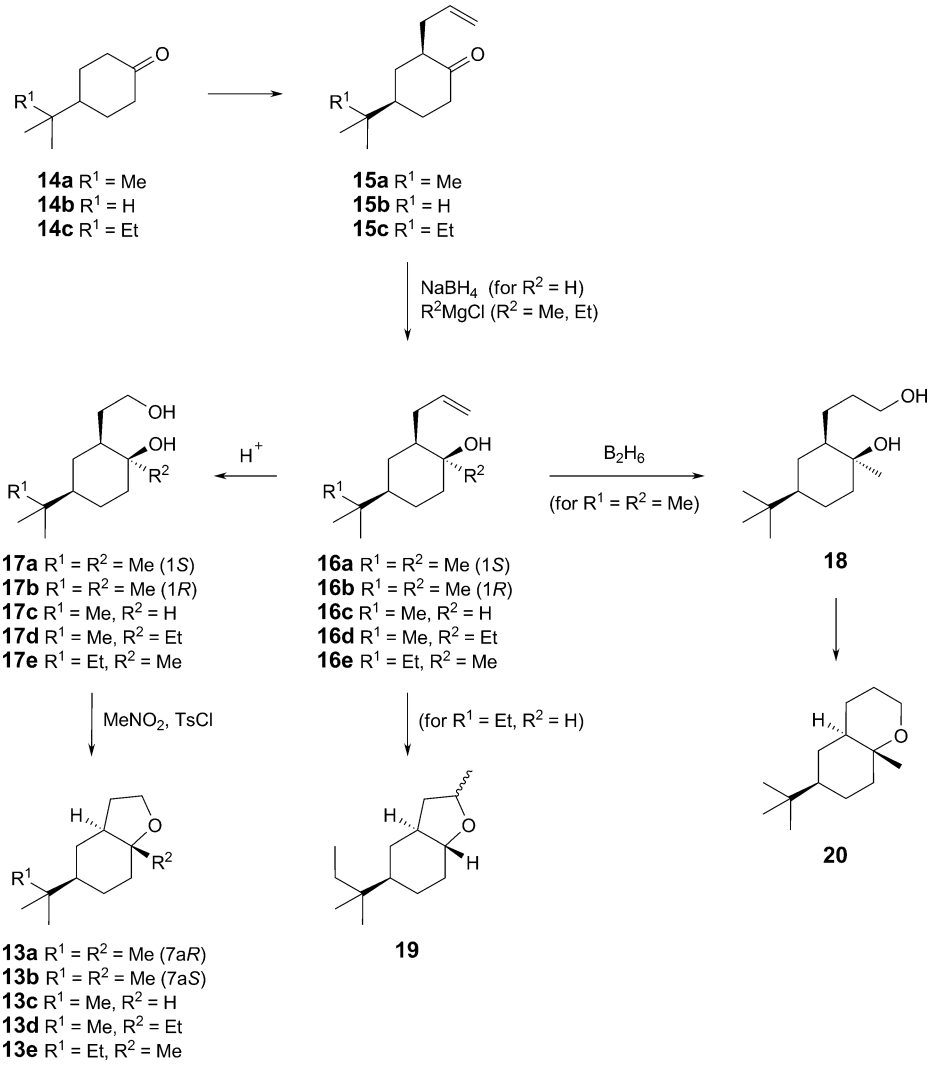


Fig. 5. *Superposition of* **13a** (lilac) *and* **2** (yellow)

(also a seco-ambroxide), indicate that the Me group at C(9a) should not be of major importance for the olfactory properties.

As **13a** exhibits a powerful strong ambergris odor, we decided to further investigate the influence of the substitution pattern of the bicyclic ring system, as well as by variation of the ^{t}Bu group. The syntheses of these molecules could be achieved almost by the same reaction sequence as described above (*Scheme 4*). Variations of the ^{t}Bu group could easily be accomplished by using 4-isopropylcyclohexanone (**14b**) or 4-isoamylcyclohexanone (**14c**) as starting material. In addition, a higher alkyl group could be incorporated at C(7a) by using EtMgBr during the *Grignard* reaction sequences. A reduction of **15** with $NaBH_4$ led to a trisubstituted molecule at 'C(7a)'

