Structure – Activity Relationship in the Domain of Odorants Having Marine Notes

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Dedicated to the memory of Dr. *Karl-Heinrich Schulte-Elte*

We synthesized or re-synthesized a large series of 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9** (*Scheme 1*), 4,5-dihydro-1-benzoxepin-3(2*H*)-ones **10** (*Schemes 3* and *4*) and 5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-ones **11** (*Schemes 5* and *6*), since the lead compound for the olfactory note of perfumes based on marine accords is a well-known benzodioxepinone named *Calone 1951*® (**9b**). We meticulously described the odor profile of each synthesized compound and discussed relevant structure – odor relationships (*Tables 1 – 3*). In particular, we revealed a correlation between the conformation of the seven-membered ring and the activities of these compounds (*Table 4* and *Fig. 3*). We also clarified the effect of the position and the size of the alkyl substituent at the aromatic ring.

1. Introduction. – In 1993, I was a young chemist at *Firmenich*, and the management asked me to 'see what is known and what is possible to do in marine-note odorants'. A rapid survey of olfactory descriptors such as marine, seabreeze, seashore, algae, oyster, ozone, watery, cucumber, watermelon, or melon in the *Arctander* reference book [1], considered as the 'Bible' of raw materials for perfumery, gave no result at all. Indeed, at that time, very few compounds possessing this kind of olfactory profile were known. However, an exhaustive bibliographic search showed that such compounds can belong to four different families[1]) (*Fig. 1*): *1*) unsaturated aldehydes, such as compounds **1** – **3** resulting from the biodegradation of fatty acids and naturally occurring in melon, watermelon, cucumber [2], and also found in algae [3]; *2*) tetraenes and trienes[2]), such as **4** – **6**, isolated from marine algae [4]; *3*) halogenated phenols, such as **7** and **8** [5]; and *4*) 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9** and 4,5-dihydro-1-benzoxepin-3(2*H*)-ones **10**. This last family, often called watermelon ketones, was patented by *Beereboom*, *Cameron*, and *Stephens* of *Pfizer* in 1966 [6].

Because it was just in those days that the use of *Calone 1951*® (= 7-methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one; **9b**) (see *Table 1*), one of the preferred compounds claimed

[1]) Note that several alkyl-substituted pyridines can have a watery profile, but this family is more reminiscent of stagnant water, sometimes with a negative connotation of 'wet dog' rather than seawater or seabreeze.

[2]) Undeca-1,3,5-triene is already used at low concentrations for the top note of many fragrances, but its odor profile is green-galbanum rather than marine-watery.

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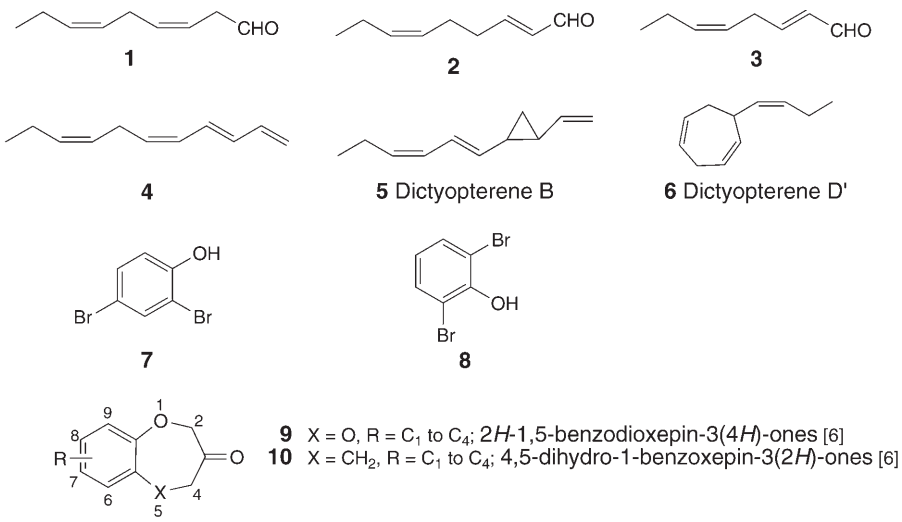
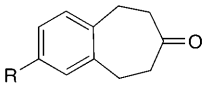


Fig. 1. *Typical compounds with marine-watery olfactory notes*

in a patent by *Pfizer*) became increasingly popular in perfumery[3]), we chose to concentrate our efforts on this lead compound. The first problem was the absence of precise olfactory descriptions for each individual compound in the original patent. Thus we decided to synthesize or re-synthesize (in the case of compounds mentioned in the *Pfizer* patent) a large set of compounds of this family, in order to rigorously compare the odors of 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9** with the corresponding carba analogues 4,5-dihydro-1-benzoxepin-3(2*H*)-ones **10**. In the course of this work, detailed herein, a valuable odorant in this family was revealed [8]. Meanwhile, other investigators were also working on this subject, and their results have been published in two patents [9][10] and a recent publication [7].

Our goal was to better understand the influence of the size and the location of the alkyl substituent at the aromatic ring. Moreover, we were interested in the role of the O-atom(s) in the seven-membered ring, and thus, undertook the synthesis of some carbocyclic analogues **11**.

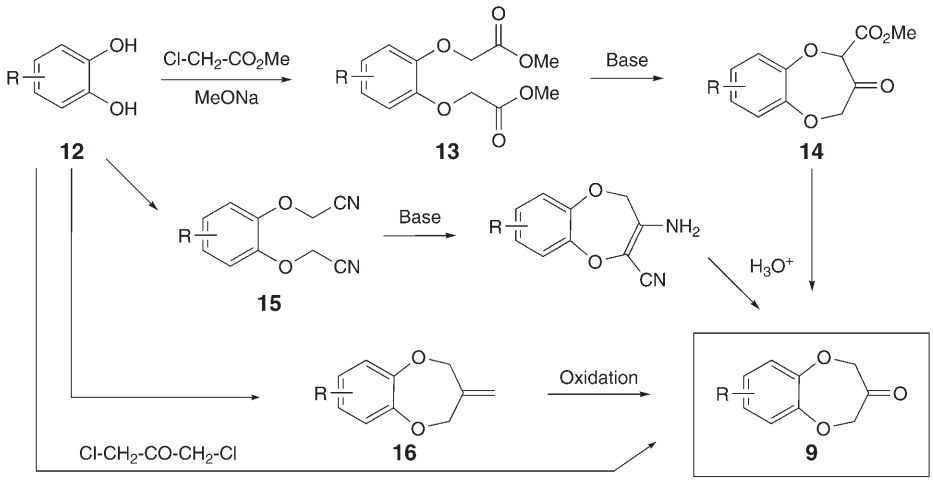


11 5,6,8,9-Tetrahydro-7*H*-benzocyclohepten-7-ones

2. Results and Discussion. – 2.1. *Synthesis and Odor Profile of 2*H*-1,5-Benzodioxepin-3(4*H*)-ones* **9**. For the synthesis of 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9**, four different pathways have been described (*Scheme 1*). The classical three-step access *via*

[3]) The success story of *Calone 1951*® and the trend of perfumes based on marine accords are documented in the excellent introduction by *P. Kraft* in his paper on this subject [7]. It is interesting to note that this trend continues to be very popular in modern perfumery, and thus represents an attractive research domain.

Scheme 1. *Different Known Pathways for the Synthesis of* 2H-*1,5-Benzodioxepin-3(4*H*)-ones* **9**



an alkylation of catechols (= benzene-1,2-diols) **12** and the *Dieckmann* condensation of the diester **13** followed by decarbomethoxylation of **14** [6] is efficient but too complicated to be used as a methodology for a screening study. The same comment is valid for a synthetic access *via* the dinitrile **15** [11]. A shorter alternative is possible *via* the 3,4-dihydro-3-methylene-2*H*-1,5-benzodioxepines **16**, by using 3-chloro-2-(chloromethyl)prop-1-ene [7][12] or a palladium-catalyzed condensation with an allylic biscarbonate [13] followed by an oxidation step.

We chose the fourth and shortest solution which consists in the direct condensation of catechols **12** with 1,3-dichloroacetone (=1,3-dichloropropan-2-one) [10]. This reaction is not very clean and selective, but careful purification by flash chromatography and vacuum distillation on a small *Fischer* column gave directly the desired products **9** (*Table 1*). As a general comment, we emphasize that the highest purity of the compounds is needed in perfumery to ensure an unambiguous olfactory evaluation; traces of impurities may have a dramatic effect. Thus, in this work, we always favored the quality of the final product over the yield, which was not optimized. Most of the starting catechols **12** are commercially available or described in the literature. For compounds **12l** and **12n**–**q**, we alkylated pyrocatechol (**12a**; R = H) with the corresponding alcohol in the presence of phosphoric acid, as already done for the synthesis of isopropylcatechols **12i** and **12j** [14]. Benzodioxepinone **9d**, the only compound substituted at position C(2), was prepared by methylation of the intermediate **14** as described [6]. Compounds **9m** and **9u**, already reported [7], were re-synthesized for olfactory comparison.

Olfactory evaluations of the 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9** (*Table 1*) resulted in the following conclusions: *i*) The presence of an alkyl group at the aromatic ring is advantageous. Compound **9a** is much more metallic and hot iron, and is hedonically less appreciated than *Calone 1951*® (**9b**). *ii*) Substitution at position 2 seems to be unfavorable (compare **9b** with **9d**), probably due to the lower accessibility of the

Table 1. *Olfactory Profiles for* 2H-*1,5-Benzodioxepin-3(*4H*)-ones* **9**

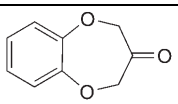
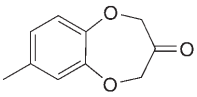
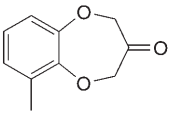
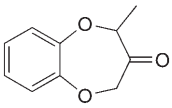
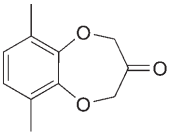
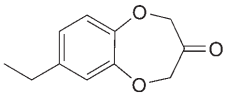
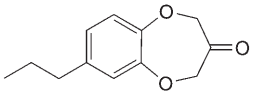
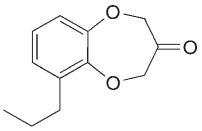
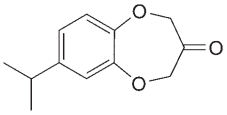
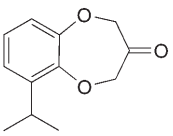
Starting catechol	Benzodioxepinone **9**		Olfactory profile[a])
12a	**9a**[b])		metallic, ozone, watery, cabbage, hot iron, more metallic-phenolic, less ozony and much weaker than *Calone 1951®*
12b	**9b**[b])		*Calone 1951®*: strongly marine, ozone, floral, oyster
12c	**9c**[b])		phenolic, leathery, earthy, close to hyacinth, *Bourgeonal®*, no ozone character in the top note, somewhat *Calone 1951®* in the base note (*Conoline®*)
12a	**9d**[b])		metallic, green, watery, by far inferior to *Calone 1951®*
12e	**9e**		swampy, fishy, reminiscent to oakmoss, crabs and mousse crystal
12f	**9f**[b])		ozone, aldehydic, watery, pleasant, weaker, less aldehydic and less characteristic than **9g**
12g	**9g**		ozone, aldehydic, *Farenal*/*Adoxal*, very powerful, stronger than *Calone 1951®*, much more aldehydic, without oyster odor (*Aldolone®*)
12h	**9h**		aldehydic, gun powder, metallic, aggressive
12i	**9i**[b])		marine, ozone, aldehydic, without the typical character of *Calone 1951®*, fair performance
12j	**9j**[b])		*Lilial®*, *Bourgeonal®*, melon, watery, very pleasant

Table 1 (cont.)

