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Structure–Activity Relationships in the Domain of Odorants Having Marine Notes[‡]

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Dedicated with best wishes to Dr. Roger Snowden on the occasion of his 65th birthday

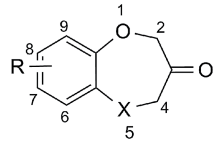
Keywords: Oxygen heterocycles / Structure–activity relationships / Fragrances / Olfactory properties

Continuing our investigations into marine note odorants, we herein describe several new scaffolds. Among them, 2,3-dihydrobenzofuran-2-carbaldehyde is particularly interesting. The results demonstrate that the seven-membered ring with a ketone functional group of the Calone 1951® family can be replaced by a five-membered ring carrying an aldehyde function. In addition, this work has allowed us to discover the valuable 2-methoxy-4-methylphenyl methyl carbonate (**20b**), which is very close to vanillin, and 2-methoxy-2,4-dimethyl-1,3-benzodioxole (**29d**), which belongs to the isoeugenol/dihydroeugenol olfactive family.

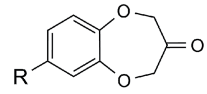
Introduction

Today marine odorants have an important place in the palette of modern perfumers. The good olfactory properties of 2*H*-1,5-benzodioxepin-3(4*H*)-ones (**1**) and 4,5-dihydro-1-benzoxepin-3(2*H*)-ones (**2**), discovered in 1966 by Beereboom et al. of Pfizer,[1] are undeniably the starting point of this story, and for 30 years (1970–2000) Calone 1951® (**1a**) was the only compound commercialized in this series (Figure 1). As mentioned by Hügel and co-workers,[2] Calone 1951® has been used in many perfumes, such as *New West for Her* (Aramis, 1990), *Escape for Her* (C. Klein, 1991), *L'eau d'Issey pour homme* (I. Miyake, 1994), *Polo Sport for Women* (R. Lauren, 1996), and *Cool Water for Women* (Davidoff, 1997), increasing the popularity of this trend in both men's and women's perfumes.

This domain was later revisited,[2–11] and now compounds such as Transluzone (**1b**), Aldolone® (**1c**), and Azurone® (**1d**) are produced on a ton scale by Firmenich and Givaudan, and used in fine fragrance as well as in body- and home-care products (e.g., shower products, air fresheners, and powder detergents).



1 2*H*-1,5-Benzodioxepin-3(4*H*)-ones (X = O)
2 4,5-Dihydro-1-benzoxepin-3(2*H*)-ones (X = CH_2)



1a R = Me, *Calone 1951*® (Pfizer)
1b R = *tert*-Bu, *Transluzone* (Firmenich)
1c R = Pr, *Aldolone*® (Firmenich)
1d R = $(CH_2)_2$-$CHMe_2$, *Azurone*® (Givaudan)

Figure 1. The Calone 1951® family.

Olfactory receptors were discovered by Buck and Axel,[12–14] but despite this important breakthrough, the mechanisms of odorant receptor interaction are yet to be understood. Predicting the odor properties of a new molecule by rational design remains challenging.[15,16] Nevertheless, the best solution to date for rationalizing the activity of odorants is the use of an olfactophore model (which corresponds to the pharmacophore in drug design). Having established the chemical space occupied by the active ligand, the olfactophore, a 3D combination of structural features, allows the generation of new candidate molecules without the benefit of the receptor's structure. For Calone 1951®, four structural features can be identified (Figure 2).

[‡] Part 2. Part 1: J. M. Gaudin, O. Nikolaenko, J. Y. de Saint Laumer, B. Winter, P. A. Blanc, *Helv. Chim. Acta* **2007**, *90*, 1245–1265.

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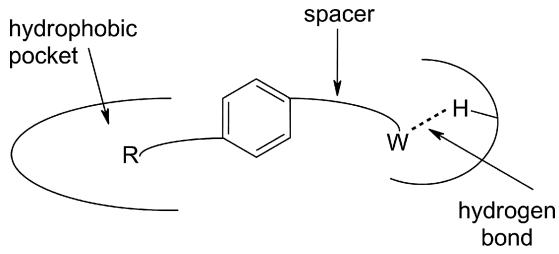


Figure 2. Structural key elements of the Calone 1951® family.

1. The hydrophobic group: The presence of an alkyl chain on the benzene ring is essential for the marine activity of the compound. Previous analyses[6,10] have shown that positions 7 and 8 (Figure 1) are the most favorable, whereas the absence of substitution decreases the intensity and leads to a different odor. The size of the alkyl substituent may vary from a methyl group to an optimal size of between C_3 and C_6.

2. The aromatic ring: This ring is present in almost all compounds having a marine odor. A beneficial interaction with the receptor is a possibility. The ring could, however, also be considered a spacer because a molecule such as Maritima® **4** (Figure 3) has a similar ozone odor but no benzene ring.

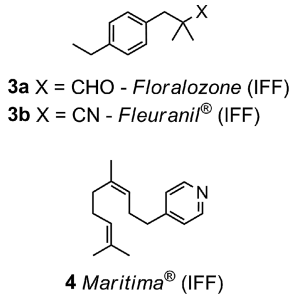


Figure 3. Typical compounds with marine-watery olfactory notes.

3. The carbonyl group: This functional group is likely involved as a hydrogen-bond acceptor in the interaction with the olfactory receptor.

4. The spacer: The spacer lies between the aromatic ring and the hydrogen-bond acceptor function.

In this context, we were interested in better understanding the role of the carbonyl group in the quality and intensity of the odor. We have good reason to believe that other functional groups, for example, aldehyde, ester, formate, methoxy, or nitrile, could be valid alternatives.

Good examples of this assessment are illustrated in Figure 3. Compounds such as Floralozone (**3a**) and Fleuranil® (**3b**) are both known to possess an ozone-watery profile even though their odors are less characteristic than those of the benzodioxepinone series.[17] This is sometimes also the case for *para*-substituted pyridines, as illustrated by Maritima® (**4**).

To evaluate the odors of these compounds, we have thus synthesized a series of molecules **5**–**7** (Figure 4) in which W represents various hydrogen-bond acceptors (the main topic of two recent studies published by Hügel and co-workers[7] and Kozlov et al.[11]). Modifying the spacer between the aromatic ring and the functional group could also provide interesting new perspectives. The position and orientation of the carbonyl group are imposed by the geometry of the seven-membered ring in the benzodioxepinone series.[6,10] Attempting to introduce more flexibility by opening the seven-membered ring, such as in **6** (Figure 4), or by replacing it with a five-membered ring, such as in **7** (Figure 4), to preserve the marine-ozone character of the compounds is also extensively described herein.

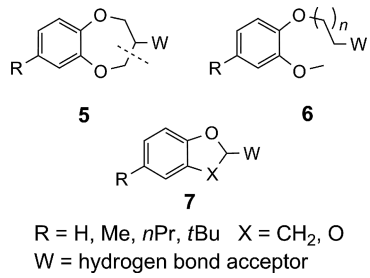


Figure 4. Targeted skeletons **5**–**7**.

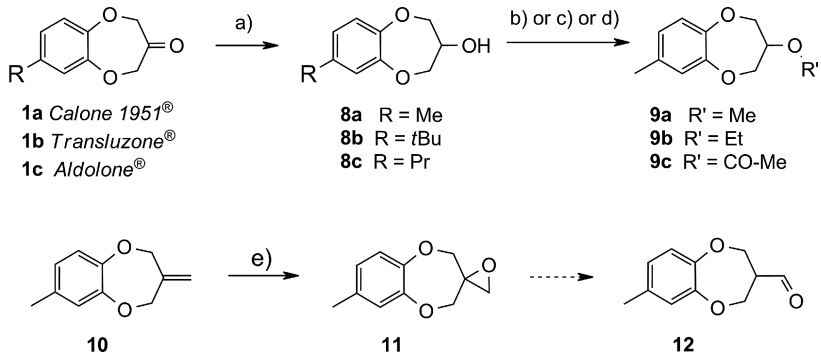
Results and Discussion

Synthesis

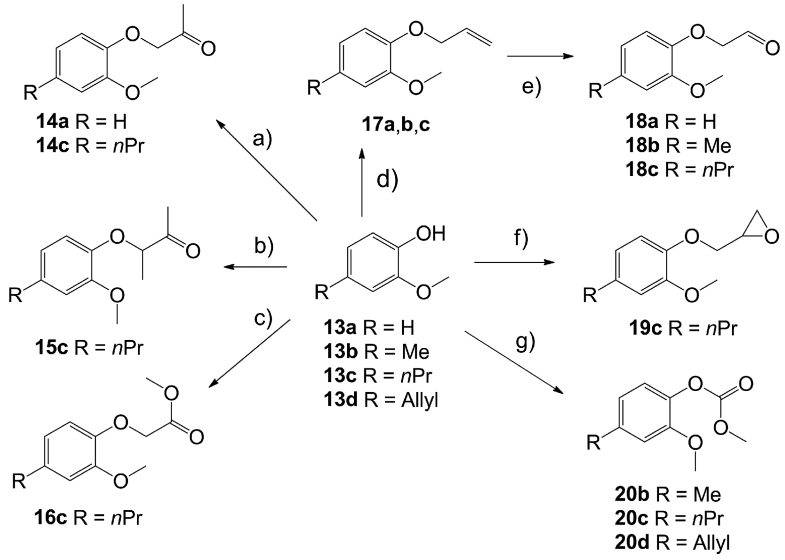
The carbonyl group of Calone 1951® (**1a**), Transluzone (**1b**), and Aldolone® (**1c**) was easily reduced by using $LiAlH_4$ to give the corresponding alcohols **8a**–**c** in very high yields[7] (Scheme 1). The alcohol **8a** was etherified or acetylated to efficiently give **9a**–**c**.[7,18] In contrast, the direct homologation of Calone 1951® to aldehyde **12** by the Corey–Chaykovsky reaction was unsuccessful in our hands. Starting from **10**,[19,20] classical epoxidation gave the expected product **11**[21] in modest yield. The isomerization of **11**, which is, surprisingly, extremely stable, to aldehyde **12** using a variety of Brønsted or Lewis acids was unsuccessful.

