Conception, Characterization and Correlation of New Marine Odorants

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Dedicated wih best wishes to Professor Andrea Vasella on the occasion of his 60th birthday

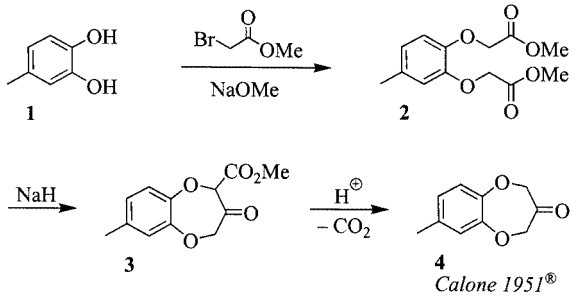
Keywords: Heterocycles / Fragrances / Olfactation / Odoriferous compounds / Marine perfumery materials / Odor−structure correlation

Via a synthetic sequence consisting of PPA-mediated Friedel–Crafts acylation of veratrol (**8**), Clemmensen reduction, demethylation with TMSI, Williamson ether synthesis employing 3-chloro-2-(chloromethyl)prop-1-ene and in-situ ruthenium tetroxide oxidation, numerous substituted benzo[*b*][1,4]dioxepinones **15**–**27** and 2,3-dihydro-1*H*-5,9-dioxacyclohepta[*f*]indenones **7**, **13** and **14** were prepared to study their odor–structure correlation. In the course of these studies, we discovered the extremely powerful new marine odorant 7-(3′-methylbutyl)benzo[*b*][1,4]dioxepin-3-one (**16**). On the basis of the measured odor threshold data, an olfactophore model was constructed that rationalizes the observed odor intensities, and indicates an aliphatic hydrophobe at a distance of 6.3 Å from the centre of the aromatic-ring binding site.

Introduction

For many years, *Calone 1951*® (7-methylbenzo[*b*]-[1,4]dioxepin-3-one, **4**), which was discovered by Beereboom, Cameron and Stephens at Pfizer in 1966,[1] played a marginal role in perfumery, for instance as a trace component in muguet accords. This changed in the early 1990ies, when the launches of "New West for her" (Aramis, 1990) and "Escape" (C. Klein, 1991) on the feminine and "Kenzo pour homme" (Kenzo, 1991) as well as "L′eau d'Issey pour homme" (I. Miyake, 1994) on the masculine side initiated a marine trend.[2] This marine trend reached its peak in 1996/97 with "Polo Sport Woman" (R. Lauren, 1996) created by Jim Krivda and "Cool Water Woman" (Davidoff, 1997) by Pierre Bourdon, but still today we see launches of extreme marine-smelling perfumes like the aquatic chypre "aquawoman" (Rochas, 2002) composed by Michel Almairac with 0.42% of **4**, and very likely the marine trend will come back to life again soon.

Calone 1951® (**4**) is the basis of all these marine accords, and though it is often blended with different ozonic, aldehydic or watermelon-like odorants, so far there is no alternative perfumery raw material to convey the typical olfactory impression of a seashore. The commercial synthesis of **4** (Scheme 1) commences with the Williamson reaction of homopyrocatechol (**1**) with two equivalents of methyl bromoacetate affording diester **2**. Dieckmann condensation, a favored 7-*exo*-*trig*-ring closure, is easily achieved to afford **3**, which is hydrolyzed and decarboxylated to provide the commercial odorant **4**. Besides the commercial product *Calone 1951*® (**4**), linear and branched C_2-C_4-substituted benzo[*b*][1,4]dioxepin-3-ones were claimed in the original patent,[1] but nothing was known about higher derivatives.



Scheme 1. Commercial synthesis of *Calone 1951*® (**4**)

We plunged into the chemistry of benzodioxepinones in an attempt to construct androgynous odorants with musky and marine characteristics. This note is present in 2,6-dibromo-3-methyl-4-nitroanisol (*Musk alpha*®, **5**; Figure 1), which however was removed from the market due to its phototoxicity. Polycyclic musk odorants, like Galaxolide® (**6**) as its most popular representative, often possess a methylated indane skeleton.[3] We thus were curious about constructing dioxacyclohepta[*f*]indenones. But in order not to go beyond the limit in molecular weight for marine odorants, and since the 7-butylbenzo[*b*][1,4]dioxepin-3-one was

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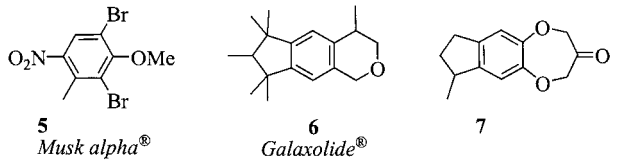
the highest-substituted marine odorant claimed in the Pfizer patent,[1] we selected **7** with almost the same molecular mass as our first target structure.

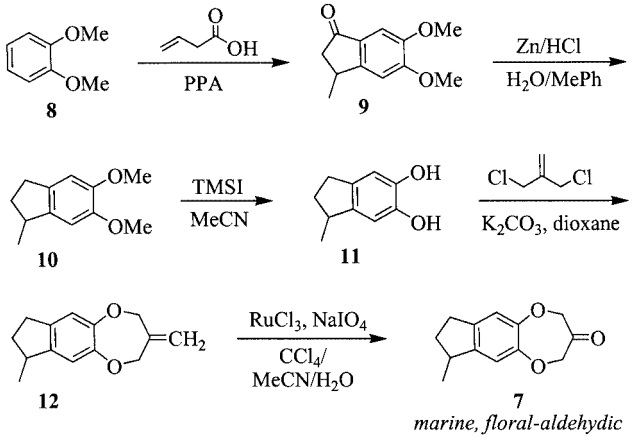


5 *Musk alpha®* **6** *Galaxolide®* **7**

Figure 1. A marine-smelling nitro musk **5**, a polycyclic nitro musk **6**, and our target structure **7**

Results and Discussion

1-Methyl-2,3-dihydro-1*H*-5,9-dioxacyclohepta[*f*]inden-7-one (**7**) can be constructed on paper simply by molding the butyl side chain into a 3-methyl-[1,2]cyclopentano bridge, and also our chemical synthesis depicted in Scheme 2 was straightforward.



Scheme 2. Synthesis of the initial target compound **7** from veratrol (**8**)

Following the protocol of Marquardt[4] with slight modifications, Friedel−Crafts acylation of veratrol (**8**) with vinylacetic acid in the presence of polyphosphoric acid (PPA) furnished 5,6-dimethoxy-3-methylindan-1-one (**9**) after recrystallization in 74% yield. Both Alesso et al.[5] and Deslongchamps et al.[6] transformed **9** into 5,6-dimethoxy-1-methylindane (**10**) by reaction with a methyl Grignard reagent, acid-catalyzed dehydration of the methyl carbinol intermediate and subsequent hydrogenation of the formed methylindene. We found this rather circuitous, and instead submitted **9** to standard Clemmensen reduction conditions. After purification by flash chromatography (FC) on silica gel, we obtained in 75% yield the methylindane **10**, the spectroscopic data of which were identical to those reported in the literature.[5,6]

In the next step, the methyl ether protecting groups of **10** had to be cleaved. For this we decided to employ trimethylsilyl iodide (TMSI)[7] in acetonitrile.[8] The cleavage of **10** with TMSI was conducted at room temp. to afford after the usual workup and purification by silica-gel FC in 93% yield 1-methylindan-5,6-diol (**11**). This diol **11** had already been reported by Ayer and Singer[9] as the unintended product of an attempt to correlate 4-(3′,4′-dihydroxyphenyl)butan-2-one with zingerone (vanillyl acetone) by demethylation of the latter with TMSI. Yet, the reported yield was only about 30%, and the synthesis is less practical and less generally applicable than our approach. The spectroscopic data of **11** prepared on our route matched with those reported by Ayer and Singer.[9]

Williamson reaction of **11** with methyl bromoacetate, Dieckmann condensation and decarboxylation would have constituted the next transformations according to the preparation of **4** in the Pfizer patent.[1] However, we were looking for a shorter alternative to construct the [1,4]dioxepinone ring. Schirmann et al.[10] employed 3-chloro-2-(chloromethyl)prop-1-ene in a synthesis of 3-methylene-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine, which they prepared in 62% yield from pyrocatechol. An alternative reagent for this transformation of diols to 6-methylene-1,4-dioxepanes is *tris*-ω,ω,ω-bromomethylacetophenone as reported by Nerdel, Mamluk and Weyerstahl.[11] However, the synthesis of this reagent from the dibromohydrin of pentaerythrol by monobromination, nitric-acid oxidation, treatment of the tribromopivalic acid with thionyl chloride, and Friedel−Crafts acylation of benzene with the resulting acid chloride[12,13] is rather complicated, and in preliminary experiments we obtained better yields employing 3-chloro-2-(chloromethyl)prop-1-ene, which is commercially available. Thus, 1-methyl-7-methylene-2,3,7,8-tetrahydro-1*H*,6*H*-dioxacyclohepta[*f*]indene (**12**) was prepared from **11** and 3-chloro-2-(chloromethyl)prop-1-ene by slow addition of a solution of both compounds in dioxane to a refluxing suspension of potassium carbonate in diethyl ketone. Though we isolated **12** by silica-gel FC in quite moderate yield of 36%, in general better yields were obtained with the other catechols investigated (see Exp. Sect.).

