Synthesis and Properties of Conformationally Constrained Analogues of Floral-Type Odorants[1])

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Dedicated to Dr. *Günther Ohloff* on the occasion of his 80th birthday

The twelve bridged analogues **8**–**19** of floral-type odorants related to cyclamenaldehyde (**1**) were synthesized (*Schemes 1–5*) to investigate the relationship between the structural and conformational features of these compounds and their odor properties. Comparison of the data from sensory evaluation and molecular modeling suggests that the side chain of both the unconstrained and the constrained active analogues is not extended (*anti*) but rather folded (*gauche*) in the 'bioactive' conformation. However, it is mainly the nature of the substituents at the α position of the aldehyde function that critically influences the odor quality and strength. These studies provide new information that should aid ongoing efforts to develop models of odorant–receptor interactions.

1. Introduction. – A commercially significant class of floral-type odorants is represented by 3-(4-isopropylphenyl)-2-methylpropanal (**1**; cyclamenaldehyde) [2], 3-[4-(*tert*-butyl)phenyl]-2-methylpropanal (= *Lilial*®[2]); **2**) [3a] and 3-[4-(*tert*-butyl)phenyl]propanal (= *Bourgeonal*®[3]); **3**) [3b], which all exhibit a desirable lily-of-the-valley ('muguet') tonality. Though many other compounds with different functional groups (alcohols, hydroxyaldehydes, acetals) belong to this class of odorants, in the present work, we will focus on aldehydes related to compounds **1**–**3**. Structure–odor relationships in this class of odorants, among others, have been reviewed [4]. A computational model for lily-of-the-valley-scented compounds, based on AM1 calculations, was proposed by *Pelzer et al.* [5], which distinguished between two structural fragments bearing either a carbonyl or a hydroxy functional group. More recently, conformational analysis of a series of 'muguet'-type odorants was used to design and synthesize candidates anticipated to possess a lily-of-the-valley odor [6]. Interest in this group of compounds has also been stimulated by the demonstration that a mixture of *Lilial*® (**2**) and *Lyral*®[4]) (**4**) [7], a compound related to hydroxycitronellal (**5**) and that also exhibits a characteristic 'muguet' odor, was able to stimulate a heterologously expressed rat olfactory receptor protein, OR5, and to generate second-messenger responses at submicromolar concentrations [8]. Shortly after, computer-

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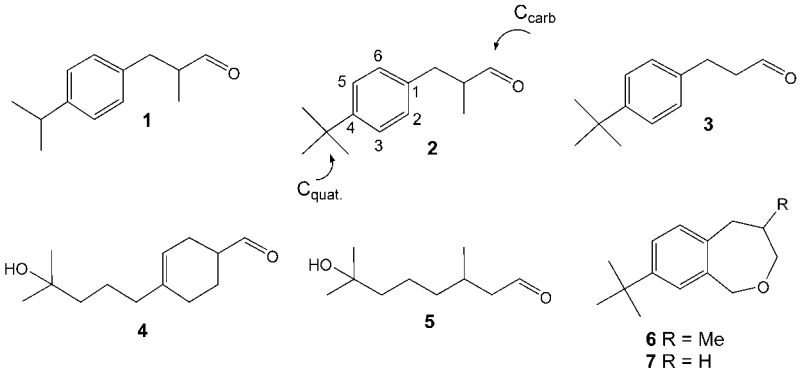
[1]) Parts of this work have been presented as a poster at the 12th Congress of the European Chemoreception Research Organization (ECRO XII), Zurich, Switzerland, August 25–31, 1996, see [1].
[2]) Trade name registered by *Givaudan*.
[3]) Trade name registered by *Quest International*.
[4]) Trade name registered by *International Flavors & Fragrances Inc.*

aided molecular-modeling studies of the interactions of OR5 with *Lyral*® (**4**) [9] and with (−)-(*R*)-*Lilial*® (**2**) [10] were published. Subsequently, specific binding of *Lilial*® (**2**) with OR5 was assessed by photoaffinity labeling experiments and by tryptophan fluorescence measurements [11]. And, more recently, *Lilial*® (**2**) and *Bourgeonal*® (**3**) were shown to be powerful agonists of an odorant receptor that may be involved in mediating human sperm chemotaxis [12]. In previous work aimed at defining the 'bioactive' conformation of floral odorants represented by compounds **1**–**3**, we had prepared the conformationally restricted ether-type analogues **6** and **7** as mimics of a folded (*gauche*) side-chain conformation of **2** and **3**, respectively, and neither **6** nor **7** exhibited the typical 'muguet' activity [13].

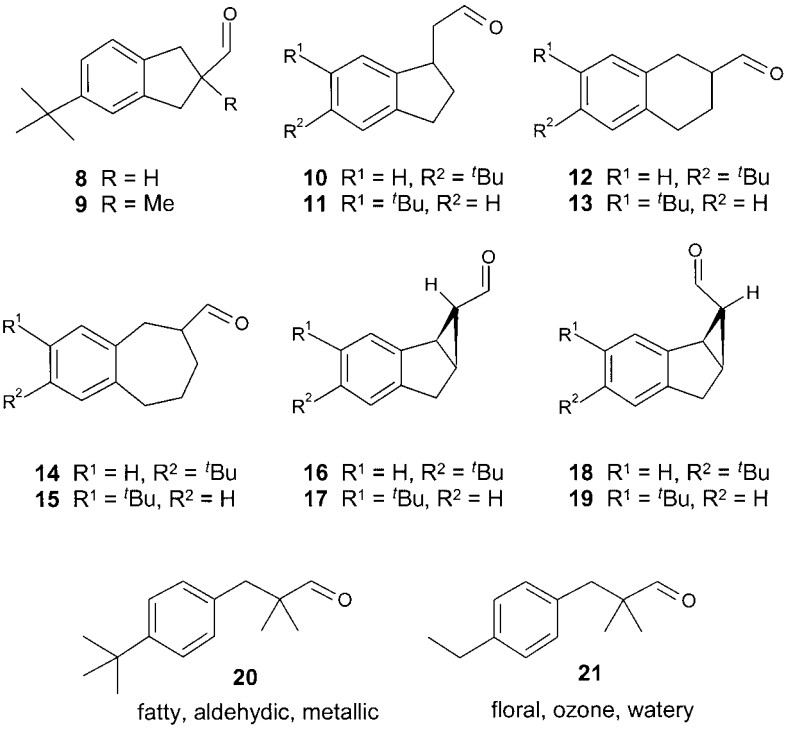


In continuation of that work, we prepared a series of aldehyde-type analogues (see **8**–**19**) of **2** and **3**, with an identical lipophilic region, and in which the side chain is constrained into a more-limited number of conformations intended to mimic extended side-chain conformations, except for analogues **18** and **19**. We now report the synthesis and sensory characterization of these novel odorants, together with the results of molecular-modeling experiments aimed at a better understanding of structure–odor relationships for this type of odorants.

2. Results. – 2.1. *Synthesis.* As shown in *Scheme 1*, we initially synthesized the indane derivative **8**, the proximate conformationally constrained analogue of *Lilial*® (**2**), and the corresponding methylated derivative **9**. Compound **9** can be seen as a conformationally restricted analogue of aldehyde **20** [14]. We note that compound **20** has been patented as a stabilizer for perfume formulations [14a] and as an odorous compound [14b] with a fresher note than **1** and **2**. The related compound **21** [15], having the same carbonyl-bearing side chain as **20**, is known as *Floralozone*®[5]).

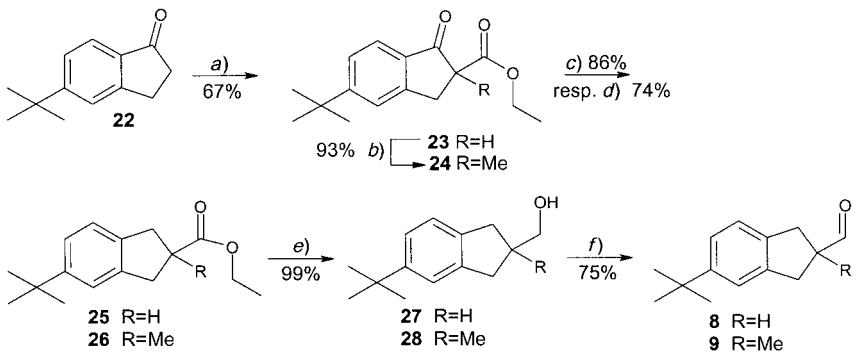
Thus, the enolate of 5-(*tert*-butyl)indan-1-one **22** [16] was treated with diethyl carbonate to afford *β*-keto ester **23**, which was methylated by reaction with MeI in the presence of K_2CO_3 to give keto ester **24**. Hydrogenation of **23** in AcOEt gave the ester **25**, while hydrogenation of **24** needed AcOH as solvent to go to completion and give ester **26**. Reduction of esters **25** and **26** to the alcohols **27** and **28**, respectively, was

[5]) Trade name registered by *International Flavors & Fragrances Inc.*



accomplished with $LiAlH_4$, and subsequent pyridinium chlorochromate (PCC) oxidation gave the desired indane-aldehydes **8** and **9**, respectively (*Scheme 1*). Analogue **8** turned out to be a valuable odorant [17a], having an odor quality very similar to that of **2** and **3**, with superior intensity. In contrast, **9** [17a] had none of the odor characteristics of **2**, **3**, or **8** (see *Table 1*).

Scheme 1



a) NaH, $(EtO)_2CO$, toluene, 60°, 8 h. *b*) MeI, K_2CO_3, THF, 65°, 3 h. *c*) H_2 (1 atm), 5% Pd/C, AcOEt, r.t., 3 h. *d*) H_2 (1 atm), 5% Pd/C, AcOH, r.t., 17 d. *e*) $LiAlH_4$, Et_2O, 25°, 2 h. *f*) PCC, CH_2Cl_2, 25°, 5 h.

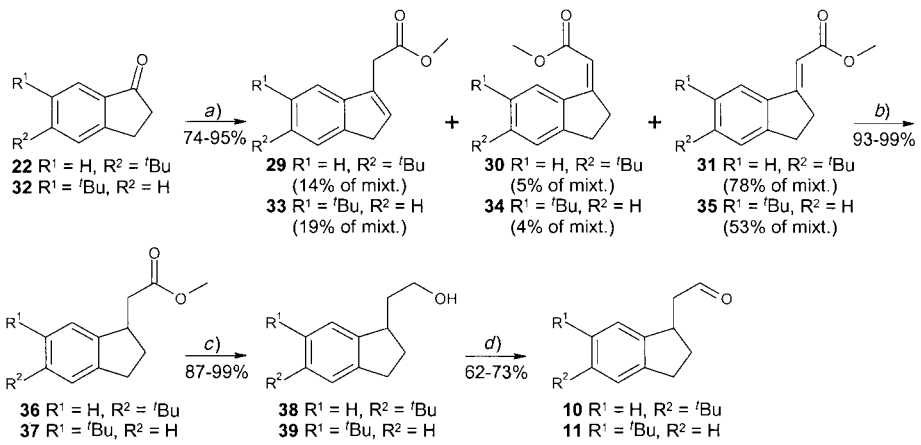
Table 1. *Odor Description of Compounds* **2**, **3**, *and* **8**–**19**. With the exception of **3**, all compounds are racemates.

	Odor description
2 (*Lilial*®)	'Sweet, yet refreshing and intensely floral; green odor of considerable radiance'[a])
3 (*Bourgeonal*®)	'Floral, lily-of-the-valley, aldehydic, green'
8	'Floral, green, 'muguet', *Bourgeonal*®, powerful, tenacious'
9	'Watery, metallic, aldehydic, green, somewhat fatty, vaguely phenolic'
10	'Floral, *Lilial*®, white flower, metallic, slightly insecticide, weak'
11	'*Bourgeonal*®, aldehydic, powerful, pleasant'
12	'Aldehydic, phenolic, leathery, waxy, green, weak'
13	'Aldehydic, phenolic, weak'
14	'*Lilial*®, *Bourgeonal*®, hydroxycitronellal, too weak'
15	'Floral, vaguely green, very weak'
16	'Woody, dry, very weak'
17	'Floral, chemical, plastic, very weak'
18	'Woody, dry, cedar, old wood, very weak'
19	'Odorless'

[a]) Taken from [17b].

Given the attractive properties of the conformationally constrained *Lilial*® analogue **8**, we next synthesized the slightly less-constrained indane analogues **10** and **11** [17a], as shown in *Scheme 2*. Compounds **10** and **11** were prepared by identical routes starting again from the indanone **22** [16] and from the indanone **32** [18], respectively. Treatment of **22** with methyl (dimethoxyphosphinyl)acetate gave a mixture of esters **29**–**31**, which was hydrogenated to afford ester **36**; $LiAlH_4$ reduction of **36** (→ **38**) followed by PCC oxidation gave aldehyde **10**. The same sequence of reactions on indanone **32** gave aldehyde **11** in good overall yield *via* **33**–**35** and **37** and **39**. Analogue **10** had only a weak floral odor with metallic side notes; analogue **11** possessed a powerful and pleasant odor close to **3** and **8** (see *Table 1*).

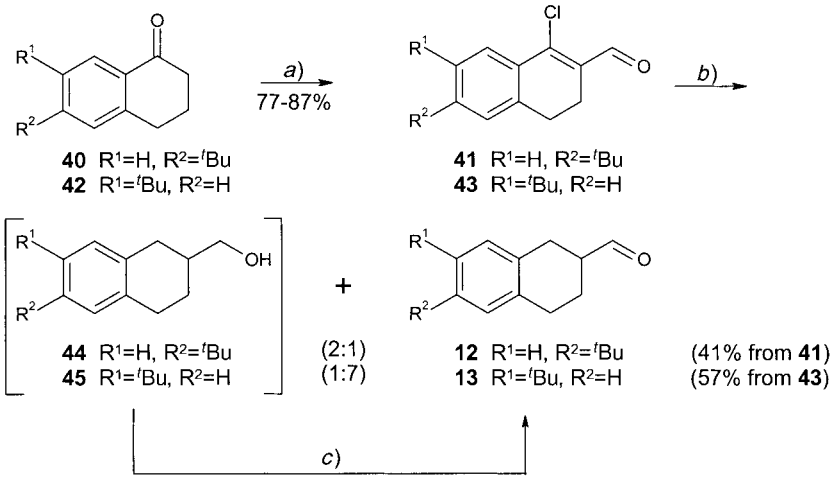
Scheme 2



a) $(MeO)_2POCH_2COOMe$, NaOMe, petroleum ether (30–50°), r.t., 24 h. *b*) H_2, 5% Pd/C, AcOEt, r.t., 1 h. *c*) $LiAlH_4$, Et_2O, r.t. to reflux, 2 h. *d*) PCC, CH_2Cl_2, r.t., 3–5 h.

We then synthesized the homologues of indane **8**, namely the tetralin derivatives **12** and **13**, again by identical routes starting from the known tetralones **40** [19] and **42** [19] [20], respectively (*Scheme 3*). Treatment of **40** with the *Vilsmeier* reagent [21] gave chloro-aldehyde **41** in good yield. Reduction and dechlorination to give a 2 : 1 mixture of alcohol **44** and the desired aldehyde **12** was accomplished by medium-pressure hydrogenation over 5% Pd/C as catalyst under basic conditions. PCC Oxidation of alcohol **44** in the mixture then gave the substituted tetralinaldehyde **12**. The same sequence of procedures, starting from **42**, afforded the target aldehyde **13** *via* **43** and **45**. Both tetralinaldehydes **12** and **13** had only weak aldehydic odors (see *Table 1*).