To synthesize compound **6** (Figure 4), we logically started from four commercial phenols: guaiacol (**13a**), 2-methoxy-4-methylphenol (**13b**), dihydroeugenol (**13c**), and eugenol (**13d**; Scheme 2). Classical reactions with chloroacetone, 3-chlorobutan-2-one, and methyl chloroacetate gave the corresponding products **14**–**16** in very good yields, while allylation using allyl bromide followed by ozonolysis gave the aldehydes **18a**–**c**. The epoxide **19c** was obtained directly by using epibromohydrin, and finally the carbonates **20b**–**d** were synthesized by reaction with methyl chloroformate.

The next targeted skeleton was 2,3-dihydro-1-benzofuran-2-carbaldehyde **25** (Scheme 3 and Figure 4, **7**: X = CH_2, W = CHO). An efficient approach to its synthesis is already known from readily accessible *ortho*-substituted phenol **23** by an epoxidation/cyclization reaction. This key transformation is possible in two successive steps[22] or in "one pot" by using either the *tert*-butyl hydroperoxide (TBHP)/[$VO(acac)_2$] system in dichloromethane in the presence of trifluoroacetic acid,[23] or with the classical *m*-



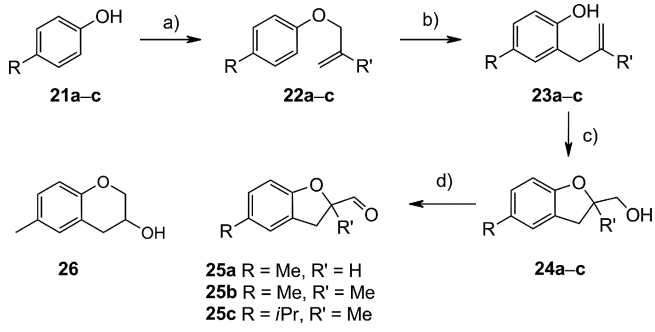
Scheme 1. Reagents and conditions: a) 0.5 equiv. $LiAlH_4$, Et_2O, room temp., 1 h; b) 1.2 equiv. NaH, 1.5 equiv. MeI, DMF (89%); c) 1.2 equiv. NaH, 1.5 equiv. EtI, DMF (86%); d) 1.2 equiv. Ac_2O, pyridine, 100 °C, 2 h (87%); e) 1.3 equiv. *m*-CPBA, CH_2Cl_2, 30 °C, 2 d (29%).



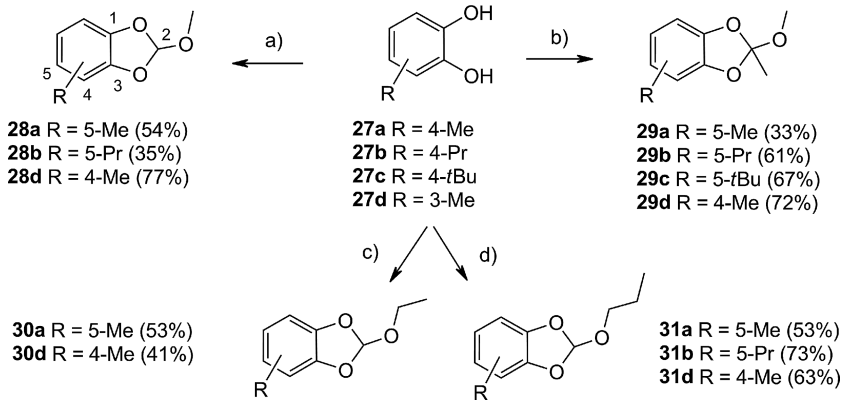
Scheme 2. Reagents and conditions: a) 1.2 equiv. chloroacetone, 1.2 equiv. K_2CO_3, acetone, reflux; b) 1.2 equiv. 3-chlorobutan-2-one, 1.2 equiv. K_2CO_3, acetone, reflux; c) 1.2 equiv. methyl chloroacetate, 1.2 equiv. K_2CO_3, acetone, reflux; d) 1.2 equiv. allyl bromide, 1.2 equiv. K_2CO_3, acetone, reflux; e) ozone, 0 °C, MeOH/CH_2Cl_2; f) 1.2 equiv. epibromohydrin, 1.2 equiv. K_2CO_3, acetone, reflux; g) 1.27 equiv. methyl chloroformate, 1.5 equiv. pyridine, 0.02 equiv. DMAP, CH_2Cl_2, room temp., 3 h.

chloroperbenzoic acid.[24] We chose to use the inexpensive and more industrial peracetic acid to perform this reaction (60–78% yields). It should also be noted that **24a** has been described by Satyanarayana et al.,[24] but with the incorrect structure **26**. Oxidation of the alcohols **24a**–**c** thus obtained was more difficult than expected. A number of well-established methods, for example, Jones, Swern, and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) oxidations, gave poor yields (10–25%) of the desired aldehydes **25a**–**c**. The 2-iodoxybenzoic acid (IBX)/DMSO method used by Ramadas and Krupadanam[23] would probably be preferable, but these conditions were never attempted.

The last targeted skeleton was 2-alkoxy-1,3-benzodioxole (Scheme 4 and Figure 4, **7**: X = O, W = OR). Compounds



Scheme 3. Reagents and conditions: a) K_2CO_3, allyl or methallyl bromide, acetone, reflux (60–78%); b) *N*,*N*-dimethylaniline, 200 °C, 48 h (95–94%); c) AcO_2H, toluene, 20 °C; d) 1.05 equiv. NaOCl, 0.02 equiv. TEMPO, 0.02 equiv. NaBr, $NaHCO_3$, AcOEt, 25 °C.



Scheme 4. Reagents and conditions: a) 5 equiv. $HC(OMe)_3$, cat. Amberlyst® 15, toluene, reflux; b) 5 equiv. $MeC(OMe)_3$, cat. Amberlyst® 15, toluene, reflux; c) 5 equiv. $HC(OEt)_3$, Amberlyst® 15, toluene, reflux; d) 5 equiv. $HC(OPr)_3$, cat. Amberlyst® 15, toluene, reflux.

28–**31** were readily accessible in one step in moderate yields (33–77%) from catechol **27** using the corresponding orthoester.[25–27]

Olfactory Evaluations

Based on the structure of Calone 1951®, an olfactophore model has been designed with the program Phase®.[28] The olfactophore model comprises the three key elements of Calone 1951®: A hydrophobic part (green), a benzenic ring (orange), and a hydrogen-bond acceptor (red). The superimposition on the olfactophore model of various molecules described as being similar to the Calone 1951® odor is presented in Figure 5.

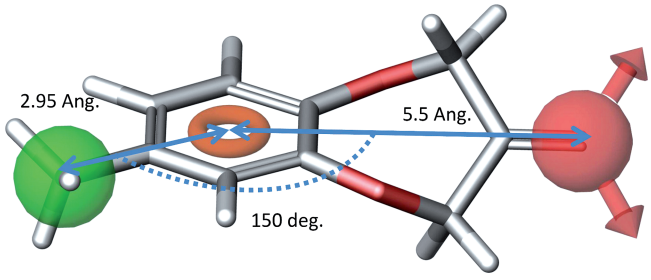


Figure 5. Olfactophore model proposed for the marine-ozone odor based on Calone 1951®. Hydrophobic part (green), benzenic ring (orange) and hydrogen-bond acceptor (red).

This model is closely related to a previous olfactophore model of the Lilial® analogues published by Winter and coworkers in 2004.[29] The main difference is the position of the hydrogen-bond acceptor element. In the present model, this olfactophore element is placed in the plane defined by the benzene ring. In the Lilial® model, the hydrogen-bond acceptor was not in the plane (2.5 Å difference). A close structural relationship exists between these two odor families (Calone® and Lilial®). For example, it is interesting to observe that Calone 1951® (carbonyl group in the benzenic plane for the preferred conformation) is described as strongly marine and ozone, whereas its carba-analogue, in which the two cyclic oxygen atoms are replaced by carbon atoms (carbonyl out of the benzenic plane for preferred conformation), is described as a Lilial®-like odor. This analysis was reported in our previous paper.[6]

The generation of the olfactophore model of Calone 1951® was performed by using the program Phase.[28] The energy penalty for superimposition on the olfactophore model is less than 3.5 kcal/mol (OPLS-2005 force field), except for Floralozone® (5.5 kcal/mol). The energies were calculated by using Macromodel[30] with constraints on the atoms involved in the olfactophore model. A large number of the molecules investigated in this work can be superimposed on the main structural features of Calone 1951®. A few of them are presented in Figure 6. For example, in mol-