Scheme 4. *Synthesis of Derivatives of* **13**

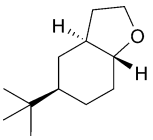
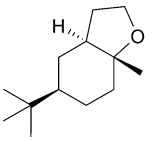
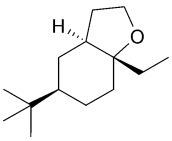
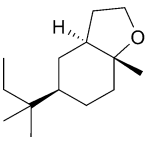
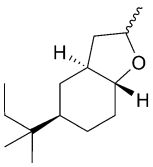
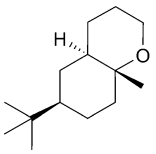


(**16c**; see also [22]). A Me substitution at C(2) could be attained by cyclization of precursor **16** with TsOH. At least by carrying out a hydroboration of **16**, alcohol **18** was successfully obtained. Cyclization of **18** resulted in the heptahydrobenzopyrane derivative **20**. All reactions were well-known and afforded good yields (generally 70–80%).

In the *Table*, all newly synthesized compounds are compiled, together with their odor descriptions.

Apparently, a substituent at C(7a) in **13a** is necessary, for ambergris odor. In analogy to a comparison of **2** and **7**, replacement of the Me group at C(7a) with an Et

Table. *Odor Descriptions of Diverse Derivatives of* **13a**, **19**, *and* **20**

Compound		Odor description
	**13c**	Tabac, tonka, green, phenolic
	**13a**	Strong ambergris, balsamic, erogenic
	**13d**	Animalic, ambergris, weaker than **13a**
	**13e**	Woody, ambergris, weaker than **13a**
	**19**	Woody, phenolic, leather, weak, cedarwood
	**20**	Woody, ambergris, creamy, powdery

group (→**13d**) decreases the strength of the ambergris odor. This is also the case for variations of the *t*Bu group at C(5), and for replacement of the tetrahydrofuran ring by a hexahydropyran ring. In summary, it was observed that none of the variations have resulted in an improved olfactory performance of **13a**.

Conclusions. – The motivation behind the design of the 'seco-*Ambroxide*' **13a** was described. This molecule has been synthesized in four-steps starting from readily available educts. The olfactory properties are very similar to those of *Ambroxide*® (**2**), but **13a** has not the same substantivity as **2**. Several molecules with structural variations at different positions of **13a** have been synthesized, to clearly demonstrate the scope of these structures as ambergris odorants.

Experimental Part

General. Unless stated otherwise, all reactions were performed under N_2. Reagents and solvents were purchased from *Sigma–Aldrich* (DE-Deisenhofen) or *Acros Organics* (DE-Schwerte), and used without further purification. All solvents were purified by distillation before use. Mixtures were washed with 5% soln. of Na_2CO_3, NaOH, and brine, or 10% H_2SO_4 and dried (Na_2SO_4), unless noted otherwise. Column chromatography (CC): *Merck* silica gel *60* (63–200 μm). Isomer (*e.g.*, (*E*)/(*Z*)) ratios were determined *via* GC unless otherwise stated. GC: *Hewlett Packard 6890* with FID and GC-sniffing-port (He; column, *DB-Wax*, 60 m × 0.25 mm × 0.25 μm; 50–240° at 4°/min; or *HP5*, 60 m × 0.25 mm × 0.25 μm; 60–250° at 4°/min). NMR Spectra: *Varian Mercury* (^{1}H: 400, ^{13}C: 100 MHz) in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. EI-MS: *Hewlett Packard 5973N* (He; column, *DB-Wax*, 60 m × 0.25 mm × 0.25 μm; 60–240° at 4°/min) in EI mode (70 eV); in *m*/*z* (%). HR-MS: *MAT-8200 Finnigan* in EI mode (70 eV).

