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Comparative Analysis of the Olfactory Properties of Silicon/Germanium/Tin Analogues of the Lily-of-the-Valley Odorants Lilial and Bourgeonal

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The silicon/germanium/tin analogues of the lily-of-the-valley odorants lilial (*rac*-**1a**), compounds *rac*-**1b**, *rac*-**1c**, and *rac*-**1d**, and bourgeonal (**2a**), compounds **2b**, **2c**, and **2d**, were synthesized and characterized for their olfactory properties, including GC–olfactometry studies. Compounds *rac*-**1a**–**c** and **2a**–**c** possess a typical lily-of-the-valley odor, whereas the stanna-analogues *rac*-**1d** and **2d**, despite some floral aspects, clearly no longer belong to the lily-of-the-valley family. In both series of the carbon/silicon/germanium/tin analogues studied, the lily-of-the-valley odor decreases in the order of carbon < silicon < germanium < tin. A HEK293 cell line with stable tetracycline-regulated expression of hOR17-4 was generated to analyze recombinant hOR17-4 activation by *rac*-**1a**–**d** and **2a**–**d** by using Ca^{2+} imaging. Bourgeonal (**2a**) showed the highest activation potency, whereas lilial (*rac*-**1a**) and sila-bourgeonal (**2b**) exhibited lower activation potencies. Sila-lilial (*rac*-**1b**), germa-lilial (*rac*-**1c**), and stanna-lilial (*rac*-**1d**), as well as germa-bourgeonal (**2c**) and stanna-bourgeonal (**2d**), did not activate heterologously expressed hOR17-4 at the concentrations tested. The carbon/silicon/germanium/tin switch strategy thus showed that the stanna-derivatives clearly exceeded the molecular dimensions of the odorant receptor(s) responsible for the recognition of lily-of-the-valley odorants, although the receptor affinity was already affected with the sila- and germa-analogues. These data could later be used in the qualitative and quantitative evaluation of computational receptor models.

Introduction

The first step in odor perception is the detection of an odorant molecule by special G-protein-coupled receptors in the cilia of olfactory sensory neurons (OSNs), the olfactory receptors (ORs). Most characterized ORs recognize a subset of odorants with chemically similar structures. A specific odorant usually activates a unique set of ORs on OSNs, and the resulting combinatorial code conveys the odor quality.[1] However, the molecular mechanism of OR selectivity is still poorly understood. The exact mechanism that controls the initial activation step when an odorant molecule interacts with an OR is discussed controversially in the literature. Frequently discussed mechanisms for odorant recognition are recognition by shape or shape components,[2] molecular vibrations,[3] a combination of both,[4] or a combination of shape recognition and matching protein–ligand dynamics.[5] To obtain further information on the qualitative structure–odor and qualitative structure–activity correlation in the family of lily-of-the-valley odorants, we focused on a strategic sila-, germa-, and stanna-substitution of the quaternary carbon atom in the hydrophobic bulk group of the lily-of-the-valley odorants lilial (**1a**→**1b**/**1c**/**1d**; compounds studied as racemates) and bourgeonal (**2a**→**2b**/**2c**/**2d**; for other studies on C/Si, C/Si/Ge, and C/Si/Ge/Sn bioisosterism, see refs. [6]–[9]). All of these model compounds share a high degree of bioisosterism and exhibit small and defined differences in their side-chain size, but considerable differences in their molecular vibrations. Lilial (**1a**) and bourgeonal (**2a**) were chosen as model compounds for this C/Si/Ge/Sn bioisosterism study, because hOR17-4 (= hOR1D2; one of only 46 deorphaned receptors of approximately 400 functional human olfactory receptors (hORs))[10] is activated by these lily-of-the-valley odorants.[11]

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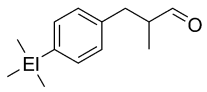
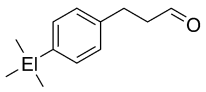


El = C: *rac*-**1a** (lilial)
El = Si: *rac*-**1b** (sila-lilial)
El = Ge: *rac*-**1c** (germa-lilial)
El = Sn: *rac*-**1d** (stanna-lilial)



