Conformational Analysis and Selection of Odor-Active Conformers: Synthesis of Molecules Designed for the Lily-of-the-Valley(Muguet)-Type Odor

by **Fumiko Yoshii**[a])*), **Tomoko Nakamura**[b]), **Shuichi Hirono**[c]), **Yumiko Shimizu**[b]),**Takashi Hoshi**[b]), **Masayoshi Ando**[b]), and **Hisahiro Hagiwara**[a])*

[a]) Graduate School of Science and Technology, Niigata University, 8050 Ikarashi 2 nocho, Niigata 950-2181, Japan

[b]) Faculty of Engineering, Niigata University, 8050 Ikarashi 2 nocho, Niigata 950-2181, Japan

[c]) Division of Physical Chemistry for Drug Design, School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-0072, Japan

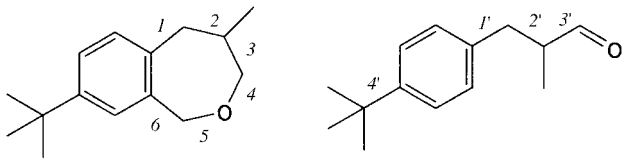
The selection of odor-active conformers and the construction of a model for a targeted odor type, *i.e.*, for the lily-of-the-valley odor, were examined. The disagreement of the odors of 1,3,4,5-tetrahydro-2-benzoxepin derivative **1** and 3-[4-(*tert*-butyl)phenyl]-2-methylpropanal (**2**) is discussed in terms of their stable conformers. The conformer active for the lily-of-the-valley odor was investigated by conformational analyses of several related compounds. Based on the integrated model consisting of the assumed active conformers (*Fig. 5*), compounds anticipated to possess the lily-of-the-valley odor were designed and synthesized. The odor of synthetic 7-(*tert*-butyl)-1,2,4,5-tetrahydro-3*H*-benzocyclohepten-3-one (**8**) and 3-[4-(*tert*-butyl)phenyl]cyclopentanone (**13**) were evaluated by perfumers to have a floral odor and to recall the lily-of-the-valley and lilac odors, respectively. Our methodology to design new odoriferous compounds, based on conformational analysis, selection of odor-active conformers, and construction of a model, proved to be satisfactory.

1. Introduction. – Recent developments of odorant chemistry promoted a study for structure-odor relationships (SOR) as described in comprehensive reviews by *Rossiter* and by *Chastrette* [1][2]. At present, the ultimate goal of SOR studies is beyond our reach, because odor types or odor categories are numerous, and understanding as well as data concerning odor are still limited. However, elucidation of relationships between odorant property and an odor type is significant to predict odor-reception mechanism and to give indications for the synthesis of odoriferous compounds of current interest.

In triggering the specific odor sensations in human beings, it was assumed that 'an odor-active conformer' of the odoriferous molecule can fit and interact with an odor-specific receptor protein. It is highly likely that there is a type of specific olfactory receptor protein that specifically relates to the lily-of-the-valley-type odorant. This assumption is based on the results by *Buck* and *Axel* [3] that putative olfactory receptor proteins exist, and by *Raming et al.* that lyral (=4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-1-carbaldehyde), which has the odor of the lily of the valley, increases the amount of the second messenger InsP3 at the OR5 putative olfactory receptor protein [4]. Molecular modeling of the interaction between lyral and its receptor in the OR5 has been carried out by *Singer* and *Shepherd* [5], though specific interactions between receptor proteins and the odorant have not yet been established. Therefore, it would be promising to find the odor-active conformer of the lily-of-the-valley odorant, to

construct a working model for odorants that have this specific odor, and to apply this model to the design of new compounds.

Skouroumounis and *Winter* synthesized the 1,3,4,5-tetrahydro-2-benzoxepin derivative **1** as a conformationally restricted analogue of 3-[4-(*tert*-butyl)phenyl]-2-methylpropanal (**2**; *Lily Aldehyde*®, trade name by *Soda Aromatic Co., Ltd.*) with the aim to develop new lily-of-the-valley-odor compounds [6] (*Fig. 1*). They examined the relevance of the compact folded conformation of **2** to the lily-of-the-valley odor. However, it was found that synthetic benzoxepin **1** had not even the slightest lily-of-the-valley odor [6].



1 (*R*) **2** (*R*)

Fig. 1. *1,3,4,5-Tetrahydro-2-benzoxepin derivative* **1** *and* LilyAldehyde® (**2**). Benzoxepin **1** is a conformationally restricted analogue of aldehyde **2**. The dihedral angles of the numbered bonds were changed for conformational analysis.

In this work, the conformational analyses of benzoxepin **1** and aldehyde **2** were carried out to re-examine this disagreement of the odor of **2** and of the proposed conformationally restricted **1**. Assumed conformers active for the lily-of-the-valley odor were selected by conformational analyses of related compounds. Based on the thus obtained model consisting of the odor-active conformers, we designed new odoriferous compounds, synthesized them, and evaluated their olfactory properties.

2. Results and Discussion. – 2.1. *Computational Analysis.* The (*R*)-aldehyde **2** was constructed as an initial structure for computational analysis, because it has been reported that the odor of the (−)-(*R*)-enantiomer is stronger than that of the (*S*)-enantiomer [7], or that the (*S*)-enantiomer is odorless [8]. The (*R*)-benzoxepin **1** was also constructed for similar reasons. Conformational analysis was then carried out by rotating the dihedral angles of bonds *1*, *2*, *3*, *4*, *5*, and *6* in benzoxepin **1** and bonds *1′*, *2′*, *3′*, and *4′* in aldehyde **2** (*Fig. 1*). The dihedral angle of bond *4′* in aldehyde **2** was rotated for further comparison with other compounds in this work. The root-mean-square (r.m.s.) threshold conditions of conformational analysis for aldehyde **2** and benzoxepin **1** were 0.3 and 0.1 Å, respectively.