Scheme 3

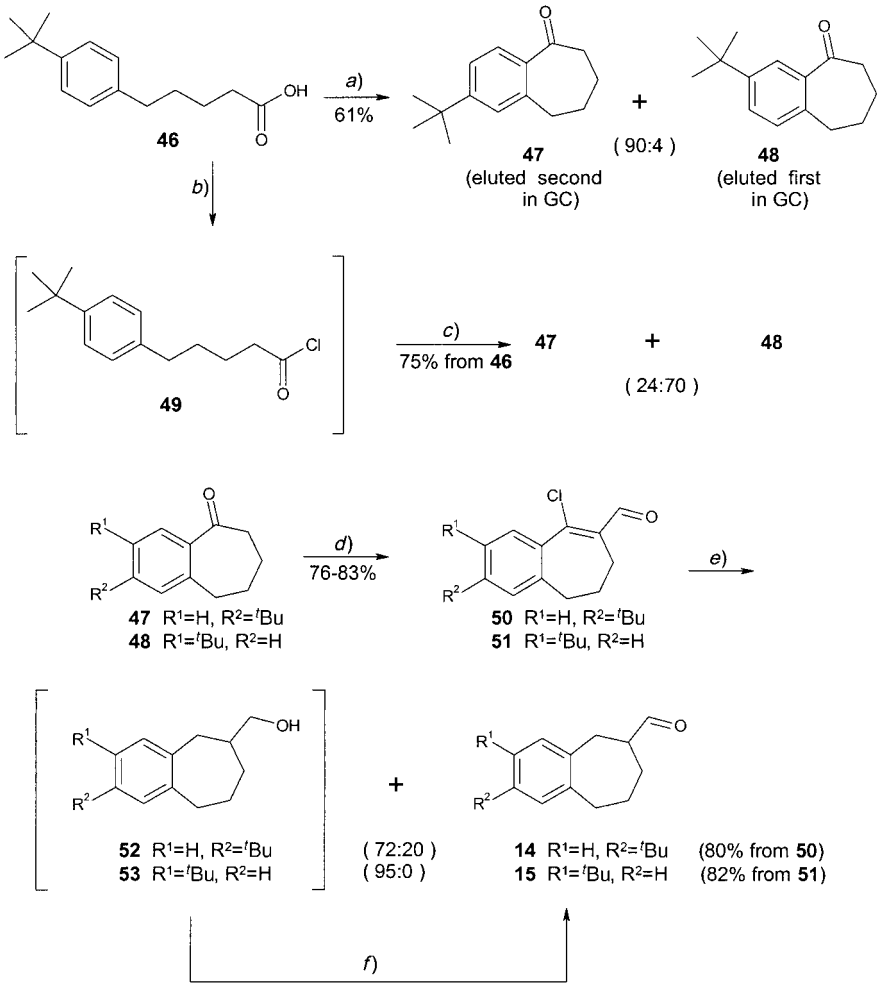


a) DMF, $POCl_3$, 80°, 4 h. *b*) H_2 (50 psi), 5% Pd/C, K_2CO_3, MeOH/H_2O, r.t., 56 h. *c*) PCC, NaOAc, CH_2Cl_2, r.t., 3 h.

Continuing on this path, we envisaged the preparation of the homologues of **12** and **13**, namely the 6,7,8,9-tetrahydro-5*H*-benzocycloheptene derivatives **14** and **15**, by a route similar to that described above, using the ketones **47** and **48**, respectively, as starting materials (see *Scheme 4*). Although the synthesis of **48** had been reported [22], its regioisomer **47** seemed unknown. Detailed examination of the literature describing the preparation of **48**, however, revealed a number of inconsistencies. For example, initial work on the cyclization of 5-[4-(*tert*-butyl)phenyl]pentanoyl chloride (**49**) with $AlCl_3$ in cold nitrobenzene was reported to give a solid product (m.p. 40°; semicarbazone, m.p. 192–193°; oxime, m.p. 122–123°), which was assigned structure **48** [22a]. Interestingly, it was also noted that the product ketone produced a powerful odor, reminiscent of that obtained when burning sandalwood, when placed on a hot plate[6]). In a subsequent paper, the same authors effected cyclization of **49** using $AlCl_3$ in CS_2 and obtained a liquid product that could not be crystallized [22b]. More importantly, no sandalwood odor was produced on heating the product on a hot plate,

[6]) Although compound **48** was meant in the odor description [23], the structure corresponding to 3-(*tert*-butyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-one was printed in error.

Scheme 4



a) CF_3SO_3H, $ClCH_2CH_2Cl$, 84°, 12 h. *b*) $SOCl_2$, 60°, 15 h. *c*) $AlCl_3$, CH_2Cl_2, 0° (1 h) → r.t. (1 h). *d*) DMF, $POCl_3$, 70–80°, 1 h. *e*) H_2 (50 psi), 5% Pd/C, K_2CO_3, MeOH/H_2O, r.t., 15 h. *f*) PCC, AcONa, CH_2Cl_2, r.t., 1.5 h.

and the semicarbazone of this compound melted at 220°. Despite these discrepancies, the product of the reaction under these conditions was also assigned as **48**. In a third study on methods for the cyclization of the acid chlorides derived from variously substituted *δ*-phenylvaleric acid, it was stated that whatever the solvent and the catalyst used, only a low yield of the desired ketones was obtained, except when working under high dilution [22c]. Therefore, an alternative method was investigated, based on work of *Gilmore* and *Horton* [24], in which the carboxylic acids were treated with a large excess of P_2O_5 in 85% phosphoric acid. Under these conditions it was claimed that the cyclized products could be obtained in 60–90% yield, including **48** from **46** [22c]. The

oxime derivative of the cyclized material **48** was, however, reported to melt at 171° rather than 122–123° as given in the initial paper on the cyclization reaction [22a]. We suspected that the structural assignments in these studies were being complicated by an unrecognized migration of the *tert*-butyl group and that, in fact, ketone **47** was being formed in these experiments. This phenomenon has been carefully investigated for the intermolecular acetylation of *p*-(*tert*-butyl)toluene [25], and was later clarified in the case of a related intramolecular cyclization [26].

To substantiate this hypothesis, we reinvestigated the acid-catalyzed cyclization of acid **46** and the cognate acid chloride **49** (*Scheme 4*). We observed indeed that ketone **48** was the major product (ratio **47**/**48** 24:70) when acid chloride **49** was treated with $AlCl_3$ in CH_2Cl_2 at 0°; moreover, as reported [22a], ketone **48** was a solid that could be purified from the reaction mixture by crystallization. By contrast, reaction of acid **46** with trifluoromethanesulfonic acid [27a][7]) in refluxing 1,2-dichloroethane (84°) predominantly afforded ketone **47** (ratio **47**/**48** 90:4), which proved to be an oil upon purification. The regioisomerism of the products **47** and **48** was assessed by using the chemical shifts of the aromatic-ring protons. Having clarified the details of the cyclization reaction, we proceeded to prepare the target aldehydes **14** and **15** by subjecting the ketones **47** and **48** to a *Vilsmeier* reaction (→ **50** and **51**, resp.), followed by hydrogenation (→ **52** and **53**, resp.) and oxidation, as used for the preparation of tetralin derivatives **12** and **13**. Aldehyde **14** had the typical 'muguet' odor present in **2**, **3**, and hydroxycitronellal **5** (used as a descriptor) but was too weak, whereas **15** was found to exhibit only a weak floral, vaguely green odor (*Table 1*).

Finally, the synthesis of the tricyclic analogues **16**–**19** was accomplished by starting again from the indanones **22** and **32** (*Scheme 5*). Thus, **22** was reduced with $LiAlH_4$ to alcohol **54**, which was dehydrated by distillation in the presence of $KHSO_4$ to indene **56**. Treatment of **56** with ethyl diazoacetate in the presence of $CuSO_4$ (*cf.* [28]) afforded a *ca.* 2:1 mixture of '*exo*'- and '*endo*'-esters **58** and **59**. After separation by column chromatography, each of the esters **58** and **59** was reduced to the alcohols **62** and **64** respectively, which in turn were oxidized to the aldehydes **16** and **18**, respectively. A similar sequence of reactions starting from indanone **32** gave aldehydes **17** and **19** *via* **55**, **57**, **60** + **61**, **63**, and **65**, respectively. The odor descriptions of compounds **16**–**19**, compared to **2** and **3**, are given in *Table 1*.

The odor descriptions for the compounds **8**–**19** synthesized in this study showed that the extremely constrained analogues **16**–**19** not only were very weak but had lost all lily-of-the-valley odor activity (*Table 1*). Among the less-constrained analogues **8**–**15**, compounds **8** and **11** were the most powerful and the most similar to **2** and **3**. In an attempt to rationalize these findings and to define more precisely the structural/conformational features associated with the odorants of this family, we carried out two series of computer-aided molecular-modeling experiments.

2.2 *Molecular Modeling*. 2.2.1. *Preamble*. Preliminary molecular-modeling calculations (MM2, Monte Carlo procedure) indicated that compounds **8**–**15** could adopt both extended and folded conformations, although at various energy costs. In contrast, for compounds **16** and **17**, the side chain is restricted to extended conformations,

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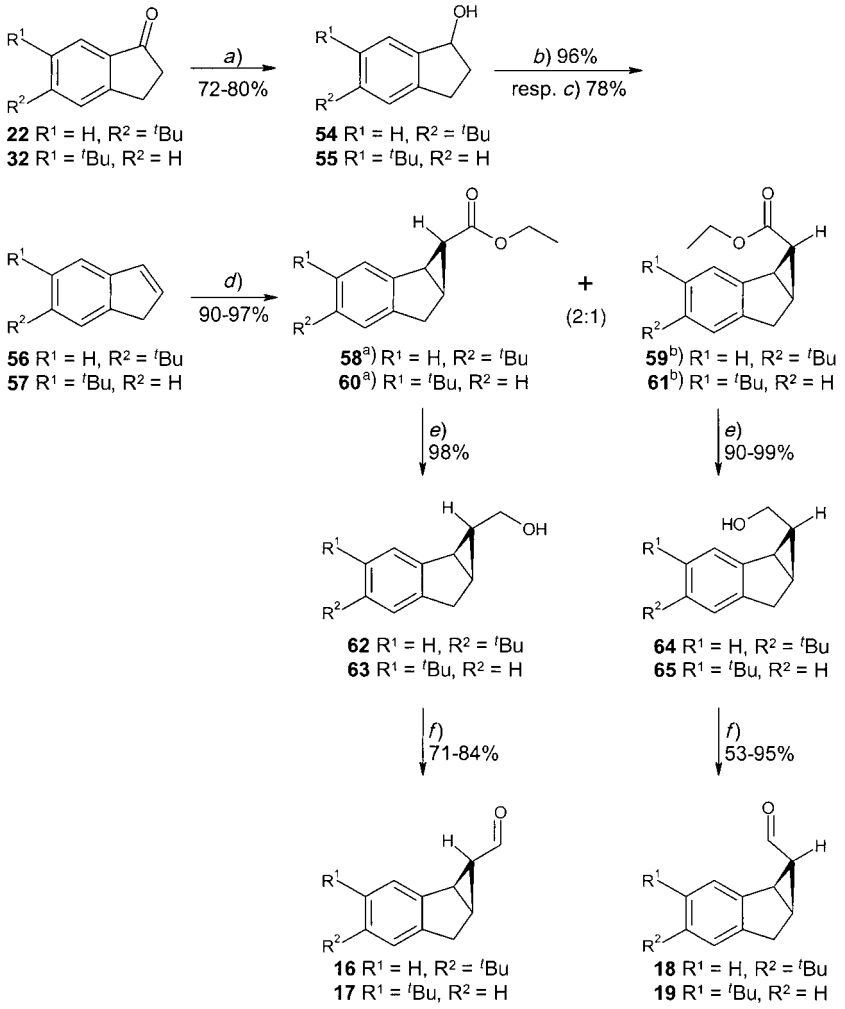
[7]) For a rare example of CF_3SO_3H-mediated intramolecular acylation of a 4-arylbutanoic acid derivative, see [27b].

Scheme 5



[a]) Eluted first on CC, but second on GC (*Sil.* and *Carb.*). [b]) Eluted second on CC, but first on GC (*Sil.* and *Carb.*).

a) $LiAlH_4$, Et_2O, r.t., 1.5 h. *b*) $KHSO_4$, 160–175°/100–25 mbar, 0.5 h. *c*) $KHSO_4$, 90–100°/0.2 mbar, 0.5 h. *d*) $N_2CHCOOEt$, $CuSO_4$, cyclohexane, 75–80°, 1 h. *e*) $LiAlH_4$, Et_2O, r.t., 0.5 h. *f*) PCC, CH_2Cl_2, r.t., 3 h.

whereas for compounds **18** and **19** the side chain is constrained into folded conformations.

2.2.2. *Investigation of the Conformational Features.* For small molecules, modern, automated conformational search methods have been developed to the extent where a complete determination of the populated conformations is feasible [29][30]. We therefore sought to determine the conformational preferences of **2** and **3**, and to

compare them to those of the constrained analogues **8**–**19**. Our approach was to use the 'jump between wells' (JBW) method, which has been successfully used to examine the conformational properties of both linear and cyclic hydrocarbons [31][32]. This method combines a 'smart' Monte Carlo algorithm for identifying energy minima populated by the molecule at a given temperature with a stochastic molecular-dynamics algorithm [33] that allows exploration of the conformational space local to these low-energy wells. Since the acceptance or rejection of a conformation is based on energetic changes, the distributions obtained reflect the *Boltzmann*-weighted populations of individual molecular conformations [31]. Assuming that all of the compounds exhibiting 'muguet'-type odors were acting at the same receptor, or set of receptors, the position of the aldehyde function with respect to the hydrophobic region of the molecule should be crucial. Therefore, we took the distance between the quaternary C-atom (C_{quat}) of the *tert*-butyl substituent and the O-atom of the aldehyde group (O_{carb}) as a simple conformational measure. The $C_{quat}-O_{carb}$ distances distribution was then evaluated from the conformer populations calculated for **2**, **3**, and **8**–**19**, and some representative examples are shown in *Fig. 1*. The computational results indicate, as expected, that the free-chain compounds **2** and **3** have the broadest conformer population, as reflected by the $C_{quat}-O_{carb}$ distance domain of 4 Å (5.5–9.5 Å). A similarly broad conformer population is shared by the more flexible of the constrained analogues, *i.e.*, by **10** (5.5–9.5 Å) and **11** (4.5–8.5 Å). In contrast, the $C_{quat}-O_{carb}$ distance domain of compounds **8** and **9** (5.7–8.7 Å), **18** (5.0–8.0 Å), and **19** (4.7–7.7 Å) covers only 3 Å, that of compound **17** (6.7–8.7 Å) only 2 Å, and that of compound **16** (7.8–9.3 Å) only 1.5 Å.

Intriguingly, the two inactive analogues **18** and **19**, constrained in a folded conformation, have a $C_{quat}-O_{carb}$ distance domain equal in breadth to **8**, the most-active constrained analogue, although for **18** and **19** the maximum $C_{quat}-O_{carb}$ distance is hardly above 7.5 Å, while for **8** it is above 8.5 Å. Nevertheless, all inactive or weakly active analogues possess $C_{quat}-O_{carb}$ distances in common with those of the most-active analogues in the present series (**2**, **3**, **8**, and **11**). Moreover, in the case of compounds **2** and **3**, which have almost identical conformational populations as reflected by the $C_{quat}-O_{carb}$ distances, it has been observed that the odor activity of **3** is approximately two- to four-times stronger than that of **2** [3b][34]. Taken together, these observations indicated that the conformational features of each individual compound, reflected by the distance parameter, were not discriminatory enough. Our hypothesis was that all the compounds eliciting a strong 'muguet'-type odor could adopt a defined conformation which was able to interact similarly with the same olfactory receptor or set of receptors. In other words, we were looking for a set of structural features responsible for a defined odor-type sensation, which has been termed 'olfactophore' [35]. Computational olfactophore models have been proposed for several families of odorants and in particular for 'muguet' alcohols and hydroxyaldehydes [4b]. Thus, we envisaged to construct a computational model ligand integrating the conformational features of the most-active compounds in this study, which we named 'consensus ligand'.