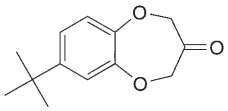
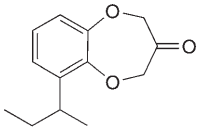
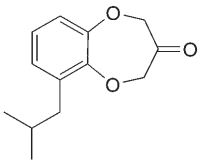
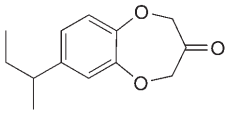
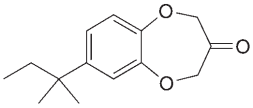
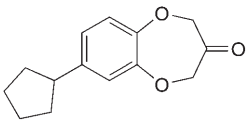
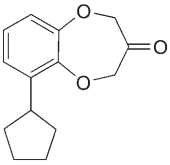
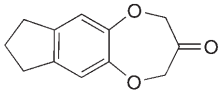
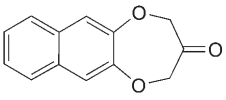
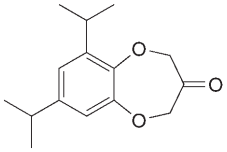
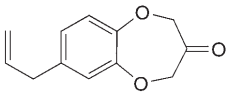
Starting catechol	Benzodioxepinone **9**	Olfactory profile[a])
12k	**9k**[b]) 	*Lilial*®, ozone, marine, floral, more floral than *Calone 1951*® and less watery, oyster like
12l	**9l** 	hydroxycitronellal, *Lilial*®, pleasant, very elegant but weak
12m	**9m** 	*Cyclosal*®, *Lilial*®, green-leafy, muguet, clearly weaker than similar compounds
12n	**9n** 	phenolic, chemical, white flowers, watery
12o	**9o** 	ozone, marine, *Lilial*®, aldehydic, weak
12p	**9p** 	aldehydic, farenal/*Adoxal*, spicy, mandarin, ozone, odor similar but less clean and weaker than **9g**
12q	**9q** 	white flowers, hydroxycitronellal, very weak
12r	**9r** 	watery, seaweed, metallic, fairly weak
12s	**9s** 	humus, aldehydic, watery, moss, phenolic, mousse cristal, ozone, nice but fairly weak

Table 1 (cont.)

Starting catechol	Benzodioxepinone **9**	Olfactory profile[a])
12t	**9t** 	*Bourgeonal*®, ozone, *Floralozone*®, nice but weak
12u	**9u**[c]) 	ozone, aldehydic, slightly phenolic and smokey, clearly inferior to **9g**, less aldehydic and weaker than **9g**

[a]) In these olfactory evaluations, the descriptors are ranked by decreasing order of importance. [b]) Mentioned in [6] without specific olfactory evaluation nor spectroscopic data. [c]) Reported in [7].

carbonyl function, but additional examples are needed to confirm that. *iii*) Substitution at position C(7) is unambiguously preferred to position C(6) for a marine-watery character of the compounds (compare **9b**,**g**,**i** with **9c**,**h**,**j**, resp.). Substitution at position C(6) affords compounds with an aldehydic character, reminiscent of *Lilial*®, *Bourgeonal*®, and *Cyclosal*®. *iv*) Increasing the length of the alkyl group (methyl to propyl) increases the perceived intensity of the odor on blotter. This observation is not in accord with the thresholds measured by *Kraft* and *Eichenberger* [7], but might be explained by the evaluation at higher concentrations[4]), *e.g.*, by saturation effects. But *Kraft* and *Eichenberger* [7] also found lower thresholds when increasing the size even further to C_6. *v*) Branched substituents at the benzylic position or disubstitution clearly decrease the odor intensity (compare **9i**,**k**,**o** with **9f**,**g**). *vi*) A propyl group is preferred over an allyl group (compare **9g** with **9u**). With regard to this last point, it is again interesting to observe that despite the fact that the experimental threshold of **9u** (0.051 ng/l) is lower than that of **9g** (0.1 ng/l) [7], for our perfumers it is evident that, at the usual levels used in perfumery, **9g** performs better than **9u** (see comments in *Table 1*).

It should be noted that, from an industrial point of view, several of these 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9** are now produced and commercialized on a large scale. The annual worldwide market for *Calone 1951*® (**9b**) is estimated to thirty tons. Compound **9c**, named *Conoline*®, is also available on the market. Compound **9g**, named *Aldolone*® and patented in 1997 [8], is much stronger than *Calone 1951*® and is different from an olfactory point of view (more aldehydic and less oyster). Benzodioxepinones **9g** and **9k** are produced by *Firmenich*. Compound **9v**, named *Azurone*® (*Fig. 2*), was patented by *Givaudan* in 2000 [9].

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4) For this study, the olfactory evaluations were made by 4 to 7 professional perfumers by comparison on blotters of the pure compounds as such and, in some cases, as mixtures with other odorants. These compounds are usually used at higher concentrations than the detection thresholds, which are the lowest level of perception. Although the detection-threshold concentrations in air give useful indicative values, we prefer to evaluate the new odorants at concentrations close to the normal usage, to judge their perfumistic performance.

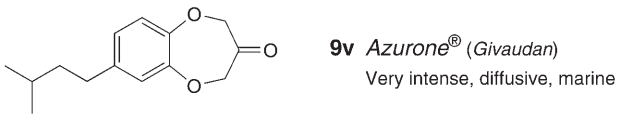


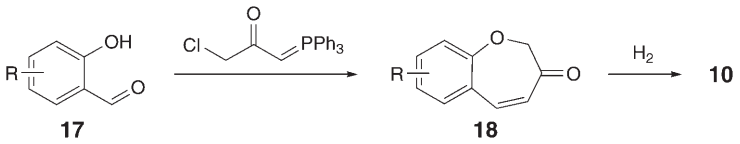
Fig. 2. *Commercial compound from* Givaudan, *available in the* Ultrazur® *base*

2.2. *Synthesis and Odor Profile of 4,5-Dihydro-1-benzoxepin-3(2*H*)-ones* **10**. As already mentioned in *Sect. 1*, *Pfizer*'s patent claims also good olfactory properties for the 4,5-dihydro-1-benzoxepin-3(2*H*)-ones **10**, but their odors were not precisely described and, up to now, they have not been used in perfumery. Are they more or less powerful than the corresponding 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9**? Do they have exactly the same odor profile? We were particularly interested to answer these questions.

It should be noted that one additional problem appears. In contrast to the symmetrical 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9**, for 4,5-dihydro-1-benzoxepin-3(2*H*)-ones **10**, all four positions C(6) to C(9) of the fused aromatic ring are different (*Fig. 1*). The same is true for the two positions adjacent to the carbonyl group. It is thus evident that testing every possible combination would demand a huge effort!

The first approach chosen was the synthesis from salicylaldehydes **17** *via* a reported tandem S_N2/*Wittig* reaction (*Scheme 2*) [15]. The advantage of this is that the intermediates **18**, unknown in perfumery and structurally halfway between coumarins (=2*H*-2-benzopyran-2-ones) and 4,5-dihydro-1-benzoxepin-3(2*H*)-ones **10**, could also have interesting olfactory properties. However, this approach was unsuccessful and, therefore, abandoned.

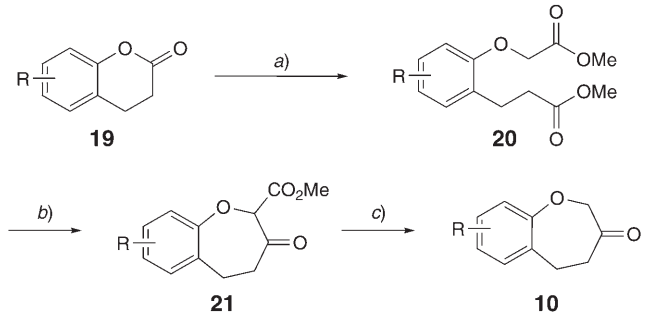
Scheme 2. *Possible Synthetic Route for the Synthesis of 4,5-Dihydro-1-benzoxepin-3(2*H*)-ones* **10**



Lecornue and *Ollivier* published another interesting approach [16], but we chose to use the more classical synthesis [6][17], starting from the dihydrocoumarins **19** *via* **20** and a *Dieckmann* reaction followed by decarbomethoxylation of the intermediates **21** (*Scheme 3*). The required dihydrocoumarins **19** can be obtained *via* different routes, and several of these compounds are already described in the literature [18–23].

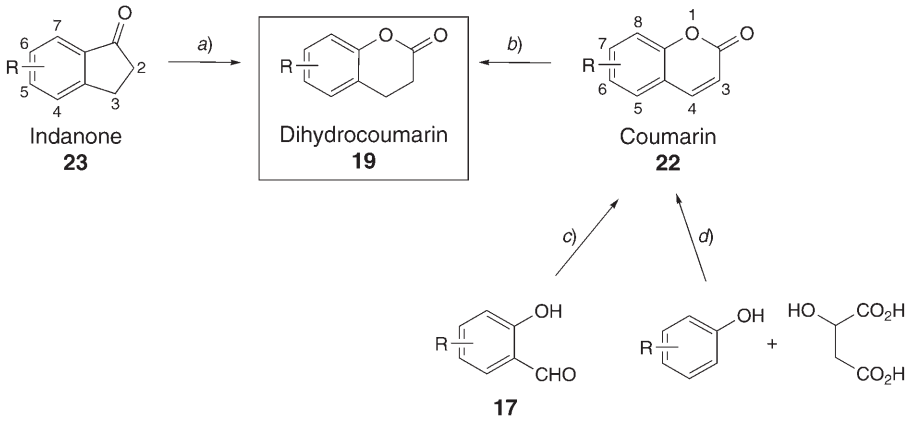
For the synthesis of coumarins, we usually employed the condensation of phenols with malic acid in concentrated sulfuric acid (*Scheme 4*). This very old reaction discovered by *von Pechmann* in 1883 is well documented [24]. Whereas *meta*-substituted phenols (3-Et and 3-^{i}Pr) reacted relatively well to give the corresponding coumarins **22** in 60–70% yields, the *para*-substituted phenols (4-Et and 4-^{i}Pr) gave lower yields. In these cases, the *Perkin* reaction from substituted salicylaldehydes **17** is probably a good alternative. When commercial sources were available, other substituted coumarins **22** (6-Me, 7-Me, 7-MeO) were directly purchased. Subsequent hydrogenation under 3 bars of H_2 (humid 5% Pd/C (*Degussa*)) in AcOEt, then afforded the dihydrocoumarins **19** in nearly quantitative yields.

Scheme 3. *Selected Pathway for the Synthesis of 4,5-Dihydro-1-benzoxepin-3(2*H*)-ones* **10**



a) MeONa, MeOH, $ClCH_2CO_2Me$, 50°, 15 h. *b*) NaH, THF, 50°, 4 h. *c*) Aq. HCl sol., EtOH, 65°, 15 h.

Scheme 4. *Different Approaches for the Synthesis of Dihydrocoumarins* **19**

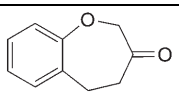
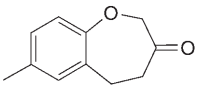
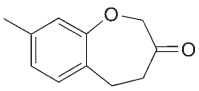
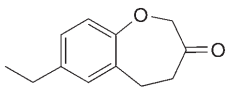
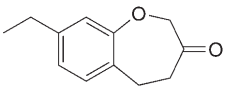
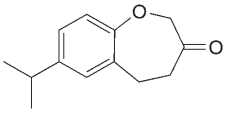
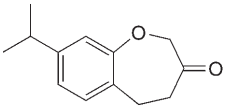
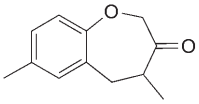
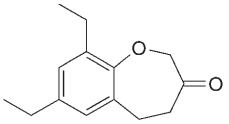
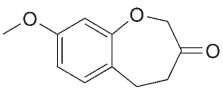


a) $MeCO_3H$, toluene, 20°, 96 h. *b*) H_2 (3 bar), 5% Pd/C, AcOEt, r.t., 60 h. *c*) *Perkin* reaction. *d*) *Pechmann* reaction.

As we had already 2,5-dimethylindanone (**23h**) [25] in hand, we decided to oxidize it with an excess of peracetic acid in toluene at 40°, affording the corresponding dihydrocoumarin **19h** in relatively modest yields (35–40%); but it is also possible to obtain **19h** as described in [22].