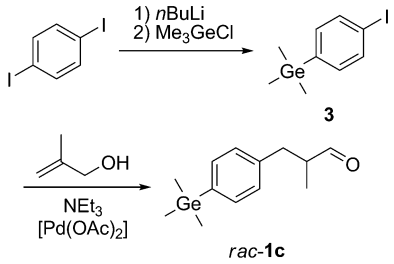
El = C: **2a** (bourgeonal)
El = Si: **2b** (sila-bourgeonal)
El = Ge: **2c** (germa-bourgeonal)
El = Sn: **2d** (stanna-bourgeonal)

Herein, we report on 1) the synthesis of *rac*-**1c**, *rac*-**1d**, **2c**, and **2d**, 2) the olfactory characterization of *rac*-**1a–d** and **2a–d**, 3) the generation of a HEK293 cell line with stable tetracycline-regulated expression of hOR17-4, and 4) the activation of heterologously expressed hOR17-4 by *rac*-**1a–d** and **2a–d**. With this combination of in vivo and in vitro data, we aimed to further elucidate the structure–odor correlation in the family of lily-of-the-valley odorants. These investigations represent a systematic extension of earlier studies on the carbon/silicon pairs **1a**/**1b** and **2a**/**2b**.[8j]

Results and Discussion

Syntheses

Germa-lilial (*rac*-**1c**) was synthesized according to Scheme 1. Thus, monolithiation of 1,4-diiodobenzene with *n*-butyllithium

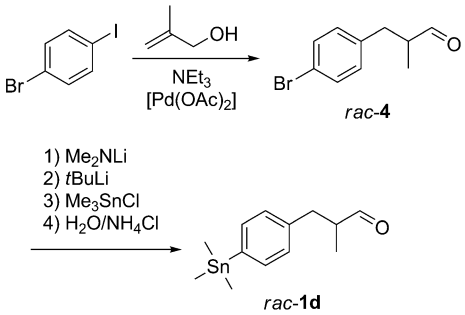


Scheme 1. Synthesis of germa-lilial (*rac*-**1c**).

and subsequent treatment with chlorotrimethylgermane afforded (4-iodophenyl)trimethylgermane (**3**; 93% yield), which, upon a palladium-catalyzed Heck cross-coupling reaction with 2-methylprop-2-en-1-ol, gave *rac*-**1c** in 68% yield.

Stanna-lilial (*rac*-**1d**) was synthesized according to Scheme 2. In the first step, a palladium-catalyzed Heck cross-coupling reaction of 1-bromo-4-iodobenzene with 2-methylprop-2-en-1-ol afforded *rac*-3-(4-bromophenyl)-2-methylpropanal (*rac*-**4**) in 87% yield. Protection of the aldehyde function of *rac*-**4** by treatment with lithium dimethylamide,[12] followed by lithiation with *tert*-butyllithium, reaction with chlorotrimethylstannane, and subsequent hydrolysis then afforded *rac*-**1d** in 51% yield.

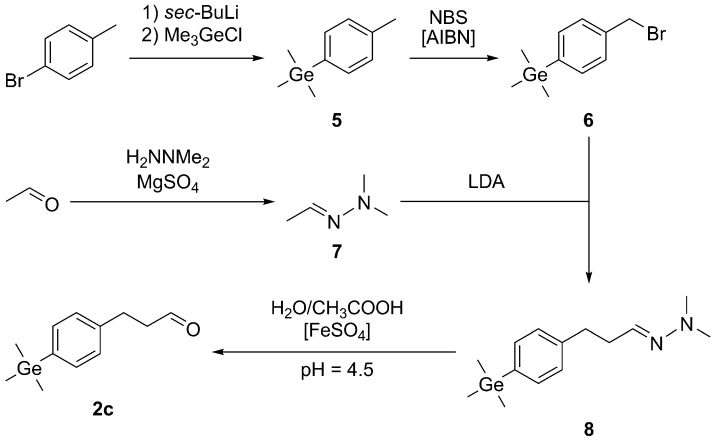
Germa-bourgeonal (**2c**) was synthesized according to Scheme 3. Thus, lithiation of 1-bromo-4-methylbenzene with *sec*-butyllithium and subsequent treatment with chlorotrimethylgermane afforded trimeth-