General Procedure for α-Alkenylation of **14** *to 4-Alkylcyclohexanone* (**15**). *4-(*tert*-Butyl)cyclohexanone* (**14**; 107.8 g, 0.7 mol), acetone dimethyl acetal (79.8 g, 0.76 mol), allyl alcohol (98 g), TsOH (0.14 g), and cyclohexane (230 ml) were heated under normal pressure until the bottom temp. raised to 91°. The org. phase was treated with a soln. of MeONa (0.15 g) in MeOH (14 ml), and hexane (200 ml) was added to the org. phase. The org. layer was washed with H_2O to neutrality and concentrated on a rotary evaporator (crude yield, 174.3 g). Crude product (174.3 g), TsOH (0.15 g), and toluene (200 ml) were heated to a bottom temp. of 135°. Allylic alcohol (35 g) passed over. For workup, the org. phase was washed with aq. Na_2CO_3 soln. to neutrality, followed by H_2O, and concentrated on a rotary evaporator (crude yield, 143.9 g). The crude oil was stirred with EtONa as described in [19]. After washing with H_2O and phase separation, the residue was purified by distillation (76°/0.2 mbar) at a 20-cm *Vigreux* column to afford pure **15a** (98.7 g, 73%).

*(2*R*,4*R*)-4-(*tert*-Butyl)-2-(prop-2-en-1-yl)cyclohexanone* (**15a**) and *(2*R*,4*R*)-4-(1-Methylethyl)-2-(prop-2-en-1-yl)cyclohexanone* (**15b**): ^{1}H-NMR: *cis* and *trans*, see [19]. ^{13}C-NMR: see [19]. MS: 137 (50), 109 (36), 95 (31), 93 (17), 83 (19), 67 (24), 57 (100), 55 (38), 41 (37), 29 (17).

General Procedure for Grignard *Reaction of α-Alkenyl-*4*-alkylcyclohexanones* **15** *to 2-Allylcyclohexanols* **16**. In a 500-ml three-necked flask, MeMgCl soln. (100 g, 0.294 mol) was placed under N_2 as a 22% soln. in THF. Then, without cooling, **15a** (44 g, 0.226 mol), dissolved in dry THF (226 ml), was added dropwise during 1–1.5 h, upon which the temp. rose to a maximum of 47°. The mixture was refluxed (66°) for a further 5 h, prior to cooling to 0–5°, and poured into 600 g of ice/H_2O 1:1. THF was removed on the rotary evaporator at 60°/150–350 mbar. ^{t}BuOMe (220 ml) and solid NH_4Cl (106 g) dissolved in H_2O (300 ml) were added. After phase separation, the aq. phase was extracted with ^{t}BuOMe (220 ml). The combined org. phases were washed twice with 5% NaCl soln. (110 ml), and the solvent was evaporated at 60° on the rotary evaporation. The crude product was purified by bulb-to-bulb distillation (120–145°/0.4 mbar) to afford pure **16a** and **16b** (40 g, 85%; GC: 93% sum of two isomers) as a colorless oil.

*(1*S*,2*R*,4*R*)- and (1*R*,2*R*,4*R*)-4-(*tert*-Butyl)-1-methyl-2-(prop-2-en-1-yl)cyclohexanol* (**16a** and **16b**, resp.). Main isomer: ^{1}H-NMR: 5.83 (*dddd*, *J* = 17.1, 10.1, 8.4, 5.8, 1 H); 5.09–4.97 (*m*, 2 H); 2.40 (*dddt*, *J* = 14.1, 5.8, 3.4, 1.7, 1 H); 1.93 (*dddt*, *J* = 14.1, 9.4, 8.4, 1.0, 1 H); 1.76–1.60 (*m*, 2 H); 1.60–1.50 (*m*, 1 H); 1.38 (*td*, *J* = 13.3, 3.6, 1 H); 1.33–1.24 (*m*, 2 H); 1.22 (*s*, 3 H); 1.03–0.94 (*m*, 2 H). ^{13}C-NMR: 138.3; 115.7; 70.9; 47.9; 45.7; 41.1; 34.7; 32.5; 28.6; 28.1; 27.6; 22.7. Peak 1 (main isomer, GC: 81%): MS: 152 (62), 111 (51), 95 (65), 83 (57), 71 (100), 69 (43), 57 (90), 55 (43), 43 (68), 41 (48); Peak 2 (GC: 12%): 135 (44), 111 (50), 95 (59), 83 (52), 71 (100), 69 (44), 57 (98), 55 (46), 43 (74), 41 (53).