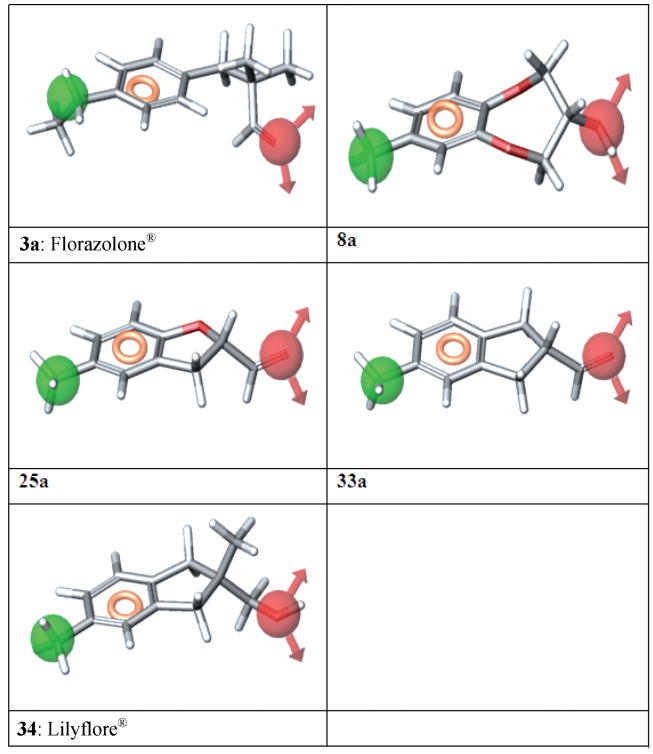
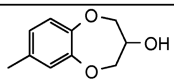
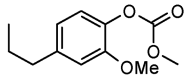
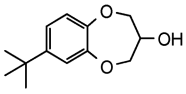
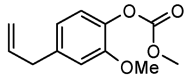
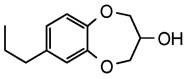
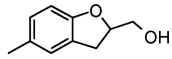
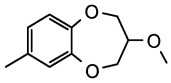
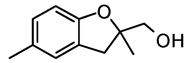
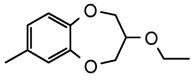
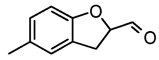
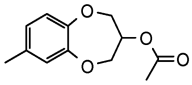
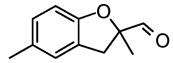
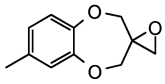
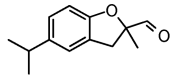
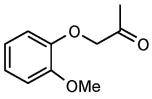
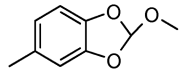
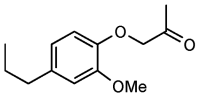
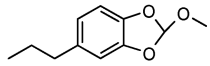
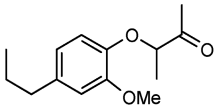
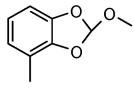
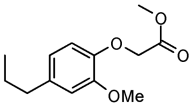
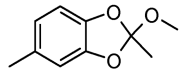
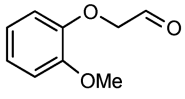
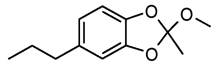
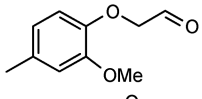
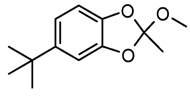
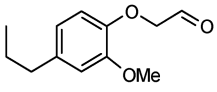
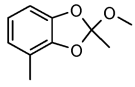
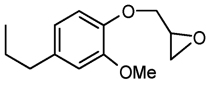
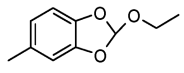
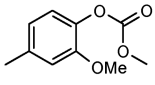
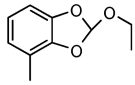
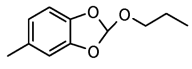
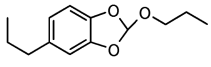
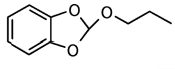


Figure 6. Superimposition of representative molecules on the olfactophore model proposed for the marine-ozone odor.

ecule **8a**, the hydroxy group that replaces the carbonyl group of Calone 1951® can play the same role of hydrogen-bond acceptor in the ligand–receptor interaction. The results of the olfactory evaluations are shown in Table 1. As a first comment, we fully confirm the results obtained by Hügel and co-workers[7] for alcohol **8a** and the correspond-

Table 1. Olfactory profiles.

Substance	Olfactory profile[a]	Substance	Olfactory profile[a]
8a 	marine, ozone, aldehydic, floral, but weak	**20c** 	spicy, phenolic, clove, slightly cresolic
8b 	fruity, without character, very weak	**20d** 	floral, white flowers, ginger, eugenol, very nice, natural
8c 	aldehydic, Farenal, ozone, but much weaker than Aldolone®	**24a** 	powdery, mimosa, heliotropine, but also metallic, aggressive
9a 	fruity, phenolic, fresh, aldehydic; not very powerful	**24b** 	coumarin, lactonic but weak
9b 	phenolic, chemical, bad	**25a** 	aldehydic, green, marine, tenacious, powerful
9c 	without character, vaguely fruity	**25b** 	phenolic, crab, oakmoss, slightly watery
11 	shellfish, algae, fresh, but not very powerful	**25c** 	watermelon, aldehydic, Aldolone®, Cyclosal, green, oyster, ozone, watery
14a 	fruity, estery, cresolic	**28a** 	solvent, bitter, almond, plastic, burnt, toluene
14c 	medicinal, hospital, weak	**28b** 	phenolic, leather, ink, orange flowers, weak
15c 	eugenol, gingerbread, cookie, guaiacol, buttery, balsamic, nice	**28d** 	shoe, polish, phenolic
16c 	whisky, smoky, woody, earthy	**29a** 	cinnamon, spicy, burnt, hot, brakes, guaiacol
18a 	green, cresolic	**29b** 	phenolic, clove oil, anisic, smoky, leather, guaiacol, eugenol.
18b 	spicy, isoeugenol, short-circuit, guaiacol, vanillic	**29c** 	phenolic, cresolic, ink
18c 	perspiration, aldehydic, slightly aldehyde muguet, vanillic, slightly metallic, nice, too weak	**29d** 	smoky, ash, tar, eugenol, isoeugenol, vetiver, geonol, saffron, lard
19c 	without character, plastic, burnt	**30a** 	terpenic, fruity, cocoa, butter, smoky
20b 	vanillin, guaiacol, isoeugenol, natural	**30d** 	terpenic, parsley, polish, metallic, phenolic
		31a 	phenolic, chemical, liquorice, cresolic
		31b 	phenolic, aldehydic, weak
		31d 	terpenic, phenolic, weak

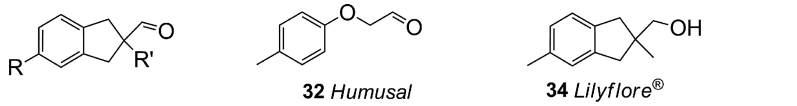
ing acetate **9c**. Alcohol **8a** fits our model (Figure 5) and has retained the marine-ozone character, but is much weaker than Calone 1951®. Moreover, we were pleased to note that the descriptors given for **8a** by Firmenich's perfumers (who were unaware of the literature description) were word-for-word identical to those used by Hügel et al. Alcohols **8b** and **8c** are also very weak, probably due to their much lower volatility compared with the parent ketones (by EPI calculations,[31] the volatility of Calone 1951® is more than 20 times higher than that of the corresponding alcohol). Acetate **9c** has completely lost the marine note. In this case, the carbonyl oxygen cannot superimpose on our model, and the sp^3 oxygen is probably too weak a hydrogen-bond acceptor.[32] Trying to replace the carbonyl group of the benzodioxepinone system with an ether functional group also has a negative effect on the quality and intensity of the odor. Compounds **9a** and **9b** are weak and have totally lost the marine-ozone-watery character. These compounds, which should in theory fit our model, may lose their activity because of the weaker ability of ethers to act as hydrogen-bond acceptors.[32] The odor of epoxide **11** (which also fits the model) is reminiscent of the fresh marine note with shellfish and algae aspects, but is not powerful. These results round off the series described by Hügel and coworkers[7] concerning Calone 1951® analogues with a substituent at position 3 of the benzodioxepine ring, and confirm that the carbonyl group is definitely the best functional group for this skeleton.

As mentioned in the introduction, allowing a degree of freedom by opening the seven-membered ring was our next idea. Doing that could allow the electron-withdrawing group to adopt the best position in space. Floralozone® (**3a**), in which the seven-membered ring is replaced by an open chain, can be superimposed on the model and still keep the ozone-watery profile. Unfortunately, the proposed new compounds **14**–**16**, **18**, and **19**, all of which fit our model, do not possess the ozone-marine odor (Table 1). A possible explanation for these observations could be the negative interaction of the free methoxy group (always present in this series) with the olfactive receptor. These observations might also indicate that the two oxygen atoms on the aromatic ring of the Calone 1951® analogues are more important for their conformation than for their electronic effect. The carbonates **20b**–**d** clearly cannot be superimposed on the model (the carbonyl being too close to the aromatic ring) and do not possess the ozone-marine odor. However, 2-methoxy-4-methylphenyl methyl carbonate (**20b**) has a particularly interesting odor that is very close to vanillin. Moreover, this compound is much more stable than vanillin and ethyl vanillin, which are well known to sometimes provoke undesired strong brown colorations. We are convinced that **20b** could sometimes be useful as a vanillin replacement in perfumery.[33]

The next question was: Is it possible to replace the seven-membered ring of the benzodioxepine and preserve the targeted marine-ozone-watery character? When the keto seven-membered ring is replaced by the combination of aldehyde five-membered ring, the superimposition on the model is preserved, as it is in structure **31a**. This is also true when the five-membered ring incorporates just one oxygen atom, as in structures **25a**–**c**.

Compound **25a**, having a methyl on the aromatic ring, has a pleasant aldehydic, green, marine odor and is particularly substantive and powerful. The introduction of a methyl group at the α position to the aldehyde is clearly unfavorable, compound **25b** having only a slightly watery odor. It should be noted that compounds **25a**–**c**, as well as **18b**, can be regarded as Humusal **32** analogues, which also fit our model and possess a fresh, marine, sea breeze character (Figure 7).