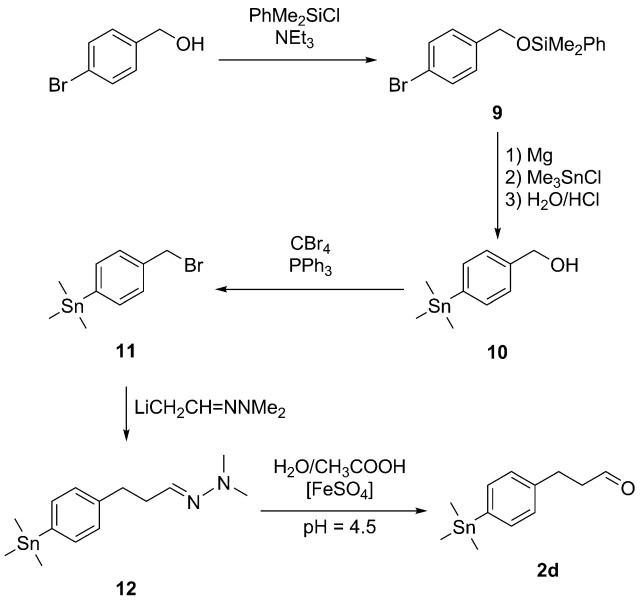
Scheme 2. Synthesis of stanna-lilial (*rac*-**1d**).

yl(4-methylphenyl)germane (**5**) in 93% yield. Radical bromination of **5** with NBS, in the presence of AIBN, gave [4-(bromomethyl)phenyl]trimethylgermane (**6**) in 76% yield. Reaction of **6** with lithiated ethanal dimethylhydrazone (obtained by lithiation of ethanal dimethylhydrazone (**7**) with LDA) then afforded 3-[4-(trimethylgermyl)phenyl]propanal dimethylhydrazone (**8**; 95% yield), which, upon treatment with water and acetic acid, in the presence of iron(II) sulfate, finally afforded **2c** in 60% yield.[13] Reagent **7** was synthesized by treatment of ethanal with 1,1-dimethylhydrazine, in the presence of anhydrous magnesium sulfate (87% yield).

Stanna-bourgeonal (**2d**) was synthesized according to Scheme 4. Thus, treatment of (4-bromophenyl)methanol with chlorodimethylphenylsilane, in the presence of triethylamine, afforded (4-bromobenzyloxy)dimethylphenylsilane (**9**) in 91% yield. Reaction of **9** with magnesium gave the corresponding Grignard reagent, which, upon treatment with chlorotrimethylstannane and subsequent hydrolysis, gave [(4-trimethylstannyl)phenyl]methanol (**10**) in 74% yield. Reaction of **10** with tetrabromomethane and triphenylphosphine afforded [4-(bromomethyl)phenyl]trimethylstannane (**11**; 69% yield), which, upon treatment with lithiated **7**, gave 3-[4-(trimethylstannyl)-phenyl]propanal dimethylhydrazone (**12**) in 94% yield. Subsequent treatment of **12** with water and acetic acid, in the presence of iron(II) sulfate, finally afforded **2d** in 60% yield.[13]



Scheme 3. Synthesis of germa-bourgeonal (**2c**). NBS = *N*-bromosuccinimide, AIBN = 2,2′-azobisisobutyronitrile, LDA = lithium diisopropylamide.



Scheme 4. Synthesis of stanna-bourgeonal (**2d**).

Compounds *rac*-**1c**, *rac*-**1d**, **2c**, and **2d** and the precursors **3**, *rac*-**4**, and **5**–**12** were isolated as colorless liquids.[14] Their identities were established by elemental analyses and by mass spectrometry (EI-MS) and NMR spectroscopy (^{1}H, ^{13}C, ^{15}N, ^{29}Si, ^{119}Sn). Experimental details of the syntheses and analytical studies are given in the Supporting Information.

