Controlled Release of Perfumery Alcohols by Neighboring-Group Participation. Comparison of the Rate Constants for the Alkaline Hydrolysis of 2-Acyl-, 2-(Hydroxymethyl)-, and 2-Carbamoylbenzoates

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Dedicated to our colleague Dr. *Sina Escher* on the occasion of her retirement

A series of 2-acylbenzoates **1** and **2**, 2-(hydroxymethyl)benzoates **3**, 2-carbamoylbenzoates **4**–**6**, as well as the carbamoyl esters **7** or **8** of maleate or succinate, respectively (see *Fig. 2*), were prepared in a few reaction steps, and the potential use of these compounds as chemical delivery systems for the controlled release of primary, secondary, and tertiary fragrance alcohols was investigated. The rate constants for the neighboring-group-assisted alkaline ester hydrolysis were determined by anal. HPLC in buffered H_2O/MeCN solution at different pH (*Table 1*). The rates of hydrolysis were found to depend on the structure of the alcohol, together with the precursor skeleton and the structure of the neighboring nucleophile that attacks the ester function. Primary alcohols were released more rapidly than secondary and tertiary alcohols, and benzoates of allylic primary alcohols (*e.g.*, geraniol) were hydrolyzed 2–4 times faster than their homologous saturated alcohols (*e.g.*, citronellol). For the same leaving alcohol, 2-[(ethylamino)carbonyl]benzoates cyclized faster than the corresponding 2-(hydroxymethyl)benzoates, and much faster than their 2-formyl and 2-acetyl analogues (see, *e.g.*, *Fig. 4*). Within the carbamoyl ester series, 2-[(ethylamino)carbonyl]benzoates were found to have the highest rate constants for the alkaline ester hydrolysis, followed by unsubstituted 2-(aminocarbonyl)benzoates, or the corresponding isopropyl derivatives. To rationalize the influence of the different structural changes on the hydrolysis kinetics, the experimental data obtained for the 2-[(alkylamino)carbonyl]benzoates were compared with the results of density-functional computer simulations (*Table 2* and *Scheme 4*). Based on a preliminary semi-empirical conformation analysis, density-functional calculations at the B3LYP/6-31G** level were carried out for the starting precursor molecules, several reaction intermediates, and the cyclized phthalimides. For the same precursor skeleton, these simple calculations were found to model the experimental data correctly. With an understanding of the influence of structural parameters on the rate constants obtained in this work, it is now possible to influence the rates of hydrolysis over several orders of magnitude, to design tailor-made precursors for a large variety of fragrance alcohols, and to predict their efficiency as controlled-release systems in practical applications.

1. Introduction. – Many perfumes contain intense-smelling primary, secondary, or tertiary alcohols such as geraniol (=(2*E*)-3,7-dimethylocta-2,6-dien-1-ol), citronellol (=3,7-dimethyloct-6-en-1-ol), or menthol (=*p*-menthan-3-ol) (*Fig. 1*), which give rise to rosy-floral and fresh notes in the final composition [1]. However, due to their high volatility, many of these fragrance molecules can be perceived only over a relatively short period of time in classical applications of functional perfumery. To increase the performance of these compounds in a broad variety of consumer products, the design of specific delivery systems for the controlled release of odorants has become an important research area in the flavor and fragrance industry [2][3]. Until now, the inclusion of active compounds into a matrix is the most widely used technique to prolong the long-lasting effect of volatile compounds and, as an additional benefit, to

increase their stability in aggressive media [3]. Chemical delivery systems which are based on the release of active molecules by cleavage of a chemical bond of a precursor molecule are an interesting alternative to encapsulation [4]. Reaction conditions, such as the action of O_2, light [5–7] or enzymes, hydrolysis [8], change in pH [9][10], or temperature, may be used to chemically transform suitable precursors to the desired flavors or fragrances. Ideally, due to their high molecular masses, the precursor compounds are odorless, increase the substantivity of the flavor or fragrance compounds to be released, and may also serve as protection for chemically unstable functionalities. Following our investigations on the controlled light-induced release of fragrance aldehydes and ketones [5], we now report the design of delivery systems for the release of perfumery alcohols by alkaline ester hydrolysis [9–11][1]).

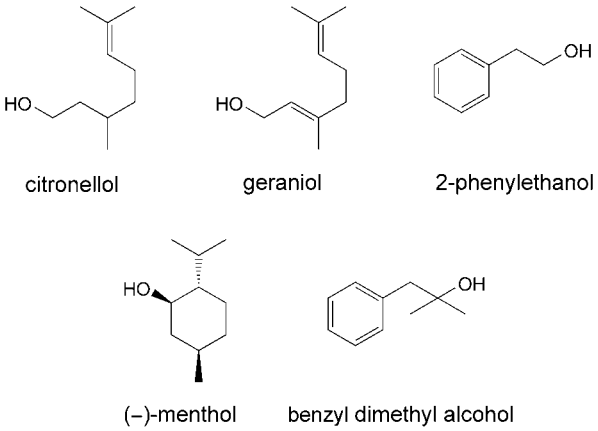

Fig. 1. *Structures and trivial names of primary, secondary, and tertiary fragrance alcohols giving rise to floral and fresh notes* [1]

The release of fragrance alcohols by lipase-triggered ester cleavage has already been described for use in laundry applications [12]. However, enzymes are not present in all washing powders and, furthermore, due to enzyme selectivity, these precursors are mainly restricted to the release of primary alcohols. In general, the efficiency of enzymatic reactions is based on the principle that specific functional groups that are held in close proximity to the substrate to be cleaved in the reactive center of the enzyme dramatically increase the reaction rates. Transferring this phenomenon to intramolecular reactions by placing a substituent that influences the rate of the targeted reaction close to the desired reaction center is known as neighboring-group participation [13] or, if this participation leads to an enhancement of the reaction rate, as intramolecular catalysis [14]. The general release principle of the precursors described in this work is based on the presence of an intermediate nucleophilic species that then intramolecularly attacks the carbonyl group of an ester function and releases the desired alcohol upon cyclization (*Scheme 1*) [15]. This effect is well-known in organic chemistry and has already been applied to the design of intramolecularly activated pro-drugs [16].

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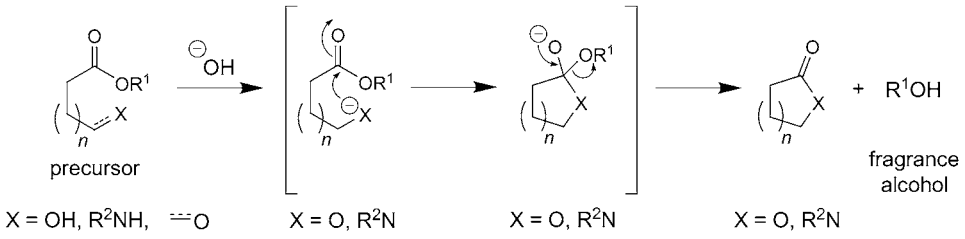
[1]) Parts of the present publication are the subject of patent applications [11].

Scheme 1. *Concept of Neighboring-Group Participation for the Controlled Release of Fragrance Alcohols*



The kinetics of alkaline ester hydrolysis of alkyl or aryl 2-acyl- or 2-benzoylbenzoates [9][17–22] and their pseudoesters (phthalides = isobenzofuran-1(3*H*)-ones) [9][18][22][23], as well as of ethyl 2-(hydroxymethyl)benzoate [24], aryl 4-hydroxybutanoates and (2-hydroxyphenyl)acetates [25], alkyl and aryl 2-(aminomethyl)benzoates [26], or different carbamoyl ester derivatives [10][27–29] by neighboring-group participation has been investigated separately by different research groups in a large variety of solvents. In most of these studies, the dependence of the rate of hydrolysis with respect to substitution at either the neighboring nucleophile or the backbone of the substrate as well as the influence of buffer catalysis was analyzed in detail. However, the influence of the leaving alcohol on the rate constants for hydrolysis, which is crucial for the targeted application in functional perfumery, has been studied in only a few cases. Phenyl 2-carbamoylbenzoates, *e.g.*, were reported to hydrolyze 30–70 times faster than their corresponding butyl esters [28], in analogy to phenyl 2-acetyl- [20] or 2-benzoylbenzoates [18], which hydrolyze 1.3 and 4.1 times faster, respectively, than their corresponding methyl esters. However, the influence of the alcohol released in the hydrolysis of the pseudoester analogues was found to be unremarkable [9] [18]. Apart from the neighboring-group participation of carbonyl groups for the hydrolysis of a series of methyl esters [30], until now, no systematic study comparing the rate constants for the alkaline hydrolysis of the same alcohols from systems with different nucleophiles acting as neighboring groups has been reported.

The goal of this work is to develop tailor-made fragrance precursors that could release different perfumery alcohols by neighboring-group-assisted alkaline ester hydrolysis at desired rate constants in typical bodycare and household applications of functional perfumery [11]. To achieve this goal, we studied the influence of the alcohol, the structure of the precursor skeleton, and the nature of the neighboring group on the rate of ester hydrolysis for a series of 2-acylbenzoates **1** and **2**, 2-(hydroxymethyl)-benzoates **3**, and carbamoyl esters **4**–**8** (*Fig. 2*) in buffered solution, and tried to rationalize our experimental data with the aid of computational calculations.

2. Results and Discussion. – 2.1. *2-Acylbenzoates and Their Corresponding Pseudoesters.* The preparation of a series of methyl and ethyl 2-acylbenzoates *via* the corresponding acid chloride [31], by esterification of 2-acylbenzoic acids in the presence of HCl or H_2SO_4 [32], or alternatively, by reaction of the carboxylic acid with alkyl halides [33][34] has already been reported. Whereas in the former two cases, the formation of the open ester form and/or the cyclic pseudoester was observed [33], the reaction with the alkyl halides generally afforded exclusively the open ester form.

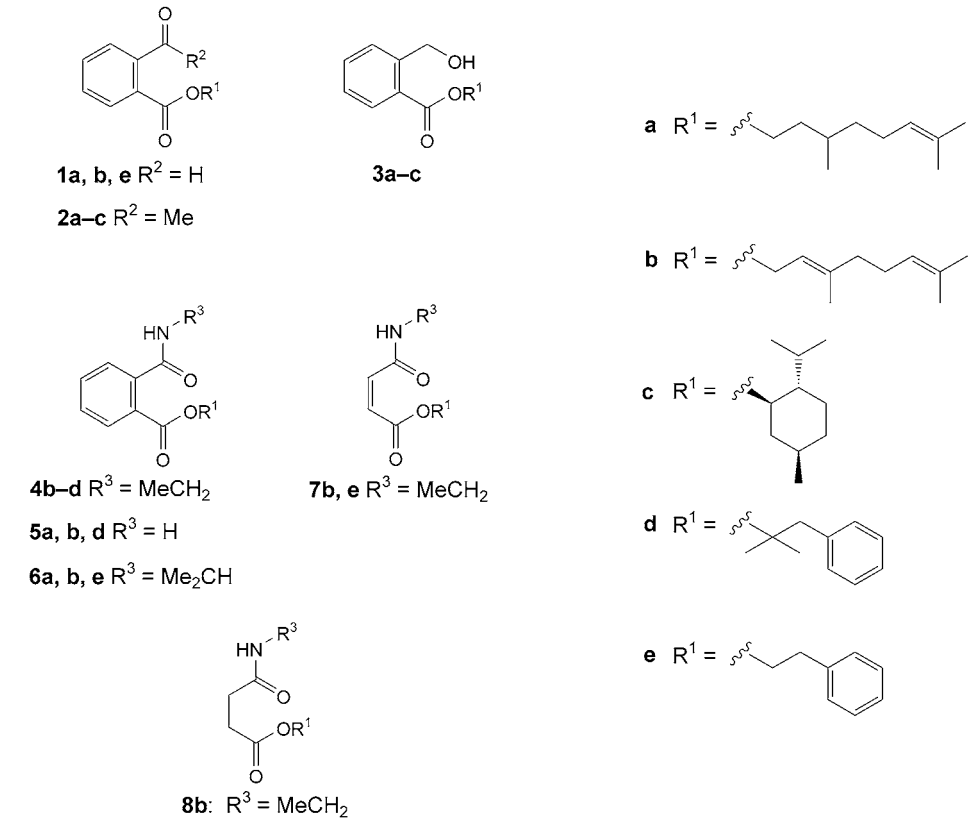
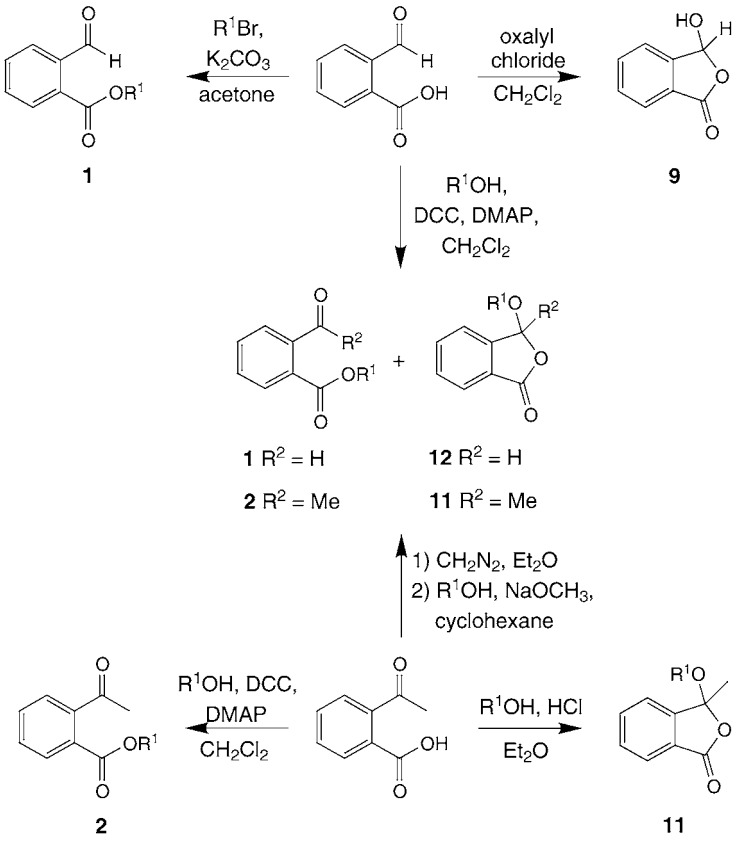


Fig. 2. *Structures of 2-acylbenzoates* **1** *and* **2**, *2-(hydroxymethyl)benzoates* **3**, *and carbamoyl esters* (**4**–**8**) *investigated as precursors for the controlled release of fragrance alcohols by alkaline hydrolysis*

Several attempts to synthesize 2-acylbenzoates from their acid chlorides and the corresponding perfumery alcohol failed, presumably due to the ring–chain tautomerism of the benzoic acid and the corresponding phthalide [35] during the formation of the acid chloride. For example, in the reaction of 2-formylbenzoic acid with oxalyl chloride, 3-hydroxyphthalide **9** was the only compound isolated (*Scheme 2*). Methyl 2-acetylbenzoate (**10**; see below, *Table 1*) was successfully obtained by reaction of the corresponding acid with diazomethane [21][36]; however, the attempted transesterification with geraniol and NaOMe in cyclohexane resulted in a *ca.* 1:1 mixture of the desired benzoate **2b** and phthalide derivative **11b**. Reaction of 2-formylbenzoic acid with 2-(bromoethyl)benzene and potassium carbonate in acetone according to the literature procedure of *Gautier* and *Dodd* [37] gave benzoate **1e** in 14% yield, without formation of the corresponding phthalide **12e**. The 2-formyl and 2-acetylbenzoates **1a,b,e** and **2a**–**c** as well as geranyl 4-formylbenzoate (**13**; *i.e.*, **1b** with CHO at C(4)) were finally prepared in higher yields by using dicyclohexylcarbodiimide (DCC) with *N*,*N*-dimethylpyridine-4-amine (DMAP) in CH_2Cl_2 [9][20][38] (*Scheme 2*). Whereas phthalides **12** were obtained as by-products in the DCC coupling reaction of 2-

formylbenzoic acid, the formation of 3-methylphthalides **11** in the reaction with 2-acetylbenzoic acid was not observed. All compounds were stable and could be isolated in their pure state. No evidence for equilibration between the corresponding ring–chain tautomers of the final products was obtained under the conditions described in this study [39]. Interestingly, the acidic esterification of 2-acetylbenzoic acid and menthol in the presence of HCl, as reported in the literature for the synthesis of **2c** [40], could not be reproduced in this work. Following the published conditions, we only obtained diastereoisomeric phthalide derivatives **11c** (*Scheme 2*).

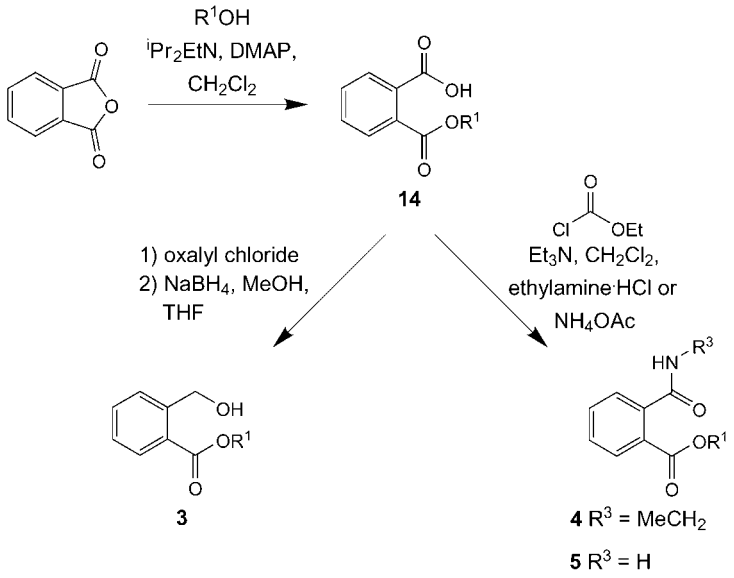
Scheme 2. *Preparation of 2-Acylbenzoates (***1** *and* **2***) and of their Corresponding Phthalides* **11** *and* **12**. For R^1, see *Fig. 2*.



2.2. *2-(Hydroxymethyl)benzoates.* A few procedures for the preparation of 2-(hydroxymethyl)benzoates such as transesterification of the corresponding lactones [41], reaction of 2-(hydroxymethyl)benzoic acid with alkyloxonium fluoroborates [24], or reduction of the corresponding alkyl hydrogen phthalates or their mixed anhydrides either with H_2 on Pd/C [42] or various borohydrides [43] have been reported in the literature. We prepared 2-(hydroxymethyl)benzoates **3a**–**c** from their corresponding alkyl hydrogen phthalates **14a**–**c**, the latter being obtained in almost quantitative yield

by reaction of a perfumery alcohol with phthalic anhydride [44] in the presence of base (*Scheme 3*). Reduction of the intermediate acyl chlorides or mixed anhydrides with sodium borohydride afforded 2-(hydroxymethyl)benzoates **3a**–**c** in 30–55% yield.