Increasing the size of the substituent on the aromatic ring leads to a compound that is particularly appreciated by perfumers. 2,3-Dihydro-5-isopropyl-1-benzofuran-2-carbaldehyde **25c** has very nice watermelon, aldehydic, green, oyster, and ozone notes. Of interest is the fact that the odors of the corresponding carba-analogues **33a**–**d** (Figure 7), which have a similar conformation, are in general more aldehydic, green, muguet and less ozone-marine.[29,34] It seems that here we are at the crossroads between lily-of-the-valley and marine-ozone-watery ingredients, which also means that the receptor for both should not be very different. All of these compounds (**25a**–**c** and **33a**–**d**) can adopt a conformation (with an energy penalty below 1 kcal) in which the carbonyl is slightly out of the plane of the benzenic ring (1.2 Å) and compatible with both models (our ozone-watery model and the previous Lilial® model[29]). Consequently, they can potentially interact with both receptors and have either the ozone-watery or Lilial odor, depending on the most favorable interaction. Again, concerning the carba-analogues, the alcohols could themselves have very good odoriferous properties,[34–36] such as compound **34**, named Lilyflore® and commercialized by Firmenich (Figure 7). Although Lilyflore® retains and magnifies the Lilial®, hydroxycitronellal, muguet notes of the parent alde-



32 *Humusal* **34** *Lilyflore®*

33a R = Me, R' = H (aldehydic, floral-muguet, soapy, fatty, slightly lemon)
33b R = R' = Me (aldehydic, green, Bourgeonal®, slightly fatty)
33c R = *i*Pr, R' = H (aldehydic, green, citrus, ozone, cyclamen aldehyde, metallic, Bourgeonal®)
33d R = *i*Pr, R' = Me (aldehydic, metallic, ozone, green, citrus)

Figure 7. Compounds **32**–**34**.

hyde, unfortunately this is not the case for alcohols **24a**,**b** with powdery, mimosa, heliotropine notes for **24a** and a curiously coumarin, lactonic odor for **24b**.

2-Alkoxy-1,3-benzodioxoles **28**–**31** cannot be superimposed on the model because the distance is too short between the oxygen atoms and the benzenic ring. Their odors are quite different from general descriptors, such as burnt, smoky, phenolic, and leather, and absolutely not ozone-watery. Increasing the length of the alkoxy chain in **30** and **31** gave compounds that are more terpenic, and even slightly aldehydic, but weaker. The presence of the methyl group at position 2 is beneficial, leading to compounds **29a**–**d** having nice guaiacol, eugenol notes. Compound **29d** is particularly interesting, reminiscent of isoeugenol and dihydroeugenol, close to cade oil, with top notes more smoky-guaiacol.

Conclusions

This report describes the continuation of our investigations concerning marine note odorants. We have shown that the seven-membered ring of the Calone family scaffold, as suggested by our model, can be replaced by a five-membered ring with retention of both the marine-ozone-watery olfactory profile and the odor intensity. In addition, the carbonyl functional group originally present in the seven-membered ring and presumably responsible for the hydrogen bond inside the active site of the olfactory receptor can be mimicked by an aldehyde. This is the case for compounds 2,3-dihydro-5-methyl-1-benzofuran-2-carbaldehyde (**25a**) and 5-isopropyl-2-methyl-2,3-dihydro-1-benzofuran-2-carbaldehyde (**25c**). The results confirm the rules already observed in our preceding work and used to design the model, but several questions remain unanswered. In particular, the need for the presence and the role of one or two oxygen atoms substituted in the aromatic ring is still confusing, and much work remains to clarify this point.

In addition, this study has allowed the unexpected discovery of two very good compounds: 2-Methoxy-4-methylphenyl methyl carbonate (**20b**), which is very close to vanillin and ethyl vanillin and is interesting as a stable substitute of these important ingredients, and 2-methoxy-2,4-dimethyl-1,3-benzodioxole (**29d**), which belongs to the isoeugenol/dihydroeugenol olfactive family.

Experimental Section

General: All reactions were performed under N_2. Gas-liquid chromatography (GLC) and prep GLC: Agilent 6890 instrument equipped with a flame ionization detector (250 °C) coupled to an Agilent Chemstation 6.03; Chrompack capillary columns DB-Wax (15 m, 0.25 mm) and DB-1 (15 m, 0.25 mm). Flash chromatography: High-quality silica gel 60 Å particle size, in prepacked cartridges from Interchim. Bulb-to-bulb distillation: Büchi GKR-50 oven; b.p. corresponds to the air temperature. NMR: Bruker WH-400, Bruker AMX-360; ^{1}H at 400 MHz and ^{13}C at 90 MHz in $CDCl_3$ when not specified; chemical shifts are in ppm relative to tetramethylsilane. MS: Varian MAT-112 spectrometer (ca. 70 eV); intensities in % relative to the base peak (100%).

(±)-7-Methyl-3,4-dihydro-2*H*-1,5-benzodioxepin-3-ol (8a): Obtained in 92% yield from **1a** following the procedure described previously.[18] ^{1}H NMR: δ = 2.24 (s, 3 H), 3.21 (d, J = 9 Hz, 1 H), 4.04 (m, 2 H), 4.23 (m, 2 H), 6.73 (dd, J = 8.0, 1.9 Hz, 1 H), 6.80 (d, J = 1.9 Hz, 1 H), 6.87 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 20.5 (q), 69.7 (d), 74.7 (t), 74.8 (t), 121.2 (d), 121.9 (d), 124.4 (d), 133.8 (s), 148.8 (s), 150.7 (s) ppm. MS: *m*/*z* (%) = 181 (11.2), 180 (100.0) $[M]^{+\cdot}$, 149 (11.7), 135 (59.8), 123 (33.9), 109 (13.8), 91 (12.9), 78 (18.6), 77 (20.9), 66 (16.7), 51 (13.5).

(±)-7-*tert*-Butyl-3,4-dihydro-2*H*-1,5-benzodioxepin-3-ol (8b): Obtained in 88% yield from **1b** following the procedure described previously.[18] ^{1}H NMR: δ = 1.26 (s, 9 H), 3.43 (d, J = 9 Hz, 1 H), 4.08 (m, 2 H), 4.21 (m, 2 H), 6.89 (d, J = 8.4 Hz, 1 H), 6.93 (dd, J = 8.4, 2.4 Hz, 1 H), 7.00 (d, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 31.3 (q), 34.2 (s), 69.7 (d), 74.6 (t), 118.4 (d), 120.5 (d), 120.7 (d), 147.2 (s), 148.3 (s), 150.2 (s) ppm. MS: *m*/*z* (%) = 223 (3.9), 222 (26.9) $[M]^{+\cdot}$, 207 (100.0), 151 (9.4), 123 (6.0), 105 (7.9), 91 (6.3), 77 (8.9), 43 (4.7).

(±)-7-Propyl-3,4-dihydro-2*H*-1,5-benzodioxepin-3-ol (8c): Obtained in 87% yield from **1c** following the procedure described previously.[18] ^{1}H NMR: δ = 0.92 (t, J = 7.3 Hz, 3 H), 1.59 (m, 2 H), 2.49 (t, J = 7.8 Hz, 2 H), 2.81 (m, 1 H), 4.05 (m, 2 H), 4.26 (m, 2 H), 6.76 (dd, J = 8.0, 2.2 Hz, 1 H), 6.83 (d, J = 2.2 Hz, 1 H), 6.91 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 13.8 (q), 24.4 (t), 37.1 (t), 69.8 (d), 74.7 (t), 74.8 (t), 121.1 (d), 121.3 (d), 123.8 (d), 138.7 (s), 148.9 (s), 150.7 (s) ppm. MS: *m*/*z* (%) = 209 (8.1), 208 (60.9) $[M]^{+\cdot}$, 179 (100.0), 135 (28.9), 123 (67.2), 105 (9.2), 91 (7.9), 77 (23.5), 57 (10.9), 51 (11.4), 43 (9.1).

(±)-3-Methoxy-7-methyl-3,4-dihydro-2*H*-1,5-benzodioxepine (9a): Obtained in 89% yield from **8a** following the procedure described previously.[18] ^{1}H NMR: δ = 2.22 (s, 3 H), 3.43 (s, 3 H), 3.75–3.82 (m, 1 H), 4.17–4.26 (m, 2 H), 4.26–4.34 (m, 2 H), 6.67 (dd, J = 8, 2 Hz, 1 H), 6.74 (d, J = 2 Hz, 1 H), 6.81 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 20.5 (q), 57.1 (q), 71.2 (t), 71.4 (t), 78.5 (d), 120.5 (d), 121.2 (d), 123.6 (d), 132.8 (s), 147.8 (s), 149.6 (s) ppm. MS: *m*/*z* (%) = 194 (100) $[M]^{+\cdot}$, 161 (6), 149 (21), 135 (67), 123 (7), 121 (10), 105 (6), 94 (10), 91 (10), 77 (18), 71 (48), 66 (15), 51 (10), 45 (10), 41 (15).