Olfactory evaluations of 4,5-dihydro-1-benzoxepin-3(2*H*)-ones **10** (*Table 2*) resulted in the following comments: *i*) Except for the disubstituted compounds **10h** (4,7-dimethyl) and **10i** (7,9-diethyl), their odors are all in the direction ozonic, marine, *Calone 1951*® (**9b**), watery, as expected. *ii*) The odor intensity of 4,5-dihydro-1-benzoxepin-3(2*H*)-ones **10** is clearly inferior to the corresponding 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9**. *iii*) As already observed for 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9**, branched substituents at the benzylic position clearly decrease the odor intensity. *iv*) There is no clear difference between a substitution at positions C(7) or C(8). *v*) In analogy to 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9**, substitution at the α-position to the carbonyl moiety seems unfavorable (compare **10b** with **10h**). This observation is in

Table 2. *Olfactory Profiles for 4,5-Dihydro-1-benzoxepin-3(2*H*)-ones* **10**

Dihydrobenzoxepinone **10**		Olfactory profile[a])
10a[b])		ozone, marine, watery, phenolic, very weak, much weaker than *Calone 1951®* and **10b**
10b[b])		ozone, watery, weakly of *Calone 1951®*, weak
10c		ozone, watery, *Calone 1951®*, more ozone-watery and slightly stronger than **10b**, but much weaker than *Calone 1951®*
10d		*Calone 1951®*, aldehydic, watery, *Heliopropanal®*/*Helional®*/ *Tropional®*, weaker than *Calone 1951®*, cleaner than **10e** and **10g**
10e[b])		*Calone 1951®*, marine, ozone, mousse cristal, aldehydic, less diffusive but more volume than *Calone 1951®*, similar but much weaker than *Calone 1951®*
10f		watery, phenolic, plaster, ozone, not special
10g		ozone, watery, shellfish, metallic, weak
10h		coumarinic, lactonic, coconut, jute, weak
10i		aldehydic, fruity, cresolic, fairly weak, no marine character
10j		phenolic, watery, not special, weak

[a]) In these olfactory evaluations, the descriptors are ranked by decreasing order of importance.
[b]) Mentioned in [6] without specific olfactory evaluation nor spectroscopic data.

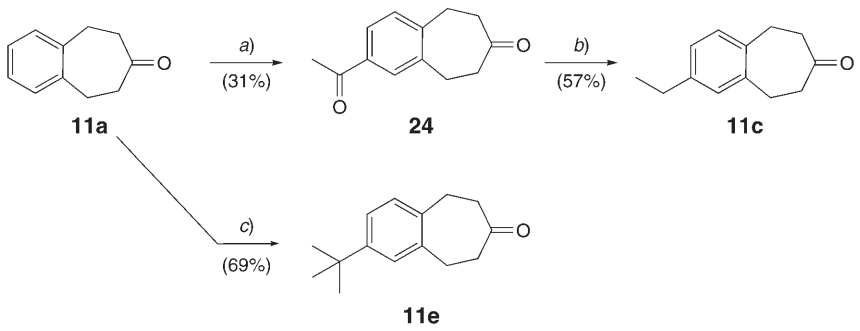
contradiction with *Pfizer*'s patent [6], in which half of the preferred compounds are substituted at this position.

Substitutions at positions 6 or 9 were not investigated.

2.3. *Synthesis and Odor Profile of 5,6,8,9-Tetrahydro-7*H*-benzocyclohepten-7-ones* **11**. Firstly, we note that the unsubstituted compound **11a** (R = H) has already been obtained in 1931 by *Kubota* and *Isemura* [26], and was described as having the odor of bitter almonds and peppermint. More recently, *Yoshii* and co-workers [27] have reported the synthesis of the 2-methyl derivative **11b** (R = Me), which was described as follows: 'recalls the note of *Cyclamenaldehyde*® and *Lily Aldehyde*®, and also has a distinctive marine note'; they also prepared the 2-(*tert*-butyl) derivative **11e** (R = ^{t}Bu), which was described as 'recalls the note of *Cyclamenaldehyde*® and *Lily Aldehyde*®, possesses the targeted lily-of-the-valley-type odor, though its intensity is weak and not adequate for perfume material'.

We have used **11a** [28] as starting material for the synthesis of the derivatives **11c** (R = Et) and **11e** (R = ^{t}Bu), as shown in *Scheme 5*. *Friedel–Crafts* acylation of **11a** with acetyl chloride furnished **24**, which was hydrogenated to **11c**. *Friedel–Crafts* alkylation of **11a** with *tert*-butyl chloride in the presence of $FeCl_3$ gave **11e**. In contrast, the same reaction with 2-chloropropane led to mixtures of mono- and disubstituted products, a fact which led us to follow an alternative and more selective route to **11d** (see below).

Scheme 5. *Synthesis of 5,6,8,9-Tetrahydro-7*H*-benzocyclohepten-7-ones* **11c** *and* **11e**

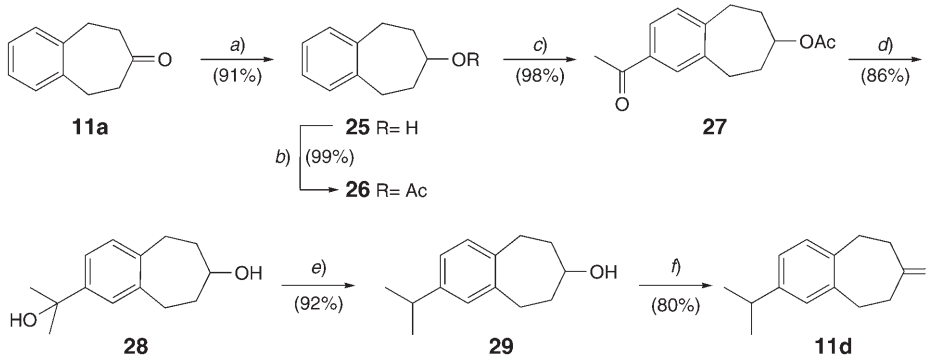


a) AcCl, $AlCl_3$, CH_2Cl_2, 0–20°, 48 h. *b*) H_2 (4.4 bar), 5% Pd/C, AcOEt, r.t., 3 h. *c*) ^{t}BuCl, $FeCl_3$, CH_2Cl_2, 0°, 1 h.

For the synthesis of **11d** (R = ^{i}Pr), **11a** was reduced to the known alcohol **25** [29], which was converted to its acetate **26** [29d]. Acylation of **26**, followed by *Grignard* reaction afforded diol **28**, which was hydrogenated to the alcohol **29** and oxidized to give **11d**.

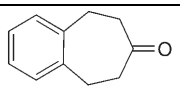
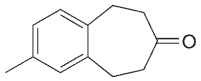
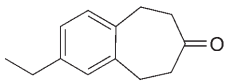
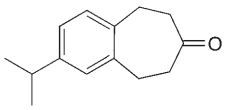
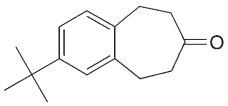
The olfactory evaluations of the 5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-ones **11** (*Table 3*) clearly established that they belong to the worst series, in which the best compound **11b** presents an odor reminiscent of the well-known *Lilial*®, *Cyclosal*®, *Heliopropanal*® family. However, in general, all these compounds are weak and do not possess the desired marine character.

Scheme 6. *Synthesis of 5,6,8,9-Tetrahydro-2-isopropyl-7*H*-benzocyclohepten-7-one* (**11d**)



a) $NaBH_4$, EtOH, r.t., 3 h. *b*) Ac_2O, pyridine, 100°, 2 h. *c*) AcCl, $AlCl_3$, CH_2Cl_2, 0°, 4 h. *d*) MeMgCl, THF, 20–60°, 2 h. *e*) H_2 (1 atm), 10% Pd/C, EtOH, r.t., 3 h. *f*) Pyridinium chlorochromate (PCC), CH_2Cl_2, r.t., 1 h.

Table 3. *Olfactory Profiles for 5,6,8,9-Tetrahydro-7*H*-benzocyclohepten-7-ones* **11**

Tetrahydrobenzocycloheptenone **11**		Olfactory profile
11a[a])		dirty, phenolic, ink, urinous
11b		*Lilial*®, *Cyclosal*®, gassy, metallic, *Heliopropanal*®/*Helional*®/*Tropional*®, green
11c		paper, green, weak
11d		vaguely floral, weak
11e[b])		vaguely phenolic, weak, without character

[a]) Reported in [26]. [b]) Reported in [27].

2.4. *Influence of the Conformation of the Seven-membered Ring and General Comments on Structure–Activity Relationships.* Analysis of the results obtained show different odor activities. While the 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9** frequently

have strong marine-ozone odors, this is not the case for the dicarba analogues **11**. The 4,5-dihydro-1-benzoxepin-3(2*H*)-ones **10** display intermediate activities. We suspected that the large difference between these three series could be partially due to the preferred conformation of the seven-membered ring.

To test this hypothesis, we investigated only the three structures substituted by a Me group at the same position: 7-methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one (=*Calone 1951*®; **9b**), 4,5-dihydro-7-methyl-1-benzoxepin-3(2*H*)-one (**10b**), and 5,6,8,9-tetrahydro-2-methyl-7*H*-benzocyclohepten-7-one (**11b**). It is evident that another substitution at this position should not dramatically influence the conformation of the seven-membered ring. Each molecule was first minimized by the standard Monte-Carlo procedure as implemented in MacroModel, by using the *Merck* molecular force field MMFF 94 [30]. For each molecule, the main conformers were then minimized at the DFT (density-functional-theory) level (B3LYP/6.31G**) by the Jaguar software [31], which usually gives the best results. The relative energies obtained are reported in *Table 4*.

Table 4. *Calculated Relative Energies of the Two Main Conformers of Compounds* **9b**, **10b**, *and* **11b**

	Pseudo-twist-boat	Pseudo-chair	Activity
7-Methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one (=*Calone 1951*®; **9b**)	0 kcal/mol	+ 2.7 kcal/mol	strong
4,5-Dihydro-7-methyl-1-benzoxepin-3(2*H*)-one (**10b**)	0 kcal/mol	+ 0.2 kcal/mol	weak
5,6,8,9-Tetrahydro-2-methyl-7*H*-benzocyclohepten-7-one (**11b**)	0 kcal/mol	– 2.9 kcal/mol	none

It can be seen that the bicyclic compounds under investigation can adopt two main conformations (see *Fig. 3*). In the first one, the seven-membered ring adopts a pseudo-twist-boat conformation where the C=O group stays in (or very close to) the plane defined by the fused benzene ring. In the second conformation, the seven-membered ring adopts a pseudo-chair conformation in which the C=O group is out of the plane defined by the benzene ring. In both cases, the C=O group points to the direction opposite to the benzene moiety and could be a key factor for a putative interaction with the receptor by H-bonding. As shown in *Table 4* and *Fig. 3*, 7-methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one (*Calone 1951*®; **9b**) prefers the pseudo-twist-boat conformation, while 5,6,8,9-tetrahydro-2-methyl-7*H*-benzocyclohepten-7-one (**11b**) adopts preferentially the pseudo-chair conformation. Perhaps the nonactivity of the series of compounds **11** could be explained by this conformational difference. According to our calculations for 4,5-dihydro-7-methyl-1-benzoxepin-3(2*H*)-one (**10b**), the two conformations are very similar in energy and could explain the intermediate activity of the family of compounds **10**.

With the data collected from the three series of bicyclic compounds **9**–**11**, we can propose some general rules for optimum marine-watery-ozone character, summarized as follows: *i*) With regard to both the strength and the marine character, 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9** are better than 4,5-dihydro-1-benzoxepin-3(2*H*)-ones **10**, which themselves are much better than 5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-