As a result, 14 conformers of benzoxepin **1** and 22 conformers of aldehyde **2** were selected (see *Exper. Part*). The features of the conformers are depicted in *Fig. 2* by the total energy [kcal/mol] *vs.* molecular size [Å] as estimated by the longest side length of a circumscribed box (LLCB). The range of LLCB of the selected conformers of aldehyde **2** and benzoxepin **1** were almost the same. As seen in these graphs, there were two different groups of conformers, one being rather short (12 Å) and the other being longer (13 Å). All 14 conformers of benzoxepin **1** were superimposed with all 22 conformers of aldehyde **2** as depicted in *Fig. 3*, showing the chosen conformers viewed

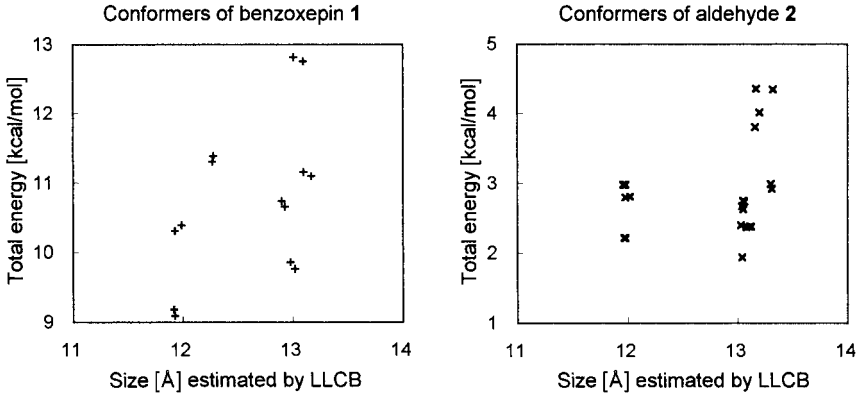


Fig. 2. *Size estimated by LLCB* [Å] vs. *total energy* [kcal/mol]. *Left:* conformers of benzoxepin **1**; *right:* conformers of aldehyde **2**.

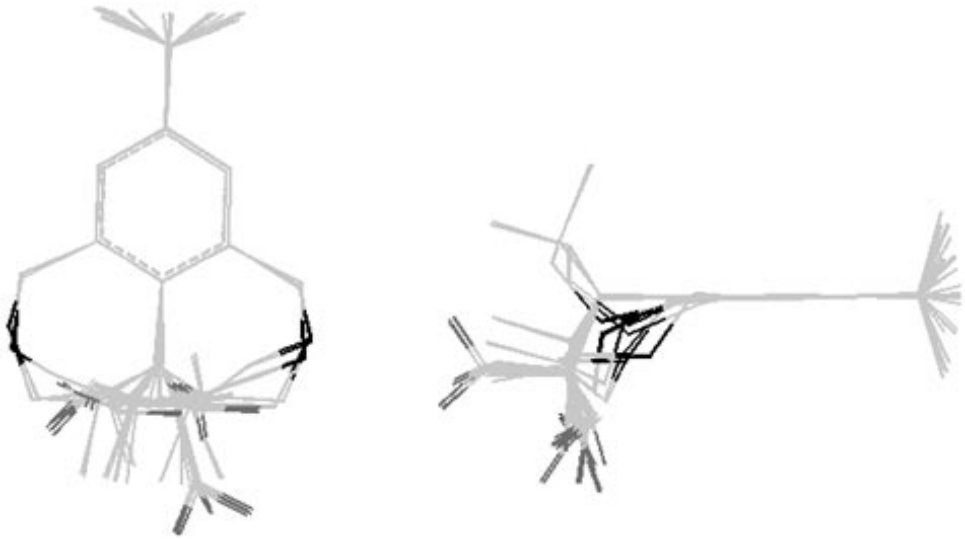
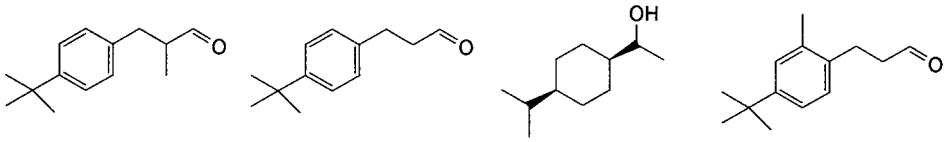


Fig. 3. *Conformers of benzoxepin* **1** *superimposed on the conformers of aldehyde* **2**. For convenience, the H-atoms are omitted. Black, O-atom of **1**; dark gray, O-atom of aldehyde **2**; light gray, skeletons, *i.e.* C-atoms and their connected bonds of **1** and **2**.

from two different directions. The quaternary C-atom of the *t*-Bu group and six atoms in the benzene ring of each compound **1** and **2** were selected for matching. In the case of several possible superimpositions of conformers, the two O-functionalities were arranged such as to be in the same direction and the two O-atoms such as to be as close as possible to each other. It is apparent from *Fig. 3* that no conformers of the benzoxepin **1** match any conformers of aldehyde **2** in terms of the spatial position of the O-functionalities. In other words, no conformer of benzoxepin **1** active for the type of odor typical of **2** would be expected to be present. The study of *Skouroumounis* and

Winter was based on the molecular-mechanics (MM2) calculation with the Macro Model [6]. We employed the molecular-mechanics parameters of Sybyl for the conformational search and the semi-empirical molecular-orbital method (PM3) for the structure optimization. In addition, the atoms used for superimposition may be different between the two studies. In our study, the benzene ring and the center of the *t*-Bu group were matched, because they are common moieties occupying a large space in benzoxepin **1** as well as in aldehyde **2**. Thus, the differences of our results from those of *Skouroumounis* and *Winter* are due to both the different calculation and the different superimposition methods.

In the next stage, in addition to aldehyde **2**, conformational analyses of three other compounds having the lily-of-the-valley odor were carried out, namely of aldehyde **3** (*Bourgeonal*®), alcohol **4** (*Mugetanol*®), and aldehyde **5** as shown in *Fig. 4*. For alcohol **4**, *cis-Mugetanol*® was selected because it has been reported that the lily-of-the-valley aspect and intensity of (−)-*cis-Mugetanol*® are far superior to those of the other isomers [9]. To gain a better superimposition with other molecules, both the (*R*) and (*S*) configurations were constructed for alcohol **4** as initial structures. Aldehyde **5** is a ring-opened analogue of the benzoxepin **1** [6].



2 **3** **4** **5**

Fig. 4. *Compounds having the lily-of-the-valley odor*

The number of conformers selected by conformational analyses were 28 for aldehyde **3**, 9 for the (*R*)- or (*S*)-configuration of alcohol **4**, and 23 for aldehyde **5** (see *Exper. Part*). The range of LLCB for the conformers of alcohol **4** was from 10.4 to 12.3 Å. The 12-Å conformers, the shorter LLCB conformers, were selected in the case of aldehydes **2**, **3**, and **5** because we presumed the existence of a common conformer of compounds **2**–**5** as the odor-active conformer, and there were no conformers at *ca.* 13 Å for alcohol **4**. The shorter conformers ($\leq$12 Å) were superimposed after PM3 optimization of the structures. Superimposition was again based on the O-functionalities, including the bulky moiety of the *t*-Bu or i-Pr group and the six-membered benzene or cyclohexane ring. Among the conformers selected and superimposed, there were some conformers that showed a good agreement in the position or the direction of the O-atoms (*Fig. 5*). The conformers in *Fig. 5* were assumed to be close to the conformer active for the lily-of-the-valley odor, because the compounds having this odor are expected to adopt a similar conformation and to fit with the specific receptor protein in the same manner. Since it is difficult to specify one active conformer for each compound from the limited information here, all the conformers in *Fig. 5* were kept as active conformers. *Fig. 5* represents an integrated model giving information regarding the size and structure of molecules having the lily-of-the-valley odor. Models for the lily-of-the-valley-type odor have been proposed by *Pelzer*, based on an AM1 calculation [9]. There are two types of fragment structures representing compounds