(±)-3-Ethoxy-7methyl-3,4-dihydro-2*H*-1,5-benzodioxepine (9b): Obtained in 86% yield from **8a** following the procedure described previously,[18] except with the use of iodoethane instead of iodomethane. ^{1}H NMR: δ = 1.24 (d, J = 7 Hz, 1 H), 2.23 (s, 3 H), 3.60 (d, J = 7 Hz, 2 H), 3.87–3.94 (m, 1 H), 4.20 (dt, J = 12, 5 Hz, 2 H), 4.32 (dt, J = 12, 5 Hz, 2 H), 6.67 (dd, J = 8, 2 Hz, 1 H), 6.74 (d, J = 2 Hz, 1 H), 6.81 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 15.5 (q), 20.5 (q), 65.1 (t), 71.8 (t), 72.0 (t), 76.9 (d), 120.5 (d), 121.2 (d), 123.5 (d), 132.7 (s), 147.8 (s), 149.6 (s) ppm. MS: *m*/*z* (%) = 208 (100) $[M]^{+\cdot}$, 179 (1), 161 (8), 149 (21), 135 (74), 123 (14), 121 (12), 105 (8), 94 (8), 91 (14), 85 (22), 77 (20), 66 (14), 57 (51), 51 (10), 43 (12), 41 (10).

(±)-7-Methylspiro[1,5-benzodioxepine-3,2′-oxirane] (11): A mixture of **10**[19,20] (1.0 equiv.) and *m*-CPBA (1.3 equiv.) in CH_2Cl_2 (4 mL/mmol) was stirred at 30 °C for 2 d. The mixture was diluted, extracted with 10% aq. $NaHSO_3$ soln., washed with satd. aq. $NaHCO_3$ soln. and brine, dried with $MgSO_4$, and concentrated under vacuum. Flash chromatography on silica gel with a mixture of ethyl acetate/heptane (3:97) gave the pure epoxide **11** (29% yield). ^{1}H NMR: δ = 2.25 (s, 3 H), 2.84 (s, 2 H), 4.18 (dd, J = 13, 7 Hz, 2 H), 4.26 (dd, J = 13, 7 Hz, 2 H), 6.72 (dd, J = 8, 2 Hz, 1 H), 6.78 (d, J = 2 Hz, 1 H), 6.85 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 20.5 (q), 50.8 (t), 57.9 (s), 73.6 (t), 73.8 (t), 120.8 (d), 121.4 (d), 124.0 (d), 133.3 (s), 147.4 (s), 149.3 (s) ppm. MS: *m*/*z* (%) = 192

(100) $[M]^{+\cdot}$, 176 (2), 162 (40), 161 (44), 135 (40), 123 (20), 105 (8), 94 (23), 91 (7), 77 (15), 70 (19), 66 (40), 55 (7), 51 (11).

1-(2-Methoxyphenoxy)-2-propanone (14a). General Procedure 1 (GP 1): Chloroacetone (6.23 g, 1.2 equiv.) was added dropwise to a mixture of guaiacol (7 g, 56.4 mmol) and potassium carbonate (9.3 g, 1.2 equiv.) in acetone (80 mL) over a period of 2 h whilst heating at reflux with stirring. The reaction mixture was heated at reflux overnight and cooled. Toluene (50 mL) was added and the mixture was distilled under reduced pressure to remove the acetone. The organic layer was washed twice with water, then dried with $MgSO_4$ and the toluene removed under reduced pressure to give 10.1 g of a dark-colored oil. Flash chromatography on silica gel with a mixture of ethyl acetate/heptane (5:95) gave 8.63 g of 1-(2-methoxyphenoxy)acetone (**14a**; yield: 85%). ^{1}H NMR: δ = 2.22 (s, 3 H), 3.88 (s, 3 H), 4.59 (s, 2 H), 6.78 (dd, J = 8.2, 1.5 Hz, 1 H), 6.88 (td, J = 8.1, 1.7 Hz, 1 H), 6.92 (dd, J = 8.0, 1.5 Hz, 1 H), 6.98 (m, 1 H) ppm. ^{13}C NMR: δ = 26.4 (q), 55.9 (q), 74.5 (t), 112.2 (d), 114.3 (d), 120.9 (d), 122.5 (d), 147.4 (s), 149.6 (s), 206.4 (s) ppm. MS: m/z (%) = 181 (7.9), 180 (68.0) $[M]^{+\cdot}$, 137 (48.7), 122 (100.0), 109 (11.0), 95 (14.9), 92 (28.8), 77 (67.5), 63 (19.0), 52 (27.2), 43 (45.6).

1-(2-Methoxy-4-propylphenoxy)acetone (14c): According to GP 1, obtained in 95% yield from dihydroeugenol (**13c**). ^{1}H NMR: δ = 0.93 (t, J = 7.2 Hz, 3 H), 1.61 (m, 2 H), 2.27 (s, 3 H), 2.53 (t, J = 7.2 Hz, 2 H), 3.86 (s, 3 H), 4.55 (s, 2 H), 6.68 (m, 2 H), 6.74 (d, J = 1.5 Hz, 1 H) ppm. ^{13}C NMR: δ = 13.8 (q), 24.7 (t), 26.4 (q), 37.7 (t), 55.8 (q), 74.8 (t), 112.6 (d), 114.3 (d), 120.4 (d), 137.2 (s), 145.4 (s), 149.4 (s), 206.7 (s) ppm. MS: m/z (%) = 223 (15.1), 222 (100.0) $[M]^{+\cdot}$, 193 (56.8), 179 (27.3), 165 (54.6), 164 (64.3), 137 (53.2), 135 (21.5), 123 (9.8), 119 (8.9), 105 (22.5), 91 (23.6), 77 (19.8), 43 (20.4).

(±)-3-(2-Methoxy-4-propylphenoxy)butan-2-one (15c): According to GP 1, obtained in 74% yield from dihydroeugenol (**13c**) using 1.2 equiv. of 3-chlorobuten-2-one. ^{1}H NMR: δ = 0.92 (t, J = 7.5 Hz, 3 H), 1.49 (d, J = 6.8 Hz, 3 H), 1.62 (m, 2 H), 2.25 (s, 3 H), 2.52 (t, J = 7.5 Hz, 2 H), 3.84 (s, 3 H), 4.52 (q, J = 6.8 Hz, 1 H), 6.65 (dd, J = 8.1, 1.8 Hz, 1 H), 6.73 (d, J = 8.1 Hz, 1 H), 6.73 (d, J = 1.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 13.8 (q), 17.7 (q), 24.6 (t), 24.8 (q), 37.7 (t), 55.8 (q), 81.2 (d), 112.8 (d), 116.0 (d), 120.4 (d), 137.4 (s), 145.0 (s), 149.8 (s), 210.9 (s) ppm. MS: m/z (%) = 237 (7.7), 236 (45.8) $[M]^{+\cdot}$, 193 (100.0), 178 (8.7), 165 (22.4), 164 (22.5), 137 (29.0), 105 (14.4), 91 (13.8), 77 (10.2), 43 (19.7).

Methyl (2-Methoxy-4-propylphenoxy)acetate (16c): According to GP 1, obtained in 83% yield from dihydroeugenol (**13c**) using 1.2 equiv. of methyl chloroacetate. ^{1}H NMR: δ = 0.93 (t, J = 7.5 Hz, 3 H), 1.62 (m, 2 H), 2.53 (t, J = 7.5 Hz, 2 H), 3.78 (s, 3 H), 3.87 (s, 3 H), 4.66 (s, 2 H), 6.67 (dd, J = 8.0, 2.1 Hz, 1 H), 6.72 (d, J = 2.1 Hz, 1 H), 6.76 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 13.8 (q), 24.6 (t), 37.7 (t), 52.1 (q), 55.8 (q), 66.8 (t), 112.6 (d), 114.7 (d), 120.3 (d), 137.3 (s), 145.3 (s), 149.5 (s), 169.7 (s) ppm. MS: m/z (%) = 239 (9.2), 238 (61.5) $[M]^{+\cdot}$, 209 (100.0), 165 (37.7), 151 (12.4), 135 (9.1), 105 (14.4), 95 (13.9), 91 (14.2), 77 (16.2), 45 (17.0).

(2-Methoxyphenoxy)acetaldehyde (18a). General Procedure 2 (GP 2): According to GP 1, the allyl intermediate 1-(allyloxy)-2-methoxybenzene (**17a**) was obtained in 98% yield as a crude oil from guaiacol (**13a**) by using 1.2 equiv. of allyl bromide. Crude **17a** (7 g, 42.7 mol) in dichloromethane (200 mL) and methanol (40 mL) at 0 °C was ozonolyzed (ozone 3.2 g/h). The reaction was purged for several minutes with pure oxygen, warmed to room temperature, and then agitated overnight with 2 g of palladium on charcoal under 1 atm of hydrogen. The reaction mixture was filtered and concentrated under vacuum to give 5.3 g of the crude product. Flash chromatography on silica gel with a mixture of diethyl ether/pentane (20:80) gave 3.83 g of (2-methoxyphenoxy)acetaldehyde (**18a**; yield: 54%). ^{1}H NMR: δ = 3.89 (s, 3 H), 4.59 (d, J = 1.1 Hz, 2 H), 6.80–7.05 (m, 4 H), 9.90 (t, J = 1.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 55.8 (q), 74.3 (t), 112.3 (d), 115.0 (d), 120.9 (d), 123.0 (d), 147.3 (s), 149.7 (s), 200.2 (d) ppm. MS: m/z (%) = 167 (8.2), 166 (81.9) $[M]^{+\cdot}$, 137 (34.7), 122 (99.3), 109 (12.2), 95 (33.0), 92 (37.2), 77 (100.0), 65 (27.4), 63 (22.4), 52 (31.5).