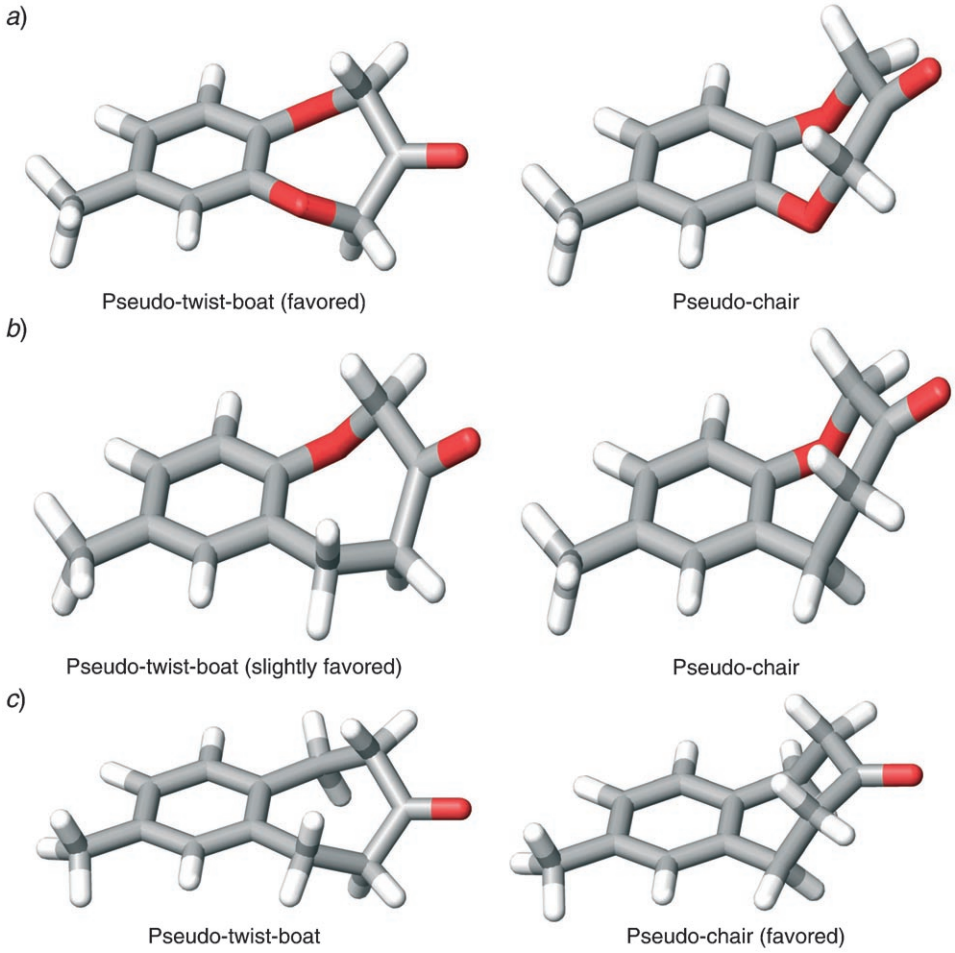


Fig. 3. *Optimized geometries of* a) *7-Methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one* (= *Calone 1951*®; **9b**), b) *4,5-dihydro-7-methyl-1-benzoxepin-3(2*H*)-one* (**10b**), *and* c) *5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-one* (**11b**)*: Comparison of the two lowest-energy conformations*

ones **11**. In our opinion, this could be due to the geometry of the seven-membered ring. *ii*) Substitution at the α-positions of the carbonyl group dramatically changes the odor profile and decreases the odor intensity. This unfavorable factor is probably not due to a change of geometry of the seven-membered ring (which was established to be similar to the unsubstituted analogue by DFT calculations) but due to the lower accessibility of the C=O group, which renders H-bonding less favorable. *iii*) The absence of an alkyl substituent at the aromatic ring decreases the intensity of the odor and leads to a phenolic note. *iv*) When the compounds are not symmetrical, as for 4,5-dihydro-1-benzoxepin-3(2*H*)-ones **9**, there is almost no difference between substitution at

position C(7) or C(8). These are the best positions for an aromatic substituent. *v*) Substitution at positions C(6) or C(9) is less favourable. *vi*) In all cases investigated, dialkylation of the aromatic ring (even in positions C(7) and C(8) has a negative effect. *vii*) To maximize the odor intensity, the optimum size of the substituent must be between C_3 and C_6. Substituents branched at the benzylic position clearly decrease the odor intensity. A ramification has a lower effect when it is further away from the aromatic ring.

3. Conclusions. – In summary, we synthesized or re-synthesized a large series of 2*H*-1,5-benzodioxepin-3(4*H*)-ones **9**, 4,5-dihydro-1-benzoxepin-3(2*H*)-ones **10**, and 5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-ones **11**. We meticulously described the odor profile of each compound and discussed relevant structure – odor relationships. In particular, we postulated a correlation between the conformation of the seven-membered ring and the activities of these compounds. We also clarified the effect of the position and the size of the alkyl substituent at the aromatic ring. The work presented here is only a part of our investigations on marine-note odorants. Other aspects of our research in this domain will be published in due course.

We wish to thank Mr. *R. Brauchli*, *Firmenich SA*, for NMR analysis, Dr. *R. L. Snowden*, *Firmenich SA,* for his daily enthusiasm and support, and also all our colleagues for the fruitful discussions and correction of this manuscript. And last but not least, we are especially grateful to all the colleagues of Dr. *P. A. Blanc*, perfumers at *Firmenich SA*, for their assistance in the olfactory evaluations.

Experimental Part

1. *General*. All reactions were performed under N_2. GLC and prep. GLC: *Hewlett-Packard 6890* instrument equipped with a flame-ionization detector (250°) coupled to a *Hewlett-Packard Chemstation 6.03*; capillary columns *Chrompack-DB-Wax* (15 m, 0.25 mm) and *-DB-1* (15 m, 0.25 mm). Flash chromatography (FC): silica gel of 60 Å quality in prepacked cartridges from *Interchim*. Bulb-to-bulb distillation: *Büchi GKR-50* oven; b.p. correspond to the air temp. NMR: *Bruker WH-400*, *Bruker AMX-360*; ^{1}H at 400 and ^{13}C at 90 MHz; $CDCl_3$ soln. when not specified; chemical shifts δ in ppm rel. to $SiMe_4$, *J* in Hz. MS: *Varian MAT-112* spectrometer (*ca.* 70 eV); intensities in % rel. to the base peak (100%).

The molecular-mechanics calculations were performed with the program MacroModel version 8.1 [30], and the *ab initio* calculations with the Jaguar software [31].

2. *Catechols* (= *Benzene-1,2-diols*) **12**. Benzene-1,2-diol (**12a**), 4-methylbenzene-1,2-diol (**12b**), 3-methylbenzene-1,2-diol (**12c**), 4-ethylbenzene-1,2-diol (**12f**), 4-(*tert*-butyl)benzene-1,2-diol (**12k**), 4-(1,1-dimethylpropyl)benzene-1,2-diol (**12o**), 2,3-dihydro-1*H*-indene-5,6-diol (**12r**), and naphthalene-2,3-diol (**12s**) were purchased from commercial sources. Several other catechols were synthesized as described in the literature: 3-isopropylbenzene-1,2-diol (**12j**), 4-isopropylbenzene-1,2-diol (**12i**) and 3,5-diisopropylbenzene-1,2-diol (**12t**) [14], 3-propylbenzene-1,2-diol (**12h**) [32], 4-propylbenzene-1,2-diol (**12g**) [33], 3,6-dimethylbenzene-1,2-diol (**12e**) [34].

4-(1-Methylpropyl)benzene-1,2-diol (**12n**) *and 3-(1-Methylpropyl)benzene-1,2-diol* (**12l**). As described in [14], with **12a** (110 g), butan-2-ol (89 g), 85% phosphoric acid (150 ml), and toluene (150 ml): 44 g (26%) of **12n**/**12l** 6 :4 which were separated by distillation.

Data of **12n**: B.p. $90°/5 \cdot 10^{-1}$ mbar. ^{1}H-NMR: 0.80 (*t*, *J* = 8, 3 H); 1.18 (*d*, *J* = 7, 3 H); 1.47 – 1.57 (*m*, 2 H); 2.20 (br. *s*, 2 H); 2.41 – 2.53 (*m*, 1 H); 6.61 (*dd*, *J* = 7, 2, 1 H); 6.71 (*d*, *J* = 2, 1 H); 6.78 (*d*, *J* = 7, 1 H). ^{13}C-NMR: 12.2 (*q*); 22.0 (*q*); 31.2 (*t*); 41.0 (*d*); 114.1 (*d*); 115.3 (*d*); 119.6 (*d*); 141.2 (*s*); 141.3 (*s*); 143.4 (*s*). MS: 166 (25, M^+), 151 (3), 138 (9), 137 (100), 123 (11), 119 (12), 91 (23), 77 (6), 65 (6), 55 (4), 51 (4), 39 (4), 29 (3), 27 (4).

Data of **12l**: B.p. $80°/5 \cdot 10^{-1}$ mbar. ^{1}H-NMR: 0.86 (*t*, *J* = 8, 3 H); 1.22 (*d*, *J* = 7, 3 H); 1.47 – 1.72 (*m*, 2 H); 2.20 (*s*, 2 H); 2.92 – 3.03 (*m*, 1 H); 6.66 – 6.80 (*m*, 3 H). ^{13}C-NMR: 12.2 (*q*); 20.5 (*q*); 29.8 (*t*); 34.1

(*d*); 112.5 (*d*); 119.0 (*d*); 120.1 (*d*); 134.1 (*s*); 141.9 (*s*); 143.1 (*s*). MS: 166 (29, M^+), 138 (9), 137 (100), 123 (14), 119 (14), 91 (32), 79 (6), 77 (8), 65 (9), 55 (4), 51 (5), 39 (7), 29 (5), 27 (6).

4-Cyclopentylbenzene-1,2-diol (**12p**) *and 3-Cyclopentylbenzene-1,2-diol* (**12q**). As described in [14], with **12a** (110 g), cyclopentanol (103 g), 85% phosphoric acid (150 ml), and toluene (150 ml): 48 g (28%) of **12p**/**12q** 55 : 45 which were separated by distillation.

Data of **12p**: B.p. $165^\circ/1 \cdot 10^{-1}$ mbar. ^{1}H-NMR: 1.42 – 1.54 (*m*, 2 H); 1.57 – 1.68 (*m*, 2 H); 1.70 – 1.81 (*m*, 2 H); 1.93 – 2.04 (*m*, 2 H); 2.21 (*s*, 2 H); 2.80 – 2.91 (*m*, 1 H); 6.66 (*dd*, $J = 8, 2$, 1 H); 6.76 (*d*, $J = 2$, 1 H); 6.77 (*d*, $J = 8$, 1 H). ^{13}C-NMR: 25.4 (*t*, 2 C); 34.6 (*t*, 2 C); 45.3 (*d*); 114.3 (*d*); 115.3 (*d*); 119.5 (*d*); 140.0 (*s*); 141.2 (*s*); 143.3 (*s*). MS: 178 (100, M^+), 160 (10), 150 (12), 149 (43), 145 (14), 137 (26), 136 (45), 135 (12), 132 (13), 131 (40), 124 (16), 123 (94), 122 (23), 117 (6), 115 (6), 110 (20), 107 (18), 104 (10), 103 (30), 94 (6), 91 (17), 89 (9), 79 (18), 78 (12), 77 (32), 67 (10), 65 (12), 63 (10), 55 (9), 53 (10), 51 (16), 41 (11), 39 (20), 29 (5), 27 (10).

Data of **12q**: B.p. $175 – 180^\circ/9 \cdot 10^{-2}$ mbar. ^{1}H-NMR: 1.53 – 1.70 (*m*, 4 H); 1.73 – 1.85 (*m*, 2 H); 1.97 – 2.09 (*m*, 2 H); 2.20 (*s*, 2 H); 3.16 – 3.28 (*m*, 1 H); 6.68 (*dd*, $J = 8, 2$, 1 H); 6.73 (*dd*, $J = 8, 8$, 1 H); 6.79 (*dd*, $J = 8$, 2, 1 H). ^{13}C-NMR: 25.4 (*t*, 2 C); 33.0 (*t*, 2 C); 39.0 (*d*); 112.7 (*d*); 119.0 (*d*); 120.2 (*d*); 132.9 (*s*); 141.9 (*s*); 143.0 (*s*). MS: 178 (100, M^+), 161 (10), 150 (15), 149 (74), 145 (9), 137 (19), 136 (69), 132 (15), 131 (61), 124 (17), 123 (66), 117 (6), 110 (25), 107 (11), 104 (12), 103 (40), 91 (16), 89 (16), 81 (5), 79 (10), 78 (10), 77 (33), 67 (9), 65 (10), 63 (11), 55 (9), 53 (11), 51 (17), 41 (11), 39 (20), 39 (20), 29 (6), 27 (12).

3. *2*H*-1,5-Benzodioxepin-3(4*H*)-ones* **9**. *General Procedure 1* (*G.P. 1*). K_2CO_3 (7.78 g, 56.4 mmol) and NaI (1.70 g, 11.3 mmol) were suspended in acetone (110 ml). To this suspension, 1,3-dichloropropan-2-one (7.16 g, 56.4 mmol) and **12g** (9.02 g, 56.4 mol) in acetone (50 ml) were added dropwise within 2 h, under reflux at 56° with stirring and under N_2. The mixture was refluxed for 2 h and then cooled down. Toluene (50 ml) was added, and the mixture was distilled under vacuum to remove the acetone. The org. layer was washed twice with H_2O, dried ($MgSO_4$), and concentrated to give 10.6 g of a dark-colored oil. FC (silica gel, AcOEt/heptane 5 : 95) gave **9g** (55%).

For a full description of **9m** and **9u**, see [7].