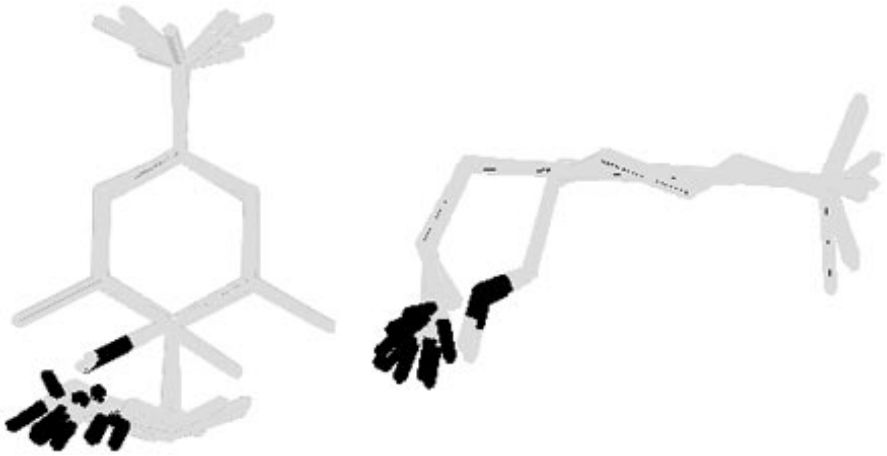


Fig. 5. *Superimposition of selected conformers of aldehyde* **2**, *aldehyde* **3**, *alcohol* **4**, *and aldehyde* **5**, *viewed from two different directions.* For convenience, H-atoms are omitted, except the H- atom of the OH group of the conformers of alcohol **4**.

with hydroxy and carbonyl functional groups, respectively. *Fig. 5* was taken as a common model for odorants that involve either fragment type.

The other molecular features of compounds **2**–**5**, such as the average electrostatic potential (*ESP*) charges of the O-atoms in selected conformers and the logarithm of the octanol/water partition coefficient (log *P*), were calculated, and the results are listed in *Table I*. *ESP* Charge is an electrostatic parameter and log *P* is a hydrophobic parameter. From odor-structure-relationship studies [1][2], electrostatic and hydrophobic factors seem to be important, in addition to steric or shape parameters. The size of odoriferous molecules would be an important parameter when they are recognized at specific olfactory receptors. In 1998, *Zhao et al.* have succeeded in driving the expression of a particular receptor gene in the rat olfactory epithelium using a recombinant adenovirus. The size specificity of odoriferous molecules was seen in the infected animal by electrophysiological recording [10]. Molecular size might be a factor to determine whether odorant-receptor interactions can be established.

Based on the superimposed model as shown in *Fig. 5*, we anticipated that compounds of two categories, *e.g.* compounds **6**–**9** of *Type A* and compounds **10**–**14** of *Type B* (*Fig. 6*), are candidates to possess a lily-of-the-valley-type odor. The spatial positions of O-functionalities of these compounds were focused on at first, and the *t*-Bu

Table 1. *Other Molecular Features of Aldehyde* **2**, *Aldehyde* **3**, *Alcohol* **4**, *and Aldehyde* **5**

	Average of *ESP*[a]) charge of the O-atom	Calculated log *P*[b])	No of conformers selected for *Fig. 5*
aldehyde **2**	– 0.26	3.56	6
aldehyde **3**	– 0.28	3.30	4
alcohol **4**	– 0.33	2.79	2
aldehyde **5**	– 0.28	3.56	4

[a]) *ESP*, electrostatic potential. [b]) *P*, octanol/H_2O partition coefficient.

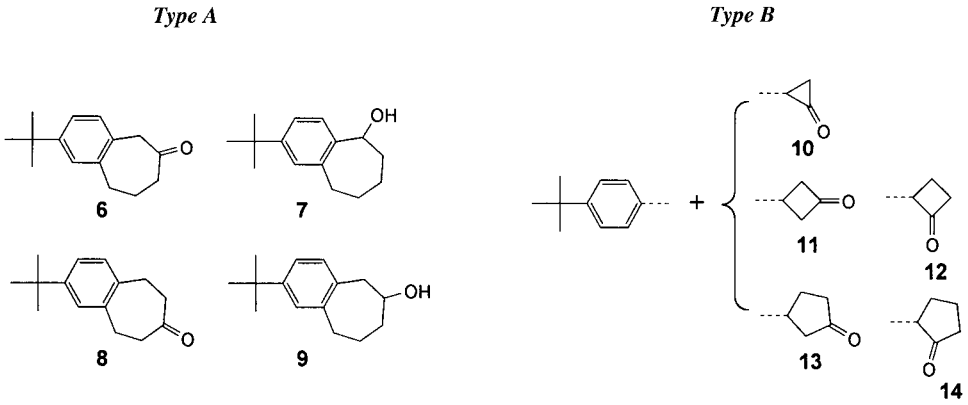


Fig. 6. *Candidate compounds* **6**–**14** *having potentially the lily-of-the-valley odor.* The two rings are connected *via* a dashed line in *Type B* compounds.

and benzene moieties were kept as is. Carbonyl or OH groups were connected to rings to restrict the position of the O-atoms. Both (*R*)- and (*S*)-configurations of the compounds in *Fig. 6* carrying a stereogenic center were considered since the spatial position and direction of O-functionalities are important. Conformational analyses and structure optimizations of all the candidate compounds **6**–**14** were then carried out. The selected conformers of each compound **6**–**14** were superimposed on the model (see *Fig. 5*) to compare them with the active conformers of compounds **2**–**5** (see *Exper. Part*).

After extensive investigations, benzocycloheptenone **8** and the (*S*)-enantiomer of cyclopentanone **13** were selected, because, among the other candidates, the conformers of compounds **8** and **13**, both fit well with the conformers in *Fig. 5*. Superimposed conformers of benzocycloheptenone **8** and cyclopentanone **13** are depicted in *Figs. 7* and *8*, respectively. The position and direction of the O-atoms in compounds **8** and **13** fit well with those of the conformers in *Fig. 5*, though not completely. The other molecular features of the best-fit conformers of benzocycloheptenone **8** and cyclopentanone **13** were also calculated and are shown in *Table 2*. Molecular size, three-dimensional structure (especially accordance with the position of the O-atoms), *ESP* charges of O-atoms, and the calculated log *P* of benzocycloheptenone **8** and cyclopentanone **13** were not significantly different from those of compounds **2**–**5** shown in the model of *Fig. 5* and in *Table I*.