The last step in our synthetic sequence was the oxidative cleavage of the methylene double bond of **12**. We chose the aqueous biphase ruthenium-tetroxide oxidation established by Carlsen, Katsuki, Martin and Sharpless.[14] This oxidation with in-situ generated ruthenium tetroxide furnished the projected target structure **7** in 50% olfactory pure yield. Disappointingly, **7** did not possess any musk-like odor facets, but instead only a marine note with distinct floral aspects. In comparison with *Calone 1951®* (**4**), these additional floral aspects were however interesting to our perfumers.

Following the same sequence, we introduced an additional methyl group in the 1- or 2- position of **7** to study this floral side note. The resulting target structures **13** and **14** were synthesized from veratrol and 3,3-dimethylacrylic acid and tiglic acid, respectively. But in comparison with **7**, the odor intensity was decreased and the floral character

diminished. 1,2-Dimethyl-2,3-dihydro-1*H*-5,9-dioxacyclohepta[*f*]inden-7-one (**14**) possessed even a blend odor of walnut and fenugreek oil with sea water and lichens (Figure 2). In order to increase the floral character, we planned to switch back from 5,9-dioxacyclohepta[*f*]indenones to benzo[*b*][1,4]dioxepinones; and thus, we cut the bond between C-1 and C-10a in **14**. The resulting *seco*-target molecule **15** was synthesized from veratrol (**8**) and 2-methylbutyric acid according to our general procedure. Indeed the floral character again increased, and the compound was also more intense than **13** and **14** with an odor threshold of 0.08 ng/L air (Figure 2). The best compound of the whole series was however the isomeric 3′-methylbutyl-substituted benzo[*b*][1,4]dioxepinone **16**, the 1(10a)-*seco* derivative of **13**, for which an odor threshold of 0.014 ng/L air was determined. It emanates a *very intense and diffusive, linear, marine odor, with some reminiscence to 2,6,10-trimethylundec-9-en-1-al (Adoxal®)*, the Darzen's glycidic ester condensate of hydrogenated *pseudo*-ionone with alkyl chloroacetate. *Adoxal®* possesses a floral-aldehydic odor, and this together with the intense marine aspects of *Calone 1951®* (**4**) makes **16** highly attractive for perfumery.[17] Besides, **16** is more intense and less salty than *Calone 1951®* (**4**), so fresher and more crisp in tonality, more closer to the actual olfactory impression of a *sea breeze* rather than that of *sea water*.

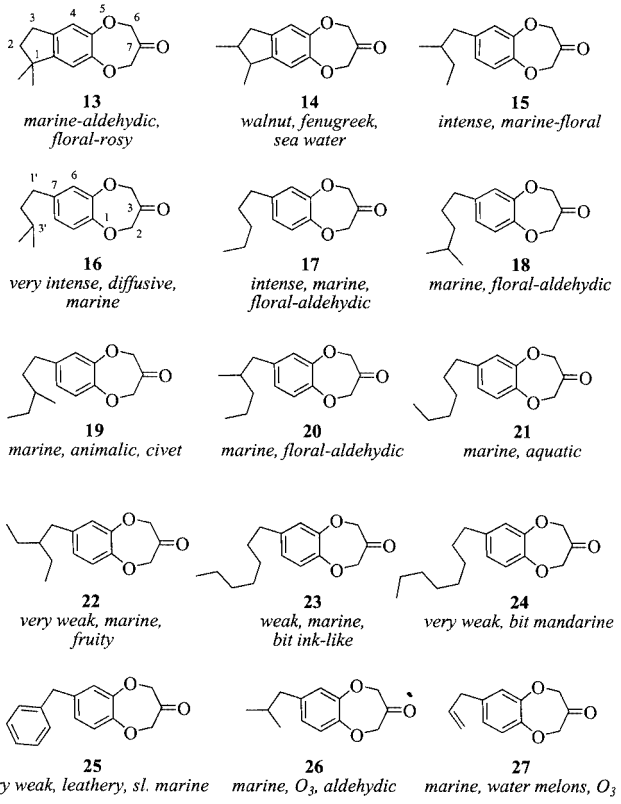


Figure 2. Overview of the marine odorants synthesized

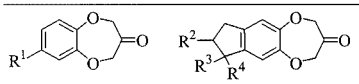
Interesting was also of course, that while the intensity of the known derivatives of **4** decreased with more heavier and bulky substituents, the C_5H_{11} group of **16** on the contrary increased the intensity dramatically. So was there a hydrophobic binding pocket that so far had been missed? This exciting question motivated us to synthesize the *n*-pentyl analogue **17** as well as the isomeric C_6-substituted derivatives **18**−**22**, all of which with the exception of the last one **22** possessed intense and interesting marine notes (Figure 2). In comparison with **18**−**21**, the 2-ethylbutyl-substituted **22** was quite weak, but still in the marine direction with a pleasant fruity twist. The *n*-heptyl analogue **23** was more powerful than **22** but its marine note was also relatively weak. With the slightly marine but mainly hesperidic, mandarin-like *n*-octyl analogue **24** we then reached the limit of the molecular dimensions of the putative marine receptor.

Often the isobutenyl moiety of terpenes can be replaced by a phenyl group without changing the overall odor characteristics.[2,18,19] So would a benzyl substituent be able to mimic the isopentyl group of **16**? The answer is no, because **25**, which was also synthesized via the general procedure developed, was found to be very weak, and mainly leathery in character, though a slight marine tonality was detectable by the evaluating perfumers. We completed our series of new marine odorants with **26** and **27**. 7-(2′-Methylpropyl)benzo[*b*][1,4]dioxepin-3-one (**26**) is interesting since it is weaker than both the known propyl and butyl analogs, so its ramification seems not to reach the postulated additional hydrophobic binding site. The allyl analogue **27** is however again very potent and possesses a pleasant marine note with some reminiscence to water melons and ozone. It was synthesized from eugenol by cleavage of the phenolic methyl ether group employing lithium chloride in refluxing DMF according to a method of Piras and co-workers.[20] 4-Allylpyrocatechol was obtained in 50% yield after 44 h reaction time, usual workup and purification by silica-gel FC. This was then transformed into **27** according to the Pfizer route[1] outlined in Scheme 1. Williamson reaction with methyl bromoacetate in the presence of sodium methoxide afforded methyl 4-allyl-2-(ethoxycarbonylmethoxy)phenoxyacetate in 65% yield, which was subjected to Dieckmann cyclization and decarboxylation to provide **27** in 42% yield (see Exp. Sect.). In this case, we could not employ our sequence because the in-situ generated ruthenium tetroxide would have cleaved not only the methylene but also the allylic double bond. In general however, the sequence presented in Scheme 2 provides a shorter, easier to perform and more flexible access to benzo[*b*][1,4]dioxepinone systems.

Olfactophore Model

With this series of marine odorants, complemented by some compounds resynthesized from the patent literature,[1,21] we had an exhaustive data set for the structure−odor correlation of the small class of marine odorants. We used this data set that is summarized in

Table 1. Experimental and calculated odor threshold values of the compounds **7** and **13**−**24** as well as those of related benchmarks



R^1	R^2	R^3	R^4	threshold	calcd.	compound
Me	—	—	—	0.031 ng/L	0.53 ng/L	**4**
Et	—	—	—	0.11 ng/L	0.53 ng/L	ref.[1]
Pr	—	—	—	0.10 ng/L	0.13 ng/L	ref.[21]
Bu	—	—	—	0.26 ng/L	0.022 ng/L	ref.[1]
*i*Bu	—	—	—	1.65 ng/L	0.42 ng/L	**26**
$CH_2CHMeCH_2CH_3$	—	—	—	0.08 ng/L	0.54 ng/L	**15**
$(CH_2)_2CHMe_2$	—	—	—	0.014 ng/L	0.044 ng/L	**16**
$(CH_2)_4CH_3$	—	—	—	0.013 ng/L	0.082 ng/L	**17**
$(CH_2)_3CHMe_2$	—	—	—	0.038 ng/L	0.071 ng/L	**18**
$(CH_2)_2CHMeCH_2CH_3$	—	—	—	0.043 ng/L	0.038 ng/L	**19**
$CH_2CHMe(CH_2)_2CH_3$	—	—	—	0.38 ng/L	0.063 ng/L	**20**
$(CH_2)_5CH_3$	—	—	—	0.019 ng/L	0.054 ng/L	**21**
$CH_2CHEtCH_2CH_3$	—	—	—	4.70 ng/L	0.55 ng/L	**22**
$(CH_2)_6CH_3$	—	—	—	0.64 ng/L	0.54 ng/L	**23**
$(CH_2)_7CH_3$	—	—	—	4.05 ng/L	0.54 ng/L	**24**
CH_2Ph	—	—	—	6.80 ng/L	0.60 ng/L	**25**
$CH_2CH{=}CH_2$	—	—	—	0.051 ng/L	0.15 ng/L	**27**
—	H	Me	H	0.26 ng/L	0.53 ng/L	**7**
—	H	Me	Me	0.55 ng/L	0.58 ng/L	**13**
—	Me	Me	H	1.16 ng/L	0.59 ng/L	**14**