*2*H*-1,5-Benzodioxepin-3(4*H*)-one* (**9a**). According to the *G.P. 1* in 55% yield from **12a**. ^{1}H-NMR: 4.71 (*s*, 4 H); 6.99 (*s*, 3 H). ^{13}C-NMR: 75.7 (2*t*); 121.0 (2*d*); 123.9 (2*d*); 148.4 (2*s*); 204.4 (*s*). MS: 164 (65, M^+), 122 (6), 121 (27), 108 (11), 80 (100), 78 (8), 77 (8), 76 (9), 64 (9), 63 (16), 52 (40), 51 (13), 50 (17), 39 (8).

*7-Methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one* (**9b**). According to the *G.P. 1* in 51% yield from **12b**. ^{1}H-NMR: 2.27 (*s*, 3 H); 4.67 (*s*, 2 H); 4.70 (*s*, 2 H); 6.76 (*dd*, $J = 8, 2, 1$ H); 6.81 (*d*, $J = 2, 1$ H); 6.89 (*d*, $J =$ 8, 1 H). ^{13}C-NMR: 20.5 (*q*); 75.5 (*t*); 75.8 (*t*); 120.7 (*d*); 121.2 (*d*); 124.3 (*d*); 133.8 (*s*); 146.1 (*s*); 148.0 (*s*); 204.8 (*s*). MS: 178 (100, M^+), 136 (7), 135 (21), 108 (7), 94 (56), 91 (11), 89 (8), 78 (6), 77(9), 66 (38), 65 (9), 63 (7), 51 (8), 39 (7).

*6-Methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one* (**9c**). According to the *G.P. 1* in 36% yield from **12c**. ^{1}H-NMR: 2.23 (*s*, 3 H); 4.67 (*s*, 2 H); 4.72 (*s*, 2 H); 6.81 – 6.88 (*m*, 3 H). ^{13}C-NMR: 16.1 (*q*); 75.5 (*t*); 75.6 (*t*); 118.8 (*d*); 122.9 (*d*); 125.4 (*d*); 130.3 (*s*); 146.9 (*s*); 148.4 (*s*); 204.9 (*s*). MS: 178 (100, M^+), 150 (4), 136 (11), 135 (31), 108 (4), 105 (4), 95 (6), 94 (78), 91 (13), 89 (11), 79 (8), 78 (7), 77 (14), 66 (65), 65 (15), 63 (12), 52 (9), 51 (15), 50 (7), 42 (5), 39 (19), 27 (5).

*2-Methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one* (**9d**). According to [6] in 42% yield from **12a**. ^{1}H-NMR: 1.48 (*d*, $J = 6$, 3 H); 4.58 (*d*, $J = 16$, 1 H); 4.81 (*d*, $J = 16$, 1 H); 5.04 (*q*, $J = 6$, 1 H); 6.88 – 7.05 (*m*, 4 H). ^{13}C-NMR: 15.1 (*q*); 75.7 (*t*); 79.6 (*d*); 120.8 (*d*); 121.0 (*d*); 123.4 (*d*); 123.8 (*d*); 148.2 (*s*); 148.2 (*s*); 205.4 (*s*). MS: 178 (81, M^+), 150 (8), 136 (3), 135 (5), 122 (9), 121 (100), 110 (16), 109 (32), 108 (6), 91 (6), 81 (14), 80 (52), 77 (9), 65 (10), 63 (17), 52 (28), 51 (14), 50 (14), 42 (13), 39 (11), 27 (11).

*6,9-Dimethyl-2*H*-1,5-benzodioxepin-3(4*H*)-one* (**9e**). According to the *G.P. 1* in 59% yield from **12e**. ^{1}H-NMR: 2.19 (*s*, 6 H); 4.70 (*s*, 4 H); 6.74 (*s*, 2 H). ^{13}C-NMR: 15.9 (2*q*); 75.5 (2*t*); 124.4 (2*d*); 127.6 (2*d*); 147.0 (2*s*); 205.4 (*s*). MS: 192 (100, M^+), 150 (12), 149 (39), 122 (7), 121 (4), 108 (67), 107 (18), 103 (6), 94 (8), 93 (10), 91 (32), 80 (38), 79 (47), 78 (10), 77 (27), 65 (18), 63 (9), 53 (9), 52 (9), 51 (16), 50 (7), 42 (7), 39 (19), 27 (10).

*7-Ethyl-2*H*-1,5-benzodioxepin-3(4*H*)-one* (**9f**). According to the *G.P. 1* in 65% yield from **12f**. ^{1}H-NMR: 1.20 (*t*, $J = 8$, 3 H); 2.57 (*q*, $J = 8, 2$ H); 4.66 (*s*, 2 H); 4.69 (*s*, 2 H); 6.79 (*dd*, $J = 8, 2, 1$ H); 6.83

(*d*, *J* = 2, 1 H); 6.91 (*d*, *J* = 8, 1 H). ^{13}C-NMR: 15.5 (*q*); 28.0 (*t*); 75.5 (*t*); 75.8 (*t*); 120.0 (*d*); 120.7 (*d*); 123.1 (*d*); 140.3 (*s*); 146.2 (*s*); 148.1 (*s*); 204.8 (*s*). MS: 192 (100, M^+), 177 (29), 150 (12), 149 (88), 136 (6), 135 (20), 123 (9), 122 (6), 121 (7), 108 (16), 105 (9), 94 (5), 91 (18), 89 (7), 80 (15), 79 (32), 78 (8), 77 (29), 67 (5), 65 (13), 63 (11), 55 (6), 51 (18), 39 (13), 27 (7).

*7-Propyl-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**9g**). According to the *G.P. 1* in 55% yield from **12g**. M.p. 32–33°. ^{1}H-NMR: 0.93 (*d*, *J* = 8, 3 H); 1.50–1.73 (*m*, 2 H); 2.50 (*t*, *J* = 6, 2 H); 4.66 (*s*, 2 H); 4.70 (*s*, 2 H); 6.76 (*dd*, *J* = 2, 8, 1 H); 6.80 (*d*, *J* = 2, 1 H); 6.90 (*d*, *J* = 2, 1 H). ^{13}C-NMR: 13.8 (*q*); 24.4 (*t*); 37.1 (*t*); 75.5 (*t*); 75.8 (*t*); 120.5 (*d*); 120.6 (*d*); 123.7 (*d*); 138.7 (*s*); 146.2 (*s*); 148.0 (*s*); 204.8 (*s*). MS: 206 (50, M^+), 178 (12), 177 (100), 149 (30), 135 (10), 123 (7), 121 (6), 105 (6), 91 (9), 79 (7), 77 (19), 65 (12), 63 (7), 55 (9), 51 (11), 39 (9), 27 (7).

*6-Propyl-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**9h**). According to the *G.P. 1* in 41% yield from **12h**. ^{1}H-NMR: 0.94 (*d*, *J* = 8, 3 H); 1.51–1.66 (*m*, 2 H); 2.59 (*t*, *J* = 7, 2 H); 4.70 (*s*, 4 H); 6.85 (br. *s*, 3 H). ^{13}C-NMR: 14.0 (*q*); 23.5 (*t*); 32.2 (*t*); 75.4 (*t*); 75.6 (*t*); 118.5 (*d*); 123.1 (*d*); 124.6 (*d*); 135.0 (*s*); 146.7 (*s*); 148.6 (*s*); 205.0 (*s*). MS: 206 (100, M^+), 178 (14), 177 (100), 164 (7), 150 (14), 149 (85), 135 (15), 121 (8), 115 (5), 107 (10), 105 (12), 103 (8), 94 (10), 93 (24), 91 (31), 89 (8), 79 (22), 78 (10), 77 (43), 65 (31), 63 (14), 55 (7), 53 (7), 51 (26), 42 (8), 39 (25), 29 (17), 27 (19).

*7-Isopropyl-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**9i**). According to the *G.P. 1* in 60% yield from **12i**. ^{1}H-NMR: 1.21 (*d*, *J* = 7, 6 H); 2.83 (*sept.*, *J* = 7, 1 H); 4.67 (*s*, 2 H); 4.70 (*s*, 2 H); 6.82 (*dd*, *J* = 7, 2, 1 H); 6.86 (*d*, *J* = 2, 1 H); 6.92 (*d*, *J* = 7, 1 H). ^{13}C-NMR: 24.0 (2*q*); 33.3 (*d*); 75.5 (*t*); 75.8 (*t*); 118.5 (*d*); 120.7 (*d*); 121.7 (*d*); 145.0 (*s*); 146.2 (*s*); 148.0 (*s*); 208.2 (*s*). MS: 206 (45, M^+), 192 (12), 191 (100), 163 (14), 121 (5), 119 (7), 107 (9), 105 (6), 91 (22), 79 (10), 77 (13), 65 (7).

*6-Isopropyl-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**9j**). According to the *G.P. 1* in 23% yield from **12j**. ^{1}H-NMR: 1.21 (*d*, *J* = 7, 6 H); 3.30 (*sept.*, *J* = 7, 1 H); 4.70 (*s*, 4 H); 6.80–6.87 (*m*, 1 H); 6.89–6.95 (*m*, 2 H). ^{13}C-NMR: 22.9 (2*q*); 27.2 (*d*); 75.4 (*t*); 75.7 (*t*); 118.3 (*d*); 120.8 (*d*); 123.4 (*d*); 140.9 (*s*); 146.1 (*s*); 148.6 (*s*); 205.0 (*s*). MS: 206 (69, M^+), 192 (12), 191 (100), 163 (36), 149 (6), 135 (12), 133 (20), 121 (5), 119 (7), 117 (5), 115 (6), 107 (21), 105 (14), 103 (8), 93 (7), 91 (41), 89 (8), 79 (26), 78 (11), 77 (33), 65 (19), 63 (11), 55 (5), 53 (9), 51 (17), 41 (10), 39 (21), 29 (8), 27 (15).

*7-(*tert-*Butyl)-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**9k**). According to the *G.P. 1* in 56% yield from **12k**. M.p. 98–99°. ^{1}H-NMR: 1.28 (*s*, 9 H); 4.68 (*s*, 2 H); 4.70 (*s*, 2 H); 6.92 (*d*, *J* = 7, 1 H); 6.98 (*dd*, *J* = 7, 2, 1 H); 7.01 (*d*, *J* = 2, 1 H). ^{13}C-NMR: 31.3 (3*q*); 34.3 (*s*); 75.6 (*t*); 75.7 (*t*); 117.8 (*d*); 120.4 (*d*); 120.7 (*d*); 145.9 (*s*); 147.4 (*s*); 147.7 (*s*); 204.8 (*s*). MS: 220 (24, M^+), 206 (14), 205 (100), 177 (13), 135 (5), 121 (5), 105 (4), 91 (7), 77 (6).

*6-(1-Methylpropyl)-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**9l**). According to the *G.P. 1* in 39% yield from **12l**. ^{1}H-NMR: 0.84 (*t*, *J* = 7, 3 H); 1.19 (*d*, *J* = 7, 3 H); 1.50–1.64 (*m*, 2 H); 3.01–3.14 (*m*, 1 H); 4.69 (*s*, 2 H); 4.71 (*s*, 2 H); 6.85–6.94 (*m*, 3 H). ^{13}C-NMR: 12.2 (*q*); 20.7 (*q*); 30.1 (*t*); 34.0 (*d*); 75.3 (*t*); 75.7 (*t*); 118.2 (*d*); 121.5 (*d*); 123.4 (*d*); 139.8 (*s*); 146.5 (*s*); 148.6 (*s*); 205.1 (*s*). MS: 220 (32, M^+), 192 (13), 191 (100), 177 (6), 135 (7), 133 (17), 107 (12), 105 (8), 91 (18), 79 (8), 77 (15), 65 (8), 51 (6), 39 (7), 29 (9), 27 (8).

*7-(1-Methylpropyl)-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**9n**). According to the *G.P. 1* in 49% yield from **12n**. ^{1}H-NMR: 0.84 (*t*, *J* = 8, 3 H); 1.19 (*d*, *J* = 7, 3 H); 1.50–1.63 (*m*, 2 H); 3.02–3.14 (*m*, 1 H); 4.69 (*s*, 2 H); 4.72 (*s*, 2 H); 6.82–6.95 (*m*, 3 H). ^{13}C-NMR: 12.2 (*q*); 21.8 (*q*); 31.1 (*t*); 40.9 (*d*); 75.5 (*t*); 75.8 (*t*); 119.1 (*d*); 120.6 (*d*); 122.3 (*d*); 143.8 (*s*); 146.2 (*s*); 148.0 (*s*); 204.9 (*s*). MS: 220 (23, M^+), 192 (13), 191 (100), 177 (5), 107 (6), 91 (13), 79 (5), 77 (10), 65 (6), 55 (5), 39 (4), 29 (5), 27 (5).