Scheme 3. *Preparation of 2-(Hydroxymethyl)benzoates* **3** *and 2-Carbamoylbenzoates* **4**–**6**. For R^1, see *Fig. 2*.



2.3 *Carbamoyl Esters.* Ring opening of *N*-alkylphthalimides with alkyl bromides under alkaline reaction conditions, or of phthalic anhydride with alkylamines, followed by esterification of the remaining free acid function, afforded 2-carbamoylbenzoates in low to moderate yields, respectively [45]. Higher amounts of 2-(aminocarbonyl)- as well as of 2-[(alkylamino)carbonyl]benzoates have been obtained from alkyl hydrogen phthalates, either *via* their acyl chlorides and reaction with hexamethyldisilazane [28] [46] or alkylamines [47], respectively, or by using peptide coupling reagents [48].

The synthesis of carbamoyl esters **4**–**8** was achieved in three consecutive reaction steps starting from commercially available acid anhydrides. In the first step, diacid monoesters (such as **14**) were obtained by reaction of the desired fragrance alcohol with the corresponding anhydride as described above for the synthesis of 2-(hydroxymethyl)benzoates. The intermediate alkyl hydrogen phthalates (see **14**), maleates, or succinates were then converted to mixed anhydrides with pivaloyl chloride or ethyl carbonochloridate, and, finally, reacted with ammonium acetate or alkyl amines to give the target compounds **4**–**8** (*Scheme 3* and *Fig. 2*). Although all three steps may be carried out in a one-pot reaction sequence, we isolated and characterized some of the intermediates common to the preparation of differently substituted products. Compounds **6a** and **6e** were obtained by a consecutive one-pot reaction of phthaloyl dichloride with the corresponding perfumery alcohols followed by addition of $^{i}PrNH_2$.

2.4. *Rate Constants for the Alkaline Hydrolysis by Neighboring-Group Participation.* To compare the rate constants for the alkaline hydrolysis of 2-formyl- or 2-acetylbenzoates **1** and **2**, 2-(hydroxymethyl)benzoates **3**, and carbamoylesters **4**–**8** (*Fig. 2*), and to study the influence of the leaving alcohol, the nature of the nucleophile, or the structure of the precursor skeleton, all kinetics measurements were carried out under the same conditions in buffered solutions at pH 7.62 (phosphate), 10.47 (borate), or 11.54 (phosphate/hydrogencarbonate) in H_2O/MeCN 2:1 (*v*/*v*) at 20°. The comparison of the rate constants obtained for the hydrolysis of 2-formyl- and 2-acetylbenzoates **1** and **2** with those of their corresponding phthalides (pseudoesters) **12** and **11**, respectively, has already been reported elsewhere [9].

In most of the cases described in the literature, rate constants for the alkaline hydrolysis of ester derivatives have been determined spectrophotometrically [20–27], but also acid-base titrimetric methods [18], conductivity measurements [19], or NMR spectroscopy [28] have been used. The rate constants can be determined graphically by plotting the logarithm of the difference of the end absorption (A_i) and the absorption at time t (A_t) against time (infinity-time method), by plotting the logarithm of the difference of absorption at time $t+\Delta t$ and time t against time (*Guggenheim* method) [49], or by plotting the absorption at time t against the absorption at time $t+\Delta t$ (*Kezdy–Mangelsdorf–Swinbourne* method) [50]. Whereas the first procedure is the one most often currently used [21][24–27][51], the latter methods have the advantage that the end absorption A_i, which is often difficult to be determined accurately, is not taken into account for the calculation of the rate constants (the reaction does not have to go to completion) [52]. Recording the UV/VIS spectra of a buffered solution of 2-acylbenzoates in H_2O/MeCN 2:1 at constant time intervals between 260 and 360 nm at 20°, as shown for citronellyl 2-formylbenzoate (**1a**) as an example, gave the plot illustrated in *Fig. 3*. Comparison of these UV/VIS spectra with those of 3-hydroxyphthalide (**9**) and 2-formylbenzoic acid suggests that, at least in the case of the formyl and acetylbenzoates, the reaction proceeds completely to the acid in the open form.

Exploitation of the same experimental data obtained for the hydrolysis of **1a** (*Fig. 3*) by all three graphical methods gave rate constants varying between $1.13\cdot10^{-4}$ and $2.35\cdot10^{-4}$ s^{-1} (at λ 280 nm) and between $1.37\cdot10^{-4}$ and $2.48\cdot10^{-4}$ s^{-1} (at λ 285 nm). Based on these large variations obtained by UV/VIS spectroscopy, and, especially because possible consecutive reactions cannot be distinguished [52], we decided to investigate the kinetics of hydrolysis by high-performance liquid chromatography (HPLC) [9][10]. Following the decrease in peak area of the precursors obtained by reinjection of the reaction solution at constant time intervals allows an accurate determination of rate constants with good reproducibility. Besides the advantage that the reaction does not have to be driven to completion, the HPLC analysis can also be carried out on considerably smaller amounts of compound and, because all the peaks are base-line-separated, several compounds may be analyzed at the same time. Furthermore, the development of new monolithic ultrafast HPLC columns allowed us to follow the kinetics of fast reactions with half-life times of only a few minutes by reinjecting the reaction samples at very short time intervals.

Since the hydroxide concentration was held constant by the buffer, the second-order rate expression $r=k_2\cdot[OH^-]\cdot[\text{precursor}]$ can be reduced to the first-order expression $r=k_0\cdot[\text{precursor}]$ [9][10][21][24–28]. Plotting the logarithm of the peak-

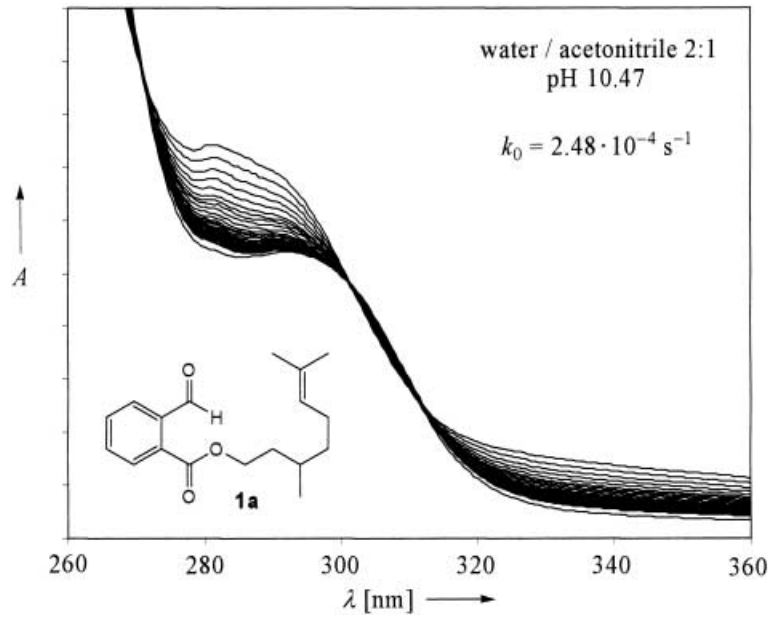


Fig. 3. *Determination of the rate constant for the alkaline hydrolysis of* **1a** *by UV/VIS spectroscopy.* k_0 was determined at λ 285 nm by the *Guggenheim* method (see text).

area quotients (A_t/A_0) of the precursors against time gave a straight line with good correlation coefficients ($r^2 > 0.99$) for all the measurements, thus justifying the general assumption of first-order kinetics. The concentrations of the precursor compounds were chosen to avoid the use of any solubilizer which, due to micelle formation in solution, may influence the reaction kinetics. Generally 0.7-1.2 $\cdot 10^{-3}$ M solutions of the compound in MeCN were prepared and added to a buffer solution in H_2O/MeCN to give the final reaction mixtures at pH 7.62, 10.47, or 11.54 in H_2O/MeCN 2 : 1 (v/v). In a typical experiment, the reaction solutions were injected at constant time intervals into a HPLC apparatus and eluted on a reversed-phase column with H_2O/MeCN. The elution conditions as well as the choice of the reversed-phase column were adapted to the speed of hydrolysis to get a minimum of eight points; in most of the analyses, 20 points were recorded. All experiments were repeated two to four times, and, in the case of precursor **4b**, the measured rate constants k_0 varied between $1.05 \cdot 10^{-4}$ and $1.10 \cdot 10^{-4}$ s^{-1} (at λ 254 nm), thus showing that good reproducibility was obtained for the data. Most of the compounds were detected at λ 254 and 280 nm simultaneously, and, as expected, the rate constants were found to be independent of the wavelength of the analysis in all cases [21]. The results obtained for the alkaline hydrolysis of esters **1**–**8** are summarized in *Table 1*.

To be able to compare the rate constants obtained in this work with other values reported in the literature and to be able to compare rate constants over a wide pH range, we calculated the second-order rate constant k_2 (obtained for constant hydroxide concentration) by dividing the measured k_0 values by $10^{(pH-pK_w)}$ [21] [24–26] using the

Table 1. *Rate Constants* k_0 *and* k_2 *and Half-Life Times* $t_{1/2}$ *for the Alkaline Hydrolysis of Precursors* **1**–**8** *in* H_2O*/MeCN 2 : 1* (*v*/*v*) *at 20°* (determined by HPLC analysis at λ 254 nm). The rate constants k_2 were obtained by dividing the measured k_0 values by $10^{(pH-pK_w)}$ (constant hydroxide concentration) by using the autoprotolysis constant $pK_w = 14.83$ obtained for H_2O/MeCN 2 : 1 [53]. All numbers are average values of at least two experiments ($r^2 > 0.99$).

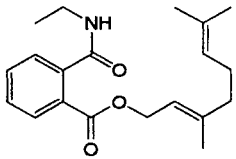
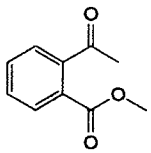
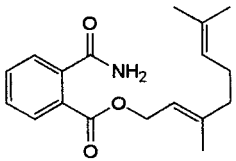
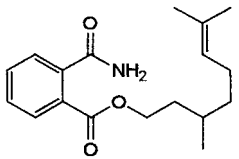
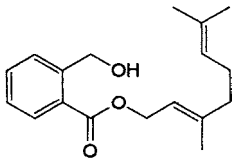
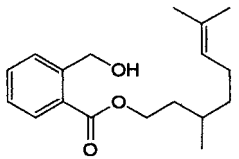
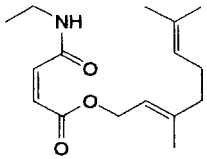
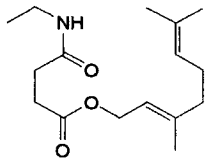
	No.	pH	$k_0 \cdot 10^5$ [s^{-1}]	k_2 [l mol^{-1} s^{-1}]	$t_{1/2}$ [h]		No.	pH	$k_0 \cdot 10^5$ [s^{-1}]	k_2 [l mol^{-1} s^{-1}]	$t_{1/2}$ [h]
	**4b**	7.62 10.47 11.54	10.7	1735.34	1.8		**10**	7.62 10.47 11.54	12.7	2.90	1.5
	**5b**	7.62 10.47 11.54	5.49	889.56	3.5		**5a**	7.62 10.47 11.54	2.13	345.45	9.0
	**3b**	7.62 10.47 11.54	5.50	892.00	3.5		**3a**	7.62 10.47 11.54	1.37	222.19	14.1
	**7b**	7.62 10.47 11.54	1.36	219.76	14.2		**8b**	7.62 10.47 11.54	3.88[a])	0.88	5.0

Table 1 (cont.)

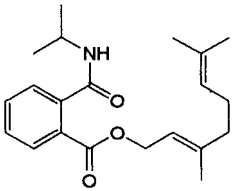
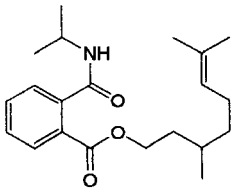
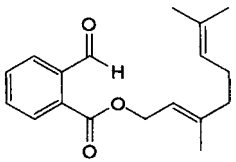
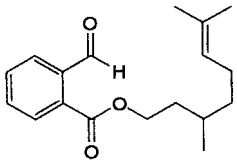
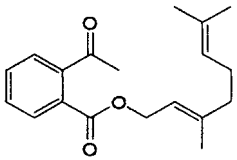
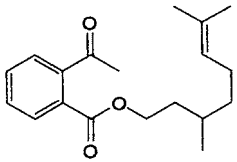
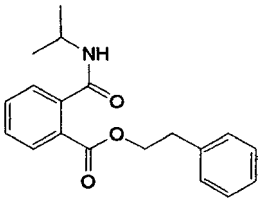
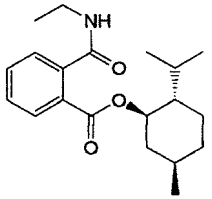
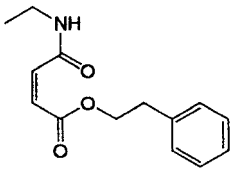
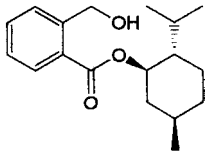
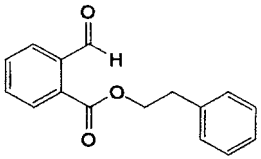
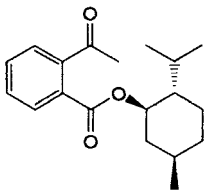
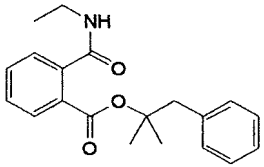
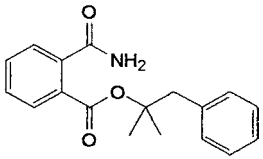
	No.	pH	$k_0 \cdot 10^5$ [s^{-1}]	k_2 [l mol^{-1} s^{-1}]	$t_{1/2}$ [h]		No.	pH	$k_0 \cdot 10^5$ [s^{-1}]	k_2 [l mol^{-1} s^{-1}]	$t_{1/2}$ [h]
	**6b**	7.62 10.47 11.54	1.11	180.02	17.4		**6a**	7.62 10.47 11.54	0.606 347	98.28 79.38	31.9 0.06
	**1b**	7.62 10.47 11.54	108	24.6	0.2		**1a**	7.62 10.47 11.54	30.0	6.85	0.6
	**2b**	7.62 10.47 11.54	3.98 38.2	0.91 0.75	4.8 0.5		**2a**	7.62 10.47 11.54	2.50 25.6	0.57 0.50	7.7 0.8
	**6e**	7.62 10.47 11.54	2.04	330.85	9.4		**4c**	7.62 10.47 11.54	1.64	265.17	11.8

Table 1 (cont.)

	No.	pH	$k_0 \cdot 10^5$ [s^{-1}]	k_2 [l mol^{-1} s^{-1}]	$t_{1/2}$ [h]		No.	pH	$k_0 \cdot 10^5$ [s^{-1}]	k_2 [l mol^{-1} s^{-1}]	$t_{1/2}$ [h]
	**7e**	7.62 10.47 11.54	1.57	253.81	12.3		**3c**	7.62 10.47 11.54	4.93 12.8	1.13 0.25	3.9 1.7
	**1e**	7.62 10.47 11.54	0.258 315	41.9 72.0	74.8 0.1		**2c**	7.62 10.47 11.54	2.89	0.06	6.7
	**4d**	7.62 10.47 11.54	31.6	7.25	0.6		**5d**	7.62 10.47 11.54	16.1	3.69	1.2

[a]) Detection at λ 220 nm.

autoprotolysis constant $pK_w = 14.83$ obtained for H_2O/MeCN 2:1 (*v*/*v*) [53][2]). Direct comparison of the rate constants k_2 measured for methyl 2-acetylbenzoate (**10**) in this study with those reported in dioxane/H_2O [19][21] shows that our reaction rates are *ca.* twice as slow as these literature values[3]). The rates of hydrolysis were found to deviate only slightly from proportionality to the hydroxide concentration. A large deviation was only measured in the case of 2-(hydroxymethyl)benzoate **3c** at pH 10–11, where the k_2 values vary by a factor of 4.5, with the reaction being faster at pH 10 than at pH 11. Doubling the borate buffer concentration (pH 10.52) did not generally influence the rate of hydrolysis of the systems within the experimental error.

2.5. *Influence of the Leaving Alcohol on the Rate of Hydrolysis.* As expected, primary alcohols were found to be released more rapidly than secondary and tertiary alcohols. This is best demonstrated by comparing the rate constants k_2 for the hydrolysis of 2-(hydroxymethyl)benzoates **3b** and **3c** or 2-[(ethylamino)carbonyl]benzoates **4b** and **4c** (*Table 1*). In the latter case, geraniol (primary) was released 6–7 times faster from **4b** than menthol (secondary) from **4c**, and 240 times faster than benzyldimethyl alcohol (tertiary) from **4d**. Comparison of the hydrolysis of menthyl 2-acetylbenzoate (**2c**) with primary alcohol derivatives **2a** or **2b** shows that the rate constants increase even more, namely by a factor of 10 and 15, respectively. Moreover, benzoates of allylic primary alcohols (geraniol) are hydrolyzed between two to four times faster than their homologous saturated alcohols (citronellol) as shown by comparing **1b** with **1a**, **2b** with **2a**, or **3b** with **3a**.

2.6. *Influence of the Neighboring Group on the Rate of Hydrolysis.* Besides the structure of the leaving alcohol, the nature of the neighboring group is an important parameter that has a strong influence on the rate constants as shown in *Fig. 4* for the series of geranyl esters **1b**–**8b**. The rate constants k_2 were found to cover several orders of magnitude between 0.75 for **2b** and 1735 for **4b**. Carbamoylbenzoate **4b** cyclizes twice as fast as 2-(hydroxymethyl)benzoate **3b**, *ca.* 70 times faster than 2-formylbenzoate **1b** and almost 2000 faster than its 2-acetyl analogue **2b**. The hydrolysis of geranyl 2-formylbenzoate (**1b**) is *ca.* 25 times faster than that of its 2-acetyl analogue **2b**, whereas citronellyl 2-formylbenzoate (**1a**) hydrolyzes *ca.* ten times faster than the corresponding 2-acetyl derivative **2a**. The release mechanism of alcohols from 2-acylbenzoates such as **1** and **2** in basic solution has been described to proceed *via* hydration of the carbonyl group followed by intramolecular nucleophilic attack to form a lactone and an alcohol [30]. For 2-acylbenzoates, the OH^- addition [19] or the cyclization [21] has been found to be the rate-determining step. Rapid ring opening gives then the anion of the corresponding carboxylic acid together with the alcohol. The mechanisms for the intramolecular cyclization of 2-(hydroxymethyl)benzoates [24], 2-carbamoylbenzoates [27][28][55], or other related systems [25][26][29][51] are very similar. However, in contrast to the 2-acylbenzoates, the internal nucleophile does not

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[2]) Note that the literature values have been reported for reaction at 25°, whereas our experiments were carried out at 20°. As compared to the pk_W values of pure H_2O (14.16 at 20°), the influence of the temperature on the absolute values is expected to be relatively small as compared to the difference in solvent. Since we are not interested in absolute rate constants but only in an estimation of the correct order of magnitude, we consider this difference to be not very important since it affects all values equally.