2.2.3. *Construction of a 'Consensus Ligand' by Induced Superimpositions.* The most active compounds (*R*)-**2**, **3**, and **8** (no chirality constraint was imposed upon compound **8**, since all evaluations employed racemic mixtures) were minimized in parallel (see

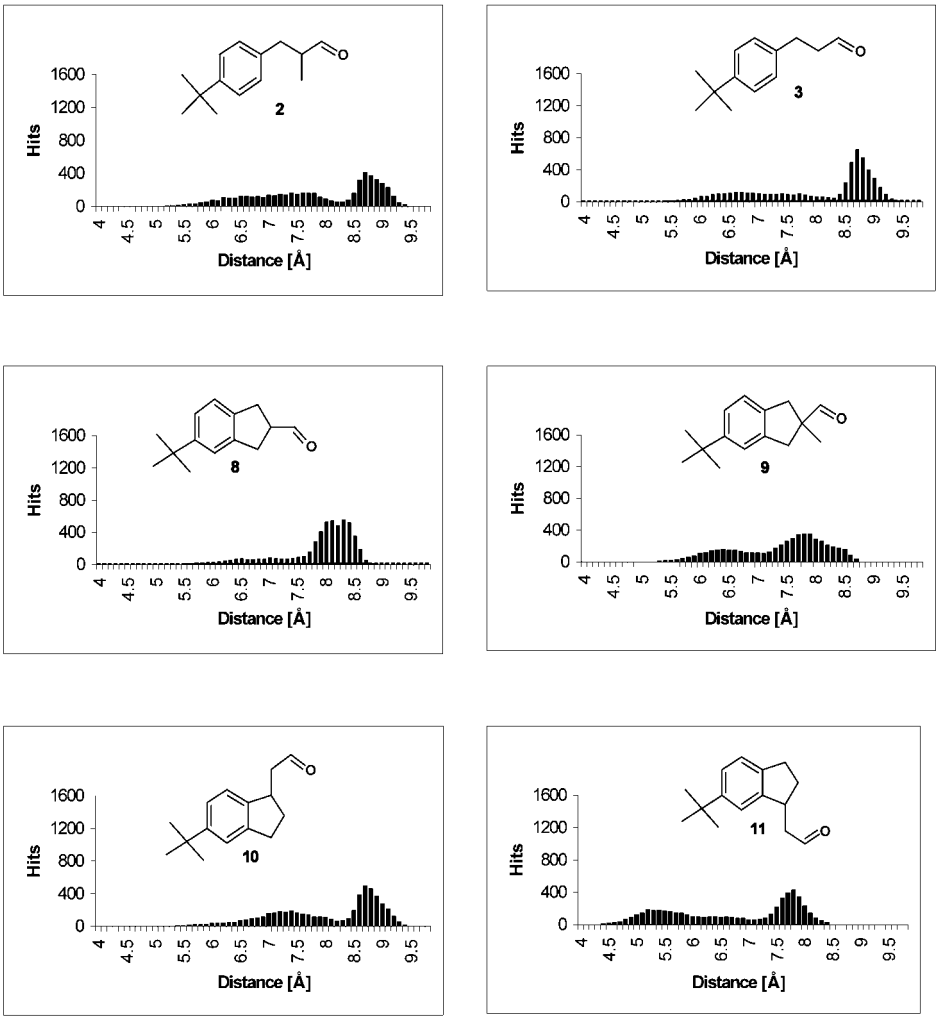


Fig. 1. *Calculated C_{quat}–O_{carb} distances* [Å] *in the conformational populations* (MM2* calculation) *of selected compounds*

Exper. Part), while a set of atoms (C_{quat}, C(1) and C(2) of the benzene ring, C_{carb} and O_{carb}) of one molecule were forced to coincide with the corresponding atoms of the other molecules. As in a classical Monte Carlo multiple conformational search, the minimizations were repeated starting from randomly chosen conformations of each individual compound. The result of this procedure was a list of superimpositions of increasing energy, which could be classified into four types (see *Fig. 2*). The lowest-energy superimposition **A** had both the carbonyl functions and the α-methyl group of (*R*)-**2** pointing towards the aromatic ring. The next, slightly higher-in-energy superimposition **B** had both the carbonyl functions and the α-methyl group pointing away from the aromatic ring, and, notably, the chiral C-atom of compound **8** adopted an

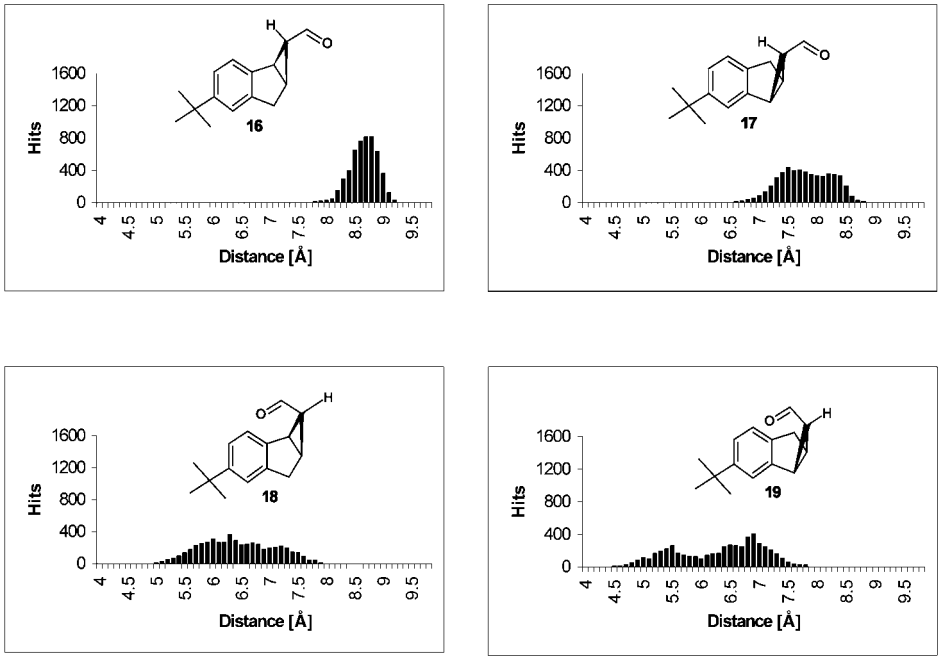


Fig. 1 (cont.)

inverse absolute configuration (we noticed that superimposition B reflected a conformation of (*R*)-**2** similar to the one seen in the published pictures [10] [35b] of (*R*)-**2** docked at a possible binding site in a model of the putative OR5 odorant receptor). The next higher-energy superimposition **C** had again the carbonyl functions turned towards the aromatic ring, but the α-methyl group of (*R*)-**2** was pointing away from the aromatic ring, and the chiral C-atom of compound **8** had again adopted an inverse absolute configuration, as in superimposition **B** (we noticed that superimposition **C** comprised a conformation of (*R*)-**2** similar to the one obtained in the superimposition of (*R*)-**2** with the inactive 1,3,4,5-tetrahydro-2-benzoxepin derivative **6**, tested earlier as a conformationally restricted analogue [13]). Finally, the highest-energy superimposition **D** had the carbonyl function turned towards the 'outside', while the α-methyl group of (*R*)-**2** was oriented towards the aromatic ring.

The conformations revealed by the superimpositions **B** and **D**, although not the lowest ones in energy, were thought to be more probable as 'bioactive' conformations because the carbonyl function would be more accessible for H-bonding. In previous studies [36], we observed a correlation between the solvent-accessible surface area (SASA) of a H-bond-acceptor atom and activity, in two series of odorants. Thus, we carried out a SASA calculation for the carbonyl O-atom of each compound in the four superimpositions **A** – **D**; the results are shown in *Table 2*. All the compounds in superimpositions **A** and **C** were in the group of small SASA values (< 42.7 Å^2), whereas all the compounds in superimpositions **B** and **D** were in the group of large SASA values (> 47.9 Å^2), except for compound (*R*)-**2** in superimposition **B**. In consequence, we

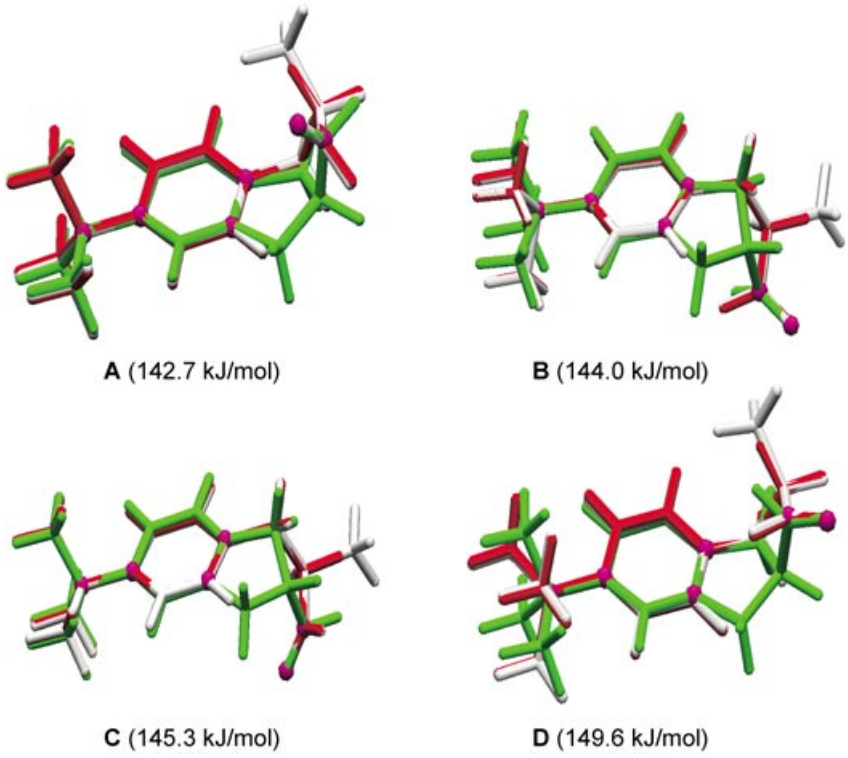


Fig. 2. *Types and energies of superimpositions of compounds* (*R*)-**2** (white), **3** (red) *and* **8** (green) *obtained by parallel minimization* (the atoms used for the superimpositions are marked in pink)

Table 2. *Solvent-Accessible Surface Areas* (SASA) *of the Carbonyl O-Atom for Compounds* (R)-**2**, **3**, *and* **8** *in the Four Superimpositions* **A**–**D** (probe radius = 1.4 Å)

	SASA [Å^2] of carbonyl O-atom			
	Superimp. **A**	Superimp. **B**	Superimp. **C**	Superimp. **D**
(*R*)-**2**	36.7	41.2	41.3	47.9
3	42.7	49.3	42.0	49.3
8	40.0	48.3	39.4	48.4

selected the set of positions obtained from superimposition **D**, in which all the carbonyl O-atoms have a large SASA value, to define our 'consensus-ligand'.

2.2.4. *Evaluation of the Energy Penalty for Each Compound of the Set to Fit to the 'Consensus Ligand'.* Compounds (*R*)- and (*S*)-**2**, **3**, and **8**–**19** were superimposed onto the 'consensus ligand' at defined positions (C_{quat}, C(1) and C(2) of the benzene ring, C_{carb}, and O_{carb}). The energy difference (ΔE) between the 'consensus-ligand'-superimposed and the ground-state conformers of a given compound, which represents how well the compound fits the model, was calculated, and the results are shown in *Table 3*. The data show that compounds **2**, **3**, **8**–**13**, **18**, and **19** can be superimposed on the 'consensus ligand' with relatively low energy penalties ($\Delta E < 11.1$ kJ/mol), whereas

analogues **14**–**17** have considerably higher ΔE values ($\Delta E > 22.5$ kJ/mol). However, among the first group of compounds, the ΔE values are not able to discriminate between active and inactive compounds. For example, (*S*)-**2** ((*S*)-*Lilial*®) has a lower penalty than (*R*)-**2** ((*R*)-*Lilial*®), which is in contradiction with the fact that (*R*)-*Lilial*® is the active compound, while (*S*)-*Lilial*® is significantly weaker [37]. Compound **9**, with no lily-of-the-valley odor activity, has a very low penalty compared to the very active compound **8**. Similarly, compound **11**, having a much more powerful and typical odor than **10**, has a higher ΔE value. These results prompted us to investigate in more detail the crucial substrate–receptor(s)-interaction event.

Table 3. *Energy Differences* (ΔE) *between the Ground-State Conformers of Compounds* **2**, **3**, *and* **8**–**19** *and Their Corresponding Conformers Superimposed onto the 'Consensus Ligand' and the 'Interaction Model'*

	Odor activity[a])	ΔE [kJ/mol]	
		'Consensus ligand'	'Interaction model'
(*R*)-**2**	1	7.1	2.6
(*S*)-**2**	0	2.1	9.2
3	1	5.7	1.2
8	1	4.5	−1.5
9	0	0.2	11.0
10	0	8.0	8.6
11	1	9.8	3.7
12	0	8.9	25.8
13	0	9.1	21.9
14	0	22.5	52.7
15	0	25.7	34.4
16	0	39.0	32.0
17	0	32.2	28.0
18	0	10.3	35.0
19	0	11.0	3.3

[a]) The compounds with a strong lily-of-the-valley odor were coded '1', those with weak or inexistent lily-of-the-valley odor were coded '0'.

2.2.5. *Generation of an 'Interaction Model'*. We added to the 'consensus ligand' the simplest possible external steric constraint, representing a steric demand of the receptor, by placing a methane molecule in proximity to the carbonyl group. The position was chosen to create unfavorable interactions with the inactive compounds (*S*)-**2**, **9**, and **10** (see *Exper. Part*), and a new model, the 'interaction model', including a methane molecule as a part of the presumed receptor protein(s) was created (see *Fig. 3*).

Again, the energy difference (ΔE) between the 'interaction-model'-superimposed and the ground-state conformers of each compound of the set was calculated, and the results are given in *Table 3*. As expected, all inactive compounds, except **19**[8]), suffered an unfavorable steric interaction with the added methane molecule, which resulted in increased ΔE values. In contrast, we found that the active compounds ((*R*)-**2**, **3**, **8**, and **11**) gained favorable *Van der Waals* interactions with the added methane molecule in

[8]) The very weak odor activity of compounds **16**–**19** puts into question the significance of this particular outcome.

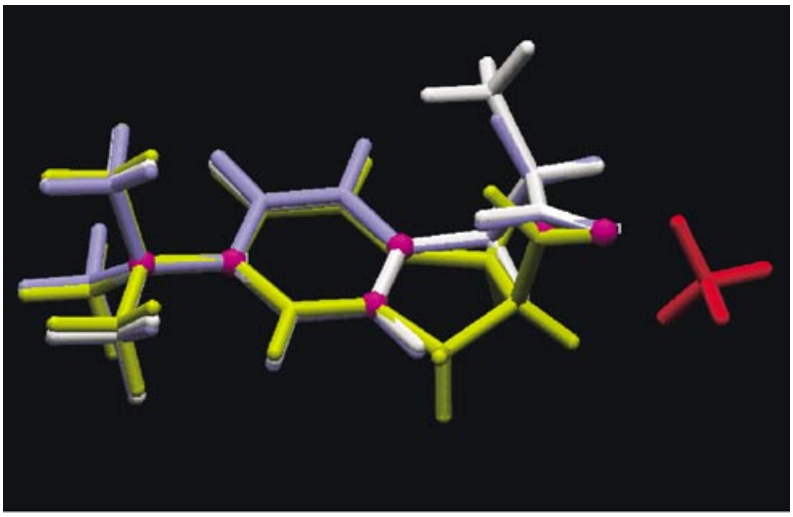


Fig. 3. *'Interaction model'*

the 'interaction model', leading to a decrease in the ΔE values. The superimpositions of some selected compounds onto the 'interaction-model' are shown in *Fig. 4*.

3. Discussion. – The cloning of the genes encoding olfactory receptors (ORs) in humans [38] and other mammals (rat, [39a]; mouse, [39b]) has permitted significant progress in elucidating the molecular mechanisms by which odorants interact with their target proteins [40]. Specifically, it is likely that receptor activation by odorant ligands proceeds by a molecular mechanism similar to that already determined for cellular receptors that interact with hormones, neurotransmitters, and light [41]. In this model, active (R*) and inactive (R) conformational forms of the OR are in an equilibrium that is perturbed by ligand binding. Hence an odorant initially binds to the R form of the OR to yield a complex that undergoes a conformational transition to give R*, which can then activate G-protein-mediated cell signaling pathways. As a result, some of the initial binding energy is employed to drive conformational changes of the OR within the membrane. Elucidation of binding-site structure is, therefore, complicated when sets of conformationally flexible ligands are employed to 'map' receptor recognition, a problem that is often overcome by preparing and characterizing the activity of conformationally constrained analogues.

Moreover, in contrast to studies on the interaction of drugs with G-protein-coupled receptors (GPCRs), the development of structure–activity relationships (SARs) for odorants is complicated by the observation that odorants can (in principle) interact with several different receptors, so that the olfactory response then arises from a combination of signals within the brain. This is a particular problem in modern structure-based methods for constructing structure–odor relationships (SOR), because all current methods require that a family of ligands all bind within an identical target site [42].