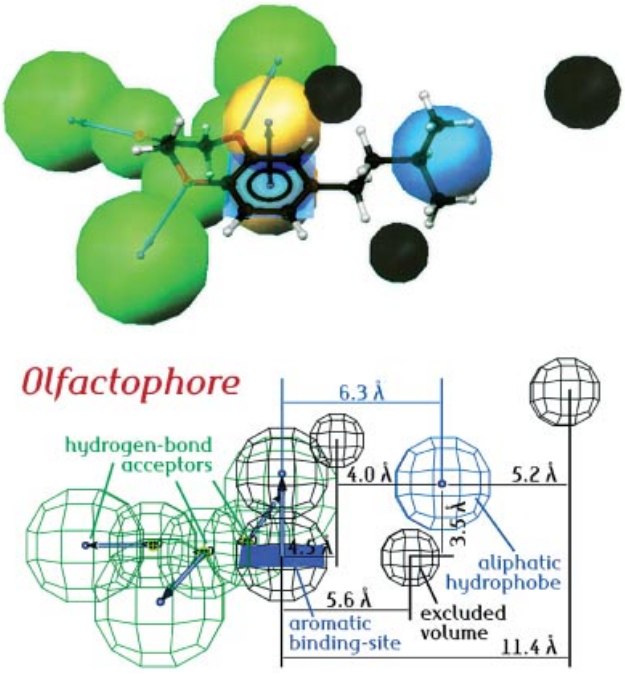


Figure 3. The olfactophore model generated with the Catalyst software

Table 1 to generate a computational olfactophore model with the Catalyst software.[22] An olfactophore model, a special case of a pharmacophore model, is a representation of generalized molecular features that are key for a certain odor.[2] It consists of hydrogen-bond acceptors (*depicted in green*) that orient the molecule on the receptor site, aromatic (*depicted in yellow*) as well as aliphatic (*depicted in blue*) binding sites, and excluded volumes (*depicted in black*) that are inaccessible for the molecule. Within a certain energy range, in this case 3 kcal·mol^{-1}, the conformer that fits the olfactophore model best is selected by the software. Its activity is then estimated on the basis of the degree of mapping of the molecular features with those of the computer receptor model. That way, odor thresholds can be calculated and compared with the experimental data.

Figure 3 shows our marine olfactophore model with **16** bound to the features of this hypothesis. The diagram below indicates the mutual distances of these features, and the calculated odor threshold values are given in Table 1, set against the experimental data. Considering the fact that most of the thresholds are very low, and distributed in a relatively narrow range, the correlation of 0.59 is quite good. In any case, we clearly see the importance of the aliphatic hydrophobe 6.3 Å away from the aromatic binding site. However, if this hydrophobe is not occupied, still a "*residual activity*' of 0.6 ng/L air is calculated, even for less active compounds like **22**, **24** and **25**. So the model could still be improved by adding more excluded volumes that would hinder these molecules from binding to the hydrogen-bond acceptors. Another major outlier is *Calone 1951*® (**4**) with a measured threshold of 0.031 ng/L air vs. 0.53 ng/L air calculated. Since **4** just bears one methyl group, it has less conformations that may hinder the docking to the receptor. It is in a way less diluted by inactive conformers, and this may account for the observed discrepancy.

In summary, more powerful and also more characteristic marine odorants were synthesized by increasing the chain length of the 7-alkyl substituent of benzo[*b*][1,4]dioxepinones beyond the bounds of the known derivatives of *Calone 1951*® (**4**).[1] This indicates the presence of a hydrophobe at a distance of 6.3 Å from the centre of the aromatic ring binding site of the receptor. The synthetic sequence presented in addition opens up a short, easy to perform and flexible access to benzo[*b*][1,4]dioxepinones.

Experimental Section

IR: Bruker VECTOR 22/Harrick SplitPea micro ATR (attenuated-total-reflection), Si. NMR: Bruker AVANCE DPX-400, TMS int. (δ = 0 ppm). MS: Finnigan MAT 95 or HP Chemstation 6890 GC/5973 Mass Sensitive Detector. FC: Merck Kieselgel 60 (particle size 40−63 μm). TLC: Merck Kieselgel 60 F_{254} (particle size 5−20 μm, layer thickness 250 μm on glass, 5 cm × 10 cm); visualization reagent: PMA spray soln. for TLC, Merck 1.00480.0100. Melting points: Büchi Melting Point B545 (uncorr.). Elemental analyses: Eidgenössische Materialprüfungs- und Forschungsanstalt (EMPA), Überlandstrasse 129, Dübendorf. All reactions were performed under nitrogen using reagents and solvents (*puriss.* or *purum* grade) from Fluka without further purification. The odor thresholds were determined by GC-olfactometry:[23,24] 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 perceiveing an odor. If the recorded time matched the retention time, the sample was further

diluted. The last concentration detected at the correct retention time is the individual odor threshold. The reported threshold values are the geometrical means of the individual odor thresholds of the different panelists.

1-Methyl-2,3-dihydro-1*H*-5,9-dioxacyclohepta[*f*]inden-7-one (7). General Procedure: A mixture of veratrol (**8**, 19.1 mL, 150 mmol) and vinylacetic acid (19.2 mL, 225 mmol) in 83% PPA (230 g) was stirred for 15 h at 60 °C prior to pouring into ice/water (1:1, 500 mL). After stirring for 30 min at room temp., the product was extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with 2 N aq. NaOH (2 × 100 mL), water (100 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated in a rotary evaporator. Crystallization (EtOAc/pentane) of the resulting residue furnished 5,6-dimethoxy-3-methylindan-1-one (**9**, 22.8 g, 74%), the physical data of which were identical with those reported in ref.[4]

Concd. aq. HCl (4 mL) was added to a suspension of Zn dust (53.3 g, 815 mmol) in water (74 mL). After stirring at room temp. for 30 min, the supernatant was decanted and water (42 mL) followed by concd. aq. HCl (55 mL) was added dropwise to the residue with cooling in an ice bath. A solution of **9** (28.0 g, 136 mmol) in toluene (53 mL) was added, and the reaction mixture was refluxed for 3d, with an additional quantity of concd. aq. HCl (55 mL) being added after 48 h. The reaction mixture was cooled down to room temp., and poured into water (200 mL), the product was extracted with Et_2O (300 mL). The combined organic extracts were washed with water (100 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated in a rotary evaporator. Silica-gel FC (pentane/Et_2O, 9:1, R_f = 0.23) of the resulting residue provided 5,6-dimethoxy-1-methylindane (**10**, 19.6 g, 75%), the spectroscopic data of which were identical to those reported in the ref.[5,6]

At room temp. under N_2, Me_3SiI (TMSI, 27.5 mL, 202 mmol) was added dropwise with stirring in the course of 90 min into a solution of **10** (19.4 g, 101 mmol) in MeCN (150 mL). Stirring was continued at room temp. for 2.5 days, with an additional quantity of Me_3SiI (TMSI, 10.0 mL, 73.5 mmol) being added after 48 h. The reaction mixture was poured into water (500 mL), and extracted with Et_2O (2 × 200 mL). The combined extracts were washed with 40% aq. $NaHSO_3$ (100 mL), water (100 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated in a rotary evaporator. Silica-gel FC (pentane/Et_2O, 2:1, R_f = 0.28) furnished 1-methylindan-5,6-diol (**11**, 15.5 g, 93%), the spectroscopic data of which matched with those reported in the ref.[9]

With vigorous stirring, a mixture of **11** (15.3 g, 93.2 mmol) and 3-chloro-2-(chloromethyl)prop-1-ene (11.6 g, 92.8 mmol) in dioxane (50 mL) was added dropwise during a period of 5 h to a refluxing suspension of K_2CO_3 (25.7 g, 186 mmol) in Et_2CO (200 mL). After completion, stirring was continued at reflux for 1 h prior to vacuum filtration of the formed inorganic precipitate after cooling. The precipitate was washed with acetone, and the combined organic solutions were concentrated under reduced pressure. By FC (pentane/Et_2O, 19:1, R_f = 0.66) on silica gel 1-methyl-7-methylene-2,3,7,8-tetrahydro-1*H*,6*H*-5,9-dioxacyclohepta[*f*]indene (**12**, 7.30 g, 36%) was isolated. IR (ATR): $\tilde{\nu}$ = 1322/1276 cm^{-1} (ν ring), 1485/1451/1419/1577 cm^{-1} (ν C=C, Ar), 1031 cm^{-1} (ν C−O−C sym.), 1155 cm^{-1} (ν C−O−C asym.). ^1H NMR ($CDCl_3$): δ = 1.22 (d, *J* = 7.2 Hz, 3 H, 1-Me), 1.60 (dddd, *J* = 16.1, 8.6, 7.8, 7.3 Hz, 1 H, 2-H_b), 2.27 (dddd, *J* = 16.1, 7.8, 7.3, 3.8 Hz, 1 H, 2-H_a), 2.74 (dt, *J* = 15.4, 7.8 Hz, 1 H, 3-H_b), 2.79 (ddd, *J* = 15.4, 8.6, 3.8 Hz, 1 H, 3-H_a), 3.07 (br. sext, *J* = 7.3 Hz, 1 H, 1-H), 4.70 (s, 4 H, 6-,8-H_2), 5.05 (t, *J* = 1.0 Hz, 2 H, =CH_2), 6.75 (s, 1 H, 4-H), 6.77 (s, 1 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.8 (q, 1-Me), 30.7 (t, C-2), 35.2 (t, C-3), 38.9 (d, C-1), 73.8/73.9 (2t, C-6,-8), 112.0 (t, = CH_2), 115.3/116.3 (2d, C-4,-10), 138.4 (s, C-7), 143.6 (s, C-10a), 144.3 (s, C-3a), 148.2/148.3 (2s, C-4a,-9a) ppm. MS (EI): *m*/*z* (%) = 91 (65) [$C_7H_7^+$], 105 (25) [$C_8H_9^+$], 117 (19)/131 (26)/145 (33) [$C_nH_{2n-9}^+$], 173 (24) [$M^+ - CH_3 - CO$], 201 (81) [$M^+ - CH_3$], 216 (100) [M^+].