[3]) The pK_w value of 15.05 used in our previous report to calculate k_2 of compound **10** [9] corresponds to a solvent mixture H_2O/MeCN *ca.* 1.2:1 (*v*/*v*) and 3:2 (*w*/*w*) at 25° [54].

have to be generated by hydration. Within the carbamoylbenzoate series, 2-[(ethylamino)carbonyl]benzoates such as **4b** were found to have the highest rate constants for the alkaline ester hydrolysis, followed by unsubstituted 2-(aminocarbonyl)benzoates (see **5b**) or the corresponding isopropyl derivatives (see **6b)**. The great diversity of available neighboring groups corresponding to various kinetics of alcohol release is presumably the most-important factor that can efficiently be varied for the tailor-made design of optimized perfume precursors. Carbamoylbenzoates have the added advantage that they are easily synthesized and, by structural modification of the amide part, can be designed to attain the optimum rate of alcohol release for the targeted application.

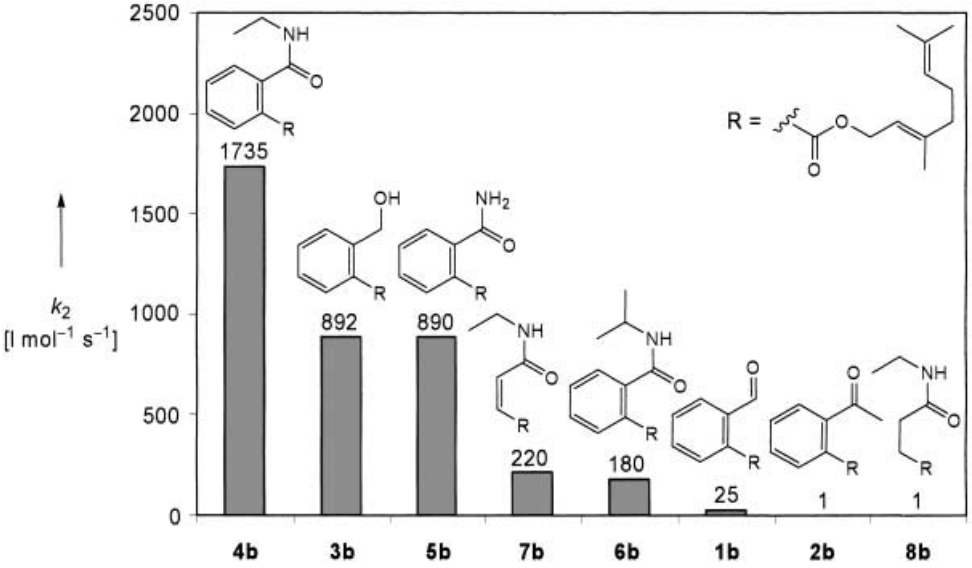


Fig. 4. *Graphical representation of the different rate constants* k_2 [l mol^{-1} s^{-1}] (see *Table 1*) *obtained for the alkaline hydrolysis of geranyl esters* **1b**–**8b**

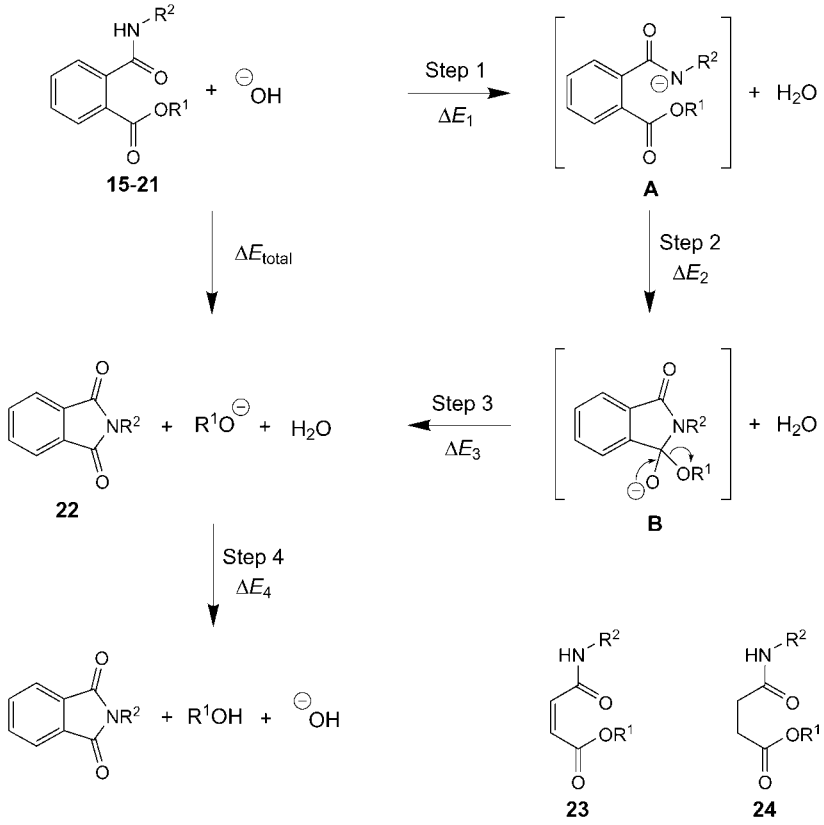
2.7. *Influence of the Precursor Skeleton on the Rate of Hydrolysis.* Another factor that strongly influences the rate of ester hydrolysis is the structure of the precursor substrate itself (*Table 1*, *Fig. 4*). First of all, the importance of the presence of a neighboring group in the 2-position is illustrated by comparing the absolute rate constants k_2 of 2-formylbenzoate **1b** ($k_2 = 24.6$ l mol^{-1} s^{-1}) and the corresponding 4-formylbenzoate **13** ($k_2 = 8.93 \cdot 10^{-3}$ l mol^{-1} s^{-1}, obtained from $k_0 = 4.58 \cdot 10^{-6}$ s^{-1} measured at pH 11.54), which results in a rate enhancement for **1b** by a factor of 2800. Generally, the rigidity of the substrate favors the cyclization of the precursor, and an increase of the rate of hydrolysis by a factor of *ca.* 250 was, thus, observed for maleate derivative **7b** as compared to succinate derivative **8b**, where free rotation between the ester group and the attacking nucleophile is possible. Surprisingly, the rate of hydrolysis increases by a factor of eight when comparing maleate derivative **7b** with benzoate **4b** (*Table 1*, *Fig. 4*).

2.8. *Calculations.* To have a general tool to predict the order of magnitude of the structural changes on the release kinetics without preparing all the compounds in question, we tried to rationalize our experimental data based on density-functional computer simulations. Since the direct comparison of the different types of nucleophiles used as the attacking neighboring groups in this work is very complicated and time-consuming, we decided to investigate only the influence of the leaving alcohols and the substitution effects on the nucleophiles in the case of the 2-carbamoylbenzoates. For simplicity, and to save computation time, the leaving fragrance alcohols citronellol, menthol, and geraniol used in the kinetics measurements were replaced by EtOH, ^{i}PrOH and 3-methylbut-2-en-1-ol, respectively. The different reaction steps that are expected to be involved in the fragrance release of compounds **15**–**21** are illustrated in *Scheme 4* as a simple model. In the first step, the OH^- ion of the buffer solution abstracts a proton from the carbamoyl moiety to form the anionic species **A**. After adopting the ideal conformation for the neighboring-group attack, **A** cyclizes to intermediate **B**, which then yields phthalimide **22** together with the corresponding alcoholate. The latter is protonated in the last step to form the final products. Based on the fact that both the leaving alcohol R^1OH and the substituent R^2 at the attacking nucleophile influence the rate constants considerably, we assume that the first and the last steps of the reaction sequence in *Scheme 4* are not rate-determining. For example, if the deprotonation of the precursor were the rate-determining step, the strong reactivity differences which were observed on varying the structure of the leaving alcohol could not be explained. Therefore, as shown for comparable cases, either the adoption of the ideal conformation for nucleophilic attack (near-attack conformation) [56] or the breakdown of the tetrahedral intermediate [57] were considered to be the rate-determining steps.

To simplify our calculations, the energies of the starting structures **15**–**18** were first minimized by systematic conformer analyses at the semi-empirical PM3 level [58] with the 'Spartan' program. Based on these minima, all reactants, products, and intermediates were then further optimized by density-functional calculations [59] in H_2O at the B3LYP/6-31G** level within the 'Jaguar' program. H_2O solvation energies were computed by using the self-consistent reaction field as implemented in 'Jaguar'. The results obtained by these methods are summarized in *Table 2*. In the first series of compounds, **15**–**18**, we investigated the influence of the leaving alcohol R^1OH (allylic, primary, and secondary) by keeping the substitution at the carbamoyl moiety the same; in the second series, **19**–**21**, we modified the substituent R^2 at the carbamoyl moiety while keeping the same leaving alcohol. The energy differences ΔE_3 and ΔE_{total} in *Table 2* are obtained by subtracting either the sum of the energies of intermediate **B** and H_2O or the sum of the energies of starting compounds **15**–**21** and the OH^- ion from the sum of energies of phthalimides **22**, the leaving alcoholate R^1O^- and H_2O.

In the case of precursor **16**, the B3LYP calculations showed that the anionic intermediate **A** is *ca.* 4.5 kcal/mol higher in energy than species **B**, thus favoring the cyclization. The reaction coordinate for the intramolecular nucleophile was explored at the semi-empirical level PM3 in the gas phase and was found to contain a very low energy barrier (0.5 kcal/mol) for the formation of **B**. We can, thus, suppose that the activation energy for the second step is probably very low and will not greatly influence the kinetics of the reaction. This, in return, suggests the third step to control the kinetics

Scheme 4. *Reaction Sequence for the Alkaline Hydrolysis of 2-[(Alkylamino)carbonyl]benzoates* **15**–**21** *Used for the Density-Functional Calculations in* H_2O. For R^1 and R^2, see *Table 2*.



of the reaction. It is out of the scope of this publication to calculate the exact transition state of this reaction, however, it can be assumed that the energy maximum of the reaction pathway is very close to the end of the third step. When comparing the different leaving alcoholates R^1O^-, the calculation of the energy difference ΔE_3 for this reaction step reflects correctly the order of the experimentally measured rate constants. However, in the case that the leaving alcoholate is kept constant and the substituent R^2 at the carbamoyl moiety varies, the experimental order of rate constants is not correctly reflected by this reaction step. We, therefore, decided to compute the total energy difference (ΔE_{total}) between the starting molecules **15**–**21** and their corresponding phthalimides **22** together with the released alcoholate (*Scheme 4*). In this case, the influence of both R^1 and R^2 should be taken into account. Again, to save computing time, the substituents R^1 were reduced to between one and five C-atoms. The significance of the absolute energy difference is probably low if we consider that it includes anionic species, which may require explicit H_2O molecules for the calculation. By taking into account relative energy differences for the entire reaction pathway, errors are probably cancelled out since for all compounds, similar intermediates are

Table 2. *Energy Differences* [kcal/mol] *Obtained by Density-Functional Calculations* (B3LYP/6-31G**) *in H_2O.* The relative energies ΔE_3 and ΔE_{total} were obtained by subtraction of the sum of energies of intermediate **B** and H_2O (ΔE_3) or the sum of energies of compounds **15**–**21** and OH^- (ΔE_{total}) from the sum of energies of compounds **22**, the leaving alcoholate R^1O^-, and H_2O, respectively, according to the reaction pathway illustrated in *Scheme 4*.

Starting compound	R^1	R^2	ΔE_3 [kcal mol^{-1}]	ΔE_{total} [kcal mol^{-1}]	Order of exper. rate constants[a])
15	$Me_2C{=}CHCH_2$	Me	13.26	– 2.55	a
16	Me	Me	12.13	– 2.50	
17	Et	Me	15.37	0.78	b
18	Me_2CH	Me	16.80	2.94	c
19	Me	Et	11.64	– 2.44	1
20	Me	H	13.53	– 2.06	2
21	Me	Me_2CH	12.73	– 0.27	3
23	Me	Me	14.90	2.94	I
24	Me	Me	10.44	– 0.54	II

[a]) See *Table 1: e.g.*, a (**4b**) > b > c (**4c**); 1 (**4b**) > 2 (**5b**) > 3 (**6b**); I (**7b**) > II (**8b**).

involved in the different reaction steps. The order of the ΔE_{total} values calculated for compounds **15**–**21** are consistent with the experimentally determined rate constants of the corresponding fragrance precursors, thus confirming our hypothesis.

The structure of the alcohol influences the reaction rate for the breakdown of the tetrahedral intermediate **B** with its ability to form an alcoholate R^1O^- (being related to the acidity of the alcohol), whereas the substituent R^2 at the carbamoyl moiety appears to influence the energy of the cyclization step. For the same precursor skeleton, these simple calculations nicely reflect the experimental reactivity of the precursors.

However, the comparison of ΔE_{total} for the corresponding maleate derivative **23** and succinate derivative **24** ($R^1 = R^2 = Me$) suggests that the saturated compound would react faster than the unsaturated one, which is not in accordance with the experimental values and, thus, illustrates the limitations of our model. The loss of entropic energy in the cyclization of saturated **24** is not taken into account in our calculations, and the computed ΔE_{total} for **24** is, thus, presumably too low[4]). Furthermore, the use of a continuum model for the solvation treatment probably overestimates the strength of the intramolecular H-bond in **23** giving rise to a higher value for ΔE_{total} in this case.

3. Conclusions. – A series of 2-acylbenzoates **1** and **2**, 2-(hydroxymethyl)benzoates **3**, and carbamoyl esters **4**–**8** were prepared in a few reaction steps as chemical delivery systems for the controlled release of primary, secondary, and tertiary fragrance alcohols. The perfumery alcohols were found to be efficiently released by neighboring-group-assisted alkaline hydrolysis of suitably designed fragrance precursors in aqueous

[4]) The calculated zero-point vibrational-energy corrections and thermodynamic properties of molecules **23** and **24**, as well as of their corresponding cyclization products, showed that the difference between the two resulting energies is not significant when compared to the computed energy differences (ΔE_{total}) given in *Table 2*. The quantification of the entropic contribution to the cyclization would, therefore, require a much more-specific evaluation (based on molecular-dynamics studies) beyond the scope of this publication.

solution. The general release principle of the precursors described in this work is based on the formation of an intermediate nucleophilic species, which then intramolecularly attacks the carbonyl group of an ester function and, upon cyclization, releases the desired alcohol. The kinetics measurements were carried out at 20° in buffered solutions in H_2O/MeCN by HPLC analysis.

The rates of hydrolysis depend on the structure of the leaving alcohol, together with the precursor skeleton and structure of the neighboring nucleophile that attacks the ester function. As a general trend, the experimental data showed that the fragrance alcohols are released more rapidly from 2-carbamoylbenzoates or 2-(hydroxymethyl)-benzoates than from 2-formyl- or 2-acetylbenzoates. The geometrically favored structure of the 2-carbamoylbenzoates cyclizes more rapidly than the corresponding conformationally mobile structure of a carbamoyl derivative of succinate. The 2-[(ethylamino)carbonyl]benzoates react faster than the corresponding 2-(aminocarbonyl)- or the bulkier 2-[(isopropylamino)carbonyl]benzoates; and allylic primary alcohols are more readily released than secondary or tertiary alcohols. A suitable choice of these different structural parameters allows one to influence the rates of hydrolysis over several orders of magnitude.

To understand and predict the order of magnitude of the structural changes on the release kinetics, the experimental data were compared to the results of density-functional computer simulations in the case of the 2-[(alkylamino)carbonyl]benzoates as an example. Based on a preliminary semi-empirical conformation analysis, density-functional calculations at the B3LYP/6-31G** level were carried out for the starting precursor molecules, several reaction intermediates, and the cyclized phthalimides. The total-energy difference (ΔE_{total}) between the starting molecules and the OH^- ion of the buffer solution, and the corresponding phthalimides together with the released alcoholate and H_2O, corresponds to the experimental reactivity of the precursors by taking into account the structural variety of the leaving alcohol and the different substitution at the attacking nucleophile. For the same precursor skeleton, these simple calculations were found to model the experimental data correctly.

Based on the solid understanding of the influence of structural parameters on the kinetic rate constants obtained in this work, it is now possible to design tailor-made precursors for a large variety of fragrance alcohols and to predict their efficiency as controlled-release systems in practical applications of functional perfumery. Furthermore, the chain length of the *N*-substituent of the 2-carbamoylbenzoates allows control of hydrophobicity ($\log P$) and, thus, the retention of the precursors on different surfaces such as fabric or hair during washing [11]. The neighboring-group-assisted release of alcohols from 2-acyl-, 2-(hydroxymethyl)-, or 2-carbamoylbenzoates investigated in this work is very generally applicable and may, therefore, be extended to the delivery of biologically active material in pharmaceutical or agrochemical research.

Experimental Part

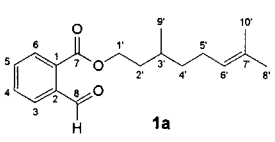
General. Commercially available reagents and solvents were used without further purification if not stated otherwise. Reactions were carried out in standard glassware under N_2 or Ar, and yields are not optimized. Demineralized water was obtained from a *Millipore Synergy-185* water purifier. Column chromatography (CC):

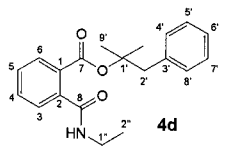
silica gel *60* (35–70 μm from *SDS*). Anal. HPLC: *Thermo Separation Products* apparatus composed of an online vacuum degasser, a *SpectraSystem P4000* quaternary pump, a *SpectraSystem AS3000* autosampler thermostatted at 20°, and a *SpectraSystem UV6000LP* diode array detector. UV/VIS Spectra: *Perkin-Elmer Lambda-14* spectrometer; λ in nm (ε). IR Spectra: *Perkin-Elmer 1600-FTIR* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker AMX-360* spectrometer; δ in ppm downfield from Me_4Si as internal standard, J in Hz; the NMR data of **1a**, **3b**, **4d**, **7e**, **8b**, and (3*R*)-**11c** are assigned as examples in *Table 3*; the signals of other structures may be attributed in analogy. GC/MS: *Hewlett-Packard 5890* or *6890-GC* system equipped with a *Supelco SPB-1* capillary column (30 m, 0.25 mm i.d.) at 70° for 10 min then to 260° (10°/min), He flow *ca.* 1 ml/min, coupled with a *Hewlett-Packard MSD-5972* or *-5973* quadrupole mass spectrometer, electron energy *ca.* 70 eV, fragment ions *m/z* (rel. int. in % of the base peak).