Olfactory studies

Compounds *rac*-**1a**–**d** and **2a**–**d** were studied for their olfactory properties (Table 1). Upon sila-substitution, the typical powerful and diffusive odor of *rac*-**1a**, which recalls the mild floral odor of lily-of-the-valley and linden blossom, becomes more rosy and fatty in tonality, and sila-lilial (*rac*-**1b**) is thus less fresh, sparkling, and watery than *rac*-**1a**. Even a spicy facet is present in the odor profile of *rac*-**1b**, which with an odor threshold of 3.3 ng L^{-1} air is much weaker than the parent carbon compound *rac*-**1a** (0.10 ng L^{-1} air). Both *rac*-**1a** and *rac*-**1b** are still olfactorily closely related, and both share the typical lily-of-the-valley character of *rac*-**1a**. Also, compound *rac*-**1c** shares this typical lily-of-the-valley character, although it is closer in smell to silvial (3-(4-isobutylphenyl)-2-methylpropanal), which of course belongs to the same odor family, than to *rac*-**1a**. Yet, in the transition from *rac*-**1b** to *rac*-**1c**, the odor again becomes more pronouncedly floral, despite still being aldehydic. Thus, compound *rac*-**1c** displays an increased volume and floral strength, and some clay-type aspects enhance the density of its smell. Thus, compound *rac*-**1c** is esthetically very pleasant; yet, with an odor threshold of 7.7 ng L^{-1} air, it is again weaker than *rac*-**1b**. Compound *rac*-**1d**, however, has a comparable intensity—its odor threshold is 6.9 ng L^{-1} air—but, despite some lilial aspects, its main odor quality now is clearly no longer in the lily-of-the-valley family. Instead, it has an oily–fatty floral character with a spicy, cuminic note.

Compound **2a**, for which an odor threshold of 0.16 ng L^{-1} air was determined,[8j] is close to *rac*-**1a** in both odor character and threshold. Its lily-of-the-valley tonality is also watery-aldehydic, but the aldehydic facets are greener in character, and hints of melons and hyacinths are discernable as well. The lily-of-the-valley note of sila-bourgeonal (**2b**) lies between that of *rac*-**1a** and **2a**; it is floral, green-aldehydic, fresh-watery, and soft. Thus, compound **2b** is more pronouncedly green than *rac*-**1a**, but less than **2a**. Its floral character is more pronounced than that of **2a**, but less distinct than that of *rac*-**1a**. With an odor threshold of 0.55 ng L^{-1} air, compound **2b** has a considerably lower odor threshold than **1b** (3.3 ng L^{-1} air). Compounds **2c** (1.1 ng L^{-1} air) and **2d** (2.0 ng L^{-1} air) also possess significantly lower odor thresholds than their lilial counterparts *rac*-**1c** (7.7 ng L^{-1} air) and *rac*-**1d** (6.9 ng L^{-1} air).

As with the lilial analogues *rac*-**1c** and *rac*-**1d**, only **2c** still possesses a typical floral-green lily-of-the-valley profile, in this case closer to *rac*-**1a** than to **2a**, with additional lilac facets and some sweet floral connotations of heliotropin. Compounds **2d** and *rac*-**1d** have only a fatty, floral odor without pro-

Table 1. Olfactory properties of compounds *rac*-**1a**–**1d** and **2a**–**d**.

Compound	Olfactory properties	Odor threshold concentration [ng L^{-1} air]	Odor threshold concentration [pmol L^{-1} air]
rac-**1a**	typical powerful and diffusive aldehydic odor reminiscent of lily-of-the-valley and linden blossom; mild floral and natural tones	0.10	0.49
rac-**1b**	lilial-like; typical aldehydic lily-of-the-valley smell; more rosy and fatty with a slightly spicy connotation; less fresh, sparkling, and watery than lilial	3.3	15
rac-**1c**	floral, aldehydic, fatty odor with 3-(4-isobutylphenyl)-2-methylpropanal (silvial) connotations and clay-type nuances	7.7	29
rac-**1d**	floral oily–fatty odor with spicy facets in the direction of cumin and some lilial aspects	6.9	22
2a	powerful and diffusive; watery-floral lily of-the-valley note with a green-aldehydic character and hints of melons and hyacinths	0.16	0.84
2b	floral, green-aldehydic, fresh-watery lily-of-the valley note; softer and less green-aldehydic than bourgeonal; between lilial and bourgeonal in floral terms	0.55	2.7
2c	natural floral-green muguet odor in the direction of lilial, with lilac facets and connotations of benzo[*d*]-[1,3]dioxole-5-carbaldehyde (heliotropin)	1.1	4.2
2d	fatty, floral, slightly green odor with anisic and slightly balsamic facets	2.0	6.7

nounced lily-of-the-valley character, but instead green, anisic, and slightly balsamic facets are perceivable.