At room temp., $NaIO_4$ (6.50 g, 30.5 mmol) was added with vigorous stirring to a mixture of **12** (6.60 g, 30.5 mmol) in MeCN (140 mL), water (140 mL) and CCl_4 (90 mL). After stirring for 30 min, $RuCl_3$ (0.30 g, 1.50 mmol, 5 mol %) was added, and stirring was continued for 48 h with another portion of $RuCl_3$ (0.30 g, 1.50 mmol, 5 mol %) being added after 6 h. The reaction mixture was poured into water (500 mL), and the product extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were washed with 20% aq. $NaHSO_3$ (200 mL) and water (200 mL), and then dried (Na_2SO_4). After evaporation of the solvent in a rotary evaporator silica-gel FC (pentane/Et_2O, 4:1, R_f = 0.32) furnished 1-methyl-2,3-dihydro-1*H*-5,9-dioxacyclohepta[*f*]inden-7-one (**7**, 3.3 g, 50%) as colorless crystals, mp. 79−80 °C. IR (ATR): $\tilde{\nu}$ = 1323/1280/1256/1351 cm^{-1} (ν ring), 1735 cm^{-1} (ν C=O), 1041 cm^{-1} (ν C−O−C sym.), 1482/1439/1577 cm^{-1} (ν C=C, Ar), 1155 cm^{-1} (ν C−O−C asym.). ^1H NMR ($CDCl_3$): δ = 1.24 (d, *J* = 7.0 Hz, 3 H, 1-Me), 1.60 (qd, *J* = 12.4, 8.7 Hz, 1 H, 2-H_b), 2.30 (tdd, *J* = 12.4, 7.7, 3.9 Hz, 1 H, 2-H_a), 2.74 (ddd, *J* = 15.7, 8.7, 7.7 Hz, 1 H, 3-H_b), 2.82 (ddd, *J* = 15.7, 8.7, 3.9 Hz, 1 H, 3-H_a), 3.10 (br. sext, *J* = 7.0 Hz, 1 H, 1-H), 4.65/4.66 (2s, 4 H, 6-,8-H_2), 6.80 (s, 1 H, 4-H), 6.83 (s, 1 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.8 (q, 1-Me), 30.7 (t, C-2), 35.1 (t, C-3), 38.9 (d, C-1), 75.4/75.5 (2t, C-6,-8), 115.2/116.2 (2d, C-4,-10), 139.2 (s, C-10a), 144.4 (s, C-3a), 146.8/147.0 (2s, C-4a,-9a), 205.0 (s, C-7) ppm. MS (EI): *m*/*z* (%) = 91 (97) [$C_7H_7^+$], 103 (20) [$C_8H_7^+$], 115 (13) [$C_8H_{19}^+$], 175 (14) [$M^+ - CH_3 - CO$], 203 (100) [$M^+ - CH_3$], 218 (57) [M^+]. $C_{13}H_{14}O_3$ (218.3): calcd. C 71.54, H 6.47; found C 71.51, H 6.38. Odor: Linear, very intense, marine with distinct floral aspects. Odor threshold: 0.26 ng/L air.

1,1-Dimethyl-2,3-dihydro-1*H*-5,9-dioxacyclohepta[*f*]inden-7-one (13): Following the general procedure, Friedel−Crafts acylation (88% yield) of veratrol (**8**, 20.7 g, 150 mmol) with 3,3-dimethylacrylic acid (22.5 g, 225 mmol), followed by Clemmensen reduction (69% yield), demethylation (9% yield), Williamson ether synthesis (39% yield) and in-situ RuO_4 oxidation (50% yield) furnished after final silica-gel FC (pentane/Et_2O, 4:1, R_f = 0.34) the odoriferous title compound **13** (300 mg). IR (ATR): $\tilde{\nu}$ = 1322/1253/1281/1350 cm^{-1} (ν ring), 1040/1067 cm^{-1} (ν C−O−C), 1484/1438 cm^{-1} (ν C=C, Ar), 1736 cm^{-1} (ν C=O). ^1H NMR ($CDCl_3$): δ = 1.22 (s, 6 H, 1-Me_2), 1.92 (t, *J* = 7.2 Hz, 2 H, 2-H_2), 2.79 (t, *J* = 7.2 Hz, 2 H, 3-H_2), 4.66/4.67 (2s, 4 H, 6-,8-H_2), 6.75 (s, 1 H, 4-H), 6.81 (s, 1 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.4 (2q, 1-Me_2), 29.3 (t, C-3), 41.7 (t, C-2), 43.6 (s, C-1), 75.4/75.5 (2t, C-6,-8), 114.0 (d, C-10), 116.3 (d, C-4), 139.0 (s, C-3a), 146.8/147.2 (2s, C-4a,-9a), 148.3 (s, C-10a), 205.1 (s, C-7) ppm. MS (EI): *m*/*z* (%) = 133 (33) [$C_9H_9O^+$], 145 (6) [$C_{11}H_{13}^+$], 161 (7) [$M^+ - CH_3 - 2CO$], 189 (2) [$M^+ - CH_3 - CO$], 217 (100) [$M^+ - CH_3$], 232 (30) [M^+]. Odor: Marine-aldehydic, floral-rosy with some reminiscence of citronellyoxy acetaldehyde [(3,7-dimethyl-6-octenyloxy)acetaldehyde]. Odor threshold: 0.55 ng/L air.

(*E*/*Z*)-1,2-Dimethyl-2,3-dihydro-1*H*-5,9-dioxacyclohepta[*f*]inden-7-one (14): Following the general procedure, Friedel−Crafts acylation of veratrol (**8**, 20.7 g, 150 mmol) with tiglic acid (22.5 g, 225 mmol) with subsequent Clemmensen reduction (80% yield), followed by demethylation (84% yield), Williamson ether synthesis

(53% yield) and in situ RuO_4 oxidation (38% yield) furnished after final silica-gel FC (pentane/Et_2O, 4:1, R_f = 0.34) the odoriferous title compound **14** (4.60 g). IR (ATR): $\tilde{\nu}$ = 1736 cm^{-1} (ν C=O), 1324/1263/1289/1352 cm^{-1} (ν ring), 1484/1439 cm^{-1} (ν C=C, Ar), 1042 cm^{-1} (ν C−O−C sym), 1159 cm^{-1} (ν C−O−C asym). ^1H NMR ($CDCl_3$): δ = 0.95/1.08/1.17/1.24 (4d, *J* = 7.0 Hz, 6 H, 1-,2-Me), 1.91−2.02 (m, 1 H, 2-H), 2.41 (dd, *J* = 15.0, 9.6 Hz)/2.49 (dd, *J* = 15.0, 6.4 Hz)/2.55 (dd, *J* = 14.0, 6.8 Hz)/2.59 (dd, *J* = 14.0, 7.2 Hz) [2 H, 3-H2], 2.89 (td, *J* = 15.7, 7.2 Hz)/3.06 (quint, *J* = 7.2 Hz) [1 H, 1-H], 4.65/4.66 (2s, 4 H, 4-,8-H2), 6.76−6.80 (m, 2 H, 4-,10-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.5/15.0/17.5/18.3 (4q, 1-,2-Me), 38.6/39.4 (2t, C-3), 38.2/41.8/44.4/46.2 (4d, C-1,-2), 75.4/75.5/75.5/75.6 (4d, C-6,-8), 115.1/115.6/116.1/116.4 (4d, C-4,-10), 138.3/138.4 (2s, C-3a), 144.2/144.4 (2s, C-10a), 146.7/146.8/146.9/147.0 (4s, C-4a,-9a), 205.0/205.1 (2s, C-7) ppm. MS (EI): *m*/*z* (%) = 77 (13)/91 (19)/105 (20)/133 (20)/161 (7)/175 (4) [$C_nH_{2n-7}^+$], 189 (18) [$M^+ - CH_3 - CO$], 203 (1) [$M^+ - C_2H_5$], 217 (100) [$M^+ - CH_3$], 232 (70) [M^+]. Odor: Blend of walnut, fenugreek oil (*Trigonella foenum-graecum*), sea water and lichens. Odor threshold: 1.16 ng/L air.