*7-(1,1-Dimethylpropyl)-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**9o**). According to the *G.P. 1* in 40% yield from **12o**. ^{1}H-NMR: 0.69 (*d*, *J* = 8, 3 H); 1.24 (*s*, 6 H); 1.49 (*d*, *J* = 8, 2 H); 4.69 (*s*, 2 H); 4.71 (*s*, 2 H); 6.89–6.94 (*m*, 2 H); 6.95 (br. *s*, 1 H). ^{13}C-NMR: 9.1 (*q*); 28.4 (2*q*); 36.8 (*t*); 37.5 (*s*); 75.5 (*t*); 75.7 (*t*); 118.5 (*d*); 120.2 (*d*); 121.3 (*d*); 145.7 (*s*); 145.8 (*s*); 147.6 (*s*); 204.8 (*s*). MS: 234 (14, M^+), 206 (15), 205 (100), 177 (15), 121 (4), 91 (10), 77 (10), 65 (5), 55 (8), 51 (5), 41 (9), 39 (7), 29 (7), 27 (7).

*7-Cyclopentyl-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**9p**). According to the *G.P. 1* in 46% yield from **12p**. ^{1}H-NMR: 1.43–1.58 (*m*, 2 H); 1.59–1.72 (*m*, 2 H); 1.73–1.84 (*m*, 2 H); 1.96–2.09 (*m*, 2 H); 2.83–2.96 (*m*, 1 H); 4.65 (*s*, 2 H); 4.67 (*s*, 2 H); 6.82 (*dd*, *J* = 7,2, 1 H); 6.87 (*d*, *J* = 2, 1 H); 6.90 (*d*, *J* = 8, 1 H). ^{13}C-NMR: 25.4 (*t*); 34.5 (*t*); 45.1 (*d*); 75.5 (*t*); 75.7 (*t*); 119.2 (*d*); 120.6 (*d*); 122.3 (*d*); 142.6 (*s*); 146.1 (*s*); 148.0 (*s*); 204.8 (*s*). MS: 232 (100, M^+), 204 (7), 203 (39), 190 (16), 177 (15), 175 (19), 162 (7), 149 (10),

147 (18), 146 (17), 135 (6), 133 (7), 131 (12), 120 (9), 119 (14), 117 (9), 115 (14), 106 (12), 103 (16), 92 (11), 91 (34), 89 (10), 78 (24), 77 (20), 65 (11), 63 (9), 55 (7), 51 (12), 41 (11), 39 (14), 29 (8), 27 (10).

*6-Cyclopentyl-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**9q**). According to the *G.P. 1* in 47% yield from **12q**. ^{1}H-NMR: 1.48–1.61 (*m*, 2 H); 1.61–1.73 (*m*, 2 H); 1.73–1.85 (*m*, 2 H); 1.95–2.07 (*m*, 2 H); 3.23–3.35 (*m*, 1 H); 4.71 (*s*, 2 H); 4.72 (*s*, 2 H); 6.84 (*dd*, *J* = 7, 2, 1 H); 6.90 (*d*, *J* = 2, 1 H); 6.93 (*d*, *J* = 8, 1 H). ^{13}C-NMR: 25.5 (*t*); 33.3 (*t*); 39.3 (*d*); 75.4 (*t*); 75.7 (*t*); 118.3 (*d*); 121.5 (*d*); 123.2 (*d*); 138.6 (*s*); 146.7 (*s*); 148.6 (*s*); 205.1 (*s*). MS: 232 (100, M^+), 203 (25), 191 (12), 190 (16), 177 (13), 175 (17), 163 (9), 161 (7), 149 (8), 147 (12), 133 (6), 131 (12), 120 (9), 117 (7), 115 (14), 106 (12), 103 (14), 92 (10), 91 (33), 89 (9), 78 (18), 77 (19), 65 (11), 63 (9), 55 (5), 51 (11), 41 (10), 39 (14), 29 (6), 27 (8).

*8,9-Dihydro-2*H,*7*H-*indeno[5,6-*b*][1,4]dioxepin-3(4*H*)-one* (**9r**). According to the *G.P. 1* in 54% yield from **12r**. ^{1}H-NMR: 2.06 (*quint.*, *J* = 8, 2 H); 2.81 (*t*, *J* = 8, 4 H); 4.65 (*s*, 4 H); 6.84 (*s*, 2 H). ^{13}C-NMR: 26.0 (*t*); 32.5 (2*t*); 75.6 (2*t*); 116.3 (2*d*); 139.7 (2*s*); 146.9 (2*s*); 204.4 (*s*). MS: 204 (100, M^+), 175 (8), 161 (8), 147 (7), 134 (22), 133 (12), 131 (10), 120 (46), 119 (10), 117 (12), 115 (19), 106 (38), 103 (19), 92 (21), 91 (61), 89 (8), 78 (12), 77 (17), 65 (11), 63 (14), 53 (6), 51 (13), 50 (8), 42 (7), 39 (15), 29 (6), 27 (10).

*2*H-*Naphtho[2,3-*b*][1,4]dioxepin-3(4*H*)-one* (**9s**). According to the *G.P. 1* in 20% yield from **12s**. ^{1}H-NMR: 4.77 (*s*, 4 H); 7.34–7.41 (*m*, 2 H); 7.44 (*s*, 2 H); 7.66–7.73 (*m*, 2 H). ^{13}C-NMR: 75.5 (2*t*); 117.2 (2*d*); 125.4 (2*d*); 126.7 (2*d*); 130.5 (2*s*); 148.3 (2*s*); 204.9 (*s*). MS: 214 (100, M^+), 172 (12), 171 (53), 131 (9), 130 (28), 128 (16), 127 (13), 126 (15), 115 (14), 114 (26), 113 (11), 102 (50), 88 (8), 76 (9), 63 (10), 51 (8).

*6,8-Diisopropyl-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**9t**). According to the *G.P. 1* in 22% yield from **12t**. ^{1}H-NMR: 1.21 (*d*, *J* = 7, 12 H); 2.82 (*sept.*, *J* = 7, 1 H); 3.27 (*sept.*, *J* = 7, 1 H); 4.68 (*s*, 2 H); 4.70 (*s*, 2 H); 6.72 (*d*, *J* = 2, 1 H); 6.78 (*d*, *J* = 2, 1 H). ^{13}C-NMR: 22.9 (2*q*); 24.0 (2*q*); 27.5 (*d*); 33.6 (*d*); 75.3 (*t*); 75.8 (*t*); 115.7 (*d*); 119.0 (*d*); 140.4 (*s*); 144.0 (*s*); 144.3 (*s*); 148.3 (*s*); 205.4 (*s*). MS: 248 (46, M^+), 234 (16), 233 (100), 205 (17), 191 (6), 177 (6), 175 (4), 163 (11), 149 (10), 147 (5), 135 (9), 133 (5), 121 (7), 119 (6), 117 (6), 115 (9), 105 (9), 91 (19), 79 (7), 77 (12), 65 (6), 55 (6), 53 (6), 51 (5), 43 (15), 41 (13), 39 (8), 29 (6), 27 (11).

4. *3,4-Dihydrocoumarins* (= *3,4-Dihydro-2*H-*1-benzopyran-2-ones*) **19**. *7-Isopropyl-2*H-*1-benzopyran-2-one* (**22g**). According to [20] in 67% yield from 3-isopropylphenol. ^{1}H-NMR: 1.28 (*d*, *J* = 7, 6 H); 2.99 (*sept.*, 1 H); 6.35 (*d*, *J* = 8, 1 H); 7.16 (*dd*, *J* = 8, 1, 1 H); 7.17 (*s*, 1 H); 7.41 (*d*, *J* = 8, 1 H); 7.69 (*d*, *J* = 8, 1 H). ^{13}C-NMR: 23.6 (2*q*); 34.3 (*t*); 114.4 (*d*); 115.5 (*d*); 116.8 (*s*); 123.1 (*d*); 127.7 (*d*); 143.4 (*d*); 154.0 (*s*); 154.3 (*s*); 161.1 (*s*). MS: 188 (43, M^+), 174 (13), 173 (100), 145 (7), 128 (10), 127 (5), 117 (9), 115 (14), 91 (6), 89 (3), 77 (2), 63 (4), 58 (2), 51 (3), 39 (2).

Hydrogenation of Coumarins **22** *into 3,4-Dihydrocoumarins* **19**. *General Procedure 2* (*G.P. 2*). A 1M soln. of the substituted coumarin **22** in AcOEt in the presence of 10% (*w*/*w*) of humid 5% Pd/C (*Degussa*) was shaken in a *Parr* apparatus under 3 bars of H_2. The mixture was filtered and the filtrate concentrated, affording the dihydrocoumarin **19** in nearly quantitative yield (95–100%).

*6-Ethyl-3,4-dihydro-2*H-*1-benzopyran-2-one* (**19d**). According to the *G.P. 2* in 96% yield from **22d** [35]. ^{1}H-NMR: 1.22 (*t*, *J* = 8, 3 H); 2.61 (*q*, *J* = 8, 2 H); 2.76 (*dd*, *J* = 9, 7, 2 H); 2.96 (*dd*, *J* = 9, 7, 2 H); 6.94 (*d*, *J* = 8, 1 H); 7.01 (br. *s*, 1 H); 7.06 (*dd*, *J* = 8, 1, 1 H). ^{13}C-NMR: 15.7 (*q*); 23.8 (*t*); 28.2 (*t*); 29.3 (*t*); 116.7 (*d*); 122.3 (*s*); 127.3 (*d*); 127.5 (*d*); 140.4 (*s*); 150.0 (*s*); 168.8 (*s*). MS: 176 (86, M^+), 162 (6), 161 (50), 148 (11), 134 (26), 133 (100), 106 (8), 105 (7), 103 (6), 91 (28), 79 (5), 78 (5), 77 (11), 65 (6), 51 (6), 39 (4), 27 (2).

*3,4-Dihydro-7-isopropyl-2*H-*1-benzopyran-2-one* (**19g**). According to the *G.P. 2* in 98% yield from **22g**. ^{1}H-NMR: 1.23 (*d*, *J* = 7, 6 H); 2.70–2.80 (*m*, 2 H); 2.89 (*sept.*, *J* = 7, 1 H); 2.91–3.00 (*m*, 2 H); 6.91 (*d*, *J* = 1, 1 H); 6.96 (*dd*, *J* = 7, 1, 1 H); 7.10 (*d*, *J* = 7, 1, 1 H). ^{13}C-NMR: 23.4 (*t*); 23.8 (2*q*); 29.4 (*t*); 33.8 (*d*); 114.8 (*d*); 119.8 (*s*); 122.5 (*d*); 127.8 (*d*); 149.7 (*s*); 152.0 (*s*); 168.8 (*s*). MS: 190 (63, M^+), 176 (12), 175 (100), 148 (15), 147 (37), 135 (11), 133 (13), 115 (6), 105 (20), 103 (6), 91 (13), 77 (10), 55 (13), 51 (4), 39 (4), 27 (2).

5. *Dihydrobenzoxepinones* **10**. *4,5-Dihydro-1-benzoxepin-3(2*H*)-one* (**10a**). According to [6] in 27% yield from the commercial 3,4-dihydro-2*H*-1-benzopyran-2-one (**19a**). B.p. 90°/4 · 10^{-2} mbar. ^{1}H-NMR: 2.93–2.99 (*m*, 2 H); 3.04–3.11 (*m*, 2 H); 4.46 (*s*, 2 H); 6.99–7.08 (*m*, 2 H); 7.12–7.20 (*m*, 2 H). ^{13}C-NMR: 27.4 (*t*); 40.1 (*t*); 78.5 (*t*); 121.4 (*d*); 124.3 (*d*); 128.0 (*d*); 130.2 (*s*); 130.7 (*d*); 158.0 (*s*); 210.8

(*s*). MS: 162 (100, M^+), 134 (17), 131 (11), 120 (12), 119 (58), 115 (6), 105 (9), 103 (12), 92 (11), 91 (65), 89 (13), 78 (26), 77 (19), 65 (8), 63 (10), 51 (15), 39 (10).