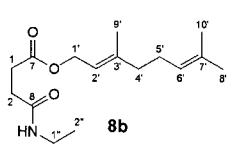
Table 3. *Assignment of ^{13}C-NMR* (90.6 MHz) *and ^1H-NMR* (360 MHz) *Data for Precursors* **1a**, **3b**, **4d**, **7e**, **8b**, *and (3*R*)-*__11c__ *in $CDCl_3$ Based on 1D and 2D NMR Measurements.* δ in ppm. Arbitrary numbering.

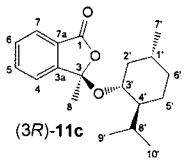
	1a[a])		**3b**		**4d**[a])		**7e**		**8b**[a])		(3*R*)-**11c**[a])	
	δ (C)	δ (H)	δ (C)	δ (H)	δ (C)	δ (H)	δ (C)	δ (H)	δ (C)	δ (H)	δ (C)	δ (H)
C(1)	132.45	–	129.29	–	130.98	–	125.03	6.07	31.07	2.47	168.01	–
C(2)	137.10	–	143.13	–	138.07	–	138.41	6.30	29.72	2.67	–	–
C(3)	128.35	7.93	130.35	7.44	127.71	7.42	–	–	–	–	109.24	–
C(3a)	–	–	–	–	–	–	–	–	–	–	148.18	–
C(4)	132.26	7.64	132.91	7.51	131.37	7.46	–	–	–	–	122.83	7.50
C(5)	132.89	7.64	127.83	7.37	129.38	7.40	–	–	–	–	134.35	7.71
C(6)	130.31	7.96	131.21	8.01	129.84	7.73	–	–	–	–	130.35	7.58
C(7)	166.33	–	168.06	–	166.27	–	166.16	–	173.12	–	125.28	7.88
C(7a)	–	–	–	–	–	–	–	–	–	–	127.50	–
C(8)	192.06	10.63	64.84	4.77	169.18	–	163.92	–	171.34	–	26.47	1.84
C(1′)	64.49	4.42	62.33	4.86	84.05	–	65.87	4.38	61.63	4.60	31.47	1.19
C(2′)	35.44	1.83, 1.63	117.94	5.48	46.16	3.21	34.84	2.98	118.18	5.33	43.83	2.11, 1.09
C(3′)	29.53	1.63	142.87	–	137.17	–	137.31	–	142.30	–	75.47	3.04
C(4′)	36.94	1.40, 1.26	39.55	2.05	130.66	7.20	128.89	7.21	39.53	2.05	48.40	1.20
C(5′)	25.37	2.01	26.27	2.09	128.00	7.25	128.58	7.30	26.30	2.09	22.80	1.55, 0.77
C(6′)	124.45	5.09	123.65	5.09	126.50	7.21	126.73	7.22	123.73	5.08	34.10	1.55, 0.77
C(7′)	131.46	–	131.92	–	128.00	7.25	128.58	7.30	131.82	–	22.21	0.86
C(8′)	25.70	1.67	25.68	1.68	130.66	7.20	128.89	7.21	25.68	1.68	24.90	2.09
C(9′)	19.46	0.98	16.58	1.78	25.88	1.56	–	–	16.47	1.69	16.08	0.37
C(10′)	17.66	1.60	17.71	1.61	–	–	–	–	17.69	1.60	21.46	0.87
C(1″)	–	–	–	–	34.91	3.40	34.52	3.33	34.43	3.27	–	–
C(2″)	–	–	–	–	14.65	1.19	14.37	1.17	14.79	1.13	–	–
OH / NH	–	–	–	3.93	–	5.84	–	8.09	–	6.08	–	–

a)









Kinetic Measurements [9]. Buffer solns. were prepared by dissolving (upon sonication) two buffer tablets pH 7.0 (phosphate) or 9.0 (borate) (*Fluka*) in a mixture of 160 ml of demineralized H_2O and 40 ml MeCN, or, by dissolving one envelope of buffer pH 11.0 (phosphate/hydrogencarbonate) (*Aldrich*) in 400 ml of demineralized

H_2O and 100 ml of MeCN. To determine the pH values of the reaction solns., 10 ml of the buffer solns. were diluted with 2 ml of MeCN (to give a mixture of H_2O/MeCN 2:1 (*v*/*v*)) and the pH values measured to be 7.62 ± 0.01, 10.47 ± 0.02 and 11.54 ± 0.02, respectively (*Mettler-Toledo MP220* apparatus with an *InLab 410*-Ag/AgCl glass electrode). For the soln. with double borate-buffer concentration, a pH value of 10.52 ± 0.01 was determined. All samples were thermostatted at 20°.

For the measurement of the rate constants, the ester (35 to 45 mg) was dissolved in MeCN (25 ml), and this soln. (0.2 ml) was added to a buffer soln. (1.0 ml) to give pH 7.62, 10.47, 10.52, or 11.54 in H_2O/MeCN 2:1. The mixture was immediately injected in a HPLC apparatus ($t = 0$), eluted on a reversed-phase column with H_2O/MeCN containing 0.1% of CF_3COOH, and analyzed at λ 254 nm. Most of the chromatograms were recorded on a *Macherey-Nagel Nucleosil-100-5-C18* column (250 × 4 mm i.d.) with H_2O/MeCN 7:3 → 2:8 during 20 min at 1 ml/min, and the reaction soln. (20 µl) was reinjected every 35 or 70 min (8–20 times). The kinetics of the fast hydrolysis reactions were measured on a *Merck Chromolith-SpeedROD-RP-C18e* column (50 × 4.6 mm i.d.) by isocratic elution with H_2O/MeCN 3:7 or 4:6 at 1 or 3 ml/min, or by using H_2O/MeCN 7:3 → 4:6 during 3 min at 3 ml/min; the reaction soln. (10 µl) was reinjected at constant time intervals varying between 3 and 6 min (8–20 times).

Computational Methods. All calculations were carried out on a *Silicon-Graphics SGI-R10000* computer. Since it is hardly possible to minimize all possible conformers at high computation levels, the starting precursor structures were obtained from systematic conformer analyses by using the 'Spartan' program (Version 02, edn. 2001; *Wavefunction Inc.*, Irvine, CA, USA) at the semi-empirical PM3 level [58]. All reactants, products, and intermediates were then further optimized by density-functional calculations [59] at the B3LYP/6-31G** level within the 'Jaguar' program (Version 4.0, edn. 2000; *Schrödinger Inc.*, Portland, OR, USA) with the previously calculated PM3 minima as the starting structures. H_2O solvation energies were computed with the self-consistent reaction field as implemented in 'Jaguar'.

Methyl 2-Acetylbenzoate (**10**) was prepared from 2-acetylbenzoic acid with diazomethane as described in [21][36].

(±)-3,7-Dimethyloct-6-enyl 2-Formylbenzoate (**1a**) *and (±)-3-(3,7-dimethyloct-6-enyloxy)isobenzofuran-1(3*H*)-one* (**12a**) [20][38]. A soln. of 2-formylbenzoic acid (7.50 g, 50.0 mmol), *N*,*N*-dimethylpyridin-4-amine (DMAP; 4.88 g, 40.0 mmol) and citronellol (15.60 g, 100.0 mmol) in CH_2Cl_2 (75 ml) was cooled in an ice-bath before a soln. of dicyclohexylcarbodiimide (DCC; 11.35 g, 55.0 mmol) in CH_2Cl_2 (25 ml) was added during 10–15 min. The mixture was stirred for 15 min at 0°, then at 20° for 48 h. The formed precipitate was filtered off and the filtrate washed with 10% HCl soln. (2×), sat. Na_2CO_3 soln. (2×), and H_2O, dried (Na_2SO_4), and evaporated. Repetitive CC (SiO_2, toluene/AcOEt 19:1 and toluene) gave 2.45 g (17%) of **12a** and 2.25 g (16%) of **1a** as colorless oils.

Data of **1a**: UV/VIS (hexane): 288 (1400), 241 (8500). IR (neat): 2960*m*, 2924*m*, 2854*m*, 2117*m*, 1774*w*, 1713*s*, 1697*s*, 1594*m*, 1577*w*, 1449*m*, 1379*m*, 1359*w*, 1346*w*, 1302*w*, 1264*s*, 1192*m*, 1162*w*, 1131*m*, 1077*s*, 1043*w*, 985*w*, 947*w*, 890*w*, 821*m*, 800*w*. ^{1}H-NMR (360 MHz, $CDCl_3$; *Table 3*): 10.63 (*s*, 1 H); 8.00–7.90 (*m*, 2 H); 7.70–7.60 (*m*, 2 H); 5.15–5.05 (*m*, 1 H); 4.50–4.36 (*m*, 2 H); 2.12–1.92 (*m*, 2 H); 1.92–1.78 (*m*, 1 H); 1.78–1.52 (*m*, 2 H); 1.67 (*s*, 3 H); 1.60 (*s*, 3 H); 1.48–1.34 (*m*, 1 H); 1.34–1.17 (*m*, 1 H); 0.98 (*d*, *J* = 6.3, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$; *Table 3*): 192.06 (*d*); 166.33 (*s*); 137.10 (*s*); 132.89 (*d*); 132.45 (*s*); 132.26 (*d*); 131.46 (*s*); 130.31 (*d*); 128.35 (*d*); 124.45 (*d*); 64.49 (*t*); 36.94 (*t*); 35.44 (*t*); 29.53 (*d*); 25.70 (*q*); 25.37 (*t*); 19.46 (*q*); 17.66 (*q*). EI-MS: 151 (20), 150 (15), 149 (89), 140 (3), 139 (4), 138 (41), 137 (21), 134 (17), 133 (100), 132 (12), 124 (5), 123 (53), 122 (5), 121 (7), 111 (6), 110 (6), 109 (24), 106 (4), 105 (37), 104 (32), 97 (4), 96 (15), 95 (73), 94 (7), 93 (10), 84 (7), 83 (17), 82 (58), 81 (93), 80 (9), 79 (5), 78 (3), 77 (36), 76 (17), 75 (3), 71 (5), 70 (26), 69 (91), 68 (27), 67 (49), 65 (12), 57 (12), 56 (15), 55 (46), 54 (4), 53 (12), 51 (17), 50 (7), 43 (12), 42 (10), 41 (98), 40 (3), 39 (17), 29 (14), 27 (11).

Data of **12a** (mixture of stereoisomers): UV/VIS (hexane): 295 (sh, 100), 288 (sh, 100), 278 (700), 270 (700), 264 (sh, 600), 231 (sh, 3400), 224 (4300). IR (neat): 2957*m*, 2914*m*, 2863*w*, 1770*s*, 1614*w*, 1604*w*, 1466*m*, 1410*w*, 1363*m*, 1311*m*, 1284*m*, 1213*m*, 1152*w*, 1131*m*, 1089*m*, 1056*s*, 1011*m*, 924*s*, 896*s*, 832*w*, 800*w*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.88 (*dt*, *J* = 7.5, 0.8, 1 H); 7.70 (*ddd*, *J* = 7.5, 7.5, 1.2, 1 H); 7.62–7.54 (*m*, 2 H); 6.36 (*s*, 1 H); 5.13–5.05 (*m*, 1 H); 4.42–3.90 (*m*, 1 H); 3.88–3.76 (*m*, 1 H); 2.09–1.88 (*m*, 2 H); 1.82–1.65 (*m*, 1 H); 1.68, 1.67 (2 *s*, 3 H); 1.65–1.55 (*m*, 1 H); 1.59 (*s*, 3 H); 1.55–1.44 (*m*, 1 H); 1.43–1.29 (*m*, 1 H); 1.28–1.11 (*m*, 1 H); 0.92, 0.92 (2 *d*, *J* = 6.7, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 168.72 (*s*); 145.10 (*s*); 134.33 (*d*); 131.30 (*s*); 130.74 (*d*); 129.03 (*d*); 128.22 (*d*); 127.27 (*s*); 125.42 (*d*); 124.61 (*d*); 123.40 (*d*); 102.57 (*d*); 102.45 (*d*); 68.69 (*t*); 68.62 (*t*); 37.06 (*t*); 36.39 (*t*); 36.33 (*t*); 29.40 (*d*); 29.34 (*d*); 25.71 (*q*); 25.40 (*t*); 19.46 (*q*); 17.65 (*q*). EI-MS: 151 (4), 149 (6), 138 (10), 137 (11), 136 (27), 135 (4), 134 (20), 133 (100), 123 (18), 122 (4), 121 (23), 109 (12), 105 (23), 104 (4), 96 (8), 95 (42), 94 (3), 93 (3), 83 (7), 82 (24), 81 (63), 80 (4), 79 (4), 77 (24), 76 (8), 71 (3), 70 (7), 69 (56),

68 (25), 67 (25), 65 (3), 57 (6), 56 (5), 55 (24), 54 (3), 53 (7), 51 (10), 50 (4), 43 (9), 42 (6), 41 (53), 39 (10), 29 (7), 27 (6).

*(2*E*)-3,7-Dimethylocta-2,6-dienyl 2-Formylbenzoate* (**1b**) *and (±)-3-[(2*E*)-3,7-Dimethylocta-2,6-dienyloxy]isobenzofuran-1(3*H*)-one* (**12b**) [9]. As described for **1a** and **12a**, with geraniol (15.42 g, 100.0 mmol). CC (SiO_2, heptane/Et_2O 8:2) gave 2.55 g (22%) of **1b** and 4.36 g (38%) of **12b**.

Data of **1b**: UV/VIS (hexane): 288 (1400), 241 (9000), 209 (36800). IR (neat): 2967*w*, 2914*m*, 2853*w*, 1777*w*, 1711*s*, 1695*s*, 1594*m*, 1577*m*, 1484*w*, 1446*m*, 1376*m*, 1340*w*, 1303*w*, 1253*s*, 1191*m*, 1162*w*, 1128*m*, 1071*s*, 1040*w*, 963*w*, 924*m*, 890*w*, 819*m*, 799*w*, 748*s*, 699*m*, 639*m*. ^{1}H-NMR (360 MHz, $CDCl_3$): 10.63 (*s*, 1 H); 8.01–7.90 (*m*, 2 H); 7.68–7.60 (*m*, 2 H); 5.52–5.45 (*m*, 1 H); 5.13–5.05 (*m*, 1 H); 4.90 (*d*, *J* = 7.5, 2 H); 2.18–2.03 (*m*, 4 H); 1.78 (*s*, 3 H); 1.67 (*s*, 3 H); 1.61 (*s*, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 192.14 (*d*); 166.34 (*s*); 143.48 (*s*); 136.99 (*s*); 132.91 (*d*); 132.57 (*s*); 132.23 (*d*); 131.95 (*s*); 130.41 (*d*); 128.31 (*d*); 123.63 (*d*); 117.73 (*d*); 62.75 (*t*); 39.55 (*t*); 26.26 (*t*); 25.68 (*q*); 17.71 (*q*); 16.59 (*q*). EI-MS: 151 (8), 150 (3), 149 (29), 137 (3), 136 (20), 135 (3), 134 (12), 133 (51), 123 (4), 122 (5), 121 (20), 107 (7), 106 (4), 105 (18), 104 (4), 95 (8), 94 (9), 93 (40), 92 (11), 91 (5), 81 (10), 80 (19), 79 (7), 78 (3), 77 (20), 76 (6), 70 (7), 69 (100), 68 (60), 67 (24), 65 (8), 55 (7), 53 (12), 51 (11), 50 (5), 43 (5), 42 (4), 41 (80), 39 (14), 29 (7), 27 (9).

Data of **12b** (off-white crystals): UV/VIS (hexane): 300 (sh, 9), 287 (sh, 42), 278 (800), 271 (800), 265 (sh, 610), 231 (sh, 7900), 223 (11100). IR (neat): 2967*w*, 2900*m*, 2870*m*, 2819*w*, 1804*w*, 1753*s*, 1714*w*, 1677*w*, 1604*w*, 1465*m*, 1436*w*, 1415*m*, 1376*m*, 1354*m*, 1311*m*, 1287*m*, 1239*w*, 1214*m*, 1207*m*, 1180*w*, 1139*m*, 1108*w*, 1089*m*, 1067*m*, 1011*w*, 992*m*, 963*w*, 913*m*, 893*m*, 885*m*, 801*m*, 786*m*, 778*m*, 752*m*, 713*m*, 690*m*, 639*m*, 617*w*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.88 (*dt*, *J* = 7.5, 1.2, 1 H); 7.70 (*ddd*, *J* = 7.5, 7.5, 1.2, 1 H); 7.58 (*t*, *J* = 7.5, 2 H); 6.41 (*s*, 1 H); 5.48–5.39 (*m*, 1 H); 5.13–5.05 (*m*, 1 H); 4.41 (*d*, *J* = 7.1, 2 H); 2.18–2.04 (*m*, 4 H); 1.73 (*s*, 3 H); 1.65 (*s*, 3 H); 1.60 (*s*, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 168.82 (*s*); 145.35 (*s*); 143.33 (*s*); 134.31 (*d*); 131.88 (*s*); 130.71 (*d*); 127.25 (*s*); 125.40 (*d*); 123.75 (*d*); 123.45 (*d*); 118.74 (*d*); 101.06 (*t*); 66.21 (*t*); 39.63 (*t*); 26.26 (*t*); 25.68 (*q*); 17.70 (*q*); 16.55 (*q*). EI-MS: 151 (15), 150 (3), 149 (28), 137 (3), 136 (15), 135 (3), 134 (14), 133 (70), 123 (8), 122 (6), 121 (19), 108 (5), 107 (12), 106 (4), 105 (22), 104 (4), 95 (7), 94 (15), 93 (45), 92 (14), 91 (7), 85 (4), 81 (15), 80 (17), 79 (8), 78 (3), 77 (23), 76 (7), 70 (8), 69 (86), 68 (100), 67 (31), 65 (4), 55 (7), 53 (12), 51 (11), 50 (6), 43 (7), 42 (4), 41 (72), 39 (14), 29 (8), 27 (10).

2-Phenylethyl 2-Formylbenzoate (**1e**) *and (±)-3-(2-Phenylethoxy)isobenzofuran-1(3*H*)-one* (**12e**). As described for **1a** and **12a**, with 2-formylbenzoic acid (12.72 g, 84.8 mmol), DMAP (8.27 g, 67.8 mmol), 2-phenylethanol (20.69 g, 169.6 mmol), CH_2Cl_2 (130 ml), DCC (19.25 g, 93.3 mmol), and CH_2Cl_2 (40 ml). CC (SiO_2, heptane/Et_2O 8:2) yielded 2.38 g (11%) of **1e** and 8.25 g (38%) of **12e**, containing unreacted 2-phenylethanol.