Essentially, except *rac*-**1d** and **2d**, all other derivatives of *rac*-**1a** and **2a** possess a typical lily-of-the-valley note of more or less pronounced green character; compound **2a** is most green-aldehydic in character and *rac*-**1c** is the most pronounced floral one. The fattiness increases in both series from carbon→silicon→germanium→tin, independently of the floral character and the lily-of-the-valley note. In terms of odor threshold, compounds *rac*-**1a** and **2a** display the lowest values, and thus, show the best performance.

Generation of a HEK293 cell line with stable tetracycline-regulated expression of hOR17-4

To analyze recombinant hOR17-4 activation by lily-of-the-valley odorants, we generated T-REx-293 cells that stably expressed rho-tagged hOR17-4 under the control of a tetracycline-regulated promoter. To investigate the integration of the targeted sequence into the genome of T-REx-293 cells, we analyzed *hOR17-4* expression at the RNA and protein levels. Reverse transcription polymerase chain reaction (RT-PCR) analyses with primers specific for *hOR17-4* showed that expression of *hOR17-4* could be induced in T-REx-293-hOR17-4 cells, but was absent in parental T-REx-293 cells (Figure S1 in the Supporting Information). By western blot analysis with a monoclonal antibody against the C-terminal rho tag of recombinant hOR17-4, we found that hOR17-4 protein was expressed in induced T-REx-293-hOR17-4 cells (Figure S2 in the Supporting Information). Immunocytochemical staining revealed hOR17-4 protein expression in approximately 80% of induced T-REx-293-hOR17-4 cells, but not in parental T-REx-293 cells (Figure S3 in the Supporting Information). These results indicate stable integration of the *hOR17-4-rho* construct into the genome of T-REx-293 cells. Experimental details of the studies described in this paragraph are given in the Supporting Information.