*(1*S*,2*R*,4*R*)-4-(*tert*-Butyl)-1-ethyl-2-(prop-2-en-1-yl)cyclohexanol* (**16d**). ^{1}H-NMR: 5.84 (*dddd*, *J* = 17.1, 10.1, 8.5, 5.9, 1 H); 5.07–4.98 (*m*, 2 H); 2.44–2.19 (*m*, 1 H); 1.89 (*dt*, *J* = 14.1, 9.0, 1 H); 1.69–1.57 (*m*, 3 H); 1.57 (*q*, *J* = 7.6, 2 H); 1.45–1.21 (*m*, 3 H); 1.10–0.92 (*m*, 2 H); 0.87 (*t*, *J* = 7.6, 3 H); 0.86 (*s*, 9 H). ^{13}C-NMR: 138.3; 115.8; 73.2; 47.8; 42.7; 36.4; 34.2; 33.2; 32.5; 27.9; 27.6; 27.5; 22.4; 8.3. MS: 195 (60), 95 (20), 85 (66), 83 (26), 69 (27), 57 (100), 55 (32), 43 (26), 41 (31), 29 (23).

*(1*S*,2*R*,4*R*)-4-(*tert*-Butyl)-2-(prop-2-en-1-yl)cyclohexanol* (**16c**). Compounds **15a** and **15b** (75 g, 0.387 mol) were dissolved in MeOH (300 ml) and a soln. of $NaBH_4$ (4.9 g, 0.129 mol) in NaOH (1%) (49 g) was added during 1 h at 0–10°. Stirring was continued for an additional 3 h, prior to removal of the

MeOH on the rotary evaporator. The resulting residue was dissolved in ^{t}BuOMe (200 ml), washed twice with H_2O, and concentrated *in vacuo*. The crude product was distilled on a 5-cm *Vigreux* column (108°/1 mbar) to afford **16c** (65 g, 85%, GC: 90%, two isomers). **16c**: Peak 1: ^{1}H-NMR: 5.94–5.72 (*m*, 2 H); 5.11–4.97 (*m*, 4 H); 3.86 (*q*, *J* = 2.7, 1 H); 3.22 (*td*, *J* = 10.4, 4.5, 1 H); 2.50–2.34 (*m*, 1 H); 2.16 (*dtt*, *J* = 15.1, 7.5, 1.2, 1 H); 2.10–1.95 (*m*, 3 H); 1.95–1.86 (*m*, 1 H); 1.84–1.68 (*m*, 2 H); 1.58–1.40 (*m*, 4 H); 1.40–1.24 (*m*, 3 H); 1.14–0.96 (*m*, 4 H); 0.86 (*s*, 9 H); 0.84 (*s*, 9 H); 0.79–0.68 (*m*, 1 H). ^{13}C-NMR: 137.5; 137.4; 116.1; 115.8; 74.9; 67.8; 47.9; 47.3; 44.9; 42.0; 37.9; 37.8; 35.8; 33.8; 32.5; 32.3; 31.5; 27.6; 27.5; 27.2; 25.7; 20.6. MS: Peak 1 (GC: 52%): 154 (42), 139 (62), 122 (33), 121 (58), 93 (44), 81 (95), 80 (38), 79 (51), 57 (100), 41 (43); Peak 2 (GC: 38%): 139 (38), 136 (44), 123 (38), 122 (36), 121 (64), 95 (33), 93 (33), 81 (56), 57 (100), 41 (38).

General Procedure for the Ozonolysis of 2-Alkenyl-1-alkyl-4-alkylcyclohexanols (**16**) *to* **17**. In a 500-ml three-necked flask equipped with magnetic stirrer, gas inlet, O_3 generator (*Ozonia*), and external cooling (dry ice/^{i}PrOH), **16a** (21.4 g, 0.1 mol) was dissolved in MeOH (214 mol). Then, in *ca.* 1 h at −10 to 0° O_3-containing O_2 (O_3 content, *ca.* 40 g O_3/ccm) was supplied to the soln. until no more O_3 was absorbed. For the reduction, $NaBH_4$ (5.7 g, 0.15 mol) was dissolved in 1% NaOH (57 g), and added in 1 h dropwise at −10° to 0°, upon which a strong exothermic reaction was observed. To complete the reaction, it was stirred for 3 h at r.t., H_2O (200 ml) and toluene (200 ml) were added to the mixture. After addition of solid NaCl (72 g), the mixture was stirred for additional 20 min. After phase separation, the org. layer was washed with 5% brine (50 ml), and the solvent was removed on the rotary evaporator. The crude product (20.5 g, 96%; GC: 94% sum of two isomers) was directly used in the next step.