(2-Methoxy-4-methylphenoxy)acetaldehyde (18b): According to GP 2, obtained in 51% yield from 2-methoxy-4-methylphenol (**13b**). ^{1}H NMR: δ = 2.30 (s, 3 H), 3.85 (s, 3 H), 4.55 (d, J = 1.4 Hz, 2 H), 6.60–6.75 (m, 3 H), 9.88 (t, J = 1.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 21.1 (q), 55.7 (q), 74.6 (t), 113.2 (d), 115.1 (d), 121.0 (d), 132.8 (s), 145.1 (s), 149.4 (s), 200.5 (d) ppm. MS: m/z (%) = 181 (12.0), 180 (100.0) $[M]^{+\cdot}$, 151 (16.7), 136 (66.0), 122 (13.3), 109 (24.6), 106 (14.8), 91 (52.8), 77 (25.5), 65 (17.0), 51 (9.4).

(2-Methoxy-4-propylphenoxy)acetaldehyde (18c): According to GP 2, obtained in 53% yield from dihydroeugenol (**13c**). ^{1}H NMR: δ = 0.93 (t, J = 7.3 Hz, 3 H), 1.62 (m, 2 H), 2.53 (t, J = 7.3 Hz, 2 H), 3.86 (s, 3 H), 4.54 (d, J = 1.0 Hz, 2 H), 6.68 (dd, J = 8.0, 1.9 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.74 (d, J = 1.9 Hz, 1 H), 9.88 (t, J = 1.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 13.8 (q), 24.7 (t), 37.7 (t), 55.7 (q), 74.5 (t), 112.6 (d), 115.0 (d), 120.4 (d), 137.7 (s), 145.3 (s), 149.5 (s), 200.5 (d) ppm. MS: m/z (%) = 209 (13.7), 208 (100.0) $[M]^{+\cdot}$, 179 (58.1), 165 (66.2), 151 (23.7), 137 (30.6), 135 (22.2), 121 (57.2), 105 (31.5), 95 (27.6), 91 (35.0), 77 (37.5), 65 (18.7), 51 (18.4), 43 (22.5).

(±)-2-[(2-Methoxy-4-propylphenoxy)methyl]oxirane (19c): According to GP 1, obtained in 43% yield from dihydroeugenol (**13c**) BY using 1.2 equiv. of epibromohydrin. ^{1}H NMR: δ = 0.93 (t, J = 7.4 Hz, 3 H), 1.61 (m, 2 H), 2.52 (t, J = 7.4 Hz, 2 H), 2.71 (dd, J = 5.0, 2.5 Hz, 1 H), 2.86 (dd, J = 5.0, 4.1 Hz, 1 H), 3.37 (m, 1 H), 3.85 (s, 3 H), 4.00 (dd, J = 11.5, 5.5 Hz, 1 H), 4.19 (dd, J = 11.5, 3.7 Hz, 1 H), 6.68 (dd, J = 8.1, 2.0 Hz, 1 H), 6.71 (d, J = 2.0 Hz, 1 H), 6.84 (d, J = 8.1 Hz, 1 H) ppm. ^{13}C NMR: δ = 13.8 (q), 24.7 (t), 37.7 (t), 45.0 (t), 50.3 (d), 55.9 (q), 70.5 (t), 112.4 (d), 114.4 (d), 120.3 (d), 136.6 (s), 146.0 (s), 149.4 (s) ppm. MS: m/z (%) = 223 (9.0), 222 (60.9) $[M]^{+\cdot}$, 193 (16.8), 165 (38.1), 137 (100.0), 122 (7.7), 105 (11.4), 95 (14.6), 91 (11.3), 77 (14.6).

2-Methoxy-4-methylphenyl Methyl Carbonate (20b). General Procedure 3 (GP 3): 2-Methoxy-4-methylphenol (**13b**; 250 mmol) was dissolved in dry dichloromethane (500 mL) with pyridine (392 mmol) and DMAP (4.26 mmol). Methyl chloroformate (317 mmol) was added slowly to this solution and the reaction mixture cooled to room temperature for 3 h. The mixture was then poured into a 2 M HCl solution (120 mL) and the aqueous layer extracted twice with dichloromethane (3 × 50 mL). The combined organic layers were then washed twice with water (3 × 100 mL), dried with $MgSO_4$, and filtered. The solvent was evaporated and the residue distilled under reduced pressure (120–140 °C, 0.4 mbar) to give 38 g (74% yield) of pure carbonate **20b**. ^{1}H NMR: δ = 2.33 (s, 3 H), 3.81 (s, 3 H), 3.87 (s, 3 H), 6.72 (dm, J = 8.0 Hz, 1 H), 6.77 (d, J = 1.9 Hz, 1 H), 6.98 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 21.3 (q), 55.3 (q), 56.0 (q), 114.1 (d), 121.4 (d), 122.6 (d), 137.4 (s), 139.4 (s), 152.1 (s), 154.5 (s) ppm. MS: m/z (%) = 197 (11.3), 196 (100.0), 152 (22.5), 137 (92.7), 109 (44.6), 91 (42.8), 77 (27.2), 67 (2.3), 66 (19.1), 59 (10.3).

2-Methoxy-4-propylphenyl Methyl Carbonate (20c): According to GP 3, obtained in 62% yield from dihydroeugenol (**13c**). ^{1}H NMR: δ = 0.95 (t, J = 7.4 Hz, 3 H), 1.64 (m, 2 H), 2.57 (t, J = 7.5 Hz, 2 H), 3.83 (s, 3 H), 3.89 (s, 3 H), 6.74 (dd, J = 8.0, 1.9 Hz, 1 H), 6.78 (d, J = 1.9 Hz, 1 H), 7.01 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 13.8 (q), 24.5 (t), 38.0 (t), 55.4 (q), 55.9 (q), 112.8 (d), 120.5 (d),

121.9 (d), 138.1 (s), 142.0 (s), 150.8 (s), 154.2 (s) ppm. MS: *m/z* (%) = 225 (3.6), 224 (26.6), 151 (100.0), 95 (11.4), 91 (8.6), 77 (11.6).

4-Allyl-2-methoxyphenyl Methyl Carbonate (20d): According to GP 3, obtained in 40% yield from eugenol (**13d**). ^{1}H NMR: δ = 3.37 (d, J = 7.0 Hz, 2 H), 3.83 (s, 3 H), 3.89 (s, 3 H), 5.06–5.14 (m, 2 H), 5.95 (m, 1 H), 6.76 (dd, J = 7.9, 2.0 Hz, 1 H), 6.79 (d, J = 2.0 Hz, 1 H), 7.03 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 40.1 (t), 55.5 (q), 55.9 (q), 112.8 (d), 116.2 (t), 120.6 (d), 122.1 (d), 137.0 (d), 138.4 (s), 139.3 (s), 150.9 (s), 154.1 (s) ppm. MS: *m/z* (%) = 223 (10.1), 222 (77.8), 178 (5.7), 163 (51.2), 147 (28.4), 135 (11.5), 115 (12.8), 107 (23.3), 103 (36.1), 91 (35.2), 77 (16.7), 44 (100.0).

(±)-(5-Methyl-2,3-dihydro-1-benzofuran-2-yl)methanol (24a): Obtained in 65% yield from 4-methyl-2-allylphenol (**23a**) following the procedure described previously,[24] except with the use of peracetic acid instead of *m*-CPBA. ^{1}H NMR: δ = 2.26 (s, 3 H), 2.34 (br. s, OH), 2.95 (dd, J = 16, 7 Hz, 1 H), 3.18 (dd, J = 16, 9 Hz, 1 H), 3.66–3.74 (m, 1 H), 3.76–3.84 (m, 1 H), 4.82–4.92 (m, 1 H), 6.65 (d, J = 8 Hz, 1 H), 6.89 (d, J = 8 Hz, 1 H), 6.96 (s, 1 H) ppm. ^{13}C NMR: δ = 20.7 (q), 31.3 (t), 64.9 (t), 83.1 (d), 109.0 (d), 125.6 (d), 126.6 (s), 128.3 (d), 129.9 (s), 157.0 (s) ppm. MS: *m/z* (%) = 164 (82) $[M]^{+\cdot}$, 145 (57), 133 (83), 131 (26), 121 (24), 105 (100), 91 (39), 77 (38), 65 (14), 63 (12), 51 (22).

(±)-(2,5-Dimethyl-2,3-dihydro-1-benzofuran-2-yl)methanol (24b): Obtained in 78% yield from 4-methyl-2-methallylphenol (**23b**) following the procedure described previously,[24] except with the use of peracetic acid instead of *m*-CPBA. ^{1}H NMR: δ = NMR: 1.42 (s, 3 H), 2.26 (s, 3 H), 2.85 (d, J = 15.5 Hz, 1 H), 3.20 (d, J = 15.5 Hz, 1 H), 3.60 (d, J = 11.6 Hz, 1 H), 3.65 (d, J = 11.6 Hz, 1 H), 6.63 (d, J = 8.3 Hz, 1 H), 6.90 (d, J = 8.3 Hz, 1 H), 6.96 (s, 1 H) ppm. ^{13}C NMR: δ = 20.7 (q), 23.2 (q), 37.9 (t), 68.2 (t), 88.5 (s), 109.0 (d), 125.8 (d), 126.8 (s), 128.3 (d), 129.7 (s), 156.5 (s) ppm. MS: *m/z* (%) = 179 (6.1), 178 (49.7) $[M]^{+\cdot}$, 159 (10.2), 147 (100.0), 145 (36.2), 121 (37.1), 119 (45.4), 108 (14.3), 103 (6.3), 91 (27.7), 77 (15.3), 65 (7.2), 51 (7.6).