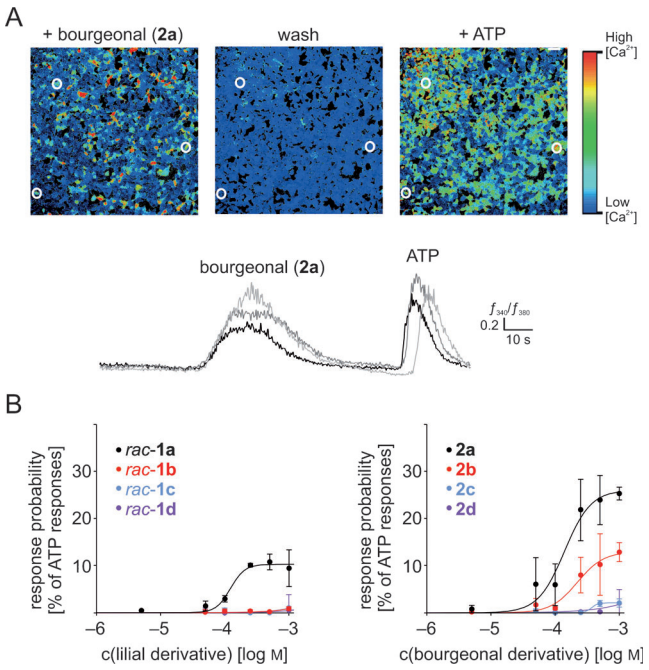


Figure 1. Activation of heterologously expressed hOR17-4 by *rac*-**1a–d** and **2a–d**. A) Representative Ca^{2+} imaging measurements of HEK293 cells stably expressing hOR17-4 (T-REx-293-hOR17-4 cells). The upper panel shows pseudocolor images of fura-2-loaded, induced T-REx-293-hOR17-4 cells that were captured during the measurements. Relative cytosolic Ca^{2+} levels are shown in pseudocolor, which indicates changes in the cytosolic Ca^{2+} concentration. In a randomly selected field of view, compound **2a** induces transient increases in the cytosolic Ca^{2+} concentration in individual fura-2-loaded cells (e.g., white circles). Compound **2a** (250 μM) was applied for 10 s, and 20 μM ATP served to control cell excitability. Cytosolic Ca^{2+} levels were monitored as integrated f_{340}/f_{380} fluorescence ratios expressed as a function of time. Traces are shown in greyish colors (lower panel). B) Dose–response relationships of heterologously expressed hOR17-4 and *rac*-**1a–d** and **2a–d**, respectively. As an indirect measure for hOR17-4 activation, the response probabilities to *rac*-**1a–d** and **2a–d** were determined in Ca^{2+} measurements of induced T-REx-293-hOR17-4 cells. The data were normalized to the response probability of 20 μM ATP in the same experiment. The means were calculated from 3 to 11 independent experiments (each with 160–900 cells) for each tested concentration; error bars indicate the standard error of the mean (SEM).

Functional characterization of hOR17-4

We analyzed the responsiveness of recombinant hOR17-4 to *rac*-**1a–d** and **2a–d** in detail by ratiofluorometric Ca^{2+} imaging measurements of induced T-REx-293-hOR17-4 cells. Application of activating odorants led to a robust transient increase in cytosolic Ca^{2+} concentration owing to hOR17-4 activation and signaling (Figure 1). As an indirect measure of the receptor's responsiveness to an odorant, we quantified the response probability in respect to ATP (positive control) and established dose–response relationships for *rac*-**1a–d** and **2a–d**. No tested compound elicited Ca^{2+} signals in control cells (here T-REx-293 cells) that were higher than background cellular activity (Figure S4 in the Supporting Information). The maximal tested odorant concentration did not exceed 1 mM, because higher concentrations induced nonspecific cellular activation. In Ca^{2+} imaging analysis of heterologously expressed hOR17-4, compounds *rac*-**1a**, **2a**, and **2b** activated the receptor. Coapplication of the hOR17-4 blocker undecanal[11] inhibited odorant-evoked Ca^{2+} responses of induced T-REx-293-hOR17-4 cells (Figure S5 in the Supporting Information); this indicated that the Ca^{2+} signals depended on hOR17-4 activation. Compound **2a** showed the highest activation potency on recombinant hOR17-4 (E_{max} = 25% of ATP response), whereas *rac*-**1a** and **2b** exhibited lower activation potencies (E_{max} = 12 and 10% of ATP response, respectively). The EC_{50} values were calculated to be in the same range for all three odorants (*rac*-**1a**, EC_{50} = 125 μM; **2a**, EC_{50} = 130 μM; **2b**, EC_{50} = 200 μM). These results indicate that the agonists bind with comparable affinities to the receptor, but differ in their abilities to activate Ca^{2+} signaling. Notably, it cannot be excluded that the hOR17-4 activation properties of the single enantiomers of *rac*-**1a–d** differ from those determined for the racemates. Compounds *rac*-**1b**, *rac*-**1c**, and *rac*-**1d**, as well as **2c** and **2d**, did not activate heterologously expressed hOR17-4 at sub-millimolar concentrations (Figure 1). These data only partially overlap with results of a previous study that compared Ca^{2+} signal amplitudes of a few transiently hOR17-4 expressing HEK293 cells that re-

sponded to *rac*-**1a**, *rac*-**1b**, **2a**, and **2b**.[8j] However, the response amplitudes may depend on the receptor expression levels in individual cells. Quantification of odorant response probabilities by using cells stably expressing hOR17-4 is therefore more accurate and enables analysis of dose–response relationships in the heterologous system in more detail. Because sperm cells, which were used in ref. [8j] to determine hOR17-4 activation potencies, may possess further sensors for **2a**, these cells are not ideal to study hOR17-4 activation.[15] A comparison of in the vitro analyses with the olfactory studies revealed that recombinant hOR17-4 was considerably activated by compounds *rac*-**1a**, **2a**, and **2b**, which all showed in vivo detection thresholds lower than 1 ng L^{-1} air. Compounds with higher