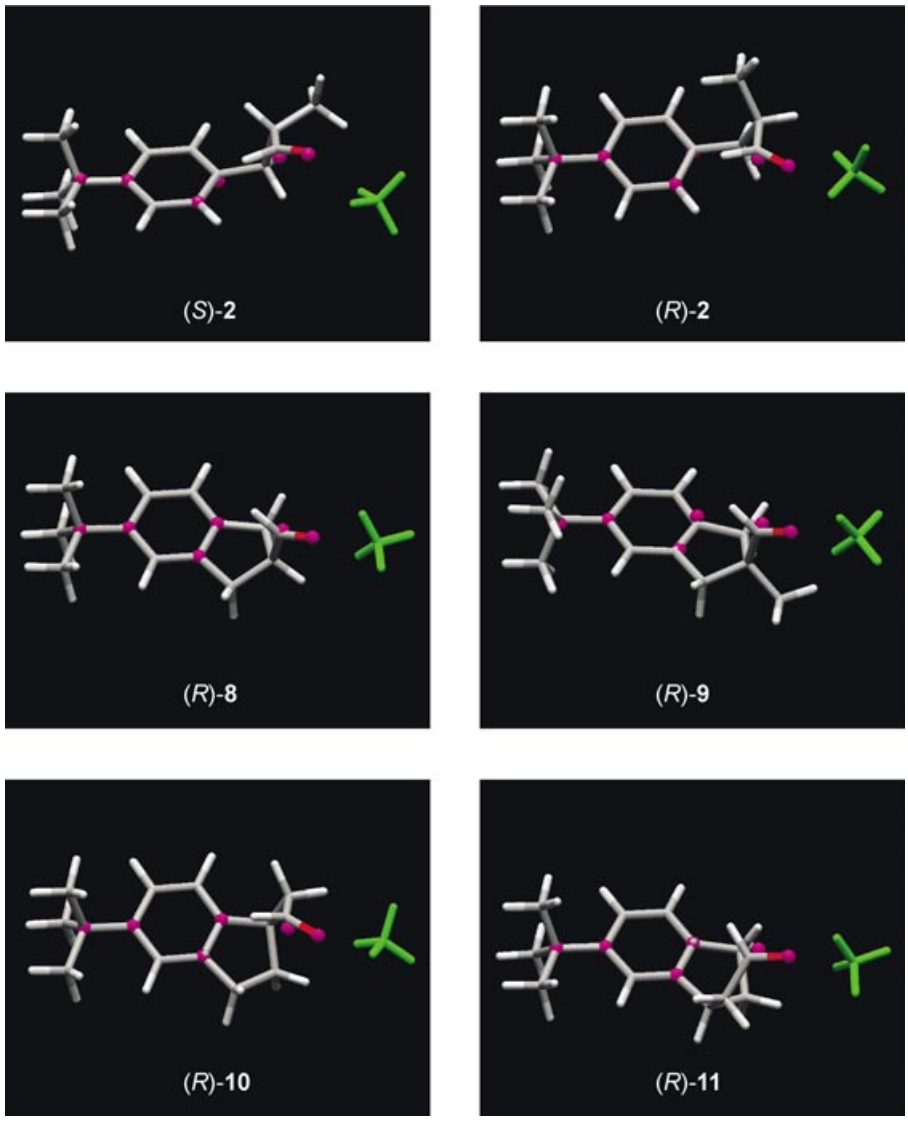


Fig. 4. *Superimposition of selected compounds onto the 'interaction model'*

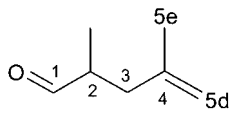
Given that there is strong evidence that the same receptor does accommodate both *Bourgeonal*® and *Lilial*® [12], however, we believed that access to conformationally constrained analogues of these odorants would permit us to develop an appropriate SOR model for this class of compounds with computational approaches. More specifically, we undertook to explore the ability of two computational approaches to rationalize the odorant qualities of a series of conformationally well-defined ligands, both of which have not been applied previously to this problem.

In our first approach, we used the JBW method to determine the conformational preferences of *Bourgeonal*®, *Lilial*®, and our series of conformationally constrained analogues. This algorithm provides an estimate of populated conformers based upon free energy rather than simple molecular-mechanics strain enthalpies. As might have been expected, however, while these calculations permitted us to evaluate the effects of molecular constraints upon the ability of a given compound to adopt multiple conformations, and therefore molecular flexibility, the SOR model developed by modeling the structural preferences of the free ligands failed to explain the olfactory-ligand set in a completely consistent manner. Efforts to identify common conformational features of our set of odorants by constrained molecular superimposition led to a 'consensus ligand' and revealed a $C_{quat}-O_{carb}$ distance of *ca.* 7.7 Å, which is in-between the fully extended (*anti*) and the fully folded (*gauche*) conformations. A comparison of the dimensions given by *Pelzer et al.* [5] for the odor-active side-chain fragment of carbonyl-type 'muguet' odorants (AM1 calculations) with the ones measured on the side chain of our 'consensus ligand' indicated slightly shorter distances in our model (*Table 4*). However, this model was also problematic, given that steric constraints imposed by receptor-based functional groups are not included in such an approach.

Table 4. *Comparison of the Dimensions for the Putative Odor-Active Side-Chain Fragment Obtained by* Pelzer's *Model*[a]) *and by the 'Consensus-Ligand'*

	Pelzer's model	'Consensus ligand' model (present work)
C(1) → C(4)	3.9+0.3 Å	3.14 Å
C(1) → C(5d)	4.4 ± 0.3 Å	3.33 Å
C(1) → C(5e)	5.0 ± 0.3 Å	4.22 Å

[a])



Structural fragment identified by *Pelzer et al.* [5] in lily-of-the-valley odorants bearing a carbonyl function.

As a result, it was necessary to introduce additional features to model the existence of such interactions, without the computational expense of modeling the three-dimensional structure of the OR explicitly, and thereby to obtain an 'interaction model' to which novel structures could be compared. Importantly, the inclusion of a methane molecule to introduce steric effects allows our model to reflect the fact that (*S*)-*Lilial*® ((*S*)-**2**) is far less intense than (*R*)-*Lilial*® ((*R*)-**2**) [37]. As far as we are aware, this represents the first ligand-based model that includes the effects of receptor environment; at this point, however, there is still room for refinement and improvement of the model with respect to this particular feature.

Work to elaborate and extend this model is continuing, and results will be reported in due course.

We gratefully acknowledge the collaboration of Mrs. *S. Gallo-Flückiger* for her experimental skill and of Mr. *W. Thommen* and Mr. *R. Brauchli* for the NMR analysis. We wish to thank Dr. *P.-A. Blanc* for the evaluation of olfactory properties and Dr. *R. L. Snowden* for stimulating discussions.

Experimental Part

General. All reactions were performed under N_2. GLC: *Hewlett-Packard-5890* instrument equipped with a flame-ionization detector coupled to a *Hewlett-Packard-3395* or *-3396A* integrator; capillary columns *Chrompack CP-Wax-52 CB* (10 m, 0.25 mm i.d.) and *CP-Sil-5 CB* (10 m, 0.25 mm i.d.). TLC: silica gel *60* (*Merck F 254*, layer thickness 0.25 mm). Column chromatography (CC): silica gel *60* (*Merck*, 0.063–0.2 mm, 70–270 mesh, ASTM). Bulb-to-bulb distillation: *Büchi-GKR-50* or *-GRK-51* oven; b.p. correspond to the air temp. IR Spectra (liquid film): *Perkin-Elmer-297* or *-1600-FTIR* spectrometers; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra ($CDCl_3$): *Bruker-AMX-360*, *-DPX-400*, or *-AV-500* spectrometers; δ in ppm downfield from $SiMe_4$, J in Hz. MS: *HP 5972* or *5973 MSD* (70 eV); in m/z (intensity in % rel. to the base peak (100%)).

1. *Computer-Aided Molecular Modeling. Conformational Properties.* All calculations were carried out with the MM2*-force-field parameters [43], and the JBW algorithm [29], as implemented in the MacroModel/BATCHMIN 6.0 software package [44]. Each simulation was run for 10'000 search steps, and all conformations that possessed a strain energy that was within 50 kJ/mol of the lowest-energy structure were sampled. Duplicate conformations were identified by using standard superimposition methods [45].

Parallel Minimization. This type of calculation, already used in a previous study [46], was performed by using the classical Monte Carlo conformational search procedure, as implemented in MacroModel. A single file containing the structures of the molecules to be superimposed was used as input. The constraints between the atoms were introduced by fixing interatomic distances equal to 0 (the force constant was 100 kJ/mol · Å^2). The force-field interactions between the atoms of different molecules were removed by using the ASNT key in the command (.com) file. The result of such calculations was a list of superimpositions classified by energy, the latter representing the summation of the force-field energy of each molecule.

Testing Molecules on the 'Consensus Ligand'. The model is constituted by the atoms fixed at positions determined in the parallel-minimization procedure. The superimposition of a molecule on the model was performed by the same procedure as above for the parallel-minimization calculations, with one exception: for the C-atom of the carbonyl function, a flat-bottom constraint was used, which started the energy penalty only when the inter-atomic distance was greater than 0.5 Å. This allowed a certain flexibility of the carbonyl-function orientation. All the atoms of the model were frozen at their initial positions. The force-field interactions between all the atoms of the molecules and the atoms of the model were removed.

Positioning of the Methane Molecule in the 'Interaction Model'. The methane molecule was placed initially to create unfavorable interactions with the inactive compounds ((*S*)-**2**, **9**, and **10**). The methane position was then optimized to best interact with the three active compounds ((*R*)-**2**, **8**, and **11**) fixed on the 'consensus ligand'. In this procedure, the energies of the three active molecules and the methane molecule was minimized; as in the parallel minimization (see above), the force-field interactions between the three active molecules were removed, but not the ones with the methane molecule. After this, the methane molecule was moved towards the C-atom in α position of the carbonyl function in compound (*R*)-**2** by 1/10 of the original distance, to maximize the unfavorable interactions with the inactive compounds, relative to the favorable interactions with the active compounds. This position of the methane molecule defined the 'interaction model'. The coordinates of this model are available; please contact *J.-Y. de Saint Laumer* (e-mail: jean-yves.de.saint.laumer@firmenich.com).

Testing Molecules on the 'Interaction Model'. The same procedure as above was used, except that the C-atom of methane was also frozen, while the H-atoms of methane were not constrained. The force-field interactions between all the atoms of the molecules and the atoms of the model, except the methane, were removed.

2. *Reduction of Esters or Ketones to Alcohols with $LiAlH_4$: General Procedure A* (*G.P. A*). To a stirred suspension of $LiAlH_4$ (1.5 equiv.) in Et_2O at r.t. was added dropwise a soln. of the ester or ketone (1.0 equiv.) in Et_2O, and the mixture was heated to reflux during 2 h. The mixture was cooled to 4°, acetone (4.0 equiv.) was added to consume the excess reagent and then a stoichiometric amount of 1N aq. NaOH. The mixture was stirred during 0.5 h ($\rightarrow$ r.t.), then Na_2SO_4 was added, the solid filtered off, and the filtrate evaporated.

3. *Oxidation of Alcohols to Aldehydes with Pyridinium Chlorochromate* (PCC): *General Procedure B* (*G.P. B*). To a stirred suspension of PCC (1.5 equiv.) in CH_2Cl_2 at r.t. was added dropwise a soln. of the alcohol (1.0 equiv.) in CH_2Cl_2, and the mixture was stirred at r.t. during 3–5 h. The mixture was diluted with an excess of Et_2O, filtered through a short column of *Florisil®* (*Acros Organics*), and evaporated.

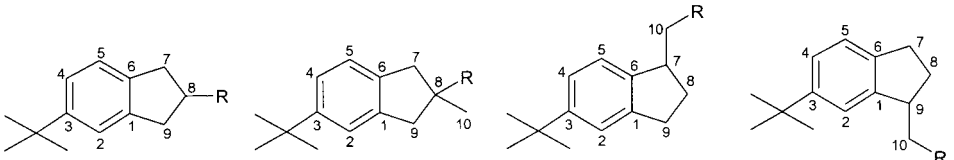
4. *Compounds* **8** *and* **9**. *(±)-Ethyl 5-(*tert*-Butyl)-2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate* (**23**). An 80% NaH dispersion in oil (4.32 g; corresponding to 3.45 g, 144 mmol) was washed with pentane. Then toluene (140 ml) and diethyl carbonate (34 g, 288 mmol) were added, and the mixture was heated to 60°. A soln. of 5-(*tert*-butyl)-2,3-dihydro-1*H*-inden-1-one (**22**; 7.52 g, 40 mmol) in toluene (20 ml) was added during 2 h, and

stirring at 60° was continued for 6 h. The mixture was poured on an excess of H_2O/AcOH 1:1 and extracted with petroleum ether (30–50°) and the extract washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4) and evaporated (10.8 g). Bulb-to-bulb distillation (oven temp. → 250°/0.1 mbar) gave **23** (7.12 g, 62%, purity (NMR) *ca.* 90%). Oil. IR: 2960, 2860, 1730–1700, 1598, 1360, 1320, 1250, 1205, 1150, 1080, 1010. ^{1}H-NMR: 7.70 (*d*, *J* = 8, 1 H); 7.50 (*s*, 1 H); 7.45 (*d*, *J* = 8, 1 H); 4.25 (*q*, *J* = 7, 2 H); 3.71 (*dd*, *J* = 8, 4, 1 H); 3.54 (*dd*, *J* = 17, 4, 1 H); 3.35 (*dd*, *J* = 17, 8, 1 H); 1.36 (*s*, 9 H); 1.32 (*t*, *J* = 7, 3 H). ^{13}C-NMR: *Table 5*. CI-MS: 260 (61, M^+), 245 (25), 215 (24), 199 (60), 186 (77), 171 (100), 157 (16), 143 (11), 131 (34), 115 (31), 91 (18), 57 (76), 41 (31).

Table 5. *^{13}C-NMR Chemical Shifts* (δ [ppm] relative to $SiMe_4$) *of Compounds in* Schemes 1 *and* 2 ($CDCl_3$ solutions)[a])

	R	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	Me_3C	Me_3C	C(R)
22	H	155.5	123.2	158.8	125.0	123.3	134.7	206.5	36.5	25.9		35.4	31.2	
23	COOEt	154.0	123.1	159.8	125.6	124.3	132.9	199.2	53.6	30.4		35.6	31.2	169.4, 61.4, 14.2
24	COOEt	152.9	123.0	159.6	125.6	124.5	132.3	203.0	56.2	40.2	21.1	35.6	31.2	172.2, 61.4, 14.0
25	COOEt	141.5	121.2	149.8	123.7	123.8	138.7	35.8	43.8	36.3		34.5	31.6	175.4, 60.6, 14.3
26	COOEt	141.2	121.5	149.7	123.6	124.1	138.3	43.6	49.6	44.1	25.2	34.5	31.6	177.7, 60.6, 14.2
27	CH_2OH	142.5	121.5	149.5	123.4	124.1	139.7	35.3	41.7	35.9		34.5	31.6	66.1
28	CH_2OH	142.3	121.7	149.4	123.3	124.2	139.4	42.9	45.0	42.4	24.1	34.5	31.6	70.7
8	CHO	141.0	121.5	150.1	124.0	124.1	138.1	32.5	50.9	33.1		34.6	31.5	203.0
9	CHO	140.8	121.6	150.1	124.0	124.2	137.9	40.6	54.4	41.1	21.1	34.6	31.5	204.1
31	COOMe	149.7	122.3	154.8	124.4	121.3	137.4	163.4	31.5	30.7	106.4	35.0	31.3	168.1, 50.9
32	H	137.0	119.9	150.8	132.5	126.3	152.6	25.3	36.6	207.4		34.8	31.3	
35	COOMe	146.9	118.0	150.1	125.2	128.8	139.7	30.1	31.6	163.8	106.7	34.7	31.4	168.0, 51.0
36	COOMe	143.7	121.5	149.9	123.4	122.9	142.7	41.0	32.7	31.3	39.7	34.6	31.6	173.3, 51.5
37	COOMe	145.5	120.2	149.5	123.9	124.1	140.9	30.7	32.6	41.5	39.9	34.6	31.6	173.3, 51.5
38	CH_2OH	143.7	121.4	149.6	123.2	123.0	144.0	41.1	32.5	31.6	38.0	34.5	31.6	61.7
39	CH_2OH	146.8	120.4	149.3	123.5	124.0	140.9	30.9	32.5	41.6	38.0	34.6	31.6	61.6
10	CHO	143.6	121.5	150.1	123.5	122.9	142.5	38.6	35.7	31.5	49.5	34.6	31.6	202.0
11	CHO	145.3	120.2	149.7	124.0	124.2	140.8	30.9	32.7	39.1	49.5	34.6	31.6	202.0

[a]) Arbitrary numbering.