(±)-(5-Isopropyl-2-methyl-2,3-dihydro-1-benzofuran-2-yl)methanol (24c): Obtained in 60% yield from 4-isopropyl-2-methallylphenol (**23c**) following the procedure described previously,[24] except with the use of peracetic acid instead of *m*-CPBA. ^{1}H NMR: δ = 1.21 (t, J = 6.8 Hz, 6 H), 1.42 (s, 3 H), 2.15 (d, J = 6.8 Hz, 1 H), 2.79–2.90 (m, 2 H), 3.58–3.66 (m, 2 H), 6.65 (d, J = 8 Hz, 1 H), 6.95 (d, J = 8 Hz, 1 H), 7.01 (s, 1 H) ppm. ^{13}C NMR: δ = 23.2 (q), 24.4 (q), 33.6 (d), 38.0 (t), 68.4 (t), 88.5 (s), 109.0 (d), 123.1 (d), 125.9 (d), 126.7 (s), 141.2 (s), 156.7 (s) ppm. MS: *m/z* (%) = 207 (8.3), 206 (63.0) $[M]^{+\cdot}$, 191 (48.7), 175 (62.7), 173 (46.2), 159 (12.1), 145 (17.5), 133 (100.0), 115 (17.0), 105 (34.9), 91 (19.2), 77 (15.8), 43 (21.4).

(±)-5-Methyl-2,3-dihydro-1-benzofuran-2-carbaldehyde (25a). General Procedure 4 (GP 4): A 13% aq. sol. of sodium hypochlorite (1.05 equiv.) was added to a mixture of alcohol **24a** (1 equiv.), sodium hydrogen carbonate, potassium bromide (0.02 equiv.) and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO; 0.02 equiv.) in ethyl acetate (3 mL/mmol) at room temperature for 1 h. The organic layer was then washed twice with brine to neutral pH. Drying over $MgSO_4$ and concentrating in vacuo gave the crude product. Flash chromatography (ethyl acetate/cyclohexane, 10:90) afforded the pure aldehyde **25a** as a colorless oil (16% yield). ^{1}H NMR: δ = 2.28 (s, 3 H), 3.29 (dd, J = 16, 6 Hz, 1 H), 3.42 (dd, J = 16, 11 Hz, 1 H), 5.00 (ddd, J = 11, 6, 1 Hz, 1 H), 6.78 (d, J = 8 Hz, 1 H), 6.95 (d, J = 8 Hz, 1 H), 6.99 (s, 1 H), 9.82 (d, J = 1 Hz, 1 H) ppm. ^{13}C NMR: δ = 20.7 (q), 31.6 (t), 84.8 (d), 109.4 (d), 124.7 (s), 125.5 (d), 128.9 (d), 130.9 (s), 156.8 (s), 201.6 (d) ppm. MS: *m/z* (%) = 162 (46) $[M]^{+\cdot}$, 145 (3), 133 (80), 131 (9), 118 (5), 105 (100), 103 (12), 91 (5), 79 (13), 77 (14), 63 (6), 51 (12).

(±)-2,5-Dimethyl-2,3-dihydro-1-benzofuran-2-carbaldehyde (25b): Obtained in 25% yield from **24b** according to GP 4. ^{1}H NMR: δ = 1.54 (s, 3 H), 2.27 (s, 3 H), 2.99 (d, J = 6 Hz, 1 H), 3.44 (d, J = 6 Hz, 1 H), 6.74 (d, J = 8 Hz, 1 H), 6.94 (d, J = 8 Hz, 1 H), 6.95 (s, 1 H), 9.72 (s, 1 H) ppm. ^{13}C NMR: δ = 20.7 (q), 21.2 (q), 37.7 (t), 90.3 (s), 109.4 (d), 125.3 (s), 125.6 (d), 128.8 (d), 130.7 (s), 156.4 (s), 201.4 (d) ppm. MS: *m/z* (%) = 176 (28) $[M]^{+\cdot}$, 148 (12), 147 (100), 131 (10), 119 (77), 117 (10), 103 (9), 91 (22), 77 (15), 65 (7), 63 (6), 51 (10), 43 (5), 41 (5).

(±)-5-Isopropyl-2-methyl-2,3-dihydro-1-benzofuran-2-carbaldehyde (25c): Obtained in 10% yield from **24c** according to GP 4. ^{1}H NMR: δ = 1.20 (d, J = 7 Hz, 6 H), 1.54 (s, 3 H), 2.15 (d, J = 7 Hz, 1 H), 2.79–2.90 (m, 2 H), 6.77 (d, J = 8 Hz, 1 H), 6.93 (d, J = 8 Hz, 1 H), 7.01 (s, 1 H), 9.73 (s, 1 H) ppm. ^{13}C NMR: δ = 21.3 (q), 24.4 (q), 24.4 (q), 33.6 (d), 37.8 (t), 90.4 (s), 109.4 (d), 122.9 (d), 125.2 (s), 126.4 (d), 142.2 (s), 156.6 (s), 201.5 (d) ppm. MS: *m/z* (%) = 204 (19.1) $[M]^{+\cdot}$, 189 (6.0), 175 (46.1), 133 (100.0), 115 (11.5), 105 (44.8), 91 (12.3), 77 (11.1), 43 (38.4).

(±)-2-Methoxy-5-methyl-1,3-benzodioxole (28a). General Procedure 5 (GP 5): A mixture of 4-methylcatechol (**27a**; 22.1 g, 178 mmol), trimethyl orthoformate (5 equiv.), Amberlyst® 15 (4 g), 3 Å molecular sieves (5 g), and toluene (400 mL) was heated at reflux for 4 h. The solvent was partially distilled during this time. The reaction was cooled to room temperature, stirred with magnesium sulfate, filtered, and concentrated under vacuum. Distillation gave pure compound **28a** (54% yield). B.p. (0.23 mbar) 155 °C. ^{1}H NMR: δ = 2.27 (s, 3 H), 3.37 (s, 3 H), 6.64 (d, J = 8 Hz, 1 H), 6.70 (s, 1 H), 6.74 (d, J = 8 Hz, 1 H), 6.80 (s, 1 H) ppm. ^{13}C NMR: δ = 21.2 (q), 49.8 (q), 107.6 (d), 109.1 (d), 119.0 (d), 121.6 (d), 131.6 (s), 143.9 (s), 146.0 (s) ppm. MS: *m/z* (%) = 167 (6.1), 166 (56.2) $[M]^{+\cdot}$, 135 (100.0), 123 (22.8), 105 (6.2), 95 (9.2), 67 (5.2), 51 (8.8).

(±)-2-Methoxy-5-propyl-1,3-benzodioxole (28b): Obtained in 35% yield from 4-*n*-propylcatechol (**27b**) according to GP 5. ^{1}H NMR: δ = 0.92 (t, J = 7 Hz, 3 H), 1.59 (m, 2 H), 2.51 (t, J = 8 Hz, 2 H), 3.39 (s, 3 H), 6.65 (dd, J = 8, 1 Hz, 1 H), 6.71 (d, J = 1 Hz, 1 H), 6.76 (d, J = 8 Hz, 1 H), 6.80 (s, 1 H) ppm. ^{13}C NMR: δ = 13.7 (q), 24.8 (t), 37.8 (t), 49.9 (q), 107.6 (d), 108.4 (d), 119.1 (d), 121.2 (d), 136.7 (s), 144.0 (s), 146.0 (s) ppm. MS: *m/z* (%) = 194 (34.8) $[M]^{+\cdot}$, 166 (11.1), 165 (100.0), 163 (35.6), 137 (13.5), 122 (5.1), 105 (12.5), 77 (15.6), 51 (7.9).

(±)-2-Methoxy-4-methyl-1,3-benzodioxole (28d): Obtained in 77% yield from 3-methylcatechol (**27d**) according to GP 5. ^{1}H NMR: δ = 2.26 (s, 3 H), 3.40 (s, 3 H), 6.70 (m, 2 H), 6.75 (dd, J = 7, 7 Hz, 1 H), 6.82 (s, 1 H) ppm. ^{13}C NMR: δ = 14.6 (q), 49.9 (q), 105.8 (d), 118.7 (d), 118.8 (s), 121.4 (d), 123.5 (d), 144.4 (s), 145.4 (s) ppm. MS: *m/z* (%) = 167 (4.8), 166 (49.6) $[M]^{+\cdot}$, 136 (8.8), 135 (100.0), 123 (15.4), 106 (6.6), 105 (7.3), 77 (15.6), 51 (7.3).

(±)-2-Methoxy-2,5-dimethyl-1,3-benzodioxole (29a): Obtained in 33% yield from 4-methylcatechol (**27a**) according to GP 5, except using trimethyl orthoacetate instead of trimethyl orthoformate. ^{1}H NMR: δ = 1.76 (s, 3 H), 2.27 (s, 3 H), 3.28 (s, 3 H), 6.61 (d, J = 8 Hz, 1 H), 6.64 (s, 1 H), 6.69 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 21.2 (q), 24.2 (q), 49.4 (q), 107.2 (d), 108.7 (d), 121.2 (d), 127.8 (s), 131.1 (s), 144.6 (s), 146.6 (s) ppm. MS: *m/z* (%) = 181 (7.6), 180 (61.7) $[M]^{+\cdot}$, 150 (12.5), 149 (100.0), 124 (47.7), 120 (21.6), 92 (6.5), 77 (11.1), 57 (7.9), 51 (8.0), 43 (29.5).