*(1*S*,2*S*,4*R*)- and (1*R*,2*S*,4*R*)-4-(*tert*-Butyl)-2-(2-hydroxyethyl)-1-methylcyclohexanol* (**17a** and **17b**, resp.). Peak 1: ^{1}H-NMR: 3.76 (*ddd*, *J* = 11.0, 7.7, 5.2, 1 H); 3.63 (*q*, *J* = 9.8, 7.7, 1 H); 1.77–1.67 (*m*, 2 H); 1.61–1.53 (*m*, 1 H); 1.52–1.37 (*m*, 3 H); 1.24 (*s*, 3 H); 1.04 (*m*, 1 H); 0.87 (*s*, 9 H). ^{13}C-NMR: 70.6; 59.9; 48.2; 43.5; 41.2; 33.2; 32.5; 28.6; 27.8; 27.6; 22.7. Main isomer (GC: 80%): MS: 129 (40), 111 (29), 83 (45), 72 (23), 71 (100), 69 (35), 57 (52), 55 (29), 43 (44), 41 (27).

*(1*S*,2*S*,4*R*)-4-(*tert*-Butyl)-2-(2-hydroxyethyl)cyclohexanol* (**17c**). MS: 83 (26), 81 (28), 80 (23), 79 (37), 69 (25), 67 (24), 57 (100), 55 (45), 41 (39), 29 (23).

*(1*S*,2*R*,4*R*)-4-(*tert*-Butyl)-2-(3-hydroxypropyl)-1-methylcyclohexanol* (**18**). Under N_2, **16a**/**16b** (10.5 g, 0.05 mol) was dissolved in THF (17 ml). Then, BH_3–THF complex (1M in THF; 20 ml, 0.02 mol) was added with slight cooling. The mixture was stirred for 1 h at r.t. After addition of H_2O (5 ml), first 3M NaOH soln. (6.7 ml) and then 30% H_2O_2 soln. (7.4 g, 0.065 mol) were added dropwise at 30–35°. The mixture was stirred for 1 h at 50°, prior to dilution with ^{t}BuOMe (50 ml), washed with 20% Na_2SO_3 soln. (40 ml), and then evaporated *in vacuo*. The crude product (12.3 g, GC: 91%) was directly used in the next step. ^{1}H-NMR: 3.64 (*t*, *J* = 6.1, 2 H); 1.74–1.70 (*m*, 5 H); 1.60–1.55 (*m*, 1 H); 1.50–1.44 (*m*, 1 H); 1.38–1.34 (*m*, 1 H); 1.27–1.24 (*m*, 1 H); 1.20 (*s*, 3 H); 1.17–1.05 (*m*, 2 H); 1.01–0.97 (*m*, 1 H); 0.86 (*s*, 9 H). ^{13}C-NMR: 71.0; 63.3; 47.9; 45.8; 41.1; 32.5; 31.1; 28.5; 28.3; 27.6; 25.8; 22.6.

General Procedure for Cyclization of Diols (**17**) *to* **13**. To **17a**/**17b** (23.3 g, 0.1 mol) as a 8.6% soln. in toluene, 50% NaOH soln. (20 g, 0.26 mol), tris(2,6-dioxaheptyl)amine (TDA-1; 1 g), and TsCl (26 g, 0.14 mol) were added at 60° in 1.5 h. The reaction was slightly exothermic and stirred for 3 h at 50° and washed two times at 50–60° with 50 ml of H_2O. Toluene was removed by rotary evaporation at 60°/200–20 mbar. The residue (24 g) was dissolved in EtOH (100 ml), and the resulting mixture was stirred for 4 h at 60° with 10% aq. NaOH soln. (44 g) to remove traces of sulfonates. EtOH was evaporated at 60°/200–50 mbar, and the resulting residue was treated with H_2O (25 ml), and then extracted twice with ^{t}BuOMe (75 ml). The org. phases were combined and washed twice with 5% NaCl soln. (50 ml). After evaporation (60°/500–20 mbar), a crude product (18 g) was obtained, which was further purified by bulb-to-bulb distillation (64–73°/2 mbar) to afford **13a**/**13b** (13 g, 66%; GC: 94%, sum of two isomers). Two g of the mixture were separated by prep. GC to afford the pure isomers.