2.2. *Synthesis of the Designed Molecules Benzocycloheptenone* **8**, *Cyclopentanone* **13**, *and Benzocycloheptenone* **23**. Benzocycloheptenone **8** was prepared according to

Table 2. *Other Molecular Features of the Designed Compounds Benzocycloheptenone* **8** *and Cyclopentanone* **13**

	ESP[a]) charge of the O-atom	Calculated log *P*[b])
Benzocycloheptenone **8**	– 0.29	3.82
Cyclopentanone **13**	– 0.29	3.43

[a]) *ESP*, electrostatic potential. [b]) *P*, octanol/H_2O partition coefficient.

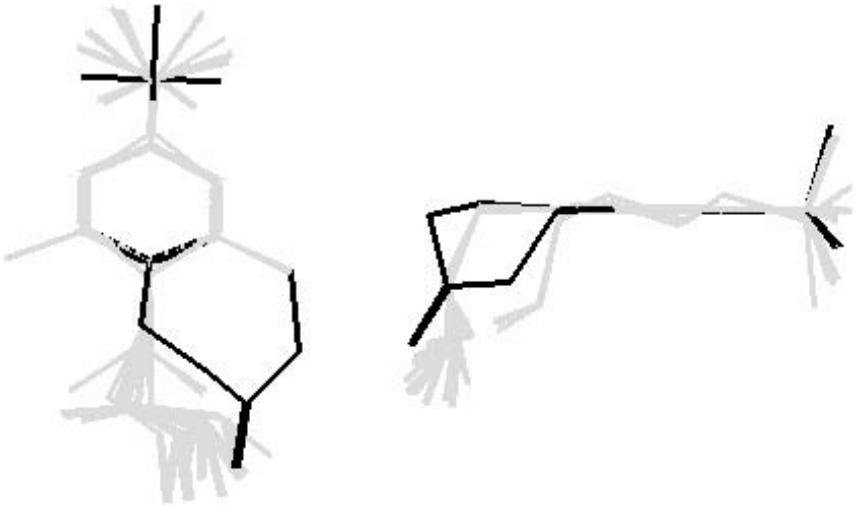


Fig. 7. *Superimposition of conformers of benzocycloheptenone* **8** *on the conformers in* Fig. 5, *viewed from two different directions.* For convenience, the H-atoms are omitted.

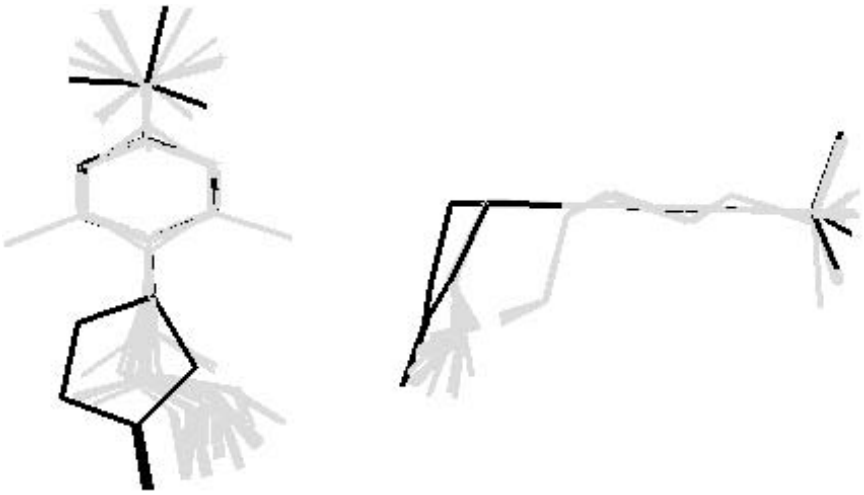
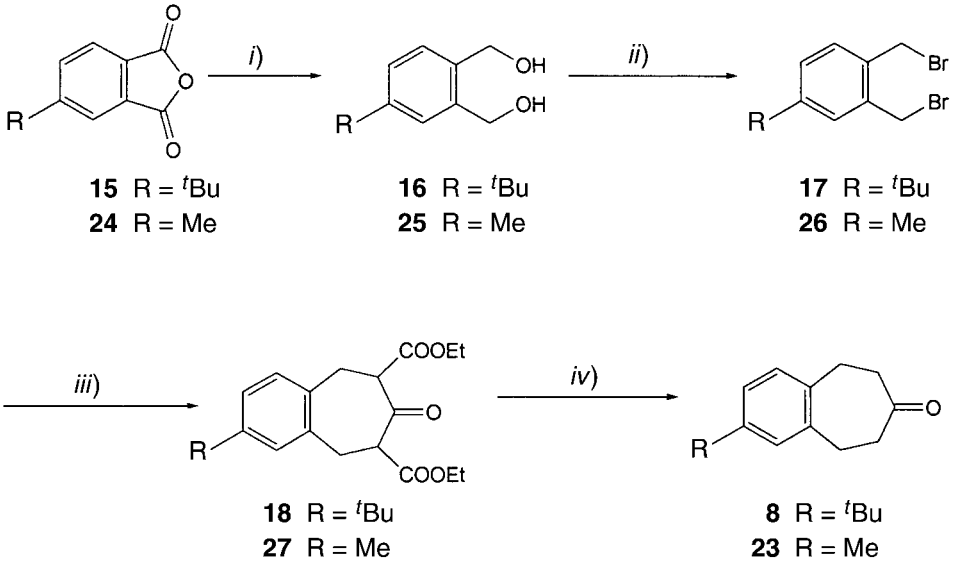


Fig. 8. *Superimposition of conformers of cyclopentanone* **13** *on the conformers in* Fig. 5, *viewed from two different directions.* For convenience, the H-atoms are omitted.

the procedure of *Mataka* and co-workers [11] as shown in *Scheme 1*. Bromination of diol **16**, prepared by lithium aluminium hydride reduction of 4-(*tert*-butyl)phthalic anhydride (**15**) was carried out with CBr_4 and triphenylphosphine to give dibromide **17** in 93% yield. Alkylation of diethyl 3-oxopentanedioate with dibromide **17** provided oxobenzocycloheptanedicarboxylate **18** in 70% yield under phase-transfer conditions, and decarboxylation of **18** in aqueous alkaline media furnished the desired benzocycloheptenone **8** in 84% yield.