Data of **1e**: UV/VIS (hexane): 336 (28), 288 (1400), 241 (8400), 209 (37700). IR (neat): 3064*w*, 3026*w*, 2953*w*, 2893*w*, 1712*s*, 1692*s*, 1593*m*, 1577*m*, 1496*m*, 1483*w*, 1465*w*, 1452*m*, 1382*m*, 1264*s*, 1253*s*, 1191*m*, 1163*w*, 1126*s*, 1075*s*, 1040*m*, 1030*m*, 989*m*, 961*m*, 908*w*, 891*w*, 863*w*, 818*m*, 799*m*, 746*s*, 698*s*. ^{1}H-NMR (360 MHz, $CDCl_3$): 10.50 (*s*, 1 H); 7.95–7.86 (*m*, 2 H); 7.66–7.57 (*m*, 2 H); 7.37–7.30 (*m*, 2 H); 7.30–7.22 (*m*, 3 H); 4.60 (*t*, *J* = 6.9, 2 H); 3.10 (*t*, *J* = 6.9, 2 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 192.06 (*d*); 166.17 (*s*); 137.44 (*s*); 137.04 (*s*); 132.91 (*d*); 132.35 (*d*); 132.18 (*s*); 130.34 (*d*); 128.92 (*d*); 128.65 (*d*); 128.35 (*d*); 126.79 (*d*); 66.36 (*t*); 35.08 (*t*). EI-MS: 150 (3), 149 (27), 134 (3), 133 (23), 121 (3), 106 (5), 105 (35), 104 (100), 91 (8), 79 (6), 78 (7), 77 (18), 76 (5), 65 (5), 51 (7), 50 (3).

Data of **12e**: ^{1}H-NMR (360 MHz, $CDCl_3$): 7.86 (*d*, *J* = 7.5, 1 H); 7.67 (*ddd*, *J* = 7.5, 7.5, 1.2, 1 H); 7.57 (*ddd*, *J* = 7.5, 7.5, 0.8, 1 H); 7.44 (*d*, *J* = 7.5, 1 H); 7.35–7.26 (*m*, 2 H); 7.26–7.18 (*m*, 3 H); 6.31 (*s*, 1 H); 4.12 (*dt*, *J* = 9.5, 6.7, 1 H); 3.97 (*dt*, *J* = 9.5, 7.3, 1 H); 2.98 (*t*, *J* = 6.9, 2 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 168.69 (*s*); 144.86 (*s*); 137.98 (*s*); 134.38 (*d*); 130.80 (*d*); 128.98 (*d*); 128.48 (*d*); 127.16 (*s*); 126.53 (*d*); 125.41 (*d*); 123.44 (*d*); 102.48 (*d*); 70.67 (*t*); 36.07 (*t*). EI-MS: 254 (1, M^+), 236 (3), 149 (11), 134 (9), 133 (100), 106 (14), 105 (18), 104 (28), 91 (11), 79 (4), 78 (7), 77 (14), 76 (3), 65 (3), 51 (5), 50 (2).

(±)-3,7-Dimethyloct-6-enyl 2-Acetylbenzoate (**2a**) [20][38]. A soln. of 2-acetylbenzoic acid (6.49 g, 39.0 mmol), DMAP (3.81 g, 31.2 mmol), and citronellol (12.48 g, 80.0 mmol) in CH_2Cl_2 (60 ml) was cooled in an ice-bath before a soln. of DCC (8.84 g, 42.9 mmol) in CH_2Cl_2 (40 ml) was added during 5 min. The mixture was stirred at 40° for 75 h. The formed precipitate was filtered off and the filtrate washed with 10% HCl soln. (2×) and sat. Na_2CO_3 soln. (2×). The org. layer was dried (Na_2SO_4) and evaporated, the excess citronellol distilled off, the residue chromatographed (SiO_2, toluene/AcOEt 9:1), and the crude product distilled at 150–155°/0.6 Torr: 7.43 g (63%) of **2a**. Colorless oil. UV/VIS (hexane): 313 (sh, 100), 281 (sh, 1000), 276 (1000), 229 (9000). IR (neat): 2961*m*, 2913*m*, 2872*w*, 2855*w*, 1717*s*, 1704*s*, 1597*w*, 1574*w*, 1446*m* (br), 1378*w*, 1354*m*, 1264*s*, 1248*m*, 1129*m*, 1100*m*, 1064*m*, 1038*w*, 1007*w*, 956*m*, 884*w*, 835*w*, 801*w*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.86 (*dd*, *J* = 7.5, 1.2, 1 H); 7.56 (*ddd*, *J* = 7.5, 7.5, 1.2, 1 H); 7.49 (*ddd*, *J* = 7.5, 7.5, 1.6, 1 H); 7.40 (*dd*, *J* = 7.5, 1.2, 1 H); 5.14–5.05 (*m*, 1 H); 4.42–4.27 (*m*, 2 H); 2.54 (*s*, 3 H); 2.12–2.18 (*m*, 2 H); 1.87–1.72 (*m*, 1 H); 1.72–1.48 (*m*, 2 H); 1.67 (*s*,

3 H); 1.60 (*s*, 3 H); 1.46–1.32 (*m*, 1 H); 1.29–1.15 (*m*, 1 H); 0.95 (*d*, *J* = 6.3, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 202.93 (*s*); 166.97 (*s*); 142.92 (*s*); 131.95 (*d*); 131.35 (*s*); 129.92 (*d*); 129.70 (*d*); 129.09 (*s*); 126.36 (*d*); 124.54 (*d*); 64.25 (*t*); 36.97 (*t*); 35.29 (*t*); 30.13 (*q*); 29.49 (*d*); 25.70 (*q*), 25.38 (*t*); 19.40 (*q*); 17.65 (*q*). EI-MS: 165 (23), 149 (12), 148 (19), 147 (100), 146 (41), 138 (18), 137 (3), 124 (3), 123 (28), 118 (6), 110 (3), 109 (13), 105 (7), 104 (18), 96 (6), 95 (30), 91 (13), 90 (9), 89 (5), 83 (5), 82 (21), 81 (33), 80 (3), 77 (5), 76 (14), 75 (3), 74 (3), 71 (4), 70 (4), 69 (26), 68 (8), 67 (16), 56 (4), 55 (11), 53 (3), 50 (4), 43 (5), 41 (15), 39 (3).

*(2*E*)-3,7-Dimethylocta-2,6-dienyl 2-Acetylbenzoate* (**2b**). As described for **2a**, with geraniol (12.32 g, 80.0 mmol). The excess geraniol was distilled off and the residue chromatographed (SiO_2, toluene/AcOEt 9 : 1): 9.08 g (78%) of **2b**. Slightly yellow oil. UV/VIS (hexane): 313 (sh, 200), 300 (sh, 200), 282 (sh, 900), 276 (900), 268 (1000), 228 (9200). IR (neat): 2966*w*, 2920*m*, 2856*w*, 1784*w*, 1715*s*, 1704*s*, 1673*w*, 1597*w*, 1574*w*, 1494*w*, 1484*w*, 1445*m*, 1376*m*, 1354*m*, 1263*s*, 1205*w*, 1163*w*, 1137*m*, 1126*m*, 1100*m*, 1062*m*, 1038*w*, 1006*w*, 955*m*, 931*m*, 886*w*, 834*w*, 799*w*, 761*m*, 731*m*, 708*m*, 696*m*, 661*w*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.90–7.84 (*m*, 1 H); 7.55 (*ddd*, *J* = 7.5, 7.5, 1.2, 1 H); 7.48 (*ddd*, *J* = 7.5, 7.5, 1.2, 1 H); 7.39 (*dd*, *J* = 7.5, 1.6, 1 H); 5.49–5.41 (*m*, 1 H); 5.13–5.05 (*m*, 1 H); 4.83 (*d*, *J* = 7.5, 2 H); 2.53 (*s*, 3 H); 2.20–1.95 (*m*, 4 H); 1.75 (*s*, 3 H); 1.67 (*s*, 3 H); 1.60 (*s*, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 203.01 (*s*); 166.92 (*s*); 143.12 (*s*); 142.94 (*s*); 131.95 (*d*); 131.85 (*s*); 129.91 (*d*); 129.78 (*d*); 129.09 (*s*); 128.23 (*s*); 126.36 (*d*); 123.73 (*d*); 117.75 (*d*); 62.51 (*t*); 39.55 (*t*); 30.17 (*q*); 26.31 (*t*); 25.66 (*q*); 17.69 (*q*); 16.54 (*q*). EI-MS: 165 (23), 149 (6), 148 (28), 147 (100), 146 (8), 137 (3), 136 (26), 123 (3), 121 (19), 107 (6), 105 (11), 104 (6), 95 (4), 94 (11), 93 (33), 92 (10), 91 (20), 81 (5), 80 (13), 79 (6), 77 (8), 76 (7), 70 (3), 69 (46), 68 (42), 67 (15), 65 (4), 55 (3), 53 (6), 43 (6), 42 (2), 41 (22), 39 (4).

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl 2-Acetylbenzoate* (**2c**). As described for **2a**, with 2-acetylbenzoic acid (11.36 g, 50.0 mmol), DMAP (4.88 g, 40.0 mmol), (−)-menthol (23.40 g, 150.0 mmol), CH_2Cl_2 (80 ml), DCC (11.36 g, 55.0 mmol), and CH_2Cl_2 (40 ml). CC (SiO_2, toluene) and recrystallization from hexane gave 1.96 g (13%) of **2c**. White crystals. M.p. 89–91°. UV/VIS (hexane): 315 (sh, 100), 281 (sh, 900), 275 (1000), 229 (9700). IR (neat): 3068*w*, 2962*m*, 2951*m*, 2924*m*, 2914*m*, 2865*m*, 2847*m*, 1716*s*, 1686*s*, 1593*w*, 1576*w*, 1488*w*, 1455*m*, 1417*w*, 1385*w*, 1360*m*, 1335*w*, 1284*m*, 1272*s*, 1259*s*, 1183*w*, 1154*w*, 1139*m*, 1106*m*, 1095*m*, 1080*w*, 1064*m*, 1035*m*, 1016*w*, 980*m*, 954*s*, 914*m*, 884*w*, 838*w*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.87 (*dd*, *J* = 7.7, 1.4, 1 H); 7.55 (*ddd*, *J* = 7.5, 7.5, 1.6, 1 H); 7.48 (*ddd*, *J* = 7.5, 7.5, 1.6, 1 H); 7.38 (*dd*, *J* = 7.5, 1.2, 1 H); 4.93 (*ddd*, *J* = 11.0, 11.0, 4.3, 1 H); 2.54 (*s*, 3 H); 2.21–2.12 (*m*, 1 H); 2.02–1.88 (*m*, 1 H); 1.78–1.67 (*m*, 2 H); 1.63–1.44 (*m*, 2 H); 1.20–1.03 (*m*, 2 H); 1.00–0.85 (*m*, 1 H); 0.94 (*d*, *J* = 6.7, 3 H); 0.92 (*d*, *J* = 7.1, 3 H); 0.80 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 203.20 (*s*); 143.20 (*s*); 131.92 (*d*); 129.76 (*d*); 129.64 (*d*); 129.26 (*s*); 126.23 (*d*); 75.84 (*d*); 47.16 (*d*); 40.59 (*t*); 34.25 (*t*); 31.49 (*d*); 30.35 (*q*); 26.30 (*d*); 23.42 (*t*); 22.02 (*q*); 20.81 (*q*); 16.26 (*q*). EI-MS: 303 (1, $[M+1]^+$), 166 (4), 165 (37), 149 (9), 148 (32), 147 (100), 146 (3), 139 (6), 138 (23), 123 (10), 105 (6), 104(4), 96 (5), 95 (20), 91 (13), 83 (9), 82 (5), 81 (13), 77 (3), 76 (4), 69 (4), 67 (3), 55 (6), 43 (4), 41 (3).

*(±)-3-[(2*E*)-3,7-Dimethylocta-2,6-dienyl]-3-methylisobenzofuran-1(3*H*)-one* (**11b**). Two drops (*ca.* 0.05 g) of 30% NaOMe in MeOH were added to a soln. of **10** (0.5 g, 2.81 mmol) and geraniol (0.43 g, 2.79 mmol) in cyclohexane (7 ml). The mixture was heated to reflux for 24h before another two drops of 30% NaOMe soln. were added. The mixture turned red. After refluxing overnight, the mixture was cooled to r.t., neutralized with 2 drops of AcOH, extracted with Et_2O (2×), washed with H_2O (2×), filtered through *Celite*, and evaporated. CC (SiO_2, heptane/Et_2O 7 : 3) afforded 0.09 g (10%) of pure **11b** as a colorless oil, besides 0.20 g of **11b**/**2b** *ca.* 1 : 1. **11b**: ^{1}H-NMR (360 MHz, $CDCl_3$): 7.89 (*dt*, *J* = 7.9, 1.0, 1 H); 7.73 (*ddd*, *J* = 7.4, 7.4, 1.2, 1 H); 7.59 (*ddd*, *J* = 7.5, 7.5, 0.8, 1 H); 7.53 (*dt*, *J* = 7.5, 0.8, 1 H); 5.30–5.21 (*m*, 1 H); 5.09–5.01 (*m*, 1 H); 3.95–3.86 (*m*, 1 H); 3.61–3.53 (*m*, 1 H); 2.10–1.94 (*m*, 4 H); 1.86 (*s*, 3 H); 1.66 (*s*, 3 H); 1.56 (*s*, 3 H); 1.49 (*s*, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 168.08 (*s*); 148.11 (*s*); 141.30 (*s*); 134.51 (*d*); 131.69 (*s*); 130.51 (*d*); 127.42 (*s*); 125.52 (*d*); 123.85 (*d*); 122.28 (*d*); 119.33 (*d*); 108.64 (*s*); 60.95 (*t*); 39.53 (*t*); 25.26 (*t*); 25.85 (*q*); 25.65 (*q*); 17.66 (*q*); 16.33 (*q*). EI-MS: 165 (29), 149 (8), 148 (25), 147 (100), 136 (11), 123 (4), 121 (10), 107 (6), 105 (7), 104 (3), 95 (3), 94 (6), 93 (26), 92 (9), 91 (20), 81 (8), 80 (11), 79 (4), 77 (8), 76 (7), 69 (36), 68 (42), 67 (13), 65 (4), 55 (3), 53 (7), 51 (3), 50 (3), 43 (11), 41 (30), 39 (7), 27 (3).

*(3*S*)- and (3*R*)-3-Methyl-3-{[1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl]oxy}isobenzofuran-1(3*H*)-one* ((3*S*)- and (3*R*)-**11c**) [40][60]. HCl was bubbled through an ice-cold soln. of 2-acetylbenzoic acid (4.10 g, 25.0 mmol) and (−)-menthol (7.80 g, 50.0 mmol) in Et_2O (75 ml). After 30 min, the exothermic reaction slowed down (*T ca.* 15–20°). The mixture was stirred at 5° for 5 min and at 20° for 1 h under a weak current of HCl gas. The soln. was slowly poured into a stirred sat. Na_2CO_3 soln. and extracted with Et_2O (2×), the extract washed with sat. Na_2CO_3 soln. and H_2O, dried (Na_2SO_4), and evaporated, and the residue submitted to CC (SiO_2, toluene): 5.45 g (72%) of a partially crystallized product. Pentane was added and the crystals were filtered off.

Washing with pentane (3×) yielded 0.55 g of pure (3*R*)-**11c**[5]). White crystals. M.p. 126°. UV/VIS (hexane): 279 (700), 271 (700), 264 (sh, 500), 231 (sh, 7200), 225 (9000). IR (neat): 2989*w*, 2960*m*, 2948*m*, 2924*m*, 2884*w*, 2862*w*, 1762*s*, 1722*w*, 1612*w*, 1602*w*, 1466*m*, 1451*m*, 1384*w*, 1377*m*, 1368*w*, 1339*m*, 1308*w*, 1284*s*, 1242*w*, 1230*w*, 1218*w*, 1183*s*, 1172*s*, 1127*m*, 1096*w*, 1074*m*, 1043*m*, 1036*m*, 1013*s*, 997*m*, 970*w*, 897*s*, 888*m*, 848*w*, 805*w*. ^{1}H-NMR (360 MHz, $CDCl_3$; *Table 3*): 7.88 (*d*, *J* = 7.5, 1 H); 7.71 (*ddd*, *J* = 7.5, 7.5, 1.2, 1 H); 7.58 (*ddd*, *J* = 7.5, 7.5, 1.2, 1 H); 7.50 (*d*, *J* = 7.5, 1 H); 3.10–2.98 (*m*, 1 H); 2.17–2.00 (*m*, 2 H); 1.84 (*s*, 3 H); 1.64–1.47 (*m*, 2 H); 1.28–1.01 (*m*, 3 H); 0.87 (*d*, *J* = 7.1, 3 H); 0.86 (*d*, *J* = 6.3, 3 H); 0.85–0.65 (*m*, 2 H); 0.37 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$, *Table 3*): 168.01 (*s*); 148.18 (*s*); 134.35 (*d*); 130.35 (*d*); 127.50 (*s*); 125.28 (*d*); 122.83 (*d*); 109.24 (*s*); 75.47 (*d*); 48.40 (*d*); 43.83 (*t*); 34.10 (*t*); 31.47 (*d*); 26.47 (*q*); 24.90 (*d*); 22.80 (*t*); 22.21 (*q*); 21.46 (*q*); 16.08 (*q*). EI-MS: 302 (2, M^+), 155 (3), 149 (10), 148 (73), 147 (100), 138 (3), 137 (8), 105 (4), 104 (3), 95 (4), 91 (10), 83 (3), 81 (5), 69 (3), 55 (4), 43 (4).

Crystallization of the concentrated mother liquor at −30° yielded (3*S*)-**11c**/(3*R*)-**11c** ≈ 44:55 (1.85 g). White crystals. M.p. 92–103°. IR (neat): 2990*w*, 2961*m*, 2950*m*, 2925*m*, 2884*w*, 2864*w*, 1763*s*, 1722*w*, 1613*w*, 1602*w*, 1466*m*, 1452*m*, 1384*w*, 1378*m*, 1368*w*, 1339*m*, 1308*w*, 1284*s*, 1243*w*, 1230*w*, 1219*w*, 1183*s*, 1173*s*, 1127*m*, 1097*w*, 1075*m*, 1043*m*, 1036*m*, 1012*s*, 998*m*, 971*w*, 896*s*, 888*m*, 848*w*, 806*w*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.91–7.84 (*m*, 2 H); 7.75–7.66 (*m*, 2 H); 7.63–7.47 (*m*, 4 H); 3.24 (*ddd*, *J* = 10.5, 10.5, 4.4, 1 H); 3.04 (*ddd*, *J* = 10.2, 10.2, 4.4, 1 H); 2.41–2.26 (*m*, 1 H); 2.18–2.00 (*m*, 2 H); 1.84 (*s*, 3 H); 1.83 (*s*, 3 H); 1.68–1.49 (*m*, 5 H); 1.30–1.00 (*m*, 5 H); 0.99–0.68 (*m*, 5 H); 0.93 (*d*, *J* = 7.1, 3 H); 0.87 (*d*, *J* = 7.1, 3 H); 0.86 (*d*, *J* = 6.3, 3 H); 0.81 (*d*, *J* = 6.7, 3 H); 0.76 (*d*, *J* = 6.7, 3 H); 0.37 (*d*, *J* = 7.1, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 168.20 (*s*); 168.00 (*s*); 149.31 (s); 148.16 (*s*); 134.36 (*d*); 134.11 (*d*); 130.35 (2 *d*); 127.49 (*s*); 127.02 (*s*); 135.31 (*d*); 125.26 (*d*); 122.85 (*d*); 109.24 (*s*); 108.24 (*s*); 75.46 (*d*); 74.46 (*d*); 48.58 (*d*); 48.39 (*d*); 43.83 (*t*); 42.91 (*t*); 34.15 (*t*); 34.10 (*t*); 31.51 (*d*); 31.46 (*d*); 26.47 (*q*); 25.61 (*q*); 25.05 (*d*); 24.89 (*d*); 23.02 (*t*); 22.79 (*t*); 22.21 (*q*); 22.18 (*q*); 21.45 (*q*); 21.42 (*q*), 16.07 (*q*); 16.01 (*q*). EI-MS: 302 (1, M^+), 149 (9), 148 (71), 147 (100), 137 (6), 105 (3), 95 (3), 91 (8), 81 (4), 55 (3), 43 (3).