7-(2′-Methylbutyl)benzo[*b*][1,4]dioxepin-3-one (15): Following the general procedure, Friedel−Crafts acylation of veratrol (**8**, 20.7 g, 150 mmol) with 2-methylbutyric acid (24.6 mL, 225 mmol) with subsequent Clemmensen reduction (16% yield), followed by demethylation (74% yield), Williamson ether synthesis (52% yield) and in-situ RuO_4 oxidation (17% yield) furnished after final silica-gel FC (pentane/Et_2O, 4:1, R_f = 0.31) the odoriferous title compound **15** (300 mg). IR (ATR): $\tilde{\nu}$ = 1501/1434/1460/1580 cm^{-1} (ν C=C, Ar), 1265/1302/1201 cm^{-1} (ν ring), 1050 cm^{-1} (ν C−O−C), 1740 cm^{-1} (ν C=O). ^1H NMR ($CDCl_3$): δ = 0.84 (d, *J* = 6.4 Hz, 3 H, 2′-Me), 0.90 (t, *J* = 7.5 Hz, 3 H, 4′-H_2), 1.16 (m_c, 1 H, 3′-H_b), 1.39 (m_c, 1 H, 3′-H_a), 1.60 (m_c, 1 H, 2′-H), 2.28 (dd, *J* = 11.6, 8.0 Hz, 1 H, 1′-H_b), 2.53 (dd, *J* = 11.6, 6.0 Hz, 1 H, 1′-H_a), 4.68/4.70 (2s, 4 H, 2-,4-H_2), 6.74 (dd, *J* = 8.0, 2.0 Hz, 1 H, 8-H), 6.78 (d, *J* = 2.0 Hz, 1 H, 6-H), 6.90 (d, *J* = 8.0 Hz, 1 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.3 (q, C-4′), 18.8 (q, 2′-Me), 29.0 (t, C-3′), 36.4 (d, C-2′), 42.2 (t, C-1′), 75.4/75.6 (2t, C-2,-4), 120.3/121.0 (2d, C-6,-9), 124.3 (d, C-8), 137.6 (s, C-7), 146.1/147.7 (2s, C-5a,-9a), 204.7 (s, C-3) ppm. MS (EI): *m*/*z* (%) = 77 (11) [$C_6H_5^+$], 91 (7) [$C_7H_7^+$], 135 (5) [$M^+ - C_4H_9 - C_2H_2O$], 149 (4) [$M^+ - C_4H_9 - CO$], 177 (100) [$M^+ - C_4H_9$], 191 (2) [$M^+ - C_3H_7$], 205 (1) [$M^+ - C_2H_5$], 219 (1) [$M^+ - CH_3$], 234 (26) [M^+]. Odor: Intense, marine-floral. Odor threshold: 0.08 ng/L air.

7-(3′-Methylbutyl)benzo[*b*][1,4]dioxepin-3-one (16): Following the general procedure, Friedel−Crafts acylation of veratrol (**8**, 20.7 g, 150 mmol) with *iso*-valeric acid (24.8 mL, 225 mmol) with subsequent Clemmensen reduction (41% yield), followed by demethylation (92% yield), Williamson ether synthesis (57% yield) and in-situ RuO_4 oxidation (32% yield) furnished after final silica-gel FC (pentane/Et_2O, 4:1, R_f = 0.38) the odoriferous title compound **16** (2.30 g). IR (ATR): $\tilde{\nu}$ = 1502/1435/1581/1467 cm^{-1} (ν C=C, Ar), 1265/1304/1201 cm^{-1} (ν ring), 1050 cm^{-1} (ν C−O−C sym), 1740 cm^{-1} (ν C=O). ^1H NMR ($CDCl_3$): δ = 0.92 (d, *J* = 6.4 Hz, 6 H, 3′-Me_2), 1.46/1.47 (2td, *J* = 8.0, 6.8 Hz, 2 H, 2′-H_2), 1.57 (nonett, *J* = 6.8 Hz, 1 H, 3′-H), 2.52 (t, *J* = 8.0 Hz, 2 H, 1′-H_2), 4.67/4.69 (2s, 4 H, 2-,4-H_2), 6.77 (dd, *J* = 8.2, 2.4 Hz, 1 H, 8-H), 6.82 (d, *J* = 2.4 Hz, 1 H, 6-H), 6.90 (d, *J* = 8.4 Hz, 1 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.36 (2q, 3′-Me_2), 27.43 (d, C-3′), 32.69 (t, C-1′), 40.53 (t, C-2′), 75.35/75.63 (2t, C-2,-4), 120.27/120.50 (d, C-6,-9), 123.45 (d, C-8), 138.99 (s, C-7), 146.00/147.86 (2s, C-5a,-9a), 204.71 (s, C-3) ppm. MS (EI): *m*/*z* (%) = 77 (26) [$C_6H_5^+$], 135 (12) [$M^+ - C_4H_9 - C_2H_2O$], 149 (21) [$M^+ - C_4H_9 - CO$], 177 (100) [$M^+ - C_4H_9$], 191 (7) [$M^+ - C_3H_7$], 234 (52) [M^+]. $C_{14}H_{18}O_3$ (234.3): calcd. C 71.77, H 7.74; found C 71.78, H 7.82. Odor: Very intense and diffusive, linear, marine, with some reminiscence of Adoxal® (2,6,10-trimethylundec-9-en-1-al). Odor threshold: 0.014 ng/L air.

7-Pentylbenzo[*b*][1,4]dioxepin-3-one (17): Following the general procedure, Friedel−Crafts acylation of veratrol (**8**, 41.5 g, 300 mmol) with valeric acid (46.0 g, 450 mmol) with subsequent Clemmensen reduction (21% yield), followed by demethylation (39% yield), Williamson ether synthesis (58% yield) and in-situ RuO_4 oxidation (17% yield) furnished after final silica-gel FC (pentane/Et_2O, 4:1, R_f = 0.25) the odoriferous title compound **17** (500 mg). IR (ATR): $\tilde{\nu}$ = 1502/1435/1580 cm^{-1} (ν C=C, Ar), 1265/1304/1201 cm^{-1} (ν ring), 1050 cm^{-1} (ν C−O−C), 1740 cm^{-1} (ν C=O). ^1H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 7.0 Hz, 3 H, 5′-H_2), 1.28−1.35 (m, 4 H, 3′-,4′-H_2), 1.59 (br. quint, *J* = 7.6 Hz, 2 H, 2′-H_2), 2.51 (t, *J* = 7.8 Hz, 2 H, 1′-H_2), 4.68/4.70 (2s, 4 H, 2-,4-H_2), 6.77 (dd, *J* = 8.0, 2.0 Hz, 1 H, 8-H), 6.81 (d, *J* = 2.0 Hz, 1 H, 6-H), 6.90 (d, *J* = 8.0 Hz, 1 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.9 (q, C-5′), 22.4 (t, C-4′), 30.9/31.3 (2t, C-2′,-3′), 34.8 (t, C-1′), 75.4/75.6 (2t, C-2,-4), 120.3/120.5 (2d, C-6,-9), 123.5 (d, C-8), 138.9 (s, C-7), 146.0/147.8 (2s, C-5a,-9a), 204.7 (s, C-3) ppm. MS (EI): *m*/*z* (%) = 77 (18) [$C_6H_5^+$], 91 (10) [$C_7H_7^+$], 135 (9) [$M^+ - C_4H_9 - C_2H_2O$], 149 (22) [$M^+ - C_4H_9 - CO$], 177 (100) [$M^+ - C_4H_9$], 191 (8) [$M^+ - C_3H_7$], 205 (1) [$M^+ - C_2H_5$], 234 (42) [M^+]. Odor: Intense, marine, floral with aldehydic nuances. Odor threshold: 0.013 ng/L air.

7-(4′-Methylpentyl)benzo[*b*][1,4]dioxepin-3-one (18): Following the general procedure, Friedel−Crafts acylation (98% yield) of veratrol (**8**, 20.7 g, 150 mmol) with *iso*-caprylic acid (26.1 g, 225 mmol) with subsequent Clemmensen reduction (11% yield), followed by demethylation (45% yield), and Williamson ether synthesis with subsequent in-situ RuO_4 oxidation (30% yield) furnished after final silica-gel FC (pentane/Et_2O, 4:1, R_f = 0.24) the odoriferous title compound **18** (500 mg). IR (ATR): $\tilde{\nu}$ = 1502/1418/1466/1580 cm^{-1} (ν C=C, Ar), 1265/1304/1201 cm^{-1} (ν ring), 1050 cm^{-1} (ν C−O−C), 1741 cm^{-1} (ν C=O). ^1H NMR ($CDCl_3$): δ = 0.88 (2d, *J* = 6.4 Hz, 6 H, 4′-Me_2), 1.18−1.24 (m, 2 H, 3′-H_2), 1.53−1.61 (m, 4 H, 2′-H_2, 4′-H), 2.50 (t, *J* = 7.8 Hz, 2 H, 1′-H_2), 4.68/4.70 (2s, 4 H, 2-,4-H_2), 6.78 (dd, *J* = 8.0, 4.0 Hz, 1 H, 8-H), 6.82 (d, *J* = 4.0 Hz, 1 H, 6-H), 6.90 (d, *J* = 8.0 Hz, 1 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.4 (2q, 4′-Me_2), 27.7 (d, C-4′), 29.1 (t, C-2′), 35.1 (t, C-1′), 38.4 (t, C-3′), 75.4/75.6 (2t, C-2,-4), 120.3/120.5 (2d, C-6,-9), 123.5 (d, C-8), 138.9 (s, C-7), 146.0/147.8 (2s, C-5a,-9a), 204.8 (s, C-3) ppm. MS (EI): *m*/*z* (%) = 77 (13) [$C_6H_5^+$], 91 (8) [$C_7H_7^+$], 135 (7) [$M^+ - C_5H_{11} - C_2H_2O$], 149 (16) [$M^+ - C_5H_{11} - CO$], 177 (100) [$M^+ - C_5H_{11}$], 191 (1) [$M^+ - C_4H_9$], 205 (3) [$M^+ - C_3H_7$], 248 (38) [$M^+$]. Odor: Marine, floral-aldehydic. Odor threshold: 0.038 ng/L air.