*(±)-Ethyl 5-(*tert*-Butyl)-2,3-dihydro-(2-methyl-1-oxo-1*H*-indene-2-carboxylate* **(24)**. To a stirred soln. of **23** (5.36 g, 20.6 mmol) in THF (75 ml) at r.t. were added K_2CO_3 (5.7 g, 41.2 mmol) and MeI (1.92 ml, 4.37 g, 31 mmol), and the mixture was heated to reflux (bath temp. → 65°) during 3 h. The cooled mixture was diluted with Et_2O and H_2O and the org. phase washed with brine (2×), dried (Na_2SO_4), and evaporated: yellow liquid (5.5 g). Bulb-to-bulb distillation (oven temp. → 110°/0.16 mbar) gave **24** (5.19 g, 94%; purity 94%). Colorless oil. IR: 2957, 1747, 1699, 1601, 1428, 1374, 1322, 1267, 1189, 1172, 1096, 1080, 965, 921, 849. ^{1}H-NMR: 7.72 (*d*, *J* = 8, 1 H); 7.47 (*s*, 1 H); 7.46 (*d*, *J* = 8, 1 H); 4.15 (*q*, *J* = 7, 2 H); 3.69 (*d*, *J* = 18, 1 H); 2.97 (*d*, *J* = 18, 1 H); 1.51 (*s*, 3 H); 1.37 (*s*, 9 H); 1.20 (*t*, *J* = 7, 3 H). ^{13}C-NMR: *Table 5*. MS: 274 (58, M^+), 259 (24), 246 (10), 229 (10), 217 (17), 201 (100), 185 (75), 171 (13), 157 (10), 143 (18), 128 (29), 115 (36), 91 (11), 77 (5), 57 (12), 41 (6).

*(±)-Ethyl 5-(*tert*-Butyl)-2,3-dihydro-1*H*-indene-2-carboxylate* (**25**). A soln. of **23** (4.65 g, 16.2 mmol; purity 90%) in AcOEt (50 ml) was shaken at r.t. in presence of 5% Pd/C (0.48 g) under H_2 (1 atm) during 12 h. The catalyst was filtered off through *Celite*® and the soln. evaporated (4.25 g). CC (SiO_2 (106 g), pentane/Et_2O 9:1), followed by bulb-to-bulb distillation (oven temp. → 160°/0.5 mbar), gave pure **25** (3.47 g, 86%). Oil. IR: 2950, 1729, 1445, 1363, 1256, 1213, 1200, 1159, 1030, 817. ^{1}H-NMR: 7.24 (*s*, 1 H); 7.20 (*d*, *J* = 8, 1 H); 7.13 (*d*, *J* = 8,

1 H); 4.18 (*q*, *J* = 7, 2 H); 3.40–3.10 (*m*, 5 H); 1.31 (*s*, 9 H); 1.28 (*t*, *J* = 7, 3 H). ^{13}C-NMR: *Table 5*. MS: 246 (25, M^+), 231 (100), 201 (3), 172 (25), 157 (60), 129 (20), 115 (20), 91 (4), 79 (4), 57 (20), 41 (7).

*(±)-Ethyl 5-(*tert*-Butyl)-2,3-dihydro-2-methyl-1*H*-indene-2-carboxylate* (**26**). To a soln. of **24** (5.19 g, 17.9 mmol, purity 94%) in AcOH (50 ml) was added 10% Pd/C (2.1 g), and the mixture was shaken under H_2 (1 atm) at r.t. during 17 days. The catalyst was filtered off and the soln. was evaporated. The residue was evaporated from toluene (3×), then treated with active charcoal in toluene soln., filtered, and evaporated: colorless oil (5.33 g). Bulb-to-bulb distillation (oven temp. → 105°/0.1 mbar) afforded **26** (4.44 g, 74%; purity 77%). Colorless oil. An anal. sample was obtained by CC (SiO_2, toluene/AcOEt 9:1). IR: 2950, 2890, 2860, 1720, 1455, 1355, 1300, 1210, 1195, 1110, 1025, 820. ^{1}H-NMR: 7.21 (*s*, 1 H); 7.19 (*d*, *J* = 8, 1 H); 7.10 (*d*, *J* = 8, 1 H); 4.16 (*q*, *J* = 7, 2 H); 3.49 (*d*, *J* = 15, 1 H); 3.44 (*d*, *J* = 15, 1 H); 2.79 (*d*, *J* = 15, 1 H); 2.77 (*d*, *J* = 15, 1 H); 1.35 (*s*, 3 H); 1.30 (*s*, 9 H); 1.26 (*t*, *J* = 7, 3 H). ^{13}C-NMR: *Table 5*. MS: 260 (18, M^+), 245 (51), 217 (3), 186 (65), 171 (100), 157 (10), 143 (13), 129 (23), 115 (16), 91 (8), 77 (4), 57 (27), 41 (11).

*(±)-5-(*tert*-Butyl)-2,3-dihydro-1*H*-indene-2-methanol* (**27**). From **25** (2.2 g, 8.9 mmol), according to the *G.P. A*. Bulb-to-bulb distillation (oven temp. → 200°/0.4 mbar) gave **27** (1.86 g, 100%). Colorless oil. IR: 3306, 2949, 2864, 1493, 1361, 1264, 1032, 816, 716. ^{1}H-NMR: 7.24 (*s*, 1 H); 7.18 (*d*, *J* = 8, 1 H); 7.13 (*d*, *J* = 8, 1 H); 3.66 (*d*, *J* = 6, 2 H); 3.04 (*m*, 2 H); 2.71 (*m*, 3 H); 1.62 (br. *s*, OH); 1.31 (*s*, 9 H). ^{13}C-NMR: *Table 5*. MS: 204 (21, M^+), 189 (100), 171 (15), 143 (14), 129 (16), 115 (13), 91 (6), 77 (3), 57 (7), 41 (5).

*(±)-5-(*tert*-Butyl)-2,3-dihydro-2-methyl-1*H*-indene-2-methanol* (**28**). From **26** (2.28 g, 8.2 mmol; purity 94%), according to the *G.P. A*. Bulb-to-bulb distillation (oven temp. → 180°/0.1 mbar) afforded **28** (1.85 g, 98%; purity 94%). Colorless oil. IR: 3330, 2960, 2920, 2880, 1605, 1490, 1455, 1360, 1255, 1040, 820. ^{1}H-NMR: 7.20 (*s*, 1 H); 7.17 (*d*, *J* = 8, 1 H); 7.09 (*d*, *J* = 8, 1 H); 3.51 (*s*, 2 H); 2.90 (*d*, *J* = 16, 1 H); 2.86 (*d*, *J* = 16, 1 H); 2.65 (*d*, *J* = 16, 1 H); 2.62 (*d*, *J* = 16, 1 H); 1.68 (*s*, OH); 1.30 (*s*, 9 H); 1.18 (*s*, 3 H). ^{13}C-NMR: *Table 5*. MS: 218 (25, M^+), 203 (100), 185 (25), 171 (4), 157 (9), 143 (15), 129 (12), 115 (8), 91 (5), 77 (3), 57 (17), 41 (8).

*(±)-5-(*tert*-Butyl)-2,3-dihydro-1*H*-indene-2-carboxaldehyde* (**8**). From **27** (2.04 g, 10 mmol), according to the *G.P. B*. Bulb-to-bulb distillation (oven temp. → 160°/0.4 mbar) gave **8** (1.47 g, 72%). Colorless oil. IR: 2950, 2713, 1720, 1494, 1436, 1391, 1361, 1265, 1200, 1056, 900, 818, 716. ^{1}H-NMR: 9.77 (*d*, *J* = 2, 1 H); 7.27 (*s*, 1 H); 7.22 (*d*, *J* = 8, 1 H); 7.16 (*d*, *J* = 8, 1 H); 3.35–3.10 (*m*, 5 H); 1.31 (*s*, 9 H). ^{13}C-NMR: *Table 5*. MS: 202 (36, M^+), 187 (100), 169 (10), 157 (10), 141 (11), 129 (18), 115 (19), 91 (6), 77 (3), 57 (6), 41 (6).

*(±)-5-(*tert*-Butyl)-2,3-dihydro-2-methyl-1*H*-indene-2-carboxaldehyde* (**9**). From **28** (1.85 g, 8 mmol; purity 94%) according to the *G.P. B*. Bulb-to-bulb distillation (oven temp. → 110°/0.1 mbar) afforded **9** (1.56 g, 81%; purity 90%). Colorless oil. IR: 2960, 2890, 2860, 2690, 1720, 1600, 1490, 1455, 1430, 1360, 1265, 885, 820. ^{1}H-NMR: 9.65 (*s*, 1 H); 7.23 (*s*, 1 H); 7.21 (*d*, *J* = 8, 1 H); 7.13 (*d*, *J* = 8, 1 H); 3.36 (*d*, *J* = 16, 1 H); 3.32 (*d*, *J* = 16, 1 H); 2.76 (*d*, *J* = 16, 1 H); 2.73 (*d*, *J* = 16, 1 H); 1.31 (*s*, 9 H); 1.30 (*s*, 3 H). ^{13}C-NMR: *Table 5*. MS: 216 (36, M^+), 201 (100), 183 (3), 171 (4), 157 (16), 141 (9), 129 (18), 115 (2), 105 (2), 91 (8), 71 (6), 57 (24), 41 (8).

5. *Compounds* **10** *and* **11**. *Methyl (*E*)-[5-(*tert*-Butyl)-2,3-dihydro-1*H*-inden-1-ylidene]acetate* (**31**) *and Isomers*. To a stirred soln. of **22** (10.2 g, 53 mmol) in petroleum ether (30–50°) (125 ml) at r.t. were added methyl (dimethoxyphosphinyl)acetate (11.6 ml, 80 mmol) and dropwise 5.4M NaOMe in MeOH (13.4 ml, 72 mmol) during 5 min. After 24 h at r.t., the mixture was heated under reflux (35°) during 17 h. The cooled mixture was diluted with Et_2O and H_2O and the org. layer washed with brine (2×), dried (Na_2SO_4), and evaporated: solidifying oil (12.6 g). GC: 2% of **22**, 14% of deconjugated isomer **29**, 5% of (*Z*)-isomer **30**, and 78% of (*E*)-isomer **31** (yield: 93%). Crystallization from Et_2O at −30° gave enriched **31** (5.56 g, 42%; purity 94%, the balance consisting of 5% of **29** and 1% of **30**). M.p. 116.5–117.5°. IR ($CHCl_3$): 2960, 1690, 1630, 1605, 1435, 1355, 1315, 1290, 1175, 1090, 830. ^{1}H-NMR: 7.53 (*d*, *J* = 8, 1 H); 7.37 (*d*, *J* = 2, 1 H); 7.30 (*dd*, *J* = 8, 2, 1 H); 6.27 (*t*, *J* = 2.5, 1 H); 3.76 (*s*, 3 H); 3.29 (*m*, 2 H); 3.06 (*m*, 2 H); 1.33 (*s*, 9 H). ^{13}C-NMR: *Table 5*. MS: 244 (43, M^+), 229 (100), 213 (15), 197 (14), 188 (9), 169 (15), 155 (27), 141 (25), 128 (34), 115 (23), 85 (10), 57 (13), 41 (7).

*Methyl (*E*)-[6-(*tert*-Butyl)-2,3-dihydro-1*H*-inden-1-ylidene]acetate* (**35**) *and Isomers*. As described for **31**, with **32** (1.4 g, 7.3 mmol; purity 98%): crude material (1.5 g). GC: 19% of deconjugated isomer **33**, 4% of (*Z*)-isomer **34**, and 53% of (*E*)-isomer **35**. Bulb-to-bulb distillation (oven temp. 110–122°/0.25 mbar) afforded a product mixture (1.20 g, 64%; purity 96%). GC: 26% of **33**, 5% of **34**, and 65% of **35**. IR: 2980, 1740, 1710, 1680, 1450, 1355, 1200, 1170, 860, 835. ^{1}H-NMR (major isomer **35**): 7.61 (*d*, *J* = 2, 1 H); 7.42 (*dd*, *J* = 8, 2, 1 H); 7.28 (*d*, *J* = 8, 1 H); 6.33 (*t*, *J* = 2, 1 H); 3.76 (*s*, 3 H); 3.31 (*m*, 2 H); 3.03 (*m*, 2 H); 1.34 (*s*, 9 H). ^{13}C-NMR: *Table 5*. MS (major isomer **35**): 244 (47, M^+), 229 (100), 213 (19), 197 (41), 188 (43), 169 (17), 155 (30), 141 (21), 129 (38), 115 (16), 85 (15), 57 (11).

*(±)-Methyl 5-(*tert*-Butyl)-2,3-dihydro-1*H*-indene-1-acetate* (**36**). A soln. of **31** (7.4 g, 30 mmol; purity 94%, the balance consisting of 5% of **29** and 1% of **30**) in AcOEt (150 ml) at r.t. was shaken under H_2 (1 atm) in the

presence of 5% Pd/C (0.68 g, 0.3 mmol) during 1 h. The catalyst was filtered off through *Celite*® and the soln. evaporated (7.39 g). Bulb-to-bulb distillation (oven temp. → 110°/0.35 mbar) gave **36** (7.1 g, 93%; purity 99%). Colorless oil. IR: 2970, 1735, 1435, 1360, 1270, 1190, 1170, 830. ^{1}H-NMR: 7.26 (*d*, *J* = 2, 1 H); 7.20 (*dd*, *J* = 8, 2, 1 H); 7.00 (*d*, *J* = 8, 1 H); 3.72 (*s*, 3 H); 3.55 (*m*, 1 H); 2.89 (*m*, 2 H); 2.79 (*m*, 1 H); 2.40 (*m*, 2 H); 1.73 (*m*, 1 H); 1.32 (*s*, 9 H). ^{13}C-NMR: *Table 5.* MS: 246 (28, M^+), 231 (58), 189 (52), 173 (74), 157 (65), 143 (32), 129 (100), 115 (54), 91 (15), 77 (7), 57 (31), 41 (7).

*(±)-Methyl 6-(*tert*-Butyl)-2,3-dihydro-1*H*-indene-1-acetate* (**37**). As described for **36**, with **35** (1.13 g, 4.4 mmol; purity 65%, the balance consisting of 26% of **33** and 5% of **34**): crude material (1.11 g) which was bulb-to-bulb distilled (oven temp. 105–110°/0.12 mbar): **37** (1.10 g, 99%; purity 98%). Colorless oil. IR: 2990, 2940, 1740, 1500, 1440, 1370, 1270, 1180, 830. ^{1}H-NMR: 7.22 (*dd*, *J* = 8, 2, 1 H); 7.20 (*d*, *J* = 2, 1 H); 7.15 (*d*, *J* = 8, 1 H); 3.72 (*s*, 3 H); 3.58 (*m*, 1 H); 2.85 (*m*, 2 H); 2.80 (*m*, 1 H); 2.40 (*m*, 2 H); 1.75 (*m*, 1 H); 1.31 (*s*, 9 H). ^{13}C-NMR: *Table 5*. MS: 246 (27, M^+), 231 (59), 189 (41), 173 (31), 157 (100), 129 (70), 115 (29), 91 (8), 57 (15).

*(±)-5-(*tert*-Butyl)-2,3-dihydro-1*H*-indene-1-ethanol* (**38**). Treatment of **36** (6.3 g, 25 mmol) according to the *G.P. A* gave crude **38**. Bulb-to-bulb distillation (oven temp. → 115°/0.3 mbar) afforded **38** (5.5 g, 99%). Colorless oil. IR: 3320, 2960, 2860, 1490, 1360, 1265, 1060, 1025, 825. ^{1}H-NMR: 7.27 (*d*, *J* = 2, 1 H); 7.21 (*dd*, *J* = 8, 2, 1 H); 7.14 (*d*, *J* = 8, 1 H); 3.81 (*m*, 2 H); 3.20 (*m*, 1 H); 2.87 (*m*, 2 H); 2.32 (*m*, 1 H); 2.15 (*m*, 1 H); 1.70 (*m*, 2 H); 1.58 (br., OH); 1.32 (*s*, 9 H). ^{13}C-NMR: *Table 5*. MS: 218 (56, M^+), 203 (99), 200 (3), 185 (25), 173 (100), 161 (34), 143 (30), 128 (22), 115 (20), 91 (8), 77 (4), 57 (25), 41 (6), 31 (9).