*(2*E*)-3,7-Dimethylocta-2,6-dienyl 4-Formylbenzoate* (**13**). A soln. of 4-formylbenzoic acid (5.00 g, 33.3 mmol), DMAP (3.3 g, 26.6 mmol), and geraniol (10.3 g, 66.6 mmol) in CH_2Cl_2 (40 ml) was cooled in an ice-bath before a soln. of DCC (7.6 g, 36.6 mmol) in CH_2Cl_2 (10 ml) was added dropwise. After the addition of more CH_2Cl_2 (50 ml), the mixture was left warming up to r.t. and stirred overnight. The formed precipitate was filtered off, the filtrate washed with 10% HCl soln. (2×), a sat. soln. of Na_2CO_3 (2×), and H_2O (pH ≈ 7), dried (Na_2SO_4), and evaporated, and 5 g of the crude mixture (14.9 g) were submitted to CC (SiO_2, heptane/Et_2O 4:1): 2.7 g (84%) of **13**. Slightly yellow oil. R_f (heptane/Et_2O 4:1): 0.34. UV/VIS (MeCN): 302 (sh, 1400), 291 (2000), 261 (sh, 16800), 251 (21100). IR (neat): 2964*m*, 2914*m*, 2850*m*, 2729*w*, 1703*s*, 1673*w*, 1609*w*, 1577*m*, 1502*m*, 1443*m*, 1418*m*, 1381*m*, 1376*m*, 1338*w*, 1297*w*, 1265*s*, 1199*s*, 1166*w*, 1100*s*, 1090*s*, 1046*w*, 1015*m*, 981*w*, 926*m*, 854*m*, 807*m*, 757*s*, 687*m*, 681*m*. ^{1}H-NMR (360 MHz, $CDCl_3$): 10.10 (*s*, 1 H); 8.20 (*d*, *J* = 8.3, 2 H); 7.95 (*d*, *J* = 8.3, 2 H); 5.53–5.45 (*m*, 1 H); 5.13–5.06 (*m*, 1 H); 4.88 (*d*, *J* = 7.1, 2 H); 2.19–2.04 (*m*, 4 H); 1.78 (*s*, 3 H); 1.67 (*s*, 3 H); 1.61 (*s*, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 191.64 (*d*); 165.57 (*s*); 143.01 (*s*); 139.08 (*s*); 135.53 (*s*); 131.89 (*s*); 130.20 (*d*); 129.46 (*d*); 123.67 (*d*); 117.98 (*d*); 62.45 (*t*); 39.55 (*t*); 26.27 (*t*); 25.68 (*q*); 17.70 (*q*); 16.58 (*q*). EI-MS: 286 (0.3, M^+), 150 (6), 149 (11), 137 (3), 136 (22), 134 (11), 133 (64), 123 (4), 122 (3), 121 (29), 107 (8), 106 (3), 105 (18), 104 (4), 95 (4), 94 (12), 93 (70), 92 (16), 91 (15), 81 (6), 80 (21), 79 (14), 78 (3), 77 (20), 76 (4), 70 (5), 69 (100), 68 (27), 67 (15), 65 (5), 55 (5), 53 (9), 51 (7), 50 (3), 43 (4), 41 (39), 40 (3), 39 (9), 29 (3), 27 (4).

*(3*R*)-3,7-Dimethyloct-6-enyl Hydrogen Benzene-1,2-dicarboxylate* (**14a**) [44]. A soln. of citronellol (10.1 g, 64.6 mmol), phthalic anhydride (= isobenzofuran-1,3-dione; 9.6 g, 64.8 mmol), DMAP (0.8 g, 6.5 mmol), and ^{i}Pr_2EtN (8.4 g, 64.8 mmol) in CH_2Cl_2 (130 ml) was left stirring at r.t. for 5 h (→ slightly yellow soln. which decolored within 15 min). The mixture was extracted with 5% $KHSO_4$ soln. (3×) and sat. NaCl soln. (3×) and the org. phase dried (Na_2SO_4) and evaporated: 15.7 g (80%) of **14a**. Slightly yellow oil that was used as such for further transformations. ^{1}H-NMR (360 MHz, $CDCl_3$): 9.63 (br. *s*, 1 H); 7.95–7.88 (*m*, 1 H); 7.73–7.66 (*m*, 1 H);

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[5]) The configuration was elucidated by ^{1}H-NMR spectroscopy in combination with computer modelling of the energy-minimized structures of the two diastereoisomers. The downfield shift of one of the Me *d* to δ 0.37 ppm could be explained if the corresponding Me group lies close above the benzene ring system. This was confirmed by computer simulation of the two diastereoisomers by using the 'Monte Carlo' procedure with the MM2 molecular force field as implemented in 'MacroModel' [61]. Only in the minimized structure of (3*R*)-**11c**, a Me group of the menthol-derived moiety was found to be in proximity to the aromatic ring system.

7.64–7.52 (*m*, 2 H); 5.12–5.03 (*m*, 1 H); 4.45–4.31 (*m*, 2 H); 2.08–1.88 (*m*, 2 H); 1.87–1.73 (*m*, 1 H); 1.71–1.49 (*m*, 2 H); 1.65 (*s*, 3 H); 1.56 (*s*, 3 H); 1.46–1.29 (*m*, 1 H); 1.28–1.13 (*m*, 1 H); 0.94 (*d*, $J = 6.7$, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 172.24 (*s*); 168.20 (*s*); 133.54 (*s*); 132.12 (*d*); 131.33 (*s*); 130.77 (*d*); 130.12 (*s*); 129.86 (*d*); 128.77 (*d*); 124.59 (*d*); 64.57 (*t*); 36.99 (*t*); 35.22 (*t*); 29.49 (*d*); 25.68 (*q*); 25.36 (*t*); 19.36 (*q*); 17.63 (*q*). CI-MS (NH_3): 306 (5), 305 (25, $[M+H]^+$), 184 (17), 174 (12), 173 (5), 171 (3), 168 (9), 167 (100), 166 (21), 158 (3), 157 (31), 155 (5), 153 (3), 149 (11), 139 (10), 138 (18), 137 (8), 124 (3), 123 (26), 121 (4), 110 (6), 109 (14), 105 (17), 104 (24), 96 (6), 95 (27), 94 (5), 93 (24), 83 (7), 82 (17), 81 (22).

*(2*E*)-3,7-Dimethylocta-2,6-dienyl Hydrogen Benzene-1,2-dicarboxylate* (**14b**). As described for **14a**, with geraniol (10.0 g, 64.9 mmol): 17.5 g (89%) of **14b**. Slightly yellow oil. IR (neat): 2965*m*, 2914*m*, 2854*m*, 2663*w*, 2541*w*, 1724*s*, 1696*s*, 1599*m*, 1578*m*, 1491*m*, 1447*m*, 1410*m*, 1376*m*, 1339*w*, 1281*s*, 1256*s*, 1164*w*, 1120*s*, 1069*s*, 1037*m*, 978*w*, 959*w*, 924*m*, 888*w*, 831*w*, 797*m*, 790*m*, 772*m*, 740*s*, 703*m*, 685*m*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.95–7.90 (*m*, 1 H); 7.72–7.67 (*m*, 1 H); 7.63–7.52 (*m*, 2 H); 5.49–5.42 (*m*, 1 H); 5.09–5.02 (*m*, 1 H); 4.86 (*d*, $J = 7.1$, 2 H); 2.20–2.00 (*m*, 4 H); 1.75 (*s*, 3 H); 1.65 (*s*, 3 H); 1.57 (*s*, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 172.33 (*s*); 168.26 (*s*); 143.17 (*s*); 133.76 (*s*); 132.21 (*d*); 131.77 (*s*); 130.66 (*d*); 129.91 (*d*); 129.85 (*s*); 128.71 (*d*); 123.78 (*d*); 117.61 (*d*); 62.82 (*t*); 39.55 (*t*); 26.29 (*t*); 25.66 (*q*); 17.66 (*q*); 16.50 (*q*). CI-MS (NH_3): 320 (2, $[M+NH_4]^+$), 185 (16), 184 (100), 167 (14), 154 (10), 138 (6), 137 (49), 81 (3).

(1,1-Dimethyl-2-phenylethyl) Hydrogen Benzene-1,2-dicarboxylate (**14d**). A 20% KH dispersion in oil (8 g, 39.9 mmol) was washed with pentane (5×10 ml) and THF (2×10 ml). Then THF (10 ml) and 2-methyl-1-phenylpropan-2-ol (5 g, 33.3 mmol) in THF (10 ml) were added dropwise during 15 min. The mixture was stirred for 1 h at r.t. and then added dropwise during 15 min to a mechanically stirred soln. of phthalic anhydride (4.93 g, 33.3 mmol), ^{i}Pr$_2$EtN (4.30 g, 33.3 mmol) and DMAP (0.40 g, 3.3 mmol) in THF (200 ml). At the end of the introduction, more THF (50 ml) was added, and the mixture was heated to 50° and left cooling to r.t. during 1 h. The reaction mixture was poured on a stirred mixture of ice (300 ml) and 5% $KHSO_4$ soln. (200 ml). Et_2O (200 ml) was added and the org. phase extracted with 5% $KHSO_4$ soln. (2×100 ml) and sat. NaCl soln. ($3 \times$). Extraction with sat. $NaHCO_3$ soln. (2×100 ml), treatment of the aq. phase with $KHSO_4$ (25 g), re-extraction with Et_2O (2×100 ml), washing with 5% $KHSO_4$ soln. (2×50 ml), drying, and evaporation gave 7.42 g (75%) of **14d**. Off-white crystals. IR (neat): 2973*w*, 2919*w*, 2866*w*, 2661*w*, 2556*w*, 1716*m*, 1689*s*, 1596*m*, 1578*m*, 1490*m*, 1467*w*, 1452*m*, 1415*m*, 1383*m*, 1370*m*, 1310*m*, 1285*s*, 1268*s*, 1237*m*, 1207*w*, 1186*w*, 1140*m*, 1114*s*, 1068*s*, 1031*w*, 1009*w*, 968*w*, 938*m*, 910*w*, 866*w*, 844*m*, 833*m*, 806*w*, 792*m*, 772*m*, 737*s*, 724*m*, 699*s*, 684*m*, 670*w*. ^{1}H-NMR (360 MHz, $CDCl_3$): 11.55 (br. *s*, 1 H); 7.91–7.85 (*m*, 1 H); 7.62–7.47 (*m*, 3 H); 7.29–7.15 (*m*, 5 H); 3.17 (*s*, 2 H); 1.58 (*s*, 6 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 172.85 (*s*); 167.26 (*s*); 136.99 (*s*); 135.02 (*s*); 132.14 (*d*); 130.66 (*d*); 130.31 (*d*); 129.74 (*d*); 129.61 (*s*); 128.62 (*d*); 127.95 (*d*); 126.50 (*d*); 84.49 (*s*); 46.67 (*t*); 25.54 (*q*). EI-MS: 167 (3), 150 (9), 149 (100), 147 (3), 146 (21), 133 (5), 132 (37), 122 (3), 121 (9), 118 (3), 117 (25), 115 (9), 105 (8), 104 (15), 93 (10), 92 (12), 91 (27), 77 (6), 76 (8), 73 (3), 70 (4), 65 (18), 61 (5), 59 (10), 57 (3), 55 (4), 51 (4), 50 (5), 45 (5), 44 (3), 43 (19), 41 (4), 39 (6).

2-Phenylethyl Hydrogen Benzene-1,2-dicarboxylate (**14e**). As described for **14a**, with 2-phenylethanol (4.00 g, 32.7 mmol), phthalic anhydride (4.85 g, 32.7 mmol), DMAP (0.40 g, 3.3 mmol), ^{i}Pr$_2$EtN (4.23 g, 32.7 mmol) and CH_2Cl_2 (80 ml): 8.60 g (97%) of **14e**. Slightly yellow oil, which slowly crystallized. ^{1}H-NMR (360 MHz, $CDCl_3$): 11.27 (br. *s*, 1 H); 7.92–7.86 (*m*, 1 H); 7.65–7.50 (*m*, 3 H); 7.32–7.16 (*m*, 5 H); 4.52 (*t*, $J = 7.1$, 2 H); 3.04 (*t*, $J = 7.1$, 2 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 172.41 (*s*); 168.02 (*s*); 137.57 (*s*); 133.37 (*s*); 132.20 (*d*); 130.83 (*d*); 129.97 (*s*); 129.87 (*d*); 128.94 (*d*); 128.75 (*d*); 128.51 (*d*); 126.58 (*d*); 66.32 (*t*); 34.77 (*t*). CI-MS (NH_3): 290 (6), 289 (21), 288 (100, $[M+NH_4]^+$), 272 (3), 271 (3), 261 (4), 246 (4), 245 (13), 244 (84), 242 (6), 229 (3), 228 (5), 227 (45).

3,7-Dimethyloct-6-enyl 2-(Hydroxymethyl)benzoate (**3a**). A soln. of **14a** (5.0 g, 16.4 mmol) in oxalyl chloride (25 ml, 18 equiv.) was heated under reflux for 3 h. The excess oxalyl chloride was distilled off under vacuum, and the crude acid chloride (5.3 g) was diluted in THF (40 ml). The soln. was cooled to −8° under Ar, and $NaBH_4$ (1.87 g, 3 equiv.) were added. The mixture was stirred at 0° for 4 h and at r.t. for another 16 h. The mixture was then cooled again to 0°, and MeOH (10 ml) was added dropwise. After 15 min, the mixture was poured into cold 5% $KHSO_4$ soln. and extracted with cold AcOEt. CC (SiO_2, toluene/Et_2O 9:1) yielded 1.41 g (31%) of **3a**. Colorless oil. UV/VIS (hexane): 287 (sh, 930), 279 (1300), 270 (sh, 1000), 231 (10400). IR (neat): 3416*m* (br.), 3067*w*, 2958*m*, 2913*m*, 2872*m*, 2854*m*, 1709*s*, 1698*s*, 1601*w*, 1576*w*, 1450*m*, 1380*m*, 1289*m*, 1255*s*, 1195*m*, 1133*s*, 1082*s*, 1029*s*, 982*w*, 949*m*, 879*w*, 832*w*, 803*w*, 737*s*, 709*m* 669*m*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.99 (*dd*, $J = 7.8$, 1.2, 1 H); 7.52 (*ddd*, $J = 7.5$, 7.2, 1.2, 1 H); 7.45 (*dd*, $J = 7.5$, 1.2, 1 H); 7.37 (*ddd*, $J = 7.8$, 7.5, 1.2, 1 H); 5.10 (*m*, 1 H); 4.78 (*d*, $J = 7.2$, 2 H); 4.38 (*m*, 2 H); 3.96 (*t*, $J = 7.2$, 1 H); 2.02 (*m*, 2 H); 1.81 (*m*, 2 H); 1.68 (*s*, 3 H); 1.63 (*m*, 1 H); 1.61 (*s*, 3 H); 1.41 (*m*, 1 H); 1.25 (*m*, 1 H); 0.98 (*d*, $J = 6.5$, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 168.08 (*s*); 143.04 (*s*); 132.93 (*d*); 131.46 (*s*); 131.08 (*d*); 130.34 (*d*); 129.22 (*s*); 127.81 (*d*); 124.49 (*d*);

64.81 (*t*); 64.03 (*t*); 36.97 (*t*); 35.45 (*t*); 29.55 (*d*); 25.71 (*q*); 25.39 (*t*); 19.53 (*q*); 17.67 (*q*). CI-MS (NH_3): 308 (l, $[M+NH_4]^+$), 291 (0.5, $[M+H]^+$), 174 (8), 169 (15), 152 (100), 135 (5), 105 (3).

*(2*E*)-3,7-Dimethylocta-2,6-dienyl 2-(Hydroxymethyl)benzoate* (**3b**). To a soln. of **14b** (5.0 g, 16.6 mmol) in CH_2Cl_2 (50 ml) $^iPr_2EtN$ (2.35 g, 1.1 equiv.) and, at 5°, isobutyl carbonochloridate (2.26 g, 1 equiv.) were added dropwise. The mixture was stirred at r.t. for 3 h, before CH_2Cl_2 (200 ml) was added. The org. phase was washed with H_2O, dried (Na_2SO_4), and evaporated to afford 6.34 g of a slightly yellow oil. At −20°, this product (1.0 g, 2.49 mmol) was then added dropwise to a soln. of $NaBH_4$ (0.38 g, 4 equiv.) in EtOH (10 ml). After reacting for 30 min, the mixture was poured into a cold mixture of AcOEt and 5% $KHSO_4$ soln.. The org. phase was washed with H_2O, dried (Na_2SO_4), and evaporated. CC (SiO_2, cyclohexane/AcOEt 4:1) yielded 0.36 g (50%) of **3b**. Colorless oil. UV/VIS (hexane): 287 (sh, 860), 278 (1200), 270 (sh, 990), 231 (11000). IR (neat): 3422*m* (br.), 3068*w*, 2964*m*, 2917*m*, 2852*m*, 1765*w*, 1709*s*, 1698*s*, 1601*w*, 1576*w*, 1483*w*, 1445*m*, 1378*m*, 1339*w*, 1286*m*, 1252*s*, 1196*m*, 1167*w*, 1132*s*, 1076*s*, 1030*s*, 985*w*, 941*m*, 880*w*, 831*w*, 803*w*, 737*s*, 709*m*, 670*w*. ^{1}H-NMR (360 MHz, $CDCl_3$; *Table 3*): 8.01 (*dd*, *J* = 7.5, 1.1, 1 H); 7.51 (*ddd*, *J* = 7.5, 7.5, 1.1, 1 H); 7.44 (*dd*, *J* = 7.5, 1.1, 1 H); 7.37 (*ddd*, *J* = 7.5, 7.5, 1.1, 1 H); 5.51–5.44 (*m*, 1 H); 5.13–5.06 (*m*, 1 H); 4.86 (*d*, *J* = 7.0, 2 H); 4.77 (*d*, *J* = 6.6, 2 H); 3.93 (*t*, *J* = 7.0, 1 H); 2.18–2.04 (*m*, 4 H); 1.78 (*s*, 3 H); 1.68 (*s*, 3 H); 1.61 (*s*, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$; *Table 3*): 168.06 (*s*); 143.13 (*s*); 142.87 (*s*); 132.91 (*d*); 131.92 (*s*); 131.21 (*d*); 130.35 (*d*); 129.29 (*s*); 127.83 (*d*); 123.65 (*d*); 117.94 (*d*); 64.84 (*t*); 62.33 (*t*); 39.55 (*t*); 26.27 (*t*); 25.68 (*q*); 17.71 (*q*); 16.58 (*q*). CI-MS (NH_3): 306 (3, $[M+NH_4]^+$), 289 (1, $[M+H]^+$), 107 (100), 152 (35), 137 (45).