*7-Methyl-4,5-dihydro-1-benzoxepin-3(2*H*)-one* (**10b**). According to [6] in 21% yield from 3,4-dihydro-6-methyl-2*H*-1-benzopyran-2-one (**19b**) [18]. B.p. 100°/5 · 10^{-1} mbar. ^{1}H-NMR: 2.28 (*s*, 3 H); 2.91–2.98 (*m*, 2 H); 3.00–3.06 (*m*, 2 H); 4.43 (*s*, 2 H); 6.89–6.98 (*m*, 3 H). ^{13}C-NMR: 20.6 (*q*); 27.3 (*t*); 40.1(*t*); 78.7 (*t*); 121.1 (*d*); 128.5 (*d*); 129.9 (*s*); 131.1 (*d*); 133.7 (*s*); 155.9 (*s*); 211.1 (*s*). MS: 176 (100, M^+), 161 (5), 148 (17), 145 (14), 134 (12), 133 (51), 119 (10), 117 (12), 115 (13), 105 (27), 103 (9), 92 (12), 91 (35), 77 (13), 65 (8), 63 (6), 51 (7), 39 (6).

*8-Methyl-4,5-dihydro-1-benzoxepin-3(2*H*)-one* (**10c**). According to [6] in 21% yield from 3,4-dihydro-7-methyl-2*H*-1-benzopyran-2-one (**19c**) [19]. B.p. 125°/6 · 10^{-1} mbar. ^{1}H-NMR: 2.29 (*s*, 3 H); 2.92–2.97 (*m*, 2 H); 3.00–3.06 (*m*, 2 H); 4.44 (*s*, 2 H); 6.82–6.88 (*m*, 2 H); 7.02 (*d*, J = 8, 1 H). ^{13}C-NMR: 20.8 (*q*); 27.1 (*t*); 40.2 (*t*); 78.4 (*t*); 121.8 (*d*); 125.0 (*d*); 126.8 (*s*); 130.5 (*d*); 138.0 (*s*); 157.8 (*s*); 211.0 (*s*). MS: 176 (100, M^+), 161 (8), 148 (16), 145 (11), 134 (15), 133 (58), 119 (28), 117 (11), 115 (16), 105 (31), 103 (12), 92 (12), 91 (46), 89 (6), 78 (11), 77 (16), 65 (10), 63 (8), 51 (9), 39 (10).

*7-Ethyl-4,5-dihydro-1-benzoxepin-3(2*H*)-one* (**10d**). According to [6] in 15% yield from 6-ethyl-3,4-dihydro-2*H*-1-benzopyran-2-one (**19d**). B.p. 160°/5 · 10^{-1} mbar. ^{1}H-NMR: 1.21 (*t*, J = 8, 3 H); 2.58 (*q*, J = 8, 2 H); 2.93–2.99 (*m*, 2 H); 3.01–3.08 (*m*, 2 H); 4.44 (*s*, 2 H); 6.94 (*d*, J = 8, 1 H); 6.96–7.02 (*m*, 2 H). ^{13}C-NMR: 15.7 (*q*); 27.4 (*t*); 28.1 (*t*); 40.2 (*t*); 78.6 (*t*); 121.2 (*d*); 127.3 (*d*); 129.9 (*d*); 140.2 (*s*); 156.0 (*s*); 211.1 (*s*). MS: 190 (100, M^+), 175 (49), 162 (17), 161 (9), 159 (8), 148 (8), 147 (56), 134 (7), 133 (53), 131 (6), 119 (10), 117 (9), 115 (11), 105 (7), 103 (7), 91 (17), 77 (10).

*8-Ethyl-4,5-dihydro-1-benzoxepin-3(2*H*)-one* (**10e**). According to [6] in 23% yield from 7-ethyl-3,4-dihydro-2*H*-1-benzopyran-2-one (**19e**) [20]. B.p. 120°/4 · 10^{-1} mbar. ^{1}H-NMR: 1.22 (*t*, J = 8, 3 H); 2.60 (*q*, J = 8, 2 H); 2.93–2.99 (*m*, 2 H); 3.01–3.08 (*m*, 2 H); 4.46 (*s*, 2 H); 6.87 (br. *s*, 1 H); 6.89 (*d*, J = 8, 1 H); 7.06 (*d*, J = 8, 1 H). ^{13}C-NMR: 15.4 (*q*); 27.1 (*t*); 28.2 (*t*); 40.2 (*t*); 78.4 (*t*); 120.6 (*d*); 123.8 (*d*); 127.0 (*s*); 130.6 (*d*); 144.5 (*s*); 157.9 (*s*); 211.1 (*s*). MS: 190 (100, M^+), 175 (6), 162 (19), 161 (18), 159 (9), 148 (14), 147 (43), 134 (9), 133 (67), 131 (6), 119 (19), 117 (12), 115 (17), 105 (14), 103 (10), 91 (28), 77 (14), 65 (6), 63 (5), 51 (6), 39 (5).

*4,5-Dihydro-7-isopropyl-1-benzoxepin-3(2*H*)-one* (**10f**). According to [6] in 17% yield from 3,4-dihydro-6-isopropyl-2*H*-1-benzopyran-2-one (**19f**) [21]. B.p. 180°/5 · 10^{-1} mbar. ^{1}H-NMR: 1.22 (*d*, J = 7, 6 H); 2.85 (*sept.*, J = 7, 1 H); 2.94–3.01 (*m*, 2 H); 3.03–3.10 (*m*, 2 H); 4.45 (*s*, 2 H); 6.95 (*d*, J = 8, 1 H); 6.98–7.05 (*m*, 2 H). ^{13}C-NMR: 24.1 (*q*); 24.1 (*q*); 27.6 (*t*); 33.4 (*d*); 40.2 (*t*); 78.6 (*t*); 121.2 (*d*); 125.8 (*d*); 128.5 (*d*); 129.8 (*s*); 144.8 (*s*); 156.0 (*s*); 211.2 (*s*). MS: 204 (39, M^+), 190 (17), 189 (100), 175 (11), 161 (7), 147 (17), 133 (9), 115 (7), 91 (9), 77 (6).

*4,5-Dihydro-8-isopropyl-1-benzoxepin-3(2*H*)-one* (**10g**). According to [6] in 26% yield from 3,4-dihydro-7-isopropyl-2*H*-1-benzopyran-2-one (**19g**). B.p. 170°/5 · 10^{-1} mbar. ^{1}H-NMR: 1.23 (*d*, J = 7, 6 H); 2.86 (*sept.*, J = 7, 1 H); 2.94–3.00 (*m*, 2 H); 3.02–3.08 (*m*, 2 H); 4.47 (*s*, 2 H); 6.89–6.95 (*m*, 2 H); 7.07 (*d*, J = 7, 1 H). ^{13}C-NMR: 23.9 (*q*); 23.9 (*q*); 27.2 (*t*); 33.6 (*d*); 40.1 (*t*); 78.4 (*t*); 119.1 (*d*); 122.4 (*d*); 127.0 (*s*); 130.6 (*d*); 149.3 (*s*); 157.9 (*s*); 211.1 (*s*). MS: 204 (100, M^+), 190 (13), 189 (95), 176 (13), 162 (10), 161 (46), 148 (9), 147 (63), 133 (26), 131 (8), 128 (10), 119 (8), 117 (11), 115 (18), 105 (11), 103 (8), 91 (21), 77 (12), 65 (6), 51 (5).

*4,5-Dihydro-4,7-dimethyl-1-benzoxepin-3(2*H*)-one* (**10h**). According to [6] in 13% yield from 3,4-dihydro-3,6-dimethyl-2*H*-1-benzopyran-2-one (**19h**) [22]. B.p. 150°/5 · 10^{-1} mbar. ^{1}H-NMR: 1.17 (*d*, J = 7, 3 H); 2.27 (*s*, 3 H); 2.80 (*dd*, J = 17, 13, 1 H); 2.95 (*dd*, J = 17, 5, 1 H); 3.49–3.59 (*m*, 1 H); 4.38 (*d*, J = 17, 1 H); 4.52 (*d*, J = 17, 1 H); 6.87–6.97 (*m*, 3 H). ^{13}C-NMR: 15.3 (*q*); 20.6 (*q*); 36.4 (*t*); 41.9 (*d*); 78.3 (*t*); 121.0 (*d*); 128.3 (*d*); 128.6 (*s*); 131.3 (*d*); 133.4 (*s*); 155.6 (*s*); 212.7 (*s*). MS: 190 (100, M^+), 175 (14), 162 (30), 159 (9), 147 (31), 145 (9), 133 (23), 131 (9), 121 (10), 119 (16), 117 (6), 115 (12), 105 (25), 103 (6), 91 (23), 77 (9), 65 (5).

*7,9-Diethyl-4,5-dihydro-1-benzoxepin-3(2*H*)-one* (**10i**). According to [6] in 15% yield from 6,8-diethyl-3,4-dihydro-2*H*-1-benzopyran-2-one (**19i**). B.p. 160°/5 · 10^{-1} mbar. ^{1}H-NMR: 1.20 (*t*, J = 7, 3 H); 1.21 (*t*, J = 7, 3 H); 2.56 (*q*, J = 7, 2 H); 2.63 (*q*, J = 7, 2 H); 2.88–2.94 (*m*, 2 H); 3.01–3.07 (*m*, 2 H); 4.42 (*s*, 2 H); 6.84 (*s*, 1 H); 6.91 (*s*, 1 H). ^{13}C-NMR: 15.0 (*q*); 15.7 (*q*); 23.4 (*t*); 27.3 (*t*); 28.2 (*t*); 40.7 (*t*); 78.56 (*t*); 127.2 (*d*); 127.4 (*d*); 130.9 (*s*); 136.2 (*s*); 140.0 (*s*); 154.0 (*s*); 211.2 (*s*). MS: 218 (100, M^+), 204 (10),

203 (67), 189 (19), 175 (36), 161 (33), 147 (15), 145 (5), 133 (9), 131 (6), 128 (7), 119 (7), 117 (8), 115 (12), 105 (9), 91 (14), 77 (7).

*8-Methoxy-4,5-dihydro-1-benzoxepin-3(2*H*)-one* (**10j**). According to [6] in 24% yield from 3,4-dihydro-7-methoxy-2*H*-1-benzopyran-2-one (**19j**) [23]. B.p. 170°/5 · 10^{-1} mbar. ^{1}H-NMR: 2.92–2.97 (*m*, 2 H); 2.98–3.04 (*m*, 2 H); 3.77 (*s*, 3 H); 4.46 (*s*, 2 H); 6.58 (*d*, *J* = 2, 1 H); 6.62 (*dd*, *J* = 8, 2, 1 H); 7.04 (*d*, *J* = 8, 1 H). ^{13}C-NMR: 26.8 (*t*); 40.2 (*t*); 55.4 (*q*); 78.4 (*t*); 106.4 (*d*); 110.5 (*d*); 121.8 (*s*); 131.2 (*d*); 158.7 (*s*); 159.2 (*s*); 210.8 (*s*). MS: 192 (100, M^+), 161 (7), 150 (30), 149 (69), 135 (9), 134 (11), 121 (28), 119 (10), 107 (8), 105 (5), 91 (17), 89 (6), 79 (7), 77 (15), 65 (9), 63 (7), 51 (8), 39 (4).

6. *Tetrahydrobenzocycloheptenones* **11**. *2-Acetyl-5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-one* (**24**). To a mixture of **11a** (1.92 g, 12 mmol) and AcCl (0.92 g, 12 mmol) in CH_2Cl_2 (20 ml) at 0° was added portionwise $AlCl_3$ (1.6 g, 12 mmol). The mixture was stirred at 0° for 1 h, then a mixture of AcCl (0.92 g, 12 mmol) and $AlCl_3$ (1.6 g, 12 mmol) was added. The mixture was stirred for 48 h at 20°, then poured slowly into an ice/H_2O mixture and extracted with CH_2Cl_2. The org. layer was washed with H_2O to pH 7, dried (Na_2SO_4), and concentrated to a residue (2.88 g) containing *ca.* 30% (GC) of **24**. Purification by CC (SiO_2 (150 g), cyclohexane/Et_2O 4:1) gave **24**, which was bulb-to-bulb distilled: **24** (0.77 g, 31%). B.p. 240°/0.2 mbar. ^{1}H-NMR: 2.61 (*s*, 3 H); 2.59–2.67 (*m*, 4 H); 2.94–3.02 (*m*, 4 H); 7.33 (*d*, *J* = 8, 1 H); 7.81 (*dd*, *J* = 8, 1, 1 H); 7.84 (*d*, *J* = 1, 1 H). ^{13}C-NMR: 26.6 (*q*); 30.4 (*t*); 30.5 (*t*); 44.1 (*t*); 127.4 (*d*); 129.0 (*d*); 129.5 (*d*); 136.2 (*s*); 141.0 (*s*); 146.2 (*s*); 197.7 (*s*); 210.2 (*s*). MS: 202 (38, M^+), 187 (100), 159 (14), 145 (21), 115 (26), 91 (16), 77 (7), 63 (6), 51 (5), 43 (19).