Scheme 1. *Synthesis of Benzocycloheptenones* **8** *and* **23**



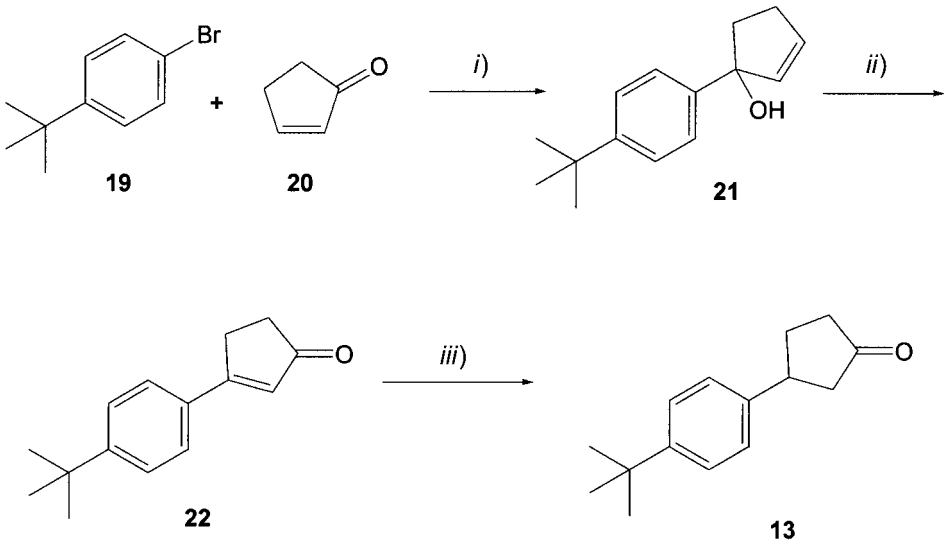
i) $LiAlH_4$, Et_2O; 92% (**16**), 90% (**25**). *ii)* CBr_4, PPh_3, CCl_4; 93% (**17**), 92% (**26**). *iii)* Bu_4NI, 5% aq. $NaHCO_3$ soln., $(EtOOCCH_2)_2CO$, CH_2Cl_2; 70% (**18**, 55% (**27**). *iv)* KOH, H_2O / EtOH; 84% (**8**), 88% (**23**).

Cyclopentanone **13** had been used to investigate the chromatographic resolution and ability of chiral recognition on methylbenzoylcellulose beads [12]. Cyclopentanone **13** was also the intermediate of a new fungicide [13]. However, its odor was not described. The first step of its synthesis, *i.e.* 1,4-conjugated addition of 4-(*tert*-butyl)phenylmagnesium bromide to cyclopentanone **20** in the presence of copper reagent did not give reproducible results. Thus, an alternative route was employed involving the *Grignard* reaction of bromide **19** with cyclopentenone **20**, which provided the tertiary alcohol **21** in 85% yield. The latter was treated with pyridinium dichromate (PDC) in CH_2Cl_2 to give cyclopentenone **22** in 82% yield. Catalytic hydrogenation of **22** provided the desired cyclopentanone **13** in 50% yield. The volatility of cyclopentanone **13** was responsible for the moderate yield after hydrogenation. Attempted reductive *Heck* reaction [14] of cyclopentenone **20** with of 4-(*tert*-butyl)phenyl bromide **19** leading to cyclopentanone **13** failed.

To increase the volatility of *tert*-butyl-substituted benzocycloheptenone **8**, the methyl-substituted benzocycloheptenone **23** was prepared *via* **24**–**27** according to the same synthetic procedure as described for **8** (see *Scheme 1*).

2.3. *Olfactory Evaluation of the Designed Molecules Benzocycloheptenone* **8**, *Cyclopentanone* **13**, *and Benzocycloheptenone* **23**. The odors of the three compounds were evaluated by eight perfumers as shown in *Fig. 9*. According to the comments of the perfumers, benzocycloheptenone **8** recalls the note of *Cyclamenaldehyde* ® and *Lily Aldehyde* ®, and cyclopentanone **13** recalls the note of lilac. The synthetic compounds **8** and **13** possess the targeted lily-of-the-valley-type odor, though their intensities are weak and not adequate for perfume materials. The additional synthetic benzocyclo-

Scheme 2. *Synthesis of Cyclopentanone* **13**



i) Mg, THF; 85%. *ii)* PDC, CH_2Cl_2; 82%. *iii)* Pd/C, H_2, EtOH; 50%.

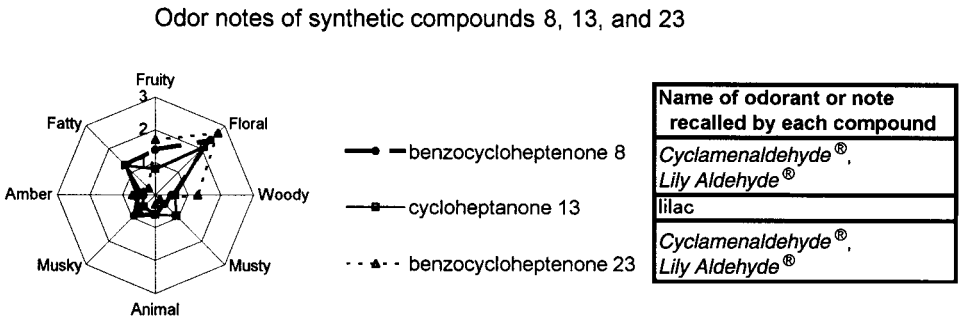


Fig. 9. *Intensity of eight odor notes of the synthetic benzocycloheptenone* **8**, *cyclopentanone* **13**, *and benzocycloheptene* **23**, *evaluated by eight perfumers.* Intensity 1: the degree of the detected feature is weak; intensity 2: the degree of the feature is rather weak; intensity 3: the degree of the feature is medium.

heptenone **23** also recalls the note of *Cyclamenaldehyde* ® and *Lily Aldehyde* ®, and also has a distinctive marine note. As a novel perfume material, the value of benzocycloheptenone **23** is rather low, because there are many other compounds having a marine note.

Concerning the odor type or odor note, the designed molecules benzocycloheptenone **8** and cyclopentanone **13** were confirmed to have floral, lily-of-the-valley-type odor by olfactory evaluation. It is worth to note that the benzocycloheptenone **8** and cyclopentanone **13** were proposed only by computational analyses. Both compounds have the lily-of-the-valley odor and did not have other strong odor notes. Therefore, our methodology to design new odoriferous compounds based on conformational

analysis proved to be satisfactory. The model obtained in this work also would predict the conformation of odorants having this odor at the receptor protein.

Concerning the intensity of odor, the model is still insufficient. Analysis of a variety of compounds having this odor may lead to a better model to design compounds having the lily-of-the-valley odor. A series of pyranyl and furanyl ether type compounds, as well as compounds having a hydroxy or carbonyl group, have been reported by *Pelosi et al.* [15][16]. Furthermore, the discovery of additional molecular parameters related to odor is expected to lead to improved models.