*(±)-6-(*tert*-Butyl)-2,3-dihydro-1*H*-indene-1-ethanol* (**39**). Treatment of **37** (0.99 g, 3.9 mmol; purity 98%) according to the *G.P. A* gave crude **39** (0.81 g), which was bulb-to-bulb distilled (oven temp. 100–115°/0.07 mbar): **39** (0.78 g, 87%; purity 97%). Colorless oil. IR: 3320, 2960, 2860, 1480, 1355, 1255, 1150, 820. ^{1}H-NMR: 7.24 (*d*, *J* = 2, 1 H); 7.21 (*dd*, *J* = 8, 2, 1 H); 7.15 (*d*, *J* = 8, 1 H); 3.81 (*m*, 2 H); 3.22 (*m*, 1 H); 2.85 (*m*, 2 H); 2.31 (*m*, 1 H); 2.16 (*m*, 1 H); 1.70 (*m*, 2 H); 1.42 (br., OH); 1.32 (*s*, 9 H). ^{13}C-NMR: *Table 5*. MS: 218 (60, M^+), 203 (100), 185 (29), 173 (84), 161 (84), 157 (52), 143 (84), 129 (60), 117 (70), 91 (22), 77 (10), 57 (50).

*(±)-5-(*tert*-Butyl)-2,3-dihydro-1*H*-indene-1-acetaldehyde* (**10**). Treatment of **38** (3.85 g, 17.6 mmol) according to the *G.P. B* gave crude **10** (2.89 g). Bulb-to-bulb distillation (oven temp. → 150°/0.4 mbar) gave **4** (2.34 g, 62%; purity 98%). Colorless oil. IR: 2960, 2900, 2860, 2710, 1490, 1360, 1260, 830. ^{1}H-NMR: 9.88 (*t*, *J* = 2, 1 H); 7.28 (*d*, *J* = 2, 1 H); 7.22 (*dd*, *J* = 8, 2, 1 H); 7.08 (*d*, *J* = 8, 1 H); 3.62 (*m*, 1 H); 2.90 (*m*, 3 H); 2.62 (*m*, 1 H); 2.43 (*m*, 1 H); 1.70 (*m*, 1 H); 1.32 (*s*, 9 H). ^{13}C-NMR: *Table 5* . MS: 216 (44, M^+), 201 (100), 173 (79), 157 (98), 143 (37), 129 (72), 115 (83), 102 (5), 91 (23), 77 (10), 57 (33), 41 (8), 29 (8).

*(±)-6-(*tert*-Butyl)-2,3-dihydro-1*H*-indene-1-acetaldehyde* (**11**). Treatment of **39** (8.53 g, 32.1 mmol; purity 82%) according to the *G.P. B* gave a crude product, which was bulb-to-bulb distilled (oven temp. → 120°/0.15 mbar): **11** (6.01 g, 72%; purity 84%). Colorless oil. CC (silica gel, cyclohexane/Et_2O 4 : 1) gave pure **11**. IR: 2980, 2880, 2620, 1730, 1495, 1370, 1270, 1125, 830. ^{1}H-NMR: 9.88 (br. *s*, 1 H); 7.22 (*dd*, *J* = 8, 2, 1 H); 7.19 (*d*, *J* = 2, 1 H); 7.17 (*d*, *J* = 8, 1 H); 3.64 (*m*, 1 H); 2.89 (*m*, 3 H); 2.62 (*m*, 1 H); 2.42 (*m*, 1 H); 1.71 (*m*, 1 H); 1.29 (*s*, 9 H). ^{13}C-NMR: *Table 5*. MS: 216 (16, M^+), 201 (42), 172 (45), 159 (27), 157 (100), 141 (21), 131 (25), 129 (61), 117 (33), 115 (51), 91 (16), 77 (6), 57 (11).

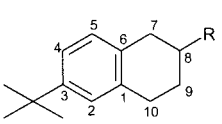
6. *Compounds* **12** *and* **13**. *6-(*tert*-Butyl)-1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde* (**41**). To stirred dimethylformamide (DMF; 2 ml, 1.89 g, 26 mmol) was added $POCl_3$ (2.31 g, 15 mmol), while maintaining the temp. below 30° with an ice-water bath. After 30 min at r.t., ketone **40** (1.01 g, 5 mmol) was added, and the mixture was heated to 80° during 4 h. The mixture was cooled to r.t., 30% aq. NaOH soln. (8.1 g) was added slowly (exothermic), and the mixture was heated to 70° during 0.5 h. H_2O (2.5 ml) was added, the mixture extracted with CH_2Cl_2, and the extract dried (Na_2SO_4) and evaporated. Bulb-to-bulb distillation (oven temp. → 190°/0.2 mbar) gave **41** (1.11 g, 77%; purity 86%). Colorless oil. IR: 2954, 2849, 1653, 1584, 1547, 1362, 1347, 1267, 1161, 969, 888, 870, 827, 820, 795, 713, 682. ^{1}H-NMR: 10.37 (*s*, 1 H); 7.78 (*d*, *J* = 8, 1 H); 7.35 (*dd*, *J* = 8, 2, 1 H); 7.23 (*d*, *J* = 2, 1 H); 2.83 (*m*, 2 H); 2.64 (*m*, 2 H); 1.33 (*s*, 9 H). ^{13}C-NMR: *Table 6.* MS: 248 (44, M^+), 235 (32), 233 (100), 205 (14), 193 (22), 191 (50), 152 (16), 141 (19), 128 (26), 115 (10), 57 (15), 41 (16), 29 (16).

*7-(*tert*-Butyl)-1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde* (**43**). As described for **41**, with 7-(*tert*-butyl)-3,4-dihydronaphthalen-1(2*H*)-one (**42**; 1.01 g, 5 mmol): crude **43** (1.57 g). Bulb-to-bulb distillation (oven temp. → 190°/0.2 mbar) afforded **43** (1.08 g, 87%; purity 97%). Yellow oil, which solidified on standing. Crystallization from heptane at −30° gave yellowish crystals. M.p. 67–68°. IR: 2957, 2855, 1659, 1582, 1555, 1351, 1250, 1130, 1228, 967, 895, 835, 818, 778, 739, 715, 655. ^{1}H-NMR: 10.40 (*s*, 1 H); 7.90 (*d*, *J* = 2, 1 H); 7.41 (*dd*, *J* = 8, 2, 1 H); 7.15 (*d*, *J* = 8, 1 H); 2.80 (*m*, 2 H); 2.63 (*m*, 2 H); 1.35 (*s*, 9 H). ^{13}C-NMR: *Table 6.* MS: 248 (36, M^+), 235 (33), 233 (100), 205 (16), 193 (20), 191 (35), 165 (8), 152 (14), 141 (14), 128 (22), 115 (9), 102 (8), 57 (10), 41 (13), 29 (10).

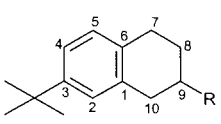
Table 6. *^{13}C-NMR Chemical Shifts* (δ [ppm] relative to $SiMe_4$) *of Compounds in* Schemes 3 *and* 4 ($CDCl_3$ solutions)[a])

	R	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C(11)	Me_3C	Me_3C	C(R)
40	H	144.3	125.4	157.1	124.0	127.1	130.3	198.2	39.2	23.4	30.1	–	35.1	31.1	
42	H	132.2	123.6	149.7	130.8	128.0	141.7	29.3	23.4	39.3	198.7	–	34.6	31.2	
41	CHO	138.7	124.9	155.3	124.1	126.1	131.3	146.1	129.4	21.7	27.4	–	35.0	31.1	190.6
43	CHO	132.0	123.3	150.2	128.5	127.5	136.2	26.5	21.8	131.5	146.5	–	34.7	31.3	190.7
12	CHO	135.4	125.7	149.0	123.2	129.0	131.3	28.1	47.1	23.1	28.4	–	34.3	31.4	204.0
13	CHO	133.7	126.0	148.9	123.3	128.6	133.0	27.7	23.1	47.0	28.8	–	34.3	31.4	203.9
47	H	141.4	126.7	155.8	123.7	128.7	136.1	205.5	40.9	21.0	25.3	33.0	34.9	31.1	
48	H	138.4	125.4	149.6	129.3	129.6	138.6	32.1	25.3	21.1	41.0	206.3	34.5	31.3	
50	CHO	140.7	126.0	154.2	123.8	128.3	135.0	147.8	136.0	22.6	33.9	32.4	34.9	31.2	190.3
51	CHO	136.3	125.3	149.7	127.8	128.8	138.0	31.4	33.7	22.6	137.3	148.0	34.6	31.3	190.3
14	CHO	142.4	126.3	149.6	123.0	129.2	136.4	34.7	50.9	31.7	26.6	36.3	34.3	31.4	203.8
15	CHO	139.8	126.6	149.2	123.4	128.9	139.1	35.3	26.6	31.7	51.0	35.6	34.3	31.4	203.7

[a]) Arbitrary numbering.



40, 41, 12



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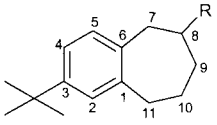

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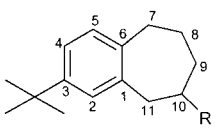


48, 51, 15

*(±)-6-(*tert*-Butyl)-1,2,3,4-tetrahydronaphthalene-2-carboxaldehyde* (**12**). In a *Parr* hydrogenation flask were placed **41** (1.12 g, 4.5 mmol), 5% Pd/C (0.1 g), K_2CO_3 (0.66 g, 4.8 mmol), H_2O (1.55 ml), and MeOH (3 ml). This mixture was shaken under H_2 (50 psi) for 6 h at r.t. The mixture was diluted with CH_2Cl_2 and filtered through *Celite®*. The aq. layer was separated, and the org. layer evaporated: crude product (1.03 g). GC: 45% of alcohol **44**, 22% of aldehyde **12**, and 26% of 6-(*tert*-butyl)-1,2,3,4-tetrahydro-2-methylnaphthalene.

This crude mixture was added at r.t. to a suspension of PCC (1.51 g, 7 mmol) and NaOAc (0.4 g, 5.5 mmol) in CH_2Cl_2 (15 ml). The mixture was stirred at r.t. for 3 h, diluted with Et_2O, filtered through *Celite®* and then through a short column of *Florisil®*, and evaporated (0.76 g). CC (SiO_2 (50 g), cyclohexane/Et_2O 9:1) gave a fraction, which was bulb-to-bulb distilled (oven temp. → 140°/0.2 mbar) **12** (0.41 g, 41% from **41**; purity 97%). Colorless oil. IR: 2954, 2707, 1720, 1610, 1503, 1435, 1361, 1271, 813, 717. ^{1}H-NMR: 9.78 (*d*, *J* = 1, 1 H); 7.18 (*dd*, *J* = 8, 2, 1 H); 7.11 (*d*, *J* = 2, 1 H); 7.08 (*d*, *J* = 8, 1 H); 2.97 (*m*, 2 H); 2.87 (*m*, 2 H); 2.68 (*m*, 1 H); 2.21 (*m*, 1 H); 1.78 (*m*, 1 H); 1.30 (*s*, 9 H). ^{13}C-NMR: *Table 6*. MS: 216 (36, M^+), 201 (100), 159 (14), 141 (10), 129 (20), 128 (18), 115 (14), 91 (10), 57 (14), 41 (8), 29 (8).

*(±)-7-(*tert*-Butyl)-1,2,3,4-tetrahydronaphthalene-2-carboxaldehyde* (**13**). To a soln. of **43** (0.86 g, 4 mmol) in MeOH (0.42 g) and H_2O (0.55 g) were added K_2CO_3 (0.55 g, 4 mmol) and 5% Pd/C (50 mg), and the mixture was shaken at r.t. in a *Parr* apparatus under H_2O (50 psi) during 22 h. The mixture was diluted with CH_2Cl_2 and filtered through *Celite®*; the aq. layer was separated and the org. layer evaporated: mixture (0.8 g). GC: 78% of aldehyde **13** and 10% of alcohol **45**. CC (SiO_2 (30 g), cyclohexane/Et_2O 4:1) gave a first fraction of **13** (0.49 g, 57%; purity > 99%), which solidified on standing. Crystallization from pentane at −30° afforded colorless crystals. M.p. 36–37°. IR: 2919, 2864, 2811, 2713, 1721, 1608, 1569, 1503, 1433, 1360, 1268, 924, 912, 819, 788, 723. ^{1}H-NMR: 9.78 (*d*, *J* = 1, 1 H); 7.17 (*dd*, *J* = 8, 2, 1 H); 7.15 (br. *s*, 1 H); 7.03 (*d*, *J* = 8, 1 H); 2.97 (*m*, 2 H); 2.83 (*m*, 2 H); 2.67 (*m*, 1 H); 2.20 (*m*, 1 H); 1.77 (*m*, 1 H); 1.30 (*s*, 9 H). ^{13}C-NMR: *Table 6*. MS: 216 (36, M^+), 201 (100), 159 (10), 155 (12), 141 (12), 129 (26), 128 (20), 115 (14), 57 (20), 41 (11), 29 (14).

7. *Compounds* **14** *and* **15**. *2-(*tert*-Butyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one* (**47**). To a stirred soln. of acid **46** (1.13 g, 4.8 mmol) in 1,2-dichloroethane (20 ml) at r.t. was added trifluoromethanesulfonic acid (*Fluka purum*; 1.5 ml, 2.58 g, 16.5 mmol), and the mixture was heated to reflux (84°, bath temp. → 90°) during 12 h. The cooled mixture was diluted with Et_2O, washed with 4% aq. NaOH soln. and brine, dried (Na_2SO_4), and evaporated: brown oil (0.77 g). Bulb-to-bulb distillation (oven temp. → 180°/0.3 mbar) gave a colorless oil (0.68 g, 61%). GC: 90% of **47** (eluted second on GC) and 4% of **48** (eluted first on GC). **47**: IR: 2960, 2860,

1665, 1595, 1450, 1400, 1360, 1290, 1260, 1100, 965, 830. ^{1}H-NMR: 7.70 (*d*, *J* = 8, 1 H); 7.32 (*dd*, *J* = 8, 2, 1 H); 7.19 (*d*, *J* = 2, 1 H); 2.94 (*m*, 2 H); 2.72 (*m*, 2 H); 1.92–1.78 (*m*, 4 H); 1.32 (*s*, 9 H). ^{13}C-NMR: *Table 6*. MS: 216 (26, M^+), 201 (100), 187 (9), 173 (18), 145 (8), 131 (22), 129 (10), 91 (12), 77 (5), 41 (7).

*3-(*tert*-Butyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one* (**48**). A stirred mixture of acid **46** (13.7 g, 57 mmol) and thionyl chloride (*Fluka*; 9.87 g, 6.02 ml, 83 mmol) was heated to 60° during 15 h. Vacuum (from the water-jet) was applied during 1 h, then the residue was dissolved in CH_2Cl_2 (100 ml) and cooled to 0–4° (ice-water bath). $AlCl_3$ (9.1 g, 68 mmol, 1.2 equiv.) was added portionwise during 10 min. (→ dark mixture). After 1 h, the mixture was allowed to reach r.t. during 1 h and then diluted with Et_2O and 5% aq. HCl soln. The org. layer was washed with brine (2 ×), sat. aq. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated: brownish oil (10.6 g). Bulb-to-bulb distillation (oven temp. → 150°/0.6 mbar) gave a mixture of **47** (eluted second on GC) and **48** (eluted first on GC) as a colorless oil (9.72 g, 75%; purity 94%; **47**/**48** 24 : 70). After three crystallizations from pentane at −30°, the major product **48** was obtained (1.68 g). Colorless crystals. M.p. 40° ([22a]: m.p. 40° (benzene)). IR: 2940, 2860, 1655, 1590, 1450, 1360, 1240, 1120, 1100, 965, 835. ^{1}H-NMR: 7.76 (*d*, *J* = 2, 1 H); 7.44 (*dd*, *J* = 8, 2, 1 H); 7.13 (*d*, *J* = 8, 1 H); 2.90 (*m*, 2 H); 2.73 (*m*, 2 H); 1.90–1.77 (*m*, 4 H); 1.32 (*s*, 9 H). ^{13}C-NMR: *Table 6*. MS: 216 (18, M^+), 201 (100), 187 (2), 173 (7), 157 (3), 145 (3), 131 (18), 129 (10), 115 (11), 91 (10), 77 (5), 41 (7).