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl 2-(Hydroxymethyl)benzoate* (**3c**). A soln. of commercially available (1*R*,3*R*,4*S*)-*p*-menthan-3-yl hydrogen phthalate (=(1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexylhydrogen benzene-1,2-dicarboxylate; **14c**; 3.78 g, 12.4 mmol) in oxalyl chloride (19 ml, 18 equiv.) was heated under reflux for 1.5 h. The excess of oxalyl chloride was distilled off under vacuum and the crude acid chloride (2.75 g) was diluted in THF (5 ml). The soln. was cooled to −8° under Ar, and $NaBH_4$ (0.97 g, 3 equiv.) was added. The mixture was stirred at 0° for 10 min and at r.t. for another 30 min. The mixture was then poured into cold 5% $KHSO_4$ soln. and extracted with Et_2O. CC (SiO_2, toluene/Et_2O 93:7) yielded 1.85 g (55%) of **3c**. Colorless oil. UV/VIS (hexane): 287 (sh, 850), 278 (1300), 271 (sh, 1000), 231 (10700). IR (neat): 3426*m* (br.), 3068*w*, 2951*m*, 2923*m*, 2866*m*, 1767*w*, 1691*s*, 1601*w*, 1577*w*, 1451*m*, 1408*w*, 1385*w*, 1366*m*, 1288*m*, 1254*s*, 1184*m*, 1132*s*, 1080*s*, 1032*s*, 980*m*, 956*s*, 915*m*, 886*w*, 844*w*, 802*w*, 736*s*, 709*m*, 670*m*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.99 (*dd*, *J* = 7.5, 1.2, 1 H); 7.52 (*ddd*, *J* = 7.5, 7.5, 1.6, 1 H); 7.45 (*dd*, *J* = 7.5, 1.2, 1 H); 7.38 (*ddd*, *J* = 7.5, 7.5, 1.6, 1 H); 4.97 (*ddd*, *J* = 11.0, 11.0, 4.3, 1 H); 4.81, 4.73 (*AB* of *ABX*, *J* = 12.6, 7.1, 2 H); 4.00 (*t*, *J* = 7.1, 1 H, exchange with D_2O); 2.13 (*m*, 1 H); 1.97 (*m*, 1 H); 1.75 (*m*, 2 H); 1.56 (*m*, 2 H); 1.14 (*m*, 1 H); 0.95 (*d*, *J* = 6.7, 3 H); 0.93 (*d*, *J* = 7.1, 3 H); 0.81 (*d*, *J* = 7.1, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 167.64 (*s*); 142.92 (*s*); 132.81 (*d*); 130.94 (*d*); 130.44 (*d*); 129.71 (*s*); 127.84 (*d*); 75.55 (*d*); 64.92 (*t*); 47.25 (*d*); 40.93 (*t*); 34.26 (*t*); 31.51 (*d*); 26.46 (*d*); 23.46 (*t*); 22.04 (*q*); 20.83 (*q*); 16.32 (*q*). CI-MS (NH_3): 291 (1), 152 (100), 135 (52), 123 (5), 105 (10), 95 (2).

*(2*E*)-3,7-Dimethylocta-2,6-dienyl 2-[(Ethylamino)carbonyl]benzoate* (**4b**). Et_3N (12 ml, *ca.* 2 equiv.) was added to a soln. of geraniol (6.16 g, 39.9 mmol) and phthalic anhydride (5.92 g, 40.0 mmol) in CH_2Cl_2 (80 ml), and the mixture was stirred under Ar at r.t. for 2 d. After the addition of more Et_3N (6 ml) and cooling to −20°, ethyl carbonochloridate (4.84 g, 44.6 mmol) in CH_2Cl_2 (10 ml) was added dropwise during 8 min. The mixture was left warming to r.t. and stirred for 4 h before 1 ml of ethyl carbonochloridate was added, and 10 min later, $EtNH_2 \cdot HCl$ (3.26 g, 40.0 mmol) was introduced. After stirring for 1 h, the mixture was acidified with 5% $KHSO_4$ soln., and the org. phase was washed with H_2O (2×), dried (Na_2SO_4), and evaporated. CC (SiO_2, cyclohexane/AcOEt 3:1) yielded 8.33 g (63%) of **4b**. Brownish yellow oil. UV/VIS (hexane): 283 (sh, 990), 276 (1200), 227 (sh, 10500). IR (neat): 3272*m*, 3065*w*, 2967*m*, 2915*m*, 2877*m*, 2853*m*, 1718*s*, 1639*s*, 1598*m*, 1577*m*, 1536*s*, 1483*m*, 1444*m*, 1376*m*, 1357*w*, 1336*w*, 1306*m*, 1283*s*, 1254*s*, 1163*w*, 1148*w*, 1123*s*, 1098*w*, 1073*s*, 1042*m*, 980*w*, 937*m*, 873*m*, 827*w*, 772*w*, 742*m*, 705*m*, 690*m*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.88–7.81 (*m*, 1 H); 7.52–7.39 (*m*, 3 H); 6.09–6.01 (*m*, 1 H); 5.42 (*dt*, *J* = 7.1, 1.2, 1 H); 5.13–5.04 (*m*, 1 H); 4.80 (*d*, *J* = 7.1, 2 H); 3.50–3.39 (*m*, 2 H); 2.17–2.00 (*m*, 4 H); 1.73 (*s*, 3 H); 1.68 (*s*, 3 H); 1.60 (*s*, 3 H); 1.22 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 169.29 (*s*); 166.83 (*s*); 142.49 (*s*); 138.37 (*s*); 131.84 (*s*); 131.75 (*d*); 130.02 (*d*); 129.43 (*s*); 129.39 (*d*); 127.64 (*d*); 123.73 (*d*); 118.04 (*d*); 62.45 (*t*); 39.58 (*t*); 34.96 (*t*); 26.30 (*t*); 25.68 (*q*); 17.69 (*q*); 16.53 (*q*); 14.63 (*q*). CI-MS (NH_3): 347 (50, $[M+NH_4]^+$), 330 (68, $[M+H]^+$, 68), 211 (100), 194 (42), 172 (21), 154 (21), 137 (6).

*(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl 2-[(Ethylamino)carbonyl]benzoate* (**4c**). A soln. of commercial **14c** (15.22 g, 49.9 mmol) and Et_3N (6.95 ml, 1 equiv.) in CH_2Cl_2 (40 ml) was cooled to −2° before ethyl carbonochloridate (5.26 ml, 1.1 equiv.) in CH_2Cl_2 (5 ml) was added during 10 min to generate the corresponding mixed carbonic anhydride. After warming to r.t. and stirring for 2 h, the formation of a white precipitate was observed. More Et_3N (6.95 ml), $EtNH_2 \cdot HCl$ (4.07 g, 1 equiv.), and 30 min later, Et_3N (2 ml)

were added. After 2 h, the mixture was diluted with AcOEt and extracted with 5% aq. $KHSO_4$ soln. (5 ×) and washed with sat. NaCl soln. (2 × 100 ml). Drying (Na_2SO_4), evaporation, and recrystallization from CH_2Cl_2 gave 5.44 g (32%) of **4c**. White crystals. M.p. 177.8–178.2°. UV/VIS (MeCN): 283 (sh, 750), 271 (1100), 222 (sh, 10900). IR (neat): 3298*m*, 3081*w*, 3060*w*, 2958*m*, 2944*m*, 2920*m*, 2864*m*, 1711*s*, 1671*w*, 1634*s*, 1597*m*, 1575*m*, 1546*s*, 1487*w*, 1463*w*, 1445*m*, 1382*w*, 1359*m*, 1347*w*, 1312*m*, 1290*s*, 1284*s*, 1181*m*, 1166*m*, 1147*m*, 1127*s*, 1096*m*, 1082*m*, 1046*m*, 1036*m*, 1007*m*, 982*m*, 959*m*, 916*m*, 891*w*, 870*m*, 846*m*, 799*m*, 782*m*, 748*m*, 688*m*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.88–7.82 (*m*, 1 H); 7.53–7.40 (*m*, 3 H); 5.94 (*m*, 1 H); 4.92 (*dt*, *J* = 10.9, 4.4, 1 H); 3.52–3.42 (*m*, 2 H); 2.19–2.10 (*m*, 1 H); 1.96 (*dquint.*, *J* = 6.9, 2.8, 1 H); 1.77–1.67 (*m*, 2 H); 1.59–1.44 (*m*, 2 H); 1.24 (*t*, *J* = 7.1, 3 H); 1.17–1.02 (*m*, 2 H); 0.98–0.83 (*m*, 1 H); 0.92 (*t*, *J* = 6.5, 6 H); 0.79 (*d*, *J* = 7.1, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 169.21 (*s*); 166.26 (*s*); 138.40 (*s*); 131.67 (*d*); 129.86 (*d*); 129.71 (*s*); 129.36 (*d*); 127.84 (*d*); 75.56 (*d*); 47.14 (*d*); 40.62 (*t*); 34.98 (*t*); 34.26 (*t*); 31.46 (*d*); 26.20 (*d*); 23.31 (*t*); 22.02 (*q*); 20.89 (*q*); 16.21 (*q*); 14.65 (*q*). CI-MS (NH_3): 349 (100, $[M+NH_4]^+$), 332 (22, $[M+H]^+$), 326 (15), 300 (100), 254 (5).

1,1-Dimethyl-2-phenylethyl 2-[(Ethylamino)carbonyl]benzoate (**4d**). As described for **4c**, with **14d** (1.00 g, 3.4 mmol), Et_3N (0.68 g, 6.7 mmol) in ^{t}BuOMe (50 ml), ethyl carbonochloridate (0.36 g, 3.4 mmol), and $EtNH_2 \cdot HCl$ (1.10 g, 13.4 mmol) in ^{t}BuOMe (50 ml): 1.07 g (98%) of **4d**. Yellow solid. UV/VIS (MeCN): 278 (sh, 1000), 268 (sh, 1200), 263 (sh, 1400), 258 (sh, 1600), 228 (sh, 9000), 218 (sh, 15100). IR (neat): 3302*m*, 3062*w*, 3032*w*, 2977*w*, 2916*w*, 2877*w*, 2850*w*, 1712*s*, 1636*s*, 1595*m*, 1575*w*, 1538*s*, 1492*m*, 1454*m*, 1444*w*, 1382*m*, 1366*m*, 1356*w*, 1295*s*, 1255*m*, 1215*m*, 1179*m*, 1163*m*, 1145*w*, 1129*m*, 1117*s*, 1088*m*, 1041*m*, 1032*m*, 978*m*, 957*w*, 939*w*, 917*w*, 904*w*, 890*w*, 874*m*, 846*m*, 798*m*, 764*m*, 751*m*, 738*m*, 715*m*, 699*s*. ^{1}H-NMR (360 MHz, $CDCl_3$; *Table 3*): 7.76–7.70 (*m*, 1 H); 7.50–7.37 (*m*, 3 H); 7.29–7.17 (*m*, 5 H); 5.84 (*m*, 1 H); 3.40 (*dq*, *J* = 7.1, 1.6, 2 H); 3.21 (*s*, 2 H); 1.56 (*s*, 6 H); 1.19 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$; *Table 3*): 169.18 (*s*); 166.27 (*s*); 138.07 (*s*); 137.17 (*s*); 131.37 (*d*); 130.98 (*s*); 130.66 (*d*); 129.84 (*d*); 129.38 (*d*); 128.00 (*d*); 127.71 (*d*); 126.50 (*d*); 84.05 (*s*); 46.16 (*t*); 34.91 (*t*); 25.88 (*q*); 14.65 (*q*). EI-MS: 194 (19), 177 (8), 176 (74), 175 (11), 161 (3), 160 (23), 149 (11), 148 (13), 133 (15), 132 (90), 131 (20), 130 (16), 129 (5), 128 (4), 118 (11), 117 (100), 116 (11), 115 (37), 105 (13), 104 (21), 103 (6), 102 (4), 92 (8), 91 (50), 89 (5), 78 (5), 77 (11), 76 (16), 75 (4), 74 (4), 66 (3), 65 (13), 64 (3), 63 (5), 52 (3), 51 (7), 50 (8), 44 (4), 41 (3), 39 (7), 30 (3).

(3R)-3,7-Dimethyloct-6-enyl 2-(Aminocarbonyl)benzoate (**5a**). As described for **4c** with **14a** (2.00 g, 6.6 mmol), Et_3N (1.3 g, 13.1 mmol) in ^{t}BuOMe (100 ml), ethyl carbonochloridate (0.7 g, 6.6 mmol), and NH_4OAc (2.00 g, 25.9 mmol). CC (SiO_2, heptane/AcOEt 1:1) gave 0.8 g (40%) of **5a**. Slightly yellow oil. UV/VIS (hexane): 283 (sh, 850), 275 (1000), 223 (sh, 8500). IR (neat): 3410*m*, 3338*m*, 3182*m*, 3072*w*, 2956*m*, 2915*m*, 2851*m*, 1718*s*, 1659*s*, 1601*m*, 1576*m*, 1492*w*, 1448*m*, 1379*s*, 1282*s*, 1261*s*, 1128*s*, 1073*s*, 1042*m*, 950*m*, 886*w*, 834*w*, 742*m*, 706*m*, 665*m*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.85 (*d*, *J* = 7.5, 1 H); 7.55–7.45 (*m*, 3 H); 6.16 (br. *d*, 2 H); 5.09 (*m*, 1 H); 4.34 (*m*, 2 H); 2.00 (*m*, 2 H); 1.79 (*m*, 1 H); 1.67 (*s*, 3 H); 1.65–1.50 (*m*, 1 H); 1.60 (*s*, 3 H); 1.39 (*m*, 1 H); 1.23 (*m*, 2 H); 0.95 (*t*, *J* = 6.3, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 171.50 (*s*); 166.94 (*s*); 137.28 (*s*); 131.77 (*d*); 131.38 (*s*); 129.92 (*d*); 129.85 (*d*); 129.63 (*s*); 127.59 (*d*); 124.57 (*d*); 64.28 (*t*); 36.99 (*t*); 35.27 (*t*); 29.49 (*d*); 25.71 (*q*); 19.40 (*q*); 17.66 (*q*). CI-MS (NH_3): 304 (100, $[M+H]^+$), 183 (10), 166 (18), 148 (20).

(2E)-3,7-Dimethylocta-2,6-dienyl 2-(Aminocarbonyl)benzoate (**5b**). As described for **4c**, with **14b** (2.00 g, 6.6 mmol), Et_3N (1.33 g, 13.2 mmol) in ^{t}BuOMe (100 ml), ethyl carbonochloridate (0.7 g, 6.6 mmol), and NH_4OAc (2.00 g, 25.9 mmol), and more Et_3N (4.0 g) and ^{t}BuOMe (100 ml). CC (SiO_2, heptane/AcOEt 1:1) gave 1.54 g (77%) of **5b**. Slightly yellow oil. UV/VIS (hexane): 283 (sh, 900), 275 (1100), 225 (sh, 9700). IR (neat): 3415*m*, 3345*m*, 3182*m*, 3067*w*, 2964*m*, 2915*m*, 2851*m*, 1716*m*, 1658*s*, 1601*m*, 1576*m*, 1490*w*, 1444*m*, 1378*m*, 1340*w*, 1282*m*, 1257*s*, 1125*s*, 1069*s*, 1037*m*, 933*m*, 874*w*, 832*w*, 743*m*, 706*m*, 666*m*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.83 (*d*, *J* = 7.1, 1 H); 7.54–7.42 (*m*, 3 H); 6.42 (br. *d*, *J* = 88.8, 2 H); 5.44 (*m*, 1 H); 5.08 (*m*, 1 H); 4.81 (*d*, *J* = 7.1, 2 H); 2.17–2.01 (*m*, 4 H); 1.74 (*s*, 3 H); 1.67 (*s*, 3 H); 1.60 (*s*, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 171.95 (*s*); 166.93 (*s*); 142.87 (*s*); 137.03 (*s*); 131.85 (*s*); 131.74 (*d*); 129.93 (*d*); 129.90 (*d*); 129.71 (*s*); 127.63 (*d*); 123.75 (*d*); 117.86 (*d*); 62.57 (*t*); 39.55 (*t*); 26.31 (*t*); 25.68 (*q*); 17.71 (*q*); 16.53 (*q*). CI-MS (NH_3): 319 (6, $[M+NH4]^+$), 302 (5, $[M+H]^+$), 183 (100), 166 (57).

1,1-Dimethyl-2-phenylethyl 2-(Aminocarbonyl)benzoate (**5d**). As described for **4c**, with **14d** (1.00 g, 3.4 mmol), Et_3N (0.68 g, 6.7 mmol) in ^{t}BuOMe (50 ml), ethyl carbonochloridate (0.36 g, 3.4 mmol), NH_4OAc (1.03 g, 13.4 mmol) in ^{t}BuOMe (50 ml), and more Et_3N (2.00 g): 0.97 g (97%) of **5d**. Yellow oil. UV/VIS (MeCN): 279 (sh, 830), 267 (1000), 263 (1100), 258 (sh, 1300), 252 (sh, 1500), 228 (sh, 7500), 218 (sh, 13000). IR (neat): 3367*m*, 3195*m*, 3175*m*, 3062*w*, 3024*w*, 2997*w*, 2968*w*, 2920*m*, 2849*w*, 1721*m*, 1708*s*, 1639*s*, 1616*m*, 1599*m*, 1573*m*, 1491*m*, 1465*w*, 1450*m*, 1397*m*, 1379*m*, 1363*m*, 1335*w*, 1301*s*, 1280*s*, 1262*w*, 1212*s*, 1175*m*, 1153*w*, 1131*s*, 1116*s*, 1068*m*, 1039*w*, 1028*w*, 987*w*, 972*m*, 934*w*, 916*w*, 892*m*, 868*m*, 845*m*, 827*w*, 798*m*, 785*m*, 768*m*, 752*m*, 731*m*, 712*m*, 697*s*, 669*m*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.76 (*d*, *J* = 7.5, 1 H); 7.52–7.40 (*m*, 3 H); 7.29–7.17 (*m*, 5 H); 5.96 (*d*, *J* = 76.5, 2 H); 3.23 (*s*, 2 H); 1.58 (*s*, 6 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 171.54 (*s*); 166.24 (*s*); 137.19

(*s*); 137.04 (*s*); 131.45 (*d*); 130.99 (*s*); 130.71 (*d*); 129.90 (*d*); 129.76 (*d*); 128.02 (*d*); 127.51 (*d*); 126.54 (*d*); 84.45 (*s*); 46.13 (*t*); 25.85 (*q*). EI-MS: 166 (6), 149 (13), 148 (100), 147 (34), 135 (3), 133 (11), 132 (95), 131 (16), 130 (17), 129 (5), 128 (4), 121 (6), 118 (9), 117 (94), 116 (10), 115 (35), 105 (12), 104 (33), 103 (11), 102 (6), 93 (4), 92 (32), 91 (56), 89 (5), 78 (5), 77 (10), 76 (28), 75 (6), 74 (6), 66 (3), 65 (17), 64 (4), 63 (5), 59 (11), 52 (3), 51 (8), 50 (11), 43 (3), 41 (3), 39 (7).