3. Conclusion – By intensive conformational analyses of 1,3,4,5-tetrahydro-2-benzoxepin derivative **1** and 3-[4-(*tert*-butyl)phenyl]-2-methylpropanal (**2**), the disagreement of odor of **1** and **2** was explained based on their stable conformers. Additional analyses of compounds **3**–**5** having the lily-of-the-valley odor established that some conformers of these compounds had a common molecular size and position of the O-functionalities. The corresponding conformers were assumed to be odor-active conformers. The synthesis of designed compounds based on our integrated model (see *Fig. 5*), *i.e.* of benzocycloheptenone **8** and cyclopentanone **13**, revealed that they possess the targeted odor of the lily of the valley. This verifies the choice of the conformers active for the lily-of-the-valley odor, as selected by conformational analysis. Our methodology to design new odoriferous compounds was successful in terms of odor type. However, in terms of odor intensity, the model has to be improved.

Investigations on the relation between odor type and odor intensity and on the additional molecular features related to odor are underway.

We thank *Soda Aromatic Co., Ltd.* for the odor evaluation of the synthetic benzocycloheptenone **8**, cyclopentanone **13**, and benzocycloheptenone **23**, and for the mass-spectral measurements. A scholarship for *F. Y.* by *Sasaki Environmental Technology Foundation* is also gratefully acknowledged.

Experimental Part

1. *Computational Analysis.* A flow-chart for the general calculation is shown in *Fig. 10. 1*) Starting structures were constructed and minimized by molecular-mechanics calculations with Tripos force field parameters in the SYBYL QSAR module (version 6.2 and 6.3) on a *Silicon Graphics IRIS 4D/420GTX*. *2*) Conformational analyses were performed by random search [17]. Standard criteria for the search were as follows: maximum cycle was from 3000 to 30000 times, depending on the structural flexibility; r.m.s. threshold was between 0.1 and 0.5 Å, according to the molecular structures; energy convergence was 0.005 kcal/mol. After the conformational analysis, the conformer with the lowest energy and those with the energy up to 5 kcal/mol from the lowest energy were selected. *3*) The size and compactness of molecules were checked by LLCB. The LLCB was calculated by our self-written program on the same workstation. The LLCB was first introduced as 'the longest side length of a hexahedron that circumscribes the *van der Waals* surface of a molecule' in our previous work [18]. The circumscribed hexahedron is made by the best plane, the intermediate plane, and the worst plane. The sum of squares of distance between the best plane and each atom of the molecule is the smallest. In other words, we can put atoms in a molecule exactly on or nearest to the best plane. The LLCB has been established to be useful in previous works [19][20][21] as a parameter for estimating molecular size. This parameter was used to select or eliminate conformers for further optimization. *4*) Structure optimizations of the conformers based on bond lengths, bond angles, and dihedral angles, by means of the PM3 method [22], were carried out in succession. *5*) Graphic images of conformers were superimposed using the least-squares-fit method for comparison of the 3-D structures in the SYBYL. *6*) Other molecular features were considered: log *P*, as a parameter of the hydrophobicity of the whole molecule, was calculated by *M*log*P* [23] on an *Apple-Macintosh LC520* computer. The *M*log*P* does not depend on the conformation of a molecule. The electrostatic-potential (*ESP*) charges of O-atoms of selected conformers were also calculated with KEY WORD, 'ESP', by the

PM3 method, because an O-atom is considered to be a requisite for the lily-of-the-valley odor. The coordinates of conformers selected in this work are available. Please contact *F. Yoshii* (fuyoshii@mb.infoweb.ne.jp) or *H. Hagiwara* (hagiwara@gs.niigata-u.ac.jp).

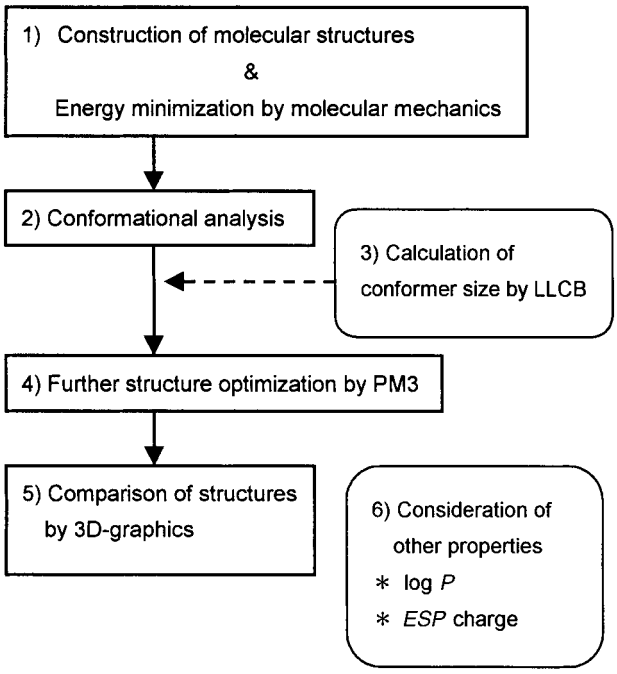


Fig. 10. *Calculation method*

2. *General:* Medium-pressure liquid chromatography (MPLC): *GL-Science PU-612* instrument, silica-gel packed column. CC = Column chromatography. M.p.s: *Yanaco MP* hot-stage apparatus; uncorrected. IR Spectra: *Shimadzu FT/IR-4200* spectrophotometer, CCl_4 solns.; in cm^{-1}. ^{1}H-NMR Spectra: *Varian Gemini 200 H* (200 MHz) instrument; $CDCl_3$ solns.; δ in ppm rel. to $SiMe_4$ as internal standard (= 0 ppm), *J* in Hz. ^{13}C-NMR Spectra: *Varian Gemini 200 H* (50 MHz) instrument. MS: *Hitachi M-4100* spectrometer; recorded at *Soda Aromatics Co., Ltd.*; *m/z* (rel. %). Microanalyses were carried out in the microanalytical laboratory of the Instrumental Analysis Center for Chemistry, Tohoku University.

3. *Syntheses. 4-(*tert*-Butyl)benzene-1,2-dimethanol* (**16**). To a soln. of 4-(*tert*-butyl)phthalic anhydride (**15**; 4634 mg, 22.7 mmol) in Et_2O (80 ml), $LiAlH_4$ (2161 mg, 56.9 mmol) was added at −78°. After 30 min stirring at −78°, the mixture was stirred for 3 h at r.t.. The reaction was quenched by addition of Et_2O and sat. aq. NH_4Cl soln. and the org. layer dried (Na_2SO_4) and evaporated CC(AcOEt/hexane 1:2) provided **16** (4050 mg, 92%). IR (CCl_4): 3535, 3080, 2966, 2907, 2872, 1614, 1477, 1020. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.32 (*s*, 9 H); 3.04 (*s*, 2 H); 4.71 (*s*, 2 H); 4.74 (*s*, 2 H); 7.30–7.37 (*m*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 31.2; 34.4; 63.3; 64.1; 76.4; 77.0; 77.6; 125.0; 126.6; 129.4; 136.3; 138.8; 151.3. EI-MS: 194 (4, M^+), 179 (28), 176 (62), 161 (100), 133 (28), 117 (7), 105 (22), 91 (16), 77 (7), 57 (8) and 41 (8) HR-MS: 194.1348 ($C_{12}H_{18}O_2^+$, M^+; calc. 194.1307).