*3-(*tert*-Butyl)-9-chloro-6,7-dihydro-5*H*-benzocycloheptene-8-carboxaldehyde* (**50**). To DMF (1.5 ml) at 0–4° (ice-water bath) was added $POCl_3$ (1 ml, 1.64 g, 11 mmol), and the mixture was stirred at 0–4° during 30 min. A soln. of **47** (0.36 g, 1.5 mmol; purity 94%) in DMF (2 ml) was added dropwise, and the mixture was heated to 70–80° (bath temp. → 83°) during 1 h (→ red). The mixture was diluted with Et_2O, and 2.5N (10%) aq. NaOH (10 ml) was added carefully (exothermicity). The org. layer was washed with H_2O, sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated: yellow oil (0.42 g), which solidified on standing. Bulb-to-bulb distillation (oven temp. → 200°/0.2 mbar) gave solid **50** (0.40 g). Crystallization from heptane (2 ml) at −30° afforded colorless crystals (0.30 g, 76%). M.p. 104–105°. IR ($CHCl_3$): 3000, 2950, 2850, 1650, 1590, 1570, 1280, 1200, 1150, 1035, 925, 720, 660. ^{1}H-NMR: 10.38 (*s*, 1 H); 7.60 (*d*, *J* = 8, 1 H); 7.40 (*dd*, *J* = 8, 2, 1 H); 7.25 (*d*, *J* = 2, 1 H); 2.61 (*t*, *J* = 7, 2 H); 2.24 (*m*, 2 H); 2.15 (*m*, 2 H); 1.35 (*s*, 9 H). ^{13}C-NMR: *Table 6*. MS: 262 (53, M^+), 247 (100), 234 (17), 227 (40), 219 (25), 211 (14), 203 (13), 197 (14), 191 (13), 183 (16), 171 (11), 165 (25), 153 (30), 141 (40), 128 (33), 115 (35), 102 (9), 91 (8), 77 (13), 57 (70), 41 (26), 29 (31).

*2-(*tert*-Butyl)-9-chloro-6,7-dihydro-5*H*-benzocycloheptene-8-carboxaldehyde* (**51**). To DMF (3 ml) at 0–4° (ice-water bath) was added dropwise $POCl_3$ (3.44 g, 2.09 ml, 22.5 mmol), and the mixture was stirred at r.t. during 30 min. Ketone **48** (1.63 g, 7.5 mmol) was added and the mixture heated to 70–80° (bath temp.). After *ca.* 15 min, an exothermic reaction took place (temp. → 95°) and the mixture became deep red. After 15 min, the temp. had decreased to 70–80° and the mixture solidified. It was cooled to 40° and covered with Et_2O (20 ml). Then 2.5N (10%) aq. NaOH (10 ml) was added dropwise and cautiously (exothermicity). The org. layer was washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4) and evaporated: red syrup (1.84 g). Bulb-to-bulb distillation (oven temp. → 180°/0.3 mbar) gave solid **51** (1.78 g, 88%; purity 97%). Crystallization from heptane (5 ml) at −30° gave colorless crystals (1.04 g). M.p. 67–69°. IR ($CHCl_3$): 2950, 2850, 1655, 1570, 1280, 1240, 1155, 1020, 950, 890, 835, 640. ^{1}H-NMR: 10.39 (*s*, 1 H); 7.67 (*d*, *J* = 2, 1 H); 7.40 (*dd*, *J* = 8, 2, 1 H); 7.18 (*d*, *J* = 8, 1 H); 2.58 (*t*, *J* = 7, 2 H); 2.23 (*m*, 2 H); 2.12 (*m*, 2 H); 1.35 (*s*, 9 H). ^{13}C-NMR: *Table 6*. MS: 262 (33, M^+), 247 (100), 234 (12), 227 (13), 219 (10), 211 (6), 205 (5), 197 (8), 191 (5), 183 (9), 171 (5), 165 (16), 153 (19), 141 (28), 128 (24), 115 (24), 102 (7), 91 (5), 77 (11), 57 (40), 41 (20), 29 (18).

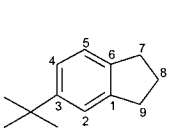
*(±)-2-(*tert*-Butyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-6-carboxaldehyde* (**14**). To a soln. of **50** (0.25 g, 0.9 mmol) in boiling MeOH (10 ml) were added H_2O (2 ml) (some product precipitated on cooling), K_2CO_3 (0.55 g, 4 mmol), and 5% Pd/C (200 mg, 0.1 mmol). The mixture was hydrogenated at r.t./60 psi (*ca.* 4 bar) in the *Parr* device during 4 h. The mixture was filtered through a short column of *Celite*®, the latter rinsed with MeOH and AcOEt, and the soln. diluted with Et_2O, washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated: colorless syrup (0.25 g) containing 20% of **14** and 74% of alcohol **52** (by GC). A soln. of this crude in CH_2Cl_2 (5 ml) was added to a stirred suspension of PCC (430 mg, 2 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred at r.t. during 2 h, diluted with Et_2O, filtered through a short column of *Florisil*®, the latter rinsed with Et_2O, and the soln. evaporated: colorless syrup (0.20 g). Bulb-to-bulb distillation (oven temp. → 190°/0.2 mbar) gave **14** (0.18 g, 80%; purity 92%). Syrup, which solidified on standing. Crystallization from pentane (1 ml) at −30° afforded colorless crystals. M.p. 63–64°. IR ($CHCl_3$): 2950, 2920, 2840, 2700, 1715, 1600, 1495, 1435, 1355, 1265, 1215, 1115, 885, 810. ^{1}H-NMR: 9.68 (*s*, 1 H); 7.14 (*dd*, *J* = 8, 2, 1 H); 7.12 (*d*, *J* = 2, 1 H); 7.09 (*d*, *J* = 8, 1 H); 3.11 (*m*, 1 H); 2.80 (*m*, 3 H); 2.30 (*m*, 2 H); 2.05 (*m*, 1 H); 1.68 (*m*, 1 H); 1.50 (*m*, 1 H); 1.30 (*s*, 9 H). ^{13}C-NMR: *Table 6*. MS: 230 (20, M^+), 215 (100), 197 (6), 184 (12), 173 (6), 169 (9), 155 (7), 145 (13), 141 (9), 128 (18), 115 (15), 91 (11), 77 (5), 57 (17), 41 (12), 29 (12).

*(±)-3-(*tert*-Butyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene-6-carboxaldehyde* (**15**). To a soln. of **51** (0.98 g, 3.6 mmol) in MeOH (10 ml) were added H_2O (2 ml), K_2CO_3 (0.55 g, 4 mmol), and 10% Pd/C (100 mg, 0.1 mmol), and the mixture was hydrogenated in the *Parr* device at r.t./50 psi during 15 h. The mixture was filtered through paper and *Celite*® and the latter rinsed with Et_2O. The org. phase was washed with sat. aq. $NaHCO_3$ soln., dried (Na_2SO_4), and evaporated: pink oil (0.9 g) containing 95% of alcohol **53** (by GC). A soln. of this crude in CH_2Cl_2 (10 ml) was added dropwise to a stirred suspension of PCC (1.07 g, 5 mmol) in CH_2Cl_2 (20 ml) at r.t., and the mixture was stirred at r.t. during 2 h. The mixture was diluted with Et_2O (150 ml) and filtered through a short column of *Florisil*®, the latter rinsed with Et_2O, and the soln. evaporated: yellowish oil (0.75 g). Bulb-to-bulb distillation (oven temp. → 180°/0.3 mbar) gave **15** (0.70 g, 82%; purity 97%). Colorless oil. IR: 2960, 2920, 2840, 2700, 1720, 1600, 1495, 1435, 1355, 1265, 1200, 1120, 820. ^{1}H-NMR: 9.70 (*s*, 1 H); 7.18 (*d*, *J* = 2, 1 H); 7.15 (*dd*, *J* = 8, 2, 1 H); 7.03 (*d*, *J* = 8, 1 H); 3.13 (*m*, 1 H); 2.83 (*m*, 1 H); 2.77 (*m*, 2 H); 2.31 (*m*, 2 H); 2.04 (*m*, 1 H); 1.67 (*m*, 1 H); 1.48 (*m*, 1 H); 1.30 (*s*, 9 H). ^{13}C-NMR: *Table 6*. MS: 230 (21, M^+), 215 (100), 197 (6), 184 (15), 169 (10), 155 (8), 145 (14), 128 (17), 115 (14), 105 (5), 91 (10), 77 (5), 57 (15), 41 (14), 29 (15).

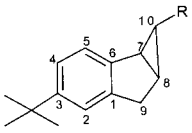
Table 7. *^{13}C-NMR Chemical Shifts* (δ [ppm] relative to $SiMe_4$) *of Compounds in* Scheme 5 ($CDCl_3$ solutions)[a])

	R	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	Me_3C	Me_3C	C(R)	$MeCH_2O$	$MeCH_2O$
54		142.2	121.7	151.7	124.0	123.7	143.3	76.2	36.1	29.9	–	34.7	31.5	–	–	–
55		144.8	120.9	150.0	125.6	124.4	140.3	29.3	36.1	76.4	–	34.7	31.6	–	–	–
56		143.7	120.8	147.7	123.3	120.3	142.2	131.7	133.6	39.1	–	34.6	31.7	–	–	–
57		144.9	117.9	149.4	121.7	123.2	140.8	38.6	134.2	132.3	–	34.6	31.7	–	–	–
58	COOEt	141.8	122.2	149.6	123.4	123.3	140.7	34.0	26.6	35.4	30.8	34.5	31.5	172.8	60.4	14.3
59	COOEt	144.3	121.0	149.5	123.1	124.1	137.2	31.1	23.5	32.6	25.2	34.5	31.5	169.8	59.8	13.8
60	COOEt	143.6	120.9	149.6	123.5	124.7	138.8	34.9	26.7	34.6	30.8	34.6	31.6	172.8	60.5	14.3
61	COOEt	139.9	121.6	149.1	123.6	123.5	141.3	32.0	23.4	31.5	25.0	34.5	31.6	169.6	59.8	13.9
62	CH_2OH	142.3[b])	122.2	148.8	123.0	122.8	142.4[b])	29.0	21.5	35.2	32.1	34.5	31.6	65.2	–	–
63	CH_2OH	145.1	120.4	149.2	122.7	124.7	139.4	34.7	21.6	29.6	32.1	34.5	31.6	65.2	–	–
64	CH_2OH	144.1	123.4	149.1	120.9	123.7	138.4	27.9	20.7	31.8	24.2	34.5	31.6	58.0	–	–
65	CH_2OH	141.4	121.2	149.6	123.0	123.4	141.0	31.2	20.8	28.5	24.1	34.5	31.6	57.9	–	–
16	CHO	141.6[b])	122.3	149.9	123.6	123.3	140.0[b])	35.1	27.5	35.3	40.5	34.6	31.5	199.3	–	–
17	CHO	138.6	120.9	149.9	123.8	124.8	142.9	34.9	27.6	35.6	40.6	34.6	31.5	199.3	–	–
18	CHO	142.5	121.4	150.4	124.2	124.3	136.8	34.0	27.4	33.3	32.5	34.6	31.5	203.1	–	–
19	CHO	139.6	121.6	150.5	124.2	123.9	139.4	32.7	27.4	34.6	32.4	34.6	31.5	203.1	–	–

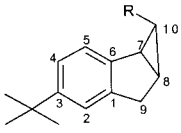
[a]) Arbitrary numbering. [b]) Interchangeable.



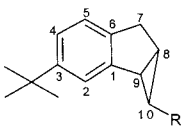
54, 55, 56, 57



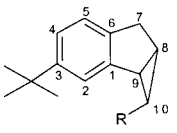
58, 62, 16



59, 64, 18



60, 63, 17



61, 65, 19

8. *Compounds* **16**–**19**. *(±)-5-(*tert*-Butyl)-2,3-dihydro-1*H*-inden-1-ol* (**54**). According to the *G.P. A*, 5-(*tert*-butyl)-2,3-dihydro-1*H*-inden-1-one (**22**; 30.08 g, 160 mmol) was converted to crude **54** (24.3 g, solid). Crystallization from petroleum ether (50–70°) at −30° gave colorless crystals (22.5 g, 72%; purity 98%). M.p. 88–90°. IR (solid): 3185 (br.), 2952, 2840, 1440, 1363, 1215, 1083, 1060, 887, 827. ^{1}H-NMR: 7.35 (*d*, *J* = 8, 1 H); 7.29 (*d*, *J* = 2, 1 H); 7.28 (*dd*, *J* = 8, 2, 1 H); 5.21 (*m*, 1 H); 3.05 (*m*, 1 H); 2.80 (*m*, 1 H); 2.48 (*m*, 1 H); 1.94 (*m*, 1 H); 1.80 (br., OH); 1.32 (*s*, 9 H). ^{13}C-NMR: *Table 7*. MS: 190 (23, M^+), 175 (100), 157 (11), 133 (25), 131 (28), 115 (12), 105 (5), 91 (9), 77 (5), 57 (3), 41 (4).

*(±)-6-(*tert*-Butyl)-2,3-dihydro-1*H*-inden-1-ol* (**55**). According to the *G.P. A*, 6-(*tert*-butyl)-2,3-dihydro-1*H*-inden-1-one (**32**; 8.83 g, 45.6 mmol; purity 97%) was converted to crude **55** (8.83 g, solid). Two crystallizations

from Et_2O/pentane at $-30°$ afforded colorless crystals (7.81 g, 90%). M.p. 77.5–78°. IR: 3560, 3400 (br.), 2950, 2850, 1480, 1355, 1255, 1075, 1035, 950, 820. ^{1}H-NMR: 7.45 (*d*, *J* = 2, 1 H); 7.30 (*dd*, *J* = 8, 2, 1 H); 7.17 (*d*, *J* = 8, 1 H); 5.18 (*m*, 1 H); 2.99 (*m*, 1 H); 2.75 (*m*, 1 H); 2.46 (*m*, 1 H); 2.08 (br., OH); 1.91 (*m*, 1 H); 1.32 (*s*, 9 H). ^{13}C-NMR: *Table 7*. MS: 190 (20, M^+), 175 (100), 173 (2), 172 (2), 157 (14), 131 (30), 129 (13), 115 (14), 91 (10), 77 (6), 57 (4), 41 (5).

*6-(*tert-*Butyl)-1*H*-indene* (**56**). To **54** (1.9 g, 10 mmol) was added $KHSO_4$ (68 mg, 0.5 mmol), and the mixture was heated in the bulb-to-bulb oven to 160° (oven temp.) at 100 mbar. After 0.5 h, no more bubbling was observed; the vacuum was lowered to 25 mbar and the oven temp. raised to 175°. After 0.5 h, nearly all product had distilled into the bulb just outside of the oven: **56** (1.65 g, 96%). IR: 3060, 2957, 2902, 1477, 1361, 1261, 868, 823, 749, 690. ^{1}H-NMR: 7.52 (*d*, *J* = 2, 1 H); 7.33 (*d*, *J* = 8, 1 H); 7.30 (*dd*, *J* = 8, 2, 1 H); 6.84 (*m*, 1 H); 6.48 (*m*, 1 H); 3.37 (br. *s*, 2 H); 1.35 (*s*, 9 H). ^{13}C-NMR: *Table 7*. MS: 172 (32, M^+), 157 (100), 142 (12), 129 (26), 115 (19), 91 (2), 77 (2), 57 (3), 41 (2).

*5-(*tert-*Butyl)-1*H*-indene* (**57**). To **55** (0.97 g, 5 mmol) was added $KHSO_4$ (35 mg, 0.25 mmol), and the mixture was heated in the bulb-to-bulb oven to 90–100° (oven temp.) at 0.2 mbar during 0.5 h. The product was collected in the bulb just outside of the oven: **57** (0.7 g, 78%; purity 96% (+4% of **56**)). Colorless liquid. IR: 3062, 2957, 2902, 1476, 1391, 1361, 1262, 944, 879, 813, 701. ^{1}H-NMR: 7.45 (*d*, *J* = 2, 1 H); 7.39 (*d*, *J* = 8, 1 H); 7.23 (*dd*, *J* = 8, 2, 1 H); 6.86 (*m*, 1 H); 6.52 (*m*, 1 H); 3.33 (br. *s*, 2 H); 1.35 (s, 9 H). ^{13}C-NMR: *Table 7*. MS: 172 (32, M^+), 157 (100), 142 (13), 129 (28), 115 (22), 91 (2), 77 (2), 57 (4), 41 (2).