*(3*R*)-3,7-Dimethyloct-6-enyl 2-{[(1-Methylethyl)amino]carbonyl}benzoate* (**6a**). A soln. of citronellol (5.0 g, 32.1 mmol) and Et_3N (4.5 ml) in CH_2Cl_2 (40 ml) was added dropwise (during 3 h) under Ar at 0° to a soln. of phthaloyl dichloride (= benzene-1,2-dicarbonyl dichloride; 6.51 g, 32.1 mmol) in CH_2Cl_2 (40 ml). After stirring for 3 h, a soln. of $^iPrNH_2$ (1.89 g, 32.0 mmol) and Et_3N (4.5 ml) in CH_2Cl_2 (20 ml) was added dropwise during 9 min, and the mixture was left stirring overnight. Extraction with H_2O (3×), drying (Na_2SO_4), and evaporation gave 10.5 g of crude product. CC (SiO_2, cyclohexane/AcOEt 3:1) yielded 5.66 g (51%) of **6a**. Yellow oil. UV/VIS (hexane): 283 (sh, 970), 276 (1100), 223 (sh, 10100). IR (neat): 3269*m*, 3064*w*, 2962*m*, 2916*m*, 2869*m*, 1721*s*, 1635*s*, 1597*m*, 1576*w*, 1536*s*, 1451*m*, 1380*m*, 1354*w*, 1327*w*, 1286*s*, 1256*s*, 1172*m*, 1125*s*, 1076*s*, 1042*m*, 951*m*, 883*m*, 829*m*, 780*w*, 740*m*, 707*m*, 687*w*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.82 (*m*, 1 H); 7.51–7.40 (*m*, 3 H); 5.84 (br. *d*, *J* = 7.8, 1 H); 5.09 (*m*, 1 H); 4.38–4.18 (*m*, 3 H); 2.08–1.90 (*m*, 3 H); 1.83–1.73 (*m*, 1 H); 1.67 (*s*, 3 H); 1.65–1.44 (*m*, 1 H); 1.59 (*s*, 3 H); 1.44–1.33 (*m*, 1 H); 1.25 (*d*, *J* = 6.7, 6 H); 1.25–1.17 (*m*, 1 H); 0.95 (*d*, *J* = 6.4, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 168.45 (*s*); 166.83 (*s*); 138.53 (*s*); 131.67 (*d*); 131.33 (*s*); 129.86 (*d*); 129.57 (*s*); 129.36 (*d*); 127.66 (*d*); 124.56 (*d*); 64.13 (*t*); 41.96 (*d*); 36.99 (*t*); 35.34 (*t*); 29.52 (*d*); 25.71 (*q*); 25.36 (*t*); 22.63 (*q*); 19.45 (*q*); 17.66 (*q*). EI-MS: 346 (5, $[M+H]^+$), 208 (100), 190 (95), 148 (75), 130 (25), 123 (20), 95 (25), 81 (30), 69 (40), 60 (25), 41 (40).

*(2*E*)-3,7-Dimethylocta-2,6-dienyl 2-{[(1-Methylethyl)amino]carbonyl}benzoate* (**6b**). A soln. of geranyl hydrogen phthalate anhydride with ethyl hydrogen carbonate (2 g, 5.34 mmol; prepared as described for **4b** and stored in the freezer) was reacted with $^iPrNH_2$ (0.43 g, 1.1 equiv.) in CH_2Cl_2 (20 ml) for 4 h at r.t. The mixture was extracted with demineralized H_2O (2×) and 5% $KHSO_4$ soln. (2×) and washed with demineralized H_2O. The org. phase was dried (Na_2SO_4) and evaporated. CC (SiO_2, cyclohexane/AcOEt 7:3) gave 1.17 g (64%) of **6b**. Colorless oil. UV/VIS (hexane): 283 (sh, 990), 275 (1200), 225 (sh, 11200). IR (neat): 3270*m*, 3064*w*, 2967*m*, 2922*m*, 2874*m*, 1719*s*, 1635*s*, 1597*m*, 1579*w*, 1536*s*, 1482*w*, 1447*m*, 1379*m*, 1329*m*, 1283*s*, 1254*s*, 1172*m*, 1123*s*, 1072*s*, 1038*m*, 981*w*, 939*m*, 882*m*, 829*m*, 777*w*, 741*m*, 708*m*, 688*w*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.86 (*m*, 1 H); 7.53–7.42 (*m*, 3 H); 5.72 (*d*, *J* = 7.5, 1 H); 5.43 (*m*, 1 H); 5.09 (*m*, 1 H); 4.82 (*d*, *J* = 7.1, 2 H); 4.26 (*m*, 1 H); 2.14–2.01 (*m*, 4 H); 1.74 (*s*, 3 H); 1.68 (*s*, 3 H); 1.60 (*s*, 3 H); 1.26 (*d*, *J* = 6.7, 6 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 168.48 (*s*); 166.83 (*s*); 142.41 (*s*); 138.52 (*s*); 131.85 (*s*); 131.71 (*d*); 130.05 (*d*); 129.51 (*s*); 129.39 (*d*); 127.64 (*d*); 123.74 (*d*); 118.08 (*d*); 62.49 (*t*); 41.99 (*d*); 39.58 (*t*); 26.30 (*t*); 25.69 (*q*); 22.66 (*q*); 17.71 (*q*); 16.56 (*q*). CI-MS (NH_3): 344 (35, $[M+H]^+$), 225 (80), 208 (100), 154 (10).

2-Phenylethyl 2-{[(1-Methylethlyl)amino]carbonyl}benzoate (**6e**). A soln. of 2-phenylethanol (5.0 g, 41.0 mmol) and Et_3N (6 ml) in CH_2Cl_2 (40 ml) was added dropwise (during 45 min) under Ar at 0° to a soln. of phthaloyl dichloride (8.32 g, 41.0 mmol) in CH_2Cl_2 (40 ml). After stirring for 2 h, a soln. of $^iPrNH_2$ (2.42 g, 40.9 mmol) and Et_3N (6 ml) in CH_2Cl_2 (20 ml) was added dropwise during 45 min, and the mixture was stirred for 2 h. Extraction with H_2O (3×), drying (Na_2SO_4), evaporation, and recrystallization of the crude product (12.3 g) from Et_2O gave 6.46 g (51%) of **6e**. White solid. UV/VIS (hexane): 275 (1100), 267 (1100), 264 (1200), 257 (sh, 1400), 225 (sh, 10500). IR (neat): 3274*m*, 3062*w*, 3030*w*, 2972*m*, 2952*w*, 2034*w*, 2889*w*, 2874*w*, 1716*s*, 1682*w*, 1632*s*, 1598*m*, 1579*m*, 1537*s*, 1498*m*, 1470*m*, 1455*m*, 1446*m*, 1380*m*, 1368*m*, 1348*m*, 1327*w*, 1292*s*, 1281*s*, 1251*s*, 1174*m*, 1167*m*, 1149*m*, 1127*s*, 1085*m*, 1038*m*, 1031*m*, 998*w*, 976*m*, 949*m*, 910*w*, 890*m*, 880*w*, 866*w*, 845*w*, 837*m*, 806*w*, 787*m*, 752*s*, 715*s*, 698*s*. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.75 (*m*, 1 H); 7.48–7.36 (*m*, 3 H); 7.32–7.18 (*m*, 5 H); 5.87 (br. *d*, *J* = 7.9, 1 H); 4.47 (*t*, *J* = 7.3, 2 H); 4.22 (*sept.d*, *J* = 7.9, 6.7, 1 H); 3.02 (*t*, *J* = 7.3, 2 H); 1.22 (*d*, *J* = 6.7, 6 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 168.38 (*s*); 166.60 (*s*); 138.57 (*s*); 137.61 (*s*); 131.73 (*d*); 129.86 (*d*); 129.34 (*d*); 128.94 (*d*); 128.51 (*d*); 127.62 (*d*); 126.59 (*d*); 65.87 (*t*); 41.92 (*d*); 35.00 (*t*); 22.56 (*q*). CI-MS (NH_3): 329 (100, $[M+NH_4]^+$), 312 (95, $[M+H]^+$), 244 (12), 207 (20), 140 (55), 117 (35).

*(2*E*)-3,7-Dimethylocta-2,6-dienyl Hydrogen (2*Z*)-But-2-enedioate.* Et_3N (50 ml, *ca.* 2 equiv.) was added to a soln. of geraniol (24.6 g, 159.5 mmol) and maleic anhydride (= furan-2,5-dione; 15.7 g, 159.9 mmol) in CH_2Cl_2 (400 ml), and the mixture was stirred under Ar at r.t. overnight. Acidification with $KHSO_4$, washing of the org. phase with H_2O, drying (Na_2SO_4), and evaporation gave 40.2 g (99%) of the hydrogen butenedioate. ^{1}H-NMR (360 MHz, $CDCl_3$): 11.78 (br. *s*, 1 H); 6.42 (*AB*, *J* = 12.7, 1 H); 6.35 (*AB*, *J* = 12.7, 1 H); 5.47–5.35 (*m*, 1 H); 5.11–5.04 (*m*, 1 H); 4.78 (*d*, *J* = 7.1, 2 H); 2.15–2.03 (*m*, 4 H); 1.74 (*s*, 3 H); 1.68 (*s*, 3 H); 1.60 (*s*, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 167.31 (*s*); 165.73 (*s*); 144.50 (*s*); 134.74 (*d*); 131.99 (*s*); 129.90 (*d*); 123.53 (*d*); 116.70 (*d*); 63.53 (*t*); 39.52 (*t*); 26.19 (*t*); 25.67 (*q*); 17.69 (*q*); 16.55 (*q*).

(2E)-3,7-Dimethylocta-2,6-dienyl (2Z)-4-(Ethylamino)-4-oxo-but-2-enoate (**7b**). A soln. of (2*E*)-3,7-dimethylocta-2,6-dienyl hydrogen (2*Z*)-but-2-enedioate (5.0 g, 19.8 mmol; see above) and Et_3N (3 ml) in CH_2Cl_2 (50 ml) was cooled to $-20°$ before pivaloyl chloride (=2,2-dimethylpropanoyl chloride; 2.6 g, 21.7 mmol) in CH_2Cl_2 (50 ml) was added dropwise during 2 min. The mixture was stirred at $-20°$ for 3.5 h and then left warming to r.t. Then Et_3N (3 ml) and $EtNH_2 \cdot HCl$ (1.7 g, 20.2 mmol) were introduced. After stirring for 1 h, the mixture was acidified with $KHSO_4$ and the org. phase washed with H_2O (2×), dried (Na_2SO_4), and evaporated. CC (SiO_2, cyclohexane/AcOEt 7:3) yielded 3.5 g (97%) of **7b**. Brownish oil. UV/VIS (hexane): 283 (sh, 1100). IR (neat): 3286*m*, 3073*w*, 2967*m*, 2926*m*, 2874*m*, 2855*w*, 1725*s*, 1654*m*, 1625*s*, 1538*s*, 1441*m*, 1403*m*, 1376*m*, 1352*w*, 1268*m*, 1205*s*, 1168*s*, 1105*m*, 1059*w*, 1047*w*, 980*m*, 940*m*, 834*m*, 805*m*, 777*w*, 740*w*. ^{1}H-NMR (360 MHz, $CDCl_3$): 8.29 (*s*, 1 H); 6.31 (*d*, *J* = 13.1, 1 H); 6.12 (*d*, *J* = 12.3, 1 H); 5.37(*t*, *J* = 7.1, 1 H); 5.08 (*t*, *J* = 6.7, 1 H); 4.70 (*d*, *J* = 7.1, 2 H); 3.36 (*dq*, *J* = 7.1, 2.0, 2 H); 2.15–2.03 (*m*, 4 H); 1.72 (*s*, 3 H); 1.68 (*s*, 3 H); 1.60 (*s*, 3 H); 1.20 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 166.31 (*s*); 163.95 (*s*); 143.36 (*s*); 138.49 (*d*); 131.92 (*d*); 125.16 (*d*); 123.61 (*d*); 117.43 (*d*); 62.36 (*t*); 39.53 (*t*); 34.53 (*t*); 26.24 (*t*); 25.68 (*q*); 17.69 (*q*); 16.53 (*q*); 14.39 (*q*). CI-MS (NH_3): 297 (26, $[M+NH_4]^+$), 280 (47, $[M+H]^+$), 178 (7), 161 (100), 144 (20).

2-Phenylethyl (2Z)-4-(ethylamino)-4-oxo-but-2-enoate (**7e**). A soln. of 2-phenylethyl hydrogen maleate (5.0 g, 22.7 mmol; synthesized as described for **7b**) and Et_3N (6 ml) in CH_2Cl_2 (30 ml) was cooled to $-20°$ before ethyl carbonochloridate (2 ml, 20.9 mmol) and CH_2Cl_2 (40 ml) were added. The mixture was stirred at $-20°$ for 10 min before Et_3N (6 ml) and $EtNH_2 \cdot HCl$ (1.7 g, 20.2 mmol) were introduced. After stirring for 75 min, the mixture was acidified with $KHSO_4$ and the org. phase washed with H_2O (2×), dried (Na_2SO_4), and evaporated. CC (SiO_2, cyclohexane/AcOEt 3:2) yielded 1.2 (24%) of **7e**. Yellow oil. IR (neat): 3286*m*, 3062*w*, 3027*w*, 2970*m*, 2932*m*, 2874*w*, 1724*s*, 1656*m*, 1621*s*, 1542*s*, 1495*m*, 1452*m*, 1403*m*, 1376*m*, 1352*m*, 1265*m*, 1212*s*, 1169*s*, 1108*w*, 1086*m*, 1048*m*, 1030*w*, 1007*w*, 994*m*, 964*w*, 909*m*, 846*m*, 828*m*, 799*m*, 748*m*, 697*s*. ^{1}H-NMR (360 MHz, $CDCl_3$; *Table 3*): 8.09 (*s*, 1 H); 7.38–7.16 (*m*, 5 H); 6.30 (*d*, *J* = 13.1, 1 H); 6.07 (*d*, *J* = 13.1, 1 H); 4.38 (*t*, *J* = 6.9, 2 H); 3.33 (*dq*, *J* = 7.1, 1.6, 2 H); 2.98 (*t*, *J* = 7.1, 2 H); 1.17 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$; *Table 3*): 166.16 (*s*); 163.92 (*s*); 138.41 (*d*); 137.31 (*s*); 128.89 (*d*); 128.58 (*d*); 126.73 (*d*); 125.03 (*d*); 65.87 (*t*); 34.84 (*t*); 34.52 (*t*); 14.37 (*q*). CI-MS (NH_3): 265 (17, $[M+NH_4]^+$), 248 (100, $[M+H]^+$), 140 (7).

(2E)-3,7-Dimethylocta-2,6-dienyl 4-(Ethylamino)-4-oxobutanoate (**8b**). Et_3N (20 ml, *ca.* 2 equiv.) was added to a soln. of geraniol (10.0 g, 64.9 mmol) and succinic anhydride (= 3,4-dihydrofuran-2,5-dione; 6.49 g, 64.9 mmol) in CH_2Cl_2 (100 ml), and the mixture was stirred under Ar at r.t. for 3 h. After cooling to $-20°$ and adding more Et_3N (10 ml), pivaloyl chloride (8.6 g, 71.3 mmol) in CH_2Cl_2 (5 ml) was introduced dropwise during 15 min. The mixture was stirred at $-20°$ for 1 h and then left warming to r.t. before Et_3N (10 ml) and $EtNH_2 \cdot HCl$ (5.3 g, 64.9 mmol) were introduced. After stirring for 30 min, the mixture was acidified with $KHSO_4$ and the org. phase washed with H_2O (2×), dried (Na_2SO_4), and evaporated. CC (SiO_2, cyclohexane/AcOEt 3:2) yielded 14.6 g (80%) of **8b**. Slightly yellow oil. IR (neat): 3302*m*, 3080*w*, 2969*m*, 2926*m*, 2875*m*, 2857*w*, 1732*s*, 1644*s*, 1540*s*, 1478*w*, 1440*m*, 1374*m*, 1358*w*, 1317*w*, 1267*m*, 1230*m*, 1205*m*, 1159*s*, 1107*m*, 1074*w*, 1046*m*, 1013*w*, 982*m*, 957*m*, 889*m*, 831*w*, 800*w*, 778*w*, 741*w*. ^{1}H-NMR (360 MHz, $CDCl_3$; *Table 3*): 6.08 (*s*, 1 H); 5.33 (*t*, *J* = 7.1, 1 H); 5.08 (*t*, *J* = 5.9, 1 H); 4.60 (*d*, *J* = 6.7, 2 H); 3.27 (*dq*, *J* = 7.1, 1.6, 2 H); 2.67 (*t*, *J* = 6.9, 2 H); 2.47 (*t*, *J* = 6.9, 2 H); 2.15–1.99 (*m*, 4 H); 1.69 (*s*, 3 H); 1.68 (*s*, 3 H); 1.60 (*s*, 3 H); 1.13 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (90.6 MHz, $CDCl_3$; *Table 3*): 173.12 (*s*); 171.34 (*s*); 142.30 (*s*); 131.82 (*s*); 123.73 (*d*); 118.18 (*d*); 61.63 (*t*); 39.53 (*t*); 34.43 (*t*); 31.07 (*t*); 29.72 (*t*); 26.30 (*t*); 25.68 (*q*); 17.69 (*q*); 16.47 (*q*); 14.79 (*q*). CI-MS (NH_3): 299 (10, $[M+NH_4]^+$), 282 (21, $[M+H]^+$), 163 (100), 153 (10), 146 (100).

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