*2-Ethyl-5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-one* (**11c**). To a soln. of **24** (0.90 g, 4.4 mmol) in AcOEt (20 ml) was added 5% Pd/C (0.21 g), and the mixture was shaken under H_2 (4.4 bar) in the *Parr* device at r.t. during 3 h. The catalyst was filtered off, the filtrate concentrated, and the residue bulb-to-bulb distilled: **11c** (0.48 g, 57%). B.p. 150°/0.2 mbar. ^{1}H.NMR: 1.24 (*t*, *J* = 8, 3 H); 2.56–2.63 (*m*, 4 H); 2.63 (*q*, *J* = 8, 2 H); 2.84–2.91 (*m*, 4 H); 7.04 (*d*, *J* = 8, 1 H); 7.06 (*s*, 1 H); 7.13 (*d*, *J* = 8, 1 H). ^{13}C-NMR: 16.6 (*q*); 28.4 (*t*); 30.2 (*t*); 30.7 (*t*); 44.6 (*t*); 44.7 (*t*); 126.4 (*d*); 128.8 (*d*); 129.2 (*d*); 137.7 (*s*); 140.5 (*s*); 143.2 (*s*); 211.5 (*s*). MS: 188 (100, M^+), 173 (22), 159 (48), 146 (63), 131 (91), 128 (32), 117 (86), 115 (61), 91 (40), 77 (18), 65 (12), 51 (13), 42 (10), 39 (15).

*2-(*tert*-Butyl)-5,6,8,9-tetrahydro-7*H*-benzocyclohepten-7-one* (**11e**). To a stirred suspension of $FeCl_3$ (3.9 g, 24 mmol) in CH_2Cl_2 (50 ml) at 0° was added dropwise a mixture of *tert*-butyl chloride (2.77 g, 30 mmol) and **11a** (1.92 g, 12 mmol). After 1 h at 0°, the mixture was diluted with CH_2Cl_2, washed with H_2O, sat. aq. $NaHCO_3$ soln., and H_2O, dried (Na_2SO_4), and concentrated. Crystallization from pentane at −16° afforded pure **11e** (1.79 g, 69%). Colorless crystals. M.p. 55–56° ([27]: m.p. 54.8–55.1°), ^{1}H- and ^{13}C-NMR: identical with those reported in [27]. MS: 216 (22, M^+), 201 (100), 173 (5), 159 (4), 143 (7), 131 (11), 115 (11), 91 (8), 77 (4), 65 (3), 41 (5).

*6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-7-ol* (**25**). To a stirred soln. of **11a** (1.60 g, 10 mmol) in EtOH (80 ml) at r.t. was added portionwise $NaBH_4$ (0.30 g, 7.9 mmol), and the mixture was stirred at r.t. during 3 h. AcOH (0.2 ml) was added and the solvent was evaporated. The residue was dissolved in Et_2O, washed with H_2O, and concentrated. The residue (1.65 g) was crystallized from Et_2O: **25** (1.47 g, 91%). Colorless crystals. M.p. 95–96° ([29c]: m.p. 96–97°). ^{1}H-NMR: 1.49 (*s*, OH); 1.46–1.61 (*m*, 2 H); 2.01–2.12 (*m*, 2 H); 2.65 (*dd*, *J* = 14, 8, 2 H); 2.90 (*dd*, *J* = 14, 8, 2 H); 7.11 (*s*, 4 H). ^{13}C-NMR: 30.3 (2*t*); 36.3 (2*t*); 73.4 (*d*); 126.4 (2*d*); 129.0 (2*d*); 142.2 (2*s*). MS: 162 (15, M^+), 144 (23), 129 (100), 115 (24), 91 (21), 77 (9), 65 (5), 51 (6), 39 (7).

*6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-7-yl Acetate* (=*6,7,8,9-Tetrahydro-5*H*-benzocyclohexen-7-ol Acetate*; **26**). A stirred soln. of **25** (1.00 g, 4.9 mmol) in pyridine (0.52 g, 6.6 mmol) and Ac_2O (0.67 g, 6.6 mmol) was heated to 100° during 2 h. After cooling, the mixture was diluted with Et_2O and H_2O, the org. layer washed with H_2O, 10% aq. HCl soln., H_2O, and sat. aq. $NaHCO_3$ soln., dried (Na_2SO_4), and concentrated. The residue (1.25 g) was crystallized from cyclohexane: **26** (1.06 g, 100%). Colorless crystals. M.p. 91–92°. ^{1}H-NMR: 1.61–1.73 (*m*, 2 H); 1.95–2.06 (*m*, 2 H); 2.06 (*s*, 3 H); 2.68 (*dd*, *J* = 14, 10, 2 H); 2.92 (*dd*, *J* = 14, 10, 2 H); 5.02–5.11 (*m*, 1 H); 7.11 (*s*, 4 H). ^{13}C-NMR: 21.4 (*q*); 30.4 (2*t*); 32.9 (2*t*); 75.3 (*d*); 126.4 (2*d*); 129.0 (2*d*); 141.9 (2*s*); 170.3 (*s*). MS: 204 (1, M^+), 144 (42), 129 (100), 115 (16), 103 (4), 91 (10), 77 (5), 65 (3), 51 (3), 43 (23), 39 (4).

*2-Acetyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-7-yl Acetate* (=*1-[7-(Acetyloxy)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-2-yl]ethanone*; **27**). To a stirred soln. of AcCl (3.69 g, 47.0 mmol) in CH_2Cl_2

(125 ml) at 0° was added $AlCl_3$ (6.27 g, 47.0 mmol), followed by dropwise addition of a soln. of **26** (4.80 g, 23.5 mmol) in CH_2Cl_2 (25 ml) during 30 min. After 2 h at 0°, more AcCl (0.36 g, 4.6 mmol) and $AlCl_3$ (0.62 g, 4.6 mmol) were added, and the mixture was stirred for 2 h at 0°. The mixture was washed with H_2O, sat. aq. $NaHCO_3$ soln., dried (Na_2SO_4), and concentrated (6.32 g). Bulb-to-bulb distillation afforded **27** (5.40 g, 93%). Colorless oil. B.p. 190°/0.1 mbar. ^{1}H-NMR: 1.63–1.77 (*m*, 2 H); 1.95–2.06 (*m*, 2 H); 2.08 (*s*, 3 H); 2.58 (*s*, 3 H); 2.67–2.79 (*m*, 2 H); 2.94–3.06 (*m*, 2 H); 7.20 (*d*, *J* = 8, 1 H); 7.71 (*dd*, *J* = 8,1, 1 H); 7.72 (br. *s*, 1 H). ^{13}C-NMR: 21.4 (*q*); 26.6 (*q*); 30.2 (*t*); 30.3 (*t*); 32.5 (*t*); 32.7 (*t*); 74.7 (*d*); 126.9 (*d*); 128.8 (*d*); 129.3 (*d*); 135.6 (*s*); 142.3 (*s*); 147.8 (*s*); 170.2 (*s*); 197.9 (*s*). MS: 246 (1, M^+), 231 (2), 186 (51), 171 (100), 143 (28), 128 (19), 115 (16), 103 (3), 91 (6), 77 (5), 65 (2), 51 (2), 43 (55), 39 (2).

*6,7,8,9-Tetrahydro-2-(1-hydroxy-1-methylethyl)-5*H*-benzocyclohepten-7-ol* (=*6,7,8,9-Tetrahydro-7-hydroxy-α,α-dimethyl-5*H*-benzocycloheptene-2-methanol*; **28**). To 22% MeMgCl in THF (13.5 g, 40 mmol), a soln. of **27** (2.4 g, 10 mmol) was added dropwise at r.t. within 10 min, and the mixture was heated to 60° during 2 h. The mixture was poured on ice/H_2O and extracted with Et_2O. The org. layer was washed with 10% aq. HCl soln., H_2O, and sat. aq. $NaHCO_3$ soln., dried (Na_2SO_4), and concentrated. The residue (2.46 g) was crystallized from toluene: **28** (1.89 g, 86%). Colorless solid. M.p. 141–145°. ^{1}H-NMR ((D$_6$)DMSO): 1.26–1.39 (*m*, 2 H); 1.39 (*s*, 6 H); 1.81–1.95 (*m*, 2 H); 2.46–2.60 (*m*, 2 H); 2.73–2.86 (*m*, 2 H); 3.68–3.78 (*m*, 1 H); 4.58 (*d*, *J* = 4, OH); 4.86 (*s*, OH); 7.00 (*d*, *J* = 8, 1 H); 7.14 (*dd*, *J* = 8, 1, 1 H); 7.19 (*d*, *J* = 1, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 29.3 (*t*); 30.1 (*t*); 31.7 (*q*); 31.8 (*q*); 36.3 (2*t*); 70.3 (*s*); 71.5 (*d*); 122.0 (*d*); 125.0 (*d*); 128.1 (*d*); 139.7 (*s*); 141.4 (*s*); 148.0 (*s*). MS: 220 (15, M^+), 205 (34), 187 (52), 171 (2), 159 (4), 145 (16), 128 (9), 115 (13), 105 (5), 91 (10), 77 (5), 65 (3), 59 (7), 43 (100), 39 (3).

5,6,8,9-Tetrahydro-2-isopropylbenzocyclohepten-7-ol (**29**). To a soln. of **28** (1.89 g, 6.6 mmol) in EtOH (100 ml) was added 10% Pd/C (0.30 g), and the mixture was shaken under H_2 (1 atm) at r.t. for 3 h. The catalyst was filtered off, and the filtrate concentrated: **29** (1.74 g, 92%). Colorless crystals. M.p. 90–92°. ^{1}H-NMR: 1.23 (*d*, *J* = 7, 6 H); 1.46–1.60 (*m*, 2 H); 1.58 (*s*, OH); 2.00–2.12 (*m*, 2 H); 2.56–2.68 (*m*, 2 H); 2.85 (*sept.*, *J* = 7, 1 H); 2.81–2.89 (*m*, 2 H); 3.88–3.98 (*m*, 1 H); 6.94–7.00 (*m*, 2 H); 7.04 (*d*, *J* = 8, 1 H). ^{13}C-NMR: 24.1 (2*q*); 29.9 (*t*); 30.5 (*t*); 33.6 (*d*); 36.4 (2*t*); 73.6 (*d*); 124.1(*d*); 127.3 (*d*); 129.1 (*d*); 139.4 (*s*); 142.0 (*s*); 146.9 (*s*). MS: 204 (31, M^+), 186 (22), 171 (100), 143 (79), 129 (35), 115 (29), 105 (9), 91 (21), 77 (9), 65 (5), 51 (4), 43 (11), 39 (7).

5,6,8,9-Tetrahydro-2-isopropylbenzocyclohepten-7-one (**11d**). To a stirred soln. of **29** (1.02 g, 5 mmol) in CH_2Cl_2 (20 ml) was added at r.t. pyridinium chlorochromate (2.15 g, 10 mmol), and the mixture was stirred at r.t. during 1 h. The mixture was diluted with Et_2O, filtered through *Celite*®, then through a short column of *Florisil*®, and concentrated. The residue (1.06 g) was crystallized from pentane at −16°: **11d** (0.82 g, 80%). Colorless crystals. M.p. 52–54°. ^{1}H-NMR: 1.25 (*d*, *J* = 7, 6 H); 2.56–2.63 (*m*, 4 H); 2.84–2.92 (*m*, 5 H); 7.07 (*d*, *J* = 8, 1 H); 7.08 (*s*, 1 H); 7.14 (*d*, *J* = 8, 1 H). ^{13}C-NMR: 24.0 (2*q*); 30.2 (*t*); 30.8 (*t*); 33.7 (*d*); 44.6 (*t*); 44.7 (*t*); 125.0 (*d*); 127.4 (*d*); 129.2 (*d*); 137.8 (*s*); 140.4 (*s*); 147.8 (*s*); 211.5 (*s*). MS: 202 (53, M^+), 187 (100), 174 (11), 159 (25), 145 (21), 141 (8), 131 (17), 128 (18), 117 (26), 105 (4), 91 (14), 77 (7), 65 (4), 51 (4), 39 (5).

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