*(3a*S*,5*R*,7a*R*)-5-(*tert*-Butyl)octahydro-7a-methyl-1-benzofuran* (**13a**). ^{1}H-NMR: 3.96–3.78 (*m*, 2 H); 2.11–1.93 (*m*, 2 H); 1.93–1.84 (*m*, 1 H); 1.84–1.76 (*m*, 1 H); 1.71–1.61 (*m*, 1 H); 1.59–1.42 (*m*, 2 H); 1.40–1.28 (*m*, 1 H); 1.27 (*s*, 3 H); 1.26–1.17 (*m*, 1 H); 0.97 (*tdd*, *J* = 13.0, 11.7, 3.9, 1 H); 0.86 (*s*, 9 H). ^{13}C-NMR: 80.32; 77.33; 77.02; 76.70; 64.70; 44.11; 41.48; 33.79; 32.11; 30.19; 27.59; 26.20; 24.81; 24.50. MS: 182 (16), 181 (100), 97 (98), 83 (10), 81 (12), 57 (29), 55 (22), 43 (30), 41 (21), 29 (11). Odor: strong ambergris, balsamic, erogenic.

*(3aS,5R,7aS)-5-(*tert-*Butyl)octahydro-7a-methyl-1-benzofuran* (**13b**). ^{1}H-NMR: 3.99–3.81 (*m*, 2 H); 2.36–2.20 (*m*, 1 H); 2.05–1.93 (*m*, 1 H); 1.77 (*dt*, *J* = 12.1, 6.3, 1 H); 1.63–1.46 (*m*, 3 H); 1.50–1.36 (*m*, 1 H); 1.25–1.11 (*m*, 1 H); 1.08 (*s*, 3 H); 1.02–0.89 (*m*, 1 H); 0.84 (*s*, 9 H); 0.89–0.77 (*m*, 1 H). ^{13}C-NMR: 80.28; 77.34; 77.02; 76.70; 64.37; 46.81; 42.90; 35.95; 32.45; 32.32; 30.79; 27.47; 26.80; 22.74. MS: 196 (9), 181 (14), 98 (11), 97 (100), 84 (9), 57 (10), 55 (9), 43 (32), 41 (12), 29 (6). Odor: weak, woody, greasy.

*5-(*tert-*Butyl)octahydro-1-benzofuran* (**13c**). Two isomers (1:1). ^{1}H-NMR: 3.99–3.88 (*m*, 3 H); 3.84–3.77 (*m*, 2 H); 2.95 (*ddd*, *J* = 11.1, 9.9, 3.9, 1 H); 2.15–2.05 (*m*, 3 H); 2.05–1.93 (*m*, 3 H); 1.93–1.80 (*m*, 2 H); 1.72–1.45 (*m*, 4 H); 1.45–1.25 (*m*, 3 H); 1.24–1.02 (*m*, 3 H); 1.01–0.89 (*m*, 2 H); 0.88 (*s*, 9 H); 0.85 (*s*, 9 H). ^{13}C-NMR: 83.5; 77.4; 67.2; 65.8; 48.0; 46.8; 45.6; 38.7; 33.1; 32.4; 32.4; 31.1; 30.8; 29.7; 29.0; 28.8; 27.9; 27.5; 25.3; 21.3. MS: 126 (33), 93 (16), 83 (98), 81 (18), 79 (25), 67 (18), 57 (100), 55 (40), 41 (36), 29 (21). Odor: tabac, tonka, green, phenolic.