*Diethyl 7-(*tert*-Butyl)-2,3,4,5-tetrahydro-3-oxo-1*H*-benzocycloheptene-2,4-dicarboxylate* (**18**). To a stirred suspension of Bu_4NI (1190 mg, 3.22 mmol) in 5% aq. $NaHCO_3$ soln. (43 ml) and CH_2Cl_2 (10 ml), a soln. of dibromide **17** (1714 mg, 5.36 mmol) and diethyl 3-oxopentanedioate (1.27 ml, 6.97 mmol) in CH_2Cl_2 (10 ml) was slowly added, and the resulting suspension was stirred vigorously at r.t. for 21 h. After addition of sat. aq. NH_4Cl soln., the org. layer was extracted with AcOEt (2×), washed with H_2O and brine, dried (Na_2SO_4), and evaporated. CC(AcOEt/hexane 1:7) provided **18** (1354 mg, 70%). IR ($CHCl_3$): 2966, 1743, 1711, 1566, 1466, 1441, 1387, 1356, 1266, 1146, 1022. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.23 (*t*, *J* = 7.0, 3 H); 1.30 (*t*, *J* = 7.0, 3 H); 1.32 (*s*,

9 H); 3.03–3.32 (*m*, 4 H); 3.48–3.74 (*m*, 2 H); 4.05–4.33 (*m*, 4 H); 7.08–7.25 (*m*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 14.0; 14.1; 31.3; 32.9; 33.8; 34.4; 58.2; 59.5; 61.3; 61.4; 124.5; 127.0; 129.8; 133.8; 136.3; 150.6; 169.4; 202.3. EI-MS: 360 (37, M^+), 315 (54), 314 (100), 286 (62), 241 (35), 240 (69), 213 (71), 173 (33), 129 (29), 58 (74). HR-MS: 360.1947 ($C_{21}H_{28}O_5^+$, M^+; calc. 360.1937).

*7-(*tert-*Butyl)-1,2,4,5-tetrahydro-3*H-*benzocyclohepten-3-one* (**8**). A soln. of **18** (1354 mg, 3.76 mmol) in 8% aq. KOH soln. (20 ml) and EtOH (30 ml) was heated to reflux for 1.5 h. After addition of 1N HCl, the mixture was extracted with $CHCl_3$ (2×) and the combined org. layer washed with H_2O and brine, dried (Na_2SO_4), and evaporated. CC(MeOH/$CHCl_3$ 1:2) afforded **8** (684 mg, 84%), which was recrystallized from hexane/$CHCl_3$. M.p. 54.8–55.1°. IR ($CHCl_3$): 2964, 2909, 2864, 1709, 1442. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.32 (*s*, 9 H); 2.58–2.66 (*m*, 4 H); 2.86–2.95 (*m*, 4 H); 7.13–7.28 (*m*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 30.1; 31.0; 31.4; 34.4; 44.6; 44.6; 123.8; 126.1; 128.9; 137.4; 140.0; 150.0; 211.6. Anal. calc. for $C_{15}H_{20}O$ (216.32): C 83.29, H 9.32; found: C 83.19, H 9.46.

*1-[4-(*tert-*Butyl)phenyl]cyclopent-2-en-1-ol* (**21**). To a stirred slurry of Mg (294 mg, 12 mmol) in THF (10 ml) under N_2, 1-bromo-4-(*tert*-butyl)benzene (1.75 ml, 10 mmol) and dibromoethane (4 µl) were added. Stirring was continued for 3 h at r.t. Then, a soln. of cyclopent-2-en-1-one (**20**) (0.57 ml, 7.0 mmol) in THF (3 ml) was added at 0°, and the resulting soln. was stirred at r.t. for 1 h. The reaction was quenched by addition of sat. aq. NH_4Cl soln. and the org. layer extracted with AcOEt (2×), washed with H_2O and brine, dried (Na_2SO_4), and evaporated. MPLC (AcOEt/hexane 1:2) purification of the residue provided **21** (1291 mg, 85%). IR (CCl_4): 3599, 2945, 2854, 1603, 1493, 1359, 1284, 1111. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.32 (*s*, 9 H); 2.25 (*m*, 2 H); 2.33 (*m*, 2 H); 5.92 (*td*, $J = 5.6, 2.4, 1$ H); 6.15 (*td*, $J = 5.6, 2.2, 1$ H); 7.42 (*m*, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 31.3; 31.5; 34.4; 41.7; 86.7; 124.5; 125.0; 134.5; 136.6; 144.0; 149.6. EI-MS: 215 (33, $[M-1]^+$), 199 (43), 198 (58), 183 (100), 161 (28), 159 (35), 155 (15), 115 (11), 57 (14). HR-MS: 215.1443 ($C_{15}H_{20}O^+$, $[M-1]^+$); calc. 215.1436).

*3-[4-(*tert-*Butyl)phenyl]cyclopent-2-en-1-one* (**22**). A slurry of PDC (568 mg, 1.51 mmol), NaOAc (126 mg, 1.53 mmol), and 4 Å molecular sieves (100 mg) in CH_2Cl_2 (6 ml) was stirred for 30 min under N_2. Then a soln. of the **21** (113 mg, 0.53 mmol) in CH_2Cl_2 (2 ml) was added, and stirring was continued for 30 min. The mixture was passed through a short SiO_2 column, the filtrate evaporated, and the residue purified by MPLC (AcOEt/hexane 1:2): **22** (90 mg, 82%), which was recrystallized from hexane/$CHCl_3$. M.p. 108.3–110.1°. IR (CCl_4): 2966, 2909, 2870, 1705, 1600, 1464, 1412, 1296, 1184. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.35 (*s*, 9 H); 2.65 (*td*, $J = 2.8, 1.9, 2$ H); 3.05 (*m*, 2 H); 6.56 (*t*, $J = 1.7, 1$ H); 7.52 (*m*, 2 H); 7.61 (*m*, 2 H). Anal. calc. for $C_{15}H_{18}O$ (214.31): C 84.07, H 8.47; found: C 83.80, H 8.77.

*3-[4-(*tert-*Butyl)phenyl]cyclopentan-1-one* (**13**). A slurry **22** (728 mg, 3.4 mmol) and Pd/C (49 mg) in EtOH (13 ml) was stirred at r.t. 20.5 h under H_2. Filtration and evaporation gave a residue, which was purified by MPLC (AcOEt/hexane 1:2): **13** (365 mg, 50%), which was recrystallized from hexane/$CHCl_3$. M.p. 68.4°. IR (CCl_4): 3057, 2966, 2870, 1748, 1462, 1408, 1329. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.32 (*s*, 9 H); 1.95 (*m*, 2 H); 2.45 (*m*, 4 H); 3.40 (*m*, 1 H); 7.20 (*m*, 2 H); 7.38 (*m*, 2 H). Anal. calc. for $C_{15}H_{20}O$ (216.32): C 83.29, H 9.32; found: C 82.83, H 9.57.