(±)-2-Methoxy-2-methyl-5-propyl-1,3-benzodioxole (29b): Obtained in 61% yield from 4-*n*-propylcatechol (**27b**) according to GP 5, except using trimethyl orthoacetate instead of trimethyl orthofor-

mate. ^{1}H NMR: δ = 0.93 (t, J = 7 Hz, 3 H), 1.60 (m, 2 H), 1.77 (s, 3 H), 2.51 (t, J = 8 Hz, 2 H), 3.29 (s, 3 H), 6.62 (dd, J = 8, 2 Hz, 1 H), 6.66 (d, J = 2 Hz, 1 H), 6.70 (d, J = 8 Hz, 1 H) ppm. ^{13}C NMR: δ = 13.8 (q), 24.2 (q), 24.8 (t), 37.9 (t), 49.4 (q), 107.2 (d), 108.0 (d), 120.8 (d), 127.8 (s), 136.2 (s), 144.7 (s), 146.7 (s) ppm. MS: *m*/*z* (%) = 209 (9.3), 208 (64.3) $[M]^{+\cdot}$, 193 (7.5), 191 (7.0), 179 (74.4), 177 (100.0), 152 (13.8), 148 (13.6), 147 (26.2), 137 (19.3), 123 (55.8), 105 (12.5), 91 (5.6), 77 (18.4), 57 (11.6), 51 (10.6), 43 (23.7).

(±)-5-*tert*-Butyl-2-methoxy-2-methyl-1,3-benzodioxole (29c): Obtained in 67% yield from 4-*tert*-butylcatechol (**27c**) according to GP 5, except using trimethyl orthoacetate instead of trimethyl orthoformate. ^{1}H NMR: δ = 1.28 (s, 9 H), 1.77 (s, 3 H), 3.30 (s, 3 H), 3.72 (d, J = 8 Hz, 1 H), 6.83 (dd, J = 8, 2 Hz, 1 H), 6.89 (d, J = 2 Hz, 1 H) ppm. ^{13}C NMR: δ = 24.2 (q), 31.6 (q), 34.6 (s), 49.4 (q), 105.5 (d), 106.8 (d), 117.5 (d), 127.8 (s), 144.3 (s), 145.0 (s), 146.5 (s) ppm. MS: *m*/*z* (%) = 223 (4.8), 222 (30.1) $[M]^{+\cdot}$, 208 (14.8), 207 (100.0), 191 (26.7), 175 (11.8), 151 (31.9), 147 (7.6), 105 (7.1), 77 (8.0), 43 (10.0).

(±)-2-Methoxy-2,4-dimethyl-1,3-benzodioxole (29d): Obtained in 72% yield from 3-methylcatechol (**27d**) according to GP 5, except using trimethyl orthoacetate instead of trimethyl orthoformate. ^{1}H NMR: δ = 1.79 (s, 3 H), 2.25 (s, 3 H), 3.28 (s, 3 H), 6.65 (d, J = 8 Hz, 1 H), 6.65 (d, J = 6 Hz, 1 H), 6.73 (dd, J = 8, 6 Hz, 1 H) ppm. ^{13}C NMR: δ = 14.6 (q), 24.3 (q), 49.4 (q), 105.3 (d), 118.3 (s), 120.9 (d), 123.1 (d), 127.3 (s), 145.0 (s), 146.1 (s) ppm. MS: *m*/*z* (%) = 181 (6.6), 180 (56.6) $[M]^{+\cdot}$, 165 (9.2), 150 (12.6), 149 (100.0), 124 (24.4), 120 (17.7), 105 (6.2), 78 (9.3), 77 (10.4), 57 (7.0), 51 (7.1), 43 (21.3).

(±)-2-Ethoxy-5-methyl-1,3-benzodioxole (30a): Obtained in 53% yield from 4-methylcatechol (**27a**) according to GP 5, except using triethyl orthoformate instead of trimethyl orthoformate. ^{1}H NMR: δ = 1.24 (t, J = 7 Hz, 3 H), 2.28 (s, 3 H), 3.70 (q, J = 7 Hz, 2 H), 6.64 (d, J = 8 Hz, 1 H), 6.69 (s, 1 H), 6.73 (d, J = 8 Hz, 1 H), 6.82 (s, 1 H) ppm. ^{13}C NMR: δ = 14.9 (q), 21.2 (q), 59.1 (t), 107.7 (d), 109.2 (d), 118.8 (d), 121.6 (d), 131.5 (s), 143.8 (s), 146.0 (s) ppm. MS: *m*/*z* (%) = 181 (8.4), 180 (75.0) $[M]^{+\cdot}$, 136 (8.9), 135 (100.0), 124 (86.3), 123 (33.0), 106 (13.0), 95 (7.6), 78 (32.1), 77 (21.1), 67 (5.7), 55 (5.9), 51 (9.5).

(±)-2-Ethoxy-4-methyl-1,3-benzodioxole (30d): Obtained in 41% yield from 3-methylcatechol (**27d**) according to GP 5, except using triethyl orthoformate instead of trimethyl orthoformate. ^{1}H NMR: δ = 1.26 (t, J = 7 Hz, 3 H), 2.25 (s, 3 H), 3.72 (q, J = 7 Hz, 2 H), 6.68 (d, J = 7 Hz, 1 H), 6.70 (d, J = 7 Hz, 1 H), 6.76 (dd, J = 7, 7 Hz, 1 H), 6.84 (s, 1 H) ppm. ^{13}C NMR: δ = 14.6 (q), 14.9 (q), 59.3 (t), 105.8 (d), 118.5 (d), 118.8 (s), 121.3 (d), 123.4 (d), 144.3 (s), 145.4 (s) ppm. MS: *m*/*z* (%) = 181 (7.7), 180 (69.9) $[M]^{+\cdot}$, 136 (8.9), 135 (100.0), 124 (77.9), 106 (12.2), 78 (30.2), 77 (19.6), 51 (8.8).

(±)-5-Methyl-2-propoxy-1,3-benzodioxole (31a): Obtained in 53% yield from 4-methylcatechol (**27a**) according to GP 5, except using tripropyl orthoformate instead of trimethyl orthoformate. ^{1}H NMR: δ = 0.93 (t, J = 7 Hz, 3 H), 1.63 (m, 2 H), 2.28 (s, 3 H), 3.59 (t, J = 7 Hz, 2 H), 6.64 (t, J = 8 Hz, 1 H), 6.69 (s, 1 H), 6.73 (d, J = 8 Hz, 1 H), 6.83 (s, 1 H) ppm. ^{13}C NMR: δ = 10.4 (q), 21.2 (q), 22.6 (t), 64.9 (t), 107.7 (d), 109.1 (d), 118.9 (d), 121.5 (d), 131.4 (s), 143.9 (s), 146.0 (s) ppm. MS: *m*/*z* (%) = 195 (5.4), 194 (44.2) $[M]^{+\cdot}$, 135 (81.5), 124 (100.0), 106 (9.5), 78 (19.7), 77 (14.5), 51 (5.2).

(±)-2-Propoxy-5-propyl-1,3-benzodioxole (31b): Obtained in 73% yield from 4-*n*-propylcatechol (**27b**) according to GP 5, except using tripropyl orthoformate instead of trimethyl orthoformate. ^{1}H NMR: δ = 0.92 (t, J = 7.4 Hz, 3 H), 0.93 (t, J = 7.3 Hz, 3 H), 1.54–1.68 (m, 4 H), 2.51 (t, J = 7.7 Hz, 2 H), 3.61 (t, J = 6.6 Hz, 2 H), 6.65 (dd, J = 7.7, 2 Hz, 1 H), 6.70 (d, J = 2 Hz, 1 H), 6.75 (d, J = 7.7 Hz, 1 H), 6.83 (s, 1 H) ppm. ^{13}C NMR: δ = 10.5 (q), 13.7 (q), 22.6 (t), 24.8 (t), 37.8 (t), 65.0 (t), 107.6 (d), 108.5 (d), 118.9 (d), 121.1 (d), 136.5 (s), 144.0 (s), 146.0 (s) ppm. MS: *m*/*z* (%) = 223 (3.5), 222 (24.0) $[M]^{+\cdot}$, 163 (41.2), 152 (26.0), 124 (8.1), 123 (100.0), 77 (6.7).

(±)-4-Methyl-2-propoxy-1,3-benzodioxole (31d): Obtained in 63% yield from 4-methylcatechol (**27d**) according to GP 5, except using tripropyl orthoformate instead of trimethyl orthoformate. ^{1}H NMR: δ = 0.94 (t, J = 7 Hz, 3 H), 1.64 (m, 2 H), 2.25 (s, 3 H), 3.61 (t, J = 7 Hz, 2 H), 6.69 (m, 2 H), 6.76 (dd, J = 8, 8 Hz, 1 H), 6.85 (s, 1 H) ppm. ^{13}C NMR: δ = 10.5 (q), 14.6 (q), 22.6 (t), 65.1 (t), 105.8 (d), 118.6 (d), 118.8 (s), 121.2 (d), 123.4 (d), 144.4 (s), 145.4 (s) ppm. MS: *m*/*z* (%) = 195 (5.7), 194 (48.1) $[M]^{+\cdot}$, 136 (7.7), 135 (88.5), 125 (7.9), 124 (100.0), 106 (9.3), 78 (20.0), 77 (15.1).

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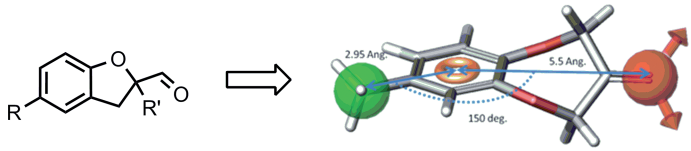
Odorants



A new class of molecules having marine, watery olfactory notes has been discovered. A model built from the Calone 1951® family shows that the seven-membered ring with a ketone group can be replaced by a five-membered ring bearing an aldehyde. Interestingly, as a side benefit, a methyl carbonate compound has been synthesized that is olfactively very close to vanillin and has interesting properties.

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Keywords: Oxygen heterocycles / Structure–activity relationships / Fragrances / Olfactory properties