*5-(*tert-*Butyl)-7a-ethyloctahydro-1-benzofuran* (**13d**). Two isomers (GC: 10:1). Main isomer: ^{1}H-NMR: 3.95–3.87 (*m*, 1 H); 3.86–3.75 (*m*, 1 H); 2.21 (*dddd*, *J* = 12.1, 9.8, 8.4, 6.7, 1 H); 1.95 (*dt*, *J* = 14.2, 3.7, 1 H); 1.89–1.77 (*m*, 1 H); 1.64–1.57 (*m*, 1 H); 1.57–1.44 (*m*, 3 H); 1.38 (*ddd*, *J* = 14.2, 12.4, 4.6, 1 H); 1.32–1.21 (*m*, 1 H); 1.21–1.09 (*m*, 1 H); 0.96–0.83 (*m*, 2 H); 0.85 (*t*, *J* = 7.5, 3 H); 0.84 (*s*, 9 H). ^{13}C-NMR: 82.6; 64.1; 46.5; 41.1; 32.6; 32.3; 31.8; 31.3; 31.0; 27.4; 22.5; 8.2. MS: 182 (13), 181 (100), 111 (16), 97 (20), 81 (7), 69 (9), 57 (25), 55 (16), 41 (11), 29 (8). Odor: animalic, ambergris, weaker than **13a**.

5-(1,1-Dimethylpropyl)octahydro-7a-methyl-1-benzofuran (**13e**). GC: Two isomers. MS: Peak 1: 196 (13), 195 (100), 97 (95), 95 (10), 81 (10), 71 (15), 69 (15), 55 (19), 43 (30), 41 (11). Peak 2: 210 (4), 195 (6), 98 (7), 97 (100), 84 (5), 71 (5), 69 (4), 55 (7), 43 (18), 41 (5). Odor: woody, ambra.

5-(1,1-Dimethylpropyl)octahydro-2-methyl-benzofuran (**19**). Starting material, **16e** (22.5 g); as described for **13a**/**13b**. Yield: 13 g (70%, GC: 98.7%, sum of two isomers). Main isomer: ^{1}H-NMR: 4.06 (*ddt*, *J* = 10.0, 6.1, 6.0, 1 H); 3.89 (*dt*, *J* = 10.0, 6.7, 1 H); 2.51 (*dddd*, *J* = 14.8, 12.8, 6.3, 2.4, 1 H); 1.93–1.68 (*m*, 3 H); 1.65–1.53 (*m*, 2 H); 1.41–1.15 (*m*, 6 H); 1.29 (*d*, *J* = 6.1, 3 H); 0.83–0.75 (*m*, 9 H). ^{13}C-NMR: 77.5; 75.3; 39.1; 38.8; 37.3; 34.6; 32.7; 31.7; 26.4; 24.3; 24.0; 23.7; 22.8; 8.1. MS: 163 (29), 150 (31), 139 (36), 121 (47), 97 (100), 95 (74), 81 (45), 79 (37), 71 (69), 43 (30). Odor: woody, phenolic, leather, weak, cedarwood.

*6-(*tert-*Butyl)octahydro-8a-methyl-2*H-*1-benzopyran* (**20**). Starting material, **18** (12.3 g, 0.05 mol); as described for **13a**/**13b**. Yield: 5.4 g (51%; GC: 98.7%, sum of two isomers). Main isomer: ^{1}H-NMR: 3.78 (*ddd*, *J* = 12.7, 11.7, 3.0, 1 H); 3.73–3.65 (*m*, 1 H); 2.03 (*ddt*, *J* = 13.1, 8.8, 4.4, 1 H); 1.92–1.80 (*m*, 1 H); 1.79–1.73 (*m*, 1 H); 1.66–1.55 (*m*, 1 H); 1.50–1.44 (*m*, 1 H); 1.40–1.25 (*m*, 5 H); 1.24 (*s*, 3 H); 1.25–1.14 (*m*, 1 H); 1.04–0.95 (*m*, 1 H); 0.86 (*s*, 9 H). ^{13}C-NMR: 71.4; 61.6; 48.3; 41.2; 38.6; 32.4; 28.0; 27.6; 25.1; 23.3; 22.60; 20.6. MS: 196 (11), 195 (81), 111 (100), 95 (11), 71 (15), 69 (11), 57 (21), 55 (14), 43 (25), 41 (22). Odor: woody, ambra.

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