*Diethyl 2,3,4,5-Tetrahydro-7-methyl-3-oxo-1*H-*benzocycloheptene-2,4-dicarboxylate* (**27**). As described for **18**, with Bu_4NI (663 mg, 1.79 mmol), 5% aq. $NaHCO_3$ soln. (15 ml), CH_2Cl_2 (10 ml), dibromide **26** (471 mg, 1.69 mmol), diethyl 3-oxopentanedioate (0.43 ml, 2.34 mmol), and CH_2Cl_2 (3 ml), at 40° for 3.5 h. CC (AcOEt/hexane 1:3) provided **27** (294 mg, 55%). IR ($CHCl_3$): 3028, 2980, 2966, 1743, 1711, 1566, 1466, 1441, 1201. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.23–1.32 (*m*, 15 H); 3.03–3.32 (*m*, 4 H); 3.48–3.74 (*m*, 2 H); 4.05–4.33 (*m*, 4 H); 7.08–7.25 (*m*, 3 H). EI-MS: 318 (31, M^+), 272 (100), 244 (51), 198 (76), 171 (68), 143 (88), 131 (66) and 115 (30), 91 (16).

*1,2,4,5-Tetrahydro-7-methyl-3*H-*benzocyclohepten-3-one* (**23**). As described for **8**, with **27** (294 mg, 0.92 mmol), 6.5% aq. KOH soln. (7 ml), and EtOH (7 ml), under reflux for 2 h: **23** (140 mg, 88%), which was recrystallized from hexane/$CHCl_3$. M.p. 61.8–63.6°. IR ($CHCl_3$): 3024, 2964, 2924, 2909, 1711, 1442. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.32 (*s*, 9 H) ; 2.58–2.66 (*m*, 4 H); 2.86–2.95 (*m*, 4 H) and 7.13–7.28 (*m*, 3 H). EI-MS: 174 (100, M^+), 159 (20), 146 (21), 132 (59), 131 (64), 117 (52), 91 (20), 77 (8). Anal. calc. for $C_{15}H_{20}O$ (216.32): C 82.72, H 8.11; found: C 82.50, H 8.32.

4. *Olfactory Evaluation of the Synthetic Molecules.* Benzocycloheptenones **8** and **23** and cyclopentanone **13** were dissolved in dipropylene glycol to give a 10% soln. Eight perfumers evaluated their odor notes using paper strips. The odor note is judged by 8 features, which are fruity, floral, woody, musty, animal, musky, amber, and fatty. Each perfumer ranked the intensity of the 8 features in a scale from 0 to 5:0, not detecting the specified feature at all; 1, the degree of the detected feature is weak; 2, the degree of the feature is rather weak; 3, the degree of the feature is medium; 4, the degree of the feature is rather strong; 5, the degree of the feature is strong. The average intensity (*A. I.*) of the eight features is calculated according to the following equation.

A. I. = {ΣN_i (number of perfumer who ranked the sample as *i)* · *i (*ranking point, *i* = *0,1,2,3,4,5)}* / 8 (total number of perfumers). We also asked the perfumers to give the names of perfume materials recalled by each synthetic compound.

REFERENCES

[1] K. J. Rossiter, *Chem. Rev.* **1996**, *96*, 3201.
[2] M. Chastrette, *SAR QSAR Environ. Res.* **1997**, *6*, 215.
[3] L. Buck, R. Axel, *Cell* **1991**, *6*, 175.
[4] K. Raming, J. Krieger, J. Strotmann, I. Boekhoff, S. Kubick, C. Baumstark, H. Breer, *Nature (London)* **1993**, *361*, 353.
[5] M. S. Singer, G. M. Shepherd, *Neuro Report* **1994**, *5*, 1297.
[6] G. Skouroumounis and B. Winter, *Helv. Chim. Acta* **1996**, *79*, 1095.
[7] D. Enders, H. Dyker, *Liebigs Ann. Chem.* **1990**, *11*, 1107.
[8] A. Mosandl, Z. *Lebensm.-Unters. Forsch. A* **1997**, *205*, 76.
[9] R. Pelzer, U. Harder, A. Krempel, H. Sommer, H. Surburg, P. Hoever, in 'Recent Developments in Flavor and Fragrance Chemistry', Proceedings of the 3rd International Haarmann & Reimer Symposium, Eds. R. Hopp and K. Mori, VCH Verlagsgesellschaft, Weinheim, 1993, p. 48.
[10] H. Zhao, L. Ivic, J. M. Otaki, M. Hashimoto, K. Mikoshiba, S. Firestein, *Science (Washington, D.C.)* **1998**, *279*, 237.
[11] S. Mataka, Y. Mitoma, T. Thiemann, T. Sawada, M. Taniguchi, M. Kobuchi, M. Tashiro, *Tetrahedron* **1997**, *53*, 3015.
[12] E. Francotte, R. M. Wolf, *J. Chromatogr.* **1992**, *595*, 63.
[13] A. Huxley-Tencer, E. Francotte, M. Bladocha-Moreau, *Pestic. Sci.* **1992** *34*, 65.
[14] H. Hagiwara, Y. Eda, K. Morohashi, T. Suzuki, M. Ando, N. Ito, *Tetrahedron Lett.*, **1998**, *39*, 4055.
[15] C. Anselmi, M. Centini, M. Mariani, A. Sega, P. Pelosi, *J. Agric. Food Chem.* **1992**, *40*, 853.
[16] C. Anselmi, M. Centini, M. Mariani, A. Sega, P. Pelosi, *J. Agric. Food Chem.* **1993**, *41*, 781.
[17] M. Saunders, *J. Am. Chem. Soc.* **1987**, *109*, 3150.
[18] F. Yoshii, Q. Liu, S. Hirono, I. Moriguchi, *Chem. Senses* **1991**, *16*, 319.
[19] F. Yoshii, S. Hirono, I. Moriguchi, *Quant. Struct.-Act. Relat.* **1994**, *13*, 144.
[20] F. Yoshii, S. Hirono, *Chem. Sens.* **1996**, *21*, 201.
[21] F. Yoshii, S. Hirono, I. Moriguchi, *Helv. Chim. Acta* **1993**, *76*, 2279.
[22] J. J. P. Stewart, 'MOPAC Ver. 6,' QCPE #455.
[23] I. Moriguchi, S. Hirono, I. Nakagome, H. Hirano, *Chem. Pharm. Bull.* **1994**, *42*, 976.

Received March 1, 2001