7-(3′-Methylpentyl)benzo[*b*][1,4]dioxepin-3-one (19): Following the general procedure, Friedel−Crafts acylation of veratrol (**8**, 20.7 g, 150 mmol) with 3-methylvalerianic acid (28.2 mL, 225 mmol) with subsequent Clemmensen reduction (10% yield), followed by demethylation (67% yield), Williamson ether synthesis (42% yield) and in-situ RuO_4 oxidation (16% yield) furnished after final silica-gel FC (pentane/Et_2O, 4:1, R_f = 0.32) the odoriferous title compound **19** (140 mg). IR (ATR): $\tilde{\nu}$ = 1502/1435/1460/1580 cm^{-1} (ν C=C, Ar), 1265/1304/1202 cm^{-1} (ν ring), 1051 cm^{-1} (ν C−O−C), 1741 cm^{-1} (ν C=O). ^1H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 3 H, 5′-H_3), 0.91 (d, *J* = 6.4 Hz, 3 H, 3′-Me), 1.18 (m_c, 1 H, 2′-H_b), 1.34−1.43 (m, 3 H, 2′-H_a, 4′-H_2), 1.56−1.62 (m, 1 H, 3′-H), 2.48 (ddd, *J* = 14.0, 10.0, 6.4 Hz, 1 H, 1′-H_a), 2.56 (ddd, *J* = 14.0, 10.4, 5.2 Hz, 1 H, 1′-H_b), 4.66/4.67 (2s, 4 H, 2-,4-H_2), 6.78 (dd, *J* =

8.2, 2.4 Hz, 1 H, 8-H), 6.82 (d, J = 2.0 Hz, 1 H, 6-H), 6.90 (d, J = 8.4 Hz, 1 H, 9-H). ^{13}C NMR ($CDCl_3$): δ = 11.1 (q, C-5′), 18.9 (q, 3′-Me), 29.2 (t, C-4′), 32.4 (t, C-1′), 33.8 (d, C-3′), 38.2 (t, C-2′), 75.4/75.6 (2t, C-2,-4), 120.3/120.5 (2d, C-6,-9), 123.5 (d, C-8), 139.1 (s, C-7), 146.0/147.9 (2s, C-5a,-9a), 204.7 (s, C-3) ppm. MS (EI): *m/z* (%) = 77 (21) [$C_6H_5^+$], 92 (14) [$C_7H_8^+$], 135 (11) [$M^+ - C_5H_{11} - C_2H_2O$], 149 (16) [$M^+ - C_5H_{11} - CO$], 177 (100) [$M^+ - C_5H_{11}$], 191 (4) [$M^+ - C_4H_9$], 205 (7) [$M^+ - C_3H_7$], 248 (45) [$M^+$]. Odor: Marine, animalic, civet-like, floral-aldehydic, slightly reminiscent of citronelloxy acetaldehyde ([3,7-dimethyl-6-octenyl]oxyacetaldehyde). Odor threshold: 0.043 ng/L air.

7-(2′-Methylpentyl)benzo[*b*][1,4]dioxepin-3-one (20): Following the general procedure, Friedel−Crafts acylation of veratrol (**8**, 20.7 g, 150 mmol) with 3-methylvalerianic acid (28.3 mL, 225 mmol) with subsequent Clemmensen reduction (23% yield), followed by demethylation (63% yield), Williamson ether synthesis (88% yield) and in-situ RuO_4 oxidation (22% yield) furnished after final silica-gel FC (pentane/Et_2O, 9:1, R_f = 0.26) the odoriferous title compound **20** (1.10 g). IR (ATR): $\tilde{\nu}$ = 1501/1434/1460/1580 cm^{-1} (ν C=C, Ar), 1265/1303/1201 cm^{-1} (ν ring), 1049 cm^{-1} (ν C−O−C), 1740 cm^{-1} (ν C=O). ^{1}H NMR ($CDCl_3$): δ = 0.83 (d, 3 H, 2′-Me), 0.88 (t, J = 7.0 Hz, 3 H, 5′-H_3), 1.11−1.40 (m, 4 H, 3′-,4′-H_2), 1.68 (m_c, 1 H, 2′-H), 2.26 (dd, J = 13.6, 8.4 Hz, 1 H, 1′-H_b), 2.54 (dd, J = 13.6, 6.0 Hz, 1 H, 1′-H_a), 4.68/4.70 (2s, 4 H, 2-,4-H_2), 6.73 (dd, J = 8.0, 2.0 Hz, 1 H, 8-H), 6.78 (d, J = 2.0 Hz, 1 H, 6-H), 6.89 (d, J = 8.0 Hz, 1 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (q, C-5′), 19.2 (q, 2′-Me), 20.0 (t, C-4′), 34.5 (d, C-2′), 38.8 (t, C-3′), 42.6 (t, C-1′), 75.4/75.6 (2t, C-2,-4), 120.3/121.0 (2d, C-6,-9), 124.3 (d, C-8), 137.6 (s, C-7), 146.1/147.7 (2s, C-5a,-9a), 204.8 (s, C-3) ppm. MS (EI): *m/z* (%) = 77 (9) [$C_6H_5^+$], 91 (6) [$C_7H_7^+$], 135 (5) [$M^+ - C_5H_{11} - C_2H_2O$], 149 (3) [$M^+ - C_5H_{11} - CO$], 177 (100) [$M^+ - C_5H_{11}$], 205 (2) [$M^+ - C_3H_7$], 248 (21) [$M^+$]. Odor: Marine, floral-aldehydic. Odor threshold: 0.38 ng/L air.

7-Hexylbenzo[*b*][1,4]dioxepin-3-one (21): Following the general procedure, Friedel−Crafts acylation of veratrol (**8**, 41.5 g, 300 mmol) with caproic acid (52.3 g, 450 mmol) with subsequent Clemmensen reduction (18% yield), followed by demethylation (86% yield), Williamson ether synthesis (55% yield) and in-situ RuO_4 oxidation (52% yield) furnished after final silica-gel FC (pentane/Et_2O, 4:1, R_f = 0.32) the odoriferous title compound **21** (2.60 g). IR (ATR): $\tilde{\nu}$ = 1502/1435/1580 cm^{-1} (ν C=C, Ar), 1265/1304/1201 cm^{-1} (ν Ring), 1051 cm^{-1} (ν C−O−C), 1741 cm^{-1} (ν C=O). ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3 H, 6′-H_3), 1.27−1.35 (m, 6 H, 3′-H_2−5′-H_2), 1.57 (br. quint, J = 8.0 Hz, 2 H, 2′-H_2), 2.51 (t, J = 7.8 Hz, 2 H, 1′-H_2), 4.67/4.69 (2s, 4 H, 2-,4-H_2), 6.77 (dd, J = 8.0, 4.0 Hz, 1 H, 8-H), 6.81 (d, J = 4.0 Hz, 1 H, 6-H), 6.90 (d, J = 8.0 Hz, 1 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0 (q, C-6′), 22.5 (t, C-5′), 28.8 (t, C-3′), 31.2/31.6 (2t, C-2′,-4′), 34.9 (t, C-1′), 75.4/75.6 (2t, C-2,-4), 120.3/120.5 (2d, C-6,-9), 123.5 (d, C-8), 138.9 (s, C-7), 146.0/147.8 (2s, C-5a,-9a), 204.7 (s, C-3) ppm. MS (EI): *m/z* (%) = 77 (16) [$C_6H_5^+$], 91 (9) [$C_7H_7^+$], 135 (9) [$M^+ - C_5H_{11} - C_2H_2O$], 149 (21) [$M^+ - C_5H_{11} - CO$], 177 (100) [$M^+ - C_5H_{11}$], 191 (2) [$M^+ - C_4H_9$], 205 (3) [$M^+ - C_3H_7$], 248 (43) [$M^+$]. Odor: Marine, aquatic. Odor threshold: 0.019 ng/L air.

7-(2′-Ethylbutyl)benzo[*b*][1,4]dioxepin-3-one (22): Following the general procedure, Friedel−Crafts acylation of veratrol (**8**, 20.7 g, 150 mmol) with 2-ethylbutyric acid (28.3 mL, 225 mmol) with subsequent Clemmensen reduction (30% yield), followed by demethylation (72% yield), and Williamson ether synthesis with subsequent in-situ RuO_4 oxidation (7% yield) furnished after final silica-gel FC (pentane/Et_2O, 9:1, R_f = 0.31) the odoriferous title compound **22** (500 mg). IR (ATR): $\tilde{\nu}$ = 1501/1434/1459/1580 cm^{-1} (ν C=C, Ar), 1265/1301/1202 cm^{-1} (ν Ring), 1050 cm^{-1} (ν C−O−C), 1740 cm^{-1} (ν C=O). ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, J = 7.4 Hz, 6 H, 4′-,2′′-H_3), 1.28 (br. quint, J = 7.4 Hz, 4 H, 3′-,1′′-H_2), 1.46 (br. sept, J = 7.4 Hz, 1 H, 2′-H), 2.44 (d, J = 7.2 Hz, 2 H, 1′-H_2), 4.68/4.70 (2s, 4 H, 2-,4-H_2), 6.74 (dd, J = 8.0, 2.0 Hz, 1 H, 8-H), 6.79 (d, J = 2.0 Hz, 1 H, 6-H), 6.89 (d, J = 8.0 Hz, 1 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.7 (2q, C-4′,-2′′), 24.8 (2t, C-3′,-1′′), 38.6 (t, C-1′), 42.4 (d, C-2′), 75.4/75.6 (2t, C-2,-4), 120.3/121.0 (2d, C-6,-9), 124.3 (d, C-8), 137.8 (s, C-7), 146.0/147.7 (2s, C-5a,-9a), 204.7 (s, C-3) ppm. MS (EI): *m/z* (%) = 77 (10) [$C_6H_5^+$], 91 (6) [$C_7H_7^+$], 135 (6) [$M^+ - C_5H_{11} - C_2H_2O$], 149 (2) [$M^+ - C_5H_{11} - CO$], 177 (100) [$M^+ - C_5H_{11}$], 191 (1) [$M^+ - C_4H_9$], 205 (2) [$M^+ - C_3H_7$], 248 (23) [$M^+$]. Odor: Very weak, marine, fruity. Odor threshold: 4.70 ng/L air.