*Ethyl (1*RS*,1a*RS*,6a*SR*)-4-(*tert-*Butyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate* (**58**; '*exo*') *and Ethyl (1*RS*,1a*SR*,6a*RS*)-4-(*tert-*Butyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate* (**59**; '*endo*'). To a stirred soln. of **56** (1.65 g, 9.6 mmol) in cyclohexane (20 ml) at r.t. was added $CuSO_4$ (25 mg, 0.15 mmol) and 20 drops of a soln. of ethyl diazoacetate *(Fluka purum*; 6.0 g, 52 mmol) in cyclohexane (15 ml). The mixture was then heated to 75–80° (bath temp. → 90°), and the rest of the reagent soln. was added dropwise during 1 h (→ N_2 evolution). At the end of the addition, no more **56** was detectable by GC. The mixture was diluted with Et_2O, washed with brine (2×), dried (Na_2SO_4), and evaporated: brown oil (6 g) containing 6% of diethyl maleate, 13% of diethyl fumarate, 20% of '*endo*'-ester **59**, and 55% of '*exo*'-ester **58** (by GC). Bulb-to-bulb distillation (oven temp. → 95°/0.1 mbar) gave a first fraction (1.73 g) of volatiles; raising the oven temp. to 180° gave a second fraction containing the desired products as a colorless oil (2.51 g, 97%; purity > 99%; **59**/**58** 26:74). CC (SiO_2 (200 g), cyclohexane/Et_2O 19:1) gave as a first fraction **58** (1.26 g, 48%). IR: 2958, 1718, 1382, 1303, 1264, 1154, 1038, 822. ^{1}H-NMR: 7.26 (*d*, *J* = 8, 1 H); 7.19 (*d*, *J* = 2, 1 H); 7.17 (*dd*, *J* = 8, 2, 1 H); 4.13 (*q*, *J* = 7, 2 H); 3.26 (*dd*, *J* = 17, 7, 1 H); 3.02 (*dd*, *J* = 17, 2, 1 H); 2.91 (*m*, 1 H); 2.42 (*m*, 1 H); 1.28 (*s*, 9 H); 1.25 (*t*, *J* = 7, 3 H); 1.22 (*m*, 1 H). ^{13}C-NMR: *Table 7*. MS: 258 (81, M^+), 243 (99), 229 (61), 213 (24), 185 (25), 169 (45), 155 (35), 129 (44), 115 (18), 57 (100), 41 (8).

After a second (mixed) fraction, a third fraction was collected, which contained **59** (0.1 g, 4%; purity 98%). Similar rechromatography of the second (mixed) fraction afforded an additional crop of **59** (0.31 g, 11%; purity 95%). IR: 2960, 1725, 1460, 1380, 1360, 1265, 1180, 1140, 1035, 825. ^{1}H-NMR: 7.22 (*d*, *J* = 8, 1 H); 7.16 (*d*, *J* = 2, 1 H); 7.14 (*dd*, *J* = 8, 2, 1 H); 3.81 (*m*, 2 H); 3.32 (*dd*, *J* = 17, 2, 1 H); 3.19 (*dd*, *J* = 17, 7, 1 H); 2.89 (*m*, 1 H); 2.23 (*m*, 1 H); 1.99 (*t*, *J* = 8, 1 H); 1.28 (*s*, 9 H); 0.86 (*t*, *J* = 7, 3 H). ^{13}C-NMR: *Table 7*. MS: 258 (35, M^+), 243 (43), 229 (26), 213 (12), 185 (12), 169 (22), 155 (17), 141 (16), 129 (25), 57 (100), 41 (9).

*Ethyl (1*RS*,1a*RS*,6a*SR*)-3-(*tert-*Butyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate* (**60**; '*exo*') *and Ethyl (1*RS*,1a*SR*,6a*RS*)-3-(*tert-*Butyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxylate* (**61**; '*endo*'). As described for **58**/**59**, with **57** (0.5 g, 2.9 mmol), cyclohexane (10 ml), $CuSO_4$ (16 mg, 0.1 mmol), and 20 drops of ethyl diazoacetate *(Fluka purum*; 2 g, 17 mmol) in cyclohexane (10 ml); addition of the rest of the reagent soln. within 15 min. Workup (washing with H_2O and brine (2×)) gave a brown oil (0.87 g) containing 8% of diethyl maleate, 8% of diethyl fumarate, 20% of '*endo*'-ester **61**, and 54% of '*exo*'-ester **60** (by GC). Bulb-to-bulb distillation (oven temp. → 100°/0.3 mbar) gave a first fraction (0.74 g) containing the volatiles. The oven temp. was raised to 180° to afford the desired products as a colorless oil (0.7 g, 90%; purity 95%; **61**/**60** 24:71). CC (SiO_2 (100 g), cyclohexane/Et_2O 9:1) gave as a 1st fraction **60** (0.34 g, 41%; purity 94%). IR: 2958, 2905, 2867, 1718, 1397, 1380, 1291, 1224, 1172, 1155, 1038, 818. ^{1}H-NMR: 7.38 (*d*, *J* = 2, 1 H); 7.16 (*dd*, *J* = 8, 2, 1 H); 7.08 (*d*, *J* = 8, 1 H); 4.14 (*q*, *J* = 7, 2 H); 3.22 (*dd*, *J* = 17, 6, 1 H); 3.00 (*dd*, *J* = 17, 2, 1 H); 2.93 (*m*, 1 H); 2.42 (*m*, 1 H); 1.30 (*s*, 9 H); 1.26 (*t*, *J* = 7, 3 H); 1.22 (*m*, 1 H). ^{13}C-NMR: *Table 7*. MS: 258 (37, M^+), 243 (43), 229 (31), 213 (12), 185 (13), 169 (24), 155 (20), 129 (31), 115 (11), 85 (8), 57 (100), 41 (10).

After a second (mixed) fraction (0.23 g), a third fraction was collected, which contained **61** (0.03 g, 3%; purity 94%). IR: 2955, 1727, 1381, 1362, 1264, 1134, 1035, 814. ^{1}H-NMR: 7.33 (*d*, *J* = 2, 1 H); 7.15 (*dd*, *J* = 8, 2, 1 H); 7 05 (*d*, *J* = 8, 1 H); 3.80 (*m*, 2 H); 3.32 (*dd*, *J* = 17, 2, 1 H); 3.15 (*dd*, *J* = 17, 7, 1 H); 2.91 (*m*, 1 H); 2.23

(*m*, 1 H); 2.00 (*t*, *J* = 8, 1 H); 1.29 (*s*, 9 H); 0.86 (*t*, *J* = 7, 3 H). ^{13}C-NMR: *Table 7*. IR: 258 (34, M^+), 243 (38), 229 (24), 213 (12), 185 (11), 169 (22), 155 (20), 141 (16), 129 (30), 57 (100), 41 (10).

*(1*RS*,1a*RS*,6a*SR*)-4-(*tert-*Butyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-methanol* (**62**). Following the *G.P. A*, **58** (2.21 g, 8.6 mmol) was converted to crude **62** (1.94 g). Bulb-to-bulb distillation (oven temp. → 160°/0.2 mbar) afforded **62** (1.8 g, 97%; purity > 99%). Colorless viscous syrup. IR: 3310 (br.), 2950, 2880, 2840, 1460, 1355, 1260, 1100, 1025, 825. ^{1}H-NMR: 7.21 (*d*, *J* = 8, 1 H); 7.16 (*d*, *J* = 2, 1 H); 7.14 (*dd*, *J* = 8, 2, 1 H); 3.55 (*d*, *J* = 7, 2 H); 3.18 (*dd*, *J* = 17, 7, 1 H); 2.95 (*d*, *J* = 17, 1 H); 2.29 (*m*, 1 H); 1.76 (*m*, 1 H); 1.54 (br., OH); 1.28 (*s*, 9 H); 0.79 (*m*, 1 H). ^{13}C-NMR: *Table 7*. MS: 216 (45, M^+), 201 (100), 185 (45), 170 (16), 155 (31), 141 (27), 129 (44), 115 (22), 91 (6), 57 (54), 41 (7).

*(1*RS*,1a*RS*,6a*SR*)-3-(*tert-*Butyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-methanol* (**63**). Following the *G.P. A*, **60** (3.04 g, 11.8 mmol) was converted to crude **63** (3.2 g). Bulb-to-bulb distillation (oven temp. → 175°/0.3 mbar) afforded **63** (2.56 g, 98%; purity 98%). Colorless oil. IR: 3300 (br.), 2940, 2890, 2840, 1480, 1350, 1255, 1100, 1025, 815. ^{1}H-NMR: 7.34 (*d*, *J* = 2, 1 H); 7.12 (*dd*, *J* = 8, 2, 1 H); 7.06 (*d*, *J* = 8, 1 H); 3.57 (*d*, *J* = 7, 2 H); 3.14 (*dd*, *J* = 17, 7, 1 H); 2.93 (*d*, *J* = 17, 1 H); 2.32 (*m*, 1 H); 1.77 (*m*, 1 H); 1.53 (br., OH); 1.31 (*s*, 9 H); 0.80 (*m*, 1 H). ^{13}C-NMR: *Table 7*. MS: 216 (52, M^+), 201 (100), 185 (62), 170 (12), 155 (32), 141 (33), 129 (56), 115 (26), 91 (7), 57 (66), 41 (9).

*(1*RS*,1a*SR*,6a*RS*)-4-(*tert-*Butyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-methanol* (**64**). Following the *G.P. A*, **59** (0.44 g, 1.7 mmol) was converted to crude **64** (0.36 g). Bulb-to-bulb distillation (oven temp. → 175°/0.25 mbar) gave **64** (0.35 g, 99%). Colorless oil. IR: 3316 (br.), 2958, 2904, 1489, 1360, 1266, 1014, 825. ^{1}H-NMR: 7.20 (*d*, *J* = 8, 1 H); 7.14 (*dd*, *J* = 8, 2, 1 H); 7.12 (*d*, *J* = 2, 1 H); 3.30 (*dd*, *J* = 11, 6.5, 1 H); 3.14 (*m*, 2 H); 2.82 (*d*, *J* = 17, 1 H); 2.60 (*m*, 1 H); 1.98 (*m*, 1 H); 1.45 (*m*, 1 H); 1.28 (*s*, 9 H); 1.20 (br., OH). ^{13}C-NMR: *Table 7*. MS: 216 (30, M^+), 201 (90), 185 (35), 170 (11), 155 (24), 141 (22), 129 (37), 115 (17), 91 (5), 57 (100), 41 (11).

*(1*RS*,1a*SR*,6a*RS*)-3-(*tert-*Butyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-methanol* (**65**). Following the *G.P. A*, **61** (0.8 g, 2.9 mmol; purity 94%) was converted to crude **65** (0.72 g). Bulb-to-bulb distillation (oven temp. → 175°/0.25 mbar) afforded **65** (0.62 g, 90%; purity 91%). Colorless oil. IR: 3311 (br.), 2957, 2902, 1490, 1361, 1262, 1014, 816. ^{1}H-NMR: 7.32 (*d*, *J* = 2, 1 H); 7.13 (*dd*, *J* = 8, 2, 1 H); 7.02 (*d*, *J* = 8, 1 H); 3.29 (*m*, 1 H); 3.17 (*m*, 1 H); 3.11 (*dd*, *J* = 17, 6, 1 H); 2.80 (*d*, *J* = 17, 1 H); 2.62 (*m*, 1 H); 1.99 (*m*, 1 H); 1.47 (*m*, 1 H); 1.30 (*s*, 9 H); 1.10 (br., OH). ^{13}C-NMR: *Table 7*. MS: 216 (18, M^+), 201 (47), 185 (27), 170 (4), 155 (17), 141 (19), 129 (33), 115 (16), 91 (4), 57 (100), 41 (11).

*(1*RS*,1a*RS*,6a*SR*)-4-(*tert-*Butyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxaldehyde* (**16**). Following the *G.P. B*, **62** (1.8 g, 8.3 mmol) was converted to crude **16** (1.57 g). Bulb-to-bulb distillation (oven temp. → 140°/0.25 mbar) afforded **16** (1.5 g, 84%). Colorless solid. Crystallization from pentane (2 ml) at −30° gave colorless crystals, M.p. 68–69°. IR: 3020, 2960, 2900, 2860, 2820, 2710, 1695, 1485, 1360, 1265, 1110, 1010, 890. ^{1}H-NMR: 9.42 (*d*, *J* = 4, 1 H); 7.26 (*d*, *J* = 8, 1 H); 7.22 (*d*, *J* = 2, 1 H); 7.19 (*dd*, *J* = 8, 2, 1 H); 3.31 (*dd*, *J* = 17, 6, 1 H); 3.07 (*m*, 1 H); 3.04 (*d*, *J* = 17, 1 H); 2.58 (*m*, 1 H); 1.52 (*m*, 1 H); 1.29 (*s*, 9 H). ^{13}C-NMR: *Table 7*. MS: 214 (36, M^+), 199 (97), 185 (100), 170 (25), 155 (42), 141 (33), 129 (65), 115 (27), 91 (7), 57 (96), 41 (12).

*(1*RS*,1a*RS*,6a*SR*)-3-(*tert-*Butyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxaldehyde* (**17**). Following the *G.P. B*, **63** (2.53 g, 11.7 mmol) was converted to **17** (2.02 g), which was bulb-to-bulb distilled (oven temp. → 140°/0.3 mbar): **17** (1.98 g; purity 95%). CC (SiO_2 (200 g), cyclohexane/Et_2O 4:1), followed by bulb-to-bulb distillation (oven temp. → 140°/0.2 mbar) afforded purified **17** (1.8 g, 71%). This material was dissolved in pentane (3 ml) and left at −30° during 7 days, whereby a solid had deposited. The cold solvent was removed and the solid allowed to reach r.t. under vacuum, whereby it melted to give pure **17** (1.01 g). IR: 3020, 3000, 2960, 2900, 2880, 2820, 2710, 1695, 1485, 1365, 1260, 1110, 1015, 920, 820. ^{1}H-NMR: 9.44 (*d*, *J* = 4, 1 H); 7.38 (*d*, *J* = 2, 1 H); 7.20 (*dd*, *J* = 8, 2, 1 H); 7.11 (*d*, *J* = 8, 1 H); 3.27 (*dd*, *J* = 17, 6, 1 H); 3.09 (*m*, 1 H); 3.03 (*d*, *J* = 17, 1 H); 2.59 (*m*, 1 H); 1.53 (*m*, 1 H); 1.31 (*s*, 9 H). ^{13}C-NMR: *Table 7*. MS: 214 (55, M^+), 199 (100), 185 (72), 171 (16), 155 (27), 141 (30), 129 (62), 115 (26), 91 (7), 57 (85), 41 (11).

*(1*RS*,1a*SR*,6a*RS*)-4-(*tert-*Butyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxaldehyde* (**18**). Following the *G.P. B*, **64** (0.36 g, 1.7 mmol) was converted to crude **18** (0.26 g). Bulb-to-bulb distillation (oven temp. → 160°/0.25 mbar) afforded **18** (0.25 g, 53%; purity 81%). Colorless oil. CC (SiO_2 (30 g), cyclohexane/Et_2O 4:1) gave purified product (0.24 g), which solidified on standing. Crystallization from pentane at −30° afforded colorless crystals. M.p. 67–68°. IR: 2958, 2913, 2866, 1693, 1490, 1466, 1438, 1362, 1267, 1190, 1065, 971, 924, 834. ^{1}H-NMR: 8.56 (*d*, *J* = 7, 1 H); 7.27 (*d*, *J* = 8, 1 H); 7.23 (*dd*, *J* = 8, 2, 1 H); 7.22 (*d*, *J* = 8, 1 H); 3.39 (*dd*, *J* = 17, 6, 1 H); 3.22 (*d*, *J* = 17, 1 H); 3.11 (*m*, 1 H); 2.52 (*m*, 1 H); 1.88 (*m*, 1 H); 1.30 (*s*, 9 H). ^{13}C-NMR: *Table 7*. MS: 214 (18, M^+), 199 (37), 185 (41), 170 (9), 155 (15), 141 (12), 129 (27), 115 (11), 57 (100), 41 (8).

*(1*RS*,1a*SR*,6a*RS*)-3-(tert-Butyl)-1,1a,6,6a-tetrahydrocyclopropa[*a*]indene-1-carboxaldehyde* (**19**). Following the *G.P. B*, **65** (0.55 g, 2.3 mmol; purity 91%) gave crude **19** (0.5 g, 95%; purity 93%). Yellowish solid. Two

crystallizations from Et_2O at $-30°$ afforded colorless crystals. M.p. 89–90°. IR: 2948, 2902, 1689, 1487, 1359, 1194, 1068, 971, 927, 889, 829, 817, 774. ^{1}H-NMR: 8.55 (*d*, *J* = 7, 1 H); 7.38 (*d*, *J* = 2, 1 H); 7.22 (*dd*, *J* = 8, 2, 1 H); 7.11 (*d*, *J* = 8, 1 H); 3.35 (*dd*, *J* = 17, 6, 1 H); 3.20 (*d*, *J* = 17, 1 H); 3.13 (*m*, 1 H); 2.53 (*m*, 1 H); 1.90 (*m*, 1 H); 1.30 (*s*, 9 H). ^{13}C-NMR: *Table 7*. MS: 214 (60, M^+), 199 (100), 185 (75), 171 (14), 155 (27), 141 (28), 129 (60), 115 (25), 57 (75), 41 (11).

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