7-Heptylbenzo[*b*][1,4]dioxepin-3-one (23): Following the general procedure, Friedel−Crafts acylation of veratrol (**8**, 20.7 g, 150 mmol) with œnanthylic acid (31.9 mL, 225 mmol) with subsequent Clemmensen reduction (10% yield), followed by demethylation (75% yield), Williamson ether synthesis (53% yield) and in-situ RuO_4 oxidation (8% yield) furnished after final silica-gel FC (pentane/Et_2O, 9:1, R_f = 0.33) the odoriferous title compound **23** (100 mg). IR (ATR): $\tilde{\nu}$ = 1502/1435/1580 cm^{-1} (ν C=C, Ar), 1265/1304/1201 cm^{-1} (ν Ring), 1051 cm^{-1} (ν C−O−C), 1741 cm^{-1} (ν C=O). ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 3 H, 7′-H_3), 1.27−1.33 (m, 8 H, 3′-H_2−6′-H_2), 1.57 (br. quint, J = 7.8 Hz, 2 H, 2′-H_2), 2.51 (t, J = 7.8 Hz, 2 H, 1′-H_2), 4.68/4.70 (2s, 4 H, 2-,4-H_2), 6.77 (dd, J = 8.4, 2.0 Hz, 1 H, 8-H), 6.81 (d, J = 2.0 Hz, 1 H, 6-H), 6.90 (d, J = 8.4 Hz, 1 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0 (q, C-7′), 22.5 (t, C-6′), 29.0/29.1 (2t, C-3′,-5′), 31.2/31.7 (2t, C-2′,-4′), 34.9 (t, C-1′), 75.4/75.6 (2t, C-2,-4), 120.3/120.5 (2d, C-6,-9), 123.5 (d, C-8), 138.9 (s, C-7), 146.0/147.8 (2s, C-5a,-9a), 204.7 (s, C-3) ppm. MS (EI): *m/z* (%) = 77 (13) [$C_6H_5^+$], 91 (9) [$C_7H_7^+$], 135 (8) [$M^+ - C_6H_{13} - C_2H_2O$], 149 (18) [$M^+ - C_6H_{13} - CO$], 177 (100) [$M^+ - C_6H_{13}$], 191 (2) [$M^+ - C_5H_{11}$], 219 (4) [$M^+ - C_3H_7$], 262 (39) [$M^+$]. Odor: Weak, mandarine, a bit ink-like. Odor threshold: 1.65 ng/L air.

7-Octylbenzo[*b*][1,4]dioxepin-3-one (24): Following the general procedure, Friedel−Crafts acylation of veratrol (**8,** 20.7 g, 150 mmol) with caprylic acid (35.7 mL, 225 mmol) with subsequent Clemmensen reduction (10% yield), followed by demethylation (68% yield), Williamson ether synthesis (48% yield) and in-situ RuO_4 oxidation (36% yield) furnished after final silica-gel FC (pentane/Et_2O, 9:1, R_f = 0.32) the odoriferous title compound **24** (1.10 g). IR (ATR): $\tilde{\nu}$ = 1502/1435/1580 cm^{-1} (ν C=C, Ar), 1265/1304/1201 cm^{-1} (ν Ring), 1052 cm^{-1} (ν C−O−C), 1741 cm^{-1} (ν C=O). ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 3 H, 7′-H_3), 1.27−1.30 (m, 10 H, 3′-H_2−7′-H_2), 1.57 (br. quint, J = 7.8 Hz, 2 H, 2′-H_2), 2.51 (t, J = 7.8 Hz, 2 H, 1′-H_2), 4.67/4.69 (2s, 4 H, 2-,4-H_2), 6.76 (dd, J = 8.4, 2.0 Hz, 1 H, 8-H), 6.81 (d, J = 2.0 Hz, 1 H, 6-H), 6.89 (d, J = 8.4 Hz, 1 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0 (q, C-8′), 22.5 (t, C-7′), 29.1/29.3/29.3 (3t, C-3′,-5′,-6′), 31.2/31.8 (2t, C-2′,-4′), 34.9 (t, C-1′), 75.3/75.6 (2t, C-2,-4), 120.3/120.5 (2d, C-6,-9), 123.5 (d, C-8), 138.8 (s, C-7), 146.0/147.8 (2s, C-5a,-9a), 204.7 (s, C-3) ppm. MS (EI): *m/z* (%) = 77 (12) [$C_6H_5^+$], 91 (8) [$C_7H_7^+$], 135 (9) [$M^+ - C_7H_{15} - C_2H_2O$], 149 (18) [$M^+ - C_7H_{15} - CO$], 177 (100) [$M^+ - C_7H_{15}$], 191 (2) [$M^+ - C_6H_{13}$], 233 (4) [$M^+ - C_3H_7$], 276 (47) [$M^+$]. Odor: Very weak, a bit of mandarines. Odor threshold: 4.05 ng/L air.

7-Benzylbenzo[*b*][1,4]dioxepin-3-one (25): Following the general procedure, Friedel−Crafts acylation of veratrol (**8,** 20.7 g, 150 mmol) with benzoic acid (27.5 g, 225 mmol) with subsequent Clemmensen reduction (15% yield), followed by demethylation

(70% yield), Williamson ether synthesis (48% yield) and in-situ RuO_4 oxidation (62% yield) furnished after final silica-gel FC (pentane/Et_2O, 4:1, R_f = 0.27) the odoriferous title compound **25** (500 mg). IR (ATR): $\tilde{\nu}$ = 1501/1435/1579/1453 cm^{-1} (ν C=C, Ar), 1265/1301/1201 cm^{-1} (ν Ring), 1049 cm^{-1} (ν C−O−C), 1739 cm^{-1} (ν C=O). ^1H NMR ($CDCl_3$): δ = 3.88 (s, 2 H, 1′-H_2), 4.65/4.66 (2s, 4 H, 2-,4-H_2), 6.78 (dd, *J* = 8.0, 2.0 Hz, 1 H, 8-H), 6.81 (d, *J* = 2.0 Hz, 1 H, 6-H), 6.91 (d, *J* = 8.0 Hz, 1 H, 9-H), 7.16−7.30 (m, 5 H, 2′′-H −6′′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 40.9 (t, C-1′), 75.4/75.6 (2t, C-2,-4), 120.7/121.0 (2d, C-6,-9), 124.0 (d, C-8), 126.1 (d, C-4′′), 128.4/128.7 (4d, C-2′′,-3′′,-5′′,-6′′), 137.1 (s, C-1′′), 140.6 (s, C-7), 146.5/148.0 (2s, C-5a,-9a), 204.5 (s, C-3) ppm. MS (EI): *m*/*z* (%) = 77 (12) [$C_6H_5^+$], 91 (22) [$C_7H_7^+$], 115 (24) [C_9H_7], 128 (9) [$C_{10}H_8$], 141 (46) [$C_{11}H_9$], 152 (20) [$C_{12}H_8$], 169 (23) [$C_{13}H_{13}$], 181 (8) [$M^+ - C_3H_5O_2$], 195 (6) [$M^+ - C_2H_3O_2$], 211 (9) [$M^+ - C_2H_3O$], 225 (12) [$M^+ - CHO$], 254 (100) [M^+]. Odor: Very weak, leathery, slightly marine. Odor threshold: 6.80 ng/L air.

7-(2′-Methylpropyl)benzo[*b*][1,4]dioxepin-3-one (26): Following the general procedure, Friedel−Crafts acylation (68% yield) of veratrol (**8,** 20.7 g, 150 mmol) with benzoic acid (27.5 g, 225 mmol) followed by Clemmensen reduction (75% yield), demethylation (68% yield), Williamson ether synthesis (63% yield) and in situ RuO_4 oxidation (53% yield) furnished after final silica-gel FC (pentane/Et_2O, 4:1, R_f = 0.31) the odoriferous title compound **26** (2.10 g). IR (ATR): $\tilde{\nu}$ = 1501/1434/1580/1466 cm^{-1} (ν C=C, Ar), 1265/1303/1202 cm^{-1} (ν Ring), 1049 cm^{-1} (ν C−O−C), 1739 cm^{-1} (ν C=O). ^1H NMR ($CDCl_3$): δ = 0.90 (d, *J* = 7.0 Hz, 6 H, 2′-Me_2), 1.82 (nonett, *J* = 7.0 Hz, 1 H, 2′-H), 2.39 (d, *J* = 7.0 Hz, 2 H, 1′-H_2), 4.68/4.70 (2s, 4 H, 2-,4-H_2), 6.74 (dd, *J* = 8.0, 2.0 Hz, 1 H, 8-H), 6.78 (d, *J* = 2.0 Hz, 1 H, 6-H), 6.90 (d, *J* = 8.0 Hz, 1 H, 9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.2 (2q, 2′-Me_2), 30.0 (d, C-2′), 44.3 (t, C-1′), 75.4/75.6 (2t, C-2,-4), 120.3/121.0 (2d, C-6,-9), 124.2 (d, C-8), 137.6 (s, C-7), 146.1/147.7 (2s, C-5a,-9a), 204.7 (s, C-3) ppm. MS (EI): *m*/*z* (%) = 71 (11) [$C_6H_5^+$], 91 (6) [$C_7H_7^+$], 135 (5) [$C_8H_7O_2^+$], 149 (5) [$C_9H_9O_2^+$], 177 (100) [$M^+ - C_3H_7$], 220 (27) [M^+]. Odor: Marine, ozone, aldehydic. Odor threshold: 1.65 ng/L air.

7-Allylbenzo[*b*][1,4]dioxepin-3-one (27): LiCl (292 g, 6.89 mol) was added to a solution of eugenol (354 mL, 2.30 mmol) in DMF (3.7 L), and the mixture was refluxed for 44 h, with additional portions of LiCl (292 g, 6.89 mol) being added after 4 h, 22 h and 29 h. The reaction mixture was allowed to cool down to room temp., and diluted with toluene (2 L). The formed precipitate was filtered off and washed with toluene, the washings were combined with the organic solution and concentrated in a rotary evaporator. Silica-gel FC (Et_2O/pentane, 1:1, R_f = 0.37) provided 4-allylpyrocatechol (173 g, 50%).

Under an atmosphere of N_2, 95% NaOMe (12.8 g, 225 mmol) was added with stirring to a solution of 4-allylpyrocatechol (16.8 g, 112 mmol) in MeOH (250 mL), followed by methyl bromoacetate (21 mL, 225 mmol). After heating to reflux for 8 h, another portion of methyl bromoacetate (21 mL, 225 mmol) was added, and after further 4 h an additional quantity of 95% NaOMe (12.8 g, 225 mmol) and methyl bromoacetate (21 mL, 225 mmol). After another 4 h of stirring at reflux, the reaction mixture was allowed to cool to room temp. and Et_2O (500 mL) was added. The formed precipitate was filtered off, the filtrate concentrated in a rotary evaporator, and the resulting residue taken up in Et_2O/water/satd. aq. NH_4Cl (1:1:1). The organic layer was separated, the aqueous one extracted with Et_2O (3 × 200 mL), and the combined organic extracts were dried (Na_2SO_4). The solvent was evaporated in a rotary evaporator, and the resulting residue purified by FC (Et_2O/pentane, 1:1, R_f = 0.35) on silica gel to afford methyl 4-allyl-2-(ethoxycarbonylmethoxy)phenoxyacetate (21.4 g, 65%).

A solution of methyl 4-allyl-2-(ethoxycarbonylmethoxy)phenoxyacetate (69.0 g, 234 mmol) in THF (500 mL) was added dropwise with stirring to a suspension of NaH (12.0 g, 500 mmol) in THF (500 mL), and the resulting mixture was refluxed for 20 h. After cooling down, the reaction mixture was poured into ice/water (1:1, 1.5 L) and by addition of 2 N aq. HCl pH 2 was adjusted. The product was extracted with Et_2O (3 × 2 L), and the combined organic solutions were dried (Na_2SO_4). After evaporation of the solvent in a rotary evaporator, the resulting residue was dissolved in EtOH (400 mL). Then 2 N aq. HCl (400 mL) was added, and the reaction mixture was heated to reflux for 20 h, prior to pouring into ice/water (1:1, 1.5 L) and extraction of the product with Et_2O (4 × 1.5 L). The combined organic extracts were washed with water (1 L) and brine (100 mL), dried (Na_2SO_4) and concentrated in a rotary evaporator. Silica-gel FC (pentane/Et_2O, 4:1, R_f = 0.37) of the resulting residue provided 7-allylbenzo[*b*][1,4]dioxepin-3-one (**27**, 20.0 g, 42%) as colorless odoriferous liquid. IR (ATR): $\tilde{\nu}$ = 1502/1581/1436/1639 cm^{-1} (ν C=C, Ar), 1742 cm^{-1} (ν C=O), 1267/1305 cm^{-1} (ν ring), 1051 cm^{-1} (ν C−O−C). ^1H NMR ($CDCl_3$): δ = 3.30 (d, *J* = 6.8 Hz, 2 H, 1′-H_2), 4.67/4.69 (2s, 2-,4-H_2), 5.05−5.10 (m, 2 H, 3′-H_2), 5.92 (m_c, 1 H, 2′-H), 6.77−6.93 (m, 3 H, 6-,8-,9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 39.2 (t, C-1′), 75.4/75.6 (2t, C-2,-4), 116.0 (t, C-3′), 120.6/120.7 (2d, C-6,-9), 123.7 (d, C-8), 135.9 (s, C-7), 136.9 (d, C-2′), 146.5 (s, C-9a), 148.0 (s, C-5a), 204.6 (s, C-3) ppm. MS (EI): *m*/*z* (%) = 91 (97) [$C_7H_7^+$], 120 (25) [$C_7H_4O_2^+$], 161 (13) [$M^+ - C_2H_3O$], 175 (6) [$M^+ - CHO$], 204 (100) [M^+]. $C_{12}H_{12}O_3$ (204.2): calcd. C 70.57, H 5.92; found C 70.59, H 5.81. Odor: Linear, very intense, marine-floral note, reminiscent of O_3, water-melons and fatty aldehydes. Odor threshold: 0.051 ng/L air.

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[1] J. J. Beereboom, D. P. Cameron, C. R. Stephens (Pfizer), US 3647479, Prior, October 28, 1969, [*Chem. Abstr.* **1972**, *76*, 152326; AN **1972**: 152326].
[2] P. Kraft, J. A. Bajgrowicz, C. Denis, G. Fráter, *Angew. Chem.* **2000**, *112*, 3106−3138; *Angew. Chem. Int. Ed.* **2000**, *39*, 2980−3010.
[3] P. J. Teisseire, *Chemistry of Fragrant Substances*, VCH Publishers, New York, **1994**, pp. 333−358; (original edition in French: P. J. Teisseire), *Chimie des substances odorantes*, Technique et Documentation − Lavoisier, Paris, **1991**, pp. 359−386.
[4] F.-H. Marquardt, *Helv. Chim. Acta* **1965**, *7*, 1476−1485.
[5] E. N. Alesso, D. G. Tombari, G. Y. Moltrasio Iglesias, J. M. Aguirre, *Can. J. Chem.* **1987**, *65*, 2568−2574.
[6] P. Deslongchamps, A. Bélanger, D. J. J. Berney, H.-J. Borschberg, R. Brosseau, A. Doutheau, R. Durand, H. Katayama, R. Lapalme, D. M. Leturc, C.-C. Liao, F.-N. MacLachlan, J.-P. Maffrand, F. Marazza, R. Martino, C. Moreau, L. Ruest, L. Saint-Laurent, R. Saintonge, P. Soucy, *Can. J. Chem.* **1990**, *68*, 127−152.

[7] M. E. Jung, M. A. Lyster, *J. Org. Chem.* **1977**, *42*, 3761−3764.
[8] G. A. Olah, S. C. Narang, B. G. Balaram Gupta, R. Malhotra, *J. Org. Chem.* **1979**, *44*, 1247−1251.
[9] W. A. Ayer, P. P. Singer, *Phytochemistry* **1980**, *19*, 2717−2721.
[10] J. P. Schirmann, A. Isard, F. Weiss, *Tetrahedron* **1968**, *24*, 6475−6483.
[11] F. Nerdel, M. Mamluk, P. Weyerstahl, *Justus Liebigs Ann. Chem.* **1970**, *736*, 75−87.
[12] F. Nerdel, A. Heymons, H. Gansau, *Justus Liebigs Ann. Chem.* **1958**, *91*, 944−948.
[13] F. Nerdel, A. Heymons, H. Croon, *Justus Liebigs Ann. Chem.* **1958**, *91*, 938−943.
[14] P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936−3938.
[15] S. R. Schow, J. D. Bloom, A. S. Thompson, K. N. Winzenberg, A. B. Smith, III, *J. Am. Chem. Soc.* **1986**, *108*, 2662−2674.
[16] A. M. Bernard, M. R. Ghiani, P. P. Piras, A. Rivoldini, *Synthesis* **1989**, 287−289.
[17] P. Kraft (Givaudan SA), EP 1136481 B1, Prior. March 23, **2000** [*Chem. Abstr.* **2001**, *135*, 262044; AN **2001**: 709739].
[18] [18a] H. Boelens, *Cosmetics and Perfumery* **1974**, *70*, 72−74 and 76−78. [18b] W. Sturm, *Parfuem. Kosmet.* **1974**, *55*, 351−355.
[19] P. Kraft, W. Eichenberger, G. Fráter, *Eur. J. Org. Chem.* **1999**, 2781−2785.
[20] A. M. Bernard, M. R. Ghiani, P. P. Piras, A. Rivoldini, *Synthesis* **1989**, 287−289.
[21] J.-M. Gaudin, P. A. Blanc (Firmenich SA), EP 902024 A1, Prior. September 9, **1997** [*Chem. Abstr.* **1999**, *130*, 227560; AN **1999**:193933].
[22] Accelrys Catalyst software; http://www.accelrys.com/catalyst/
[23] N. Neuner-Jehle, F. Etzweiler, in *Perfumes: Art, Science, and Technology*, (Eds.: P. M. Müller, D. Lamparsky), Elsevier Science Publishers, Essex, **1991**, pp. 153−212.
[24] A. Dravnieks, A. O'Donnell, *J. Agr. Food Chem.* **1971**, *19*, 1049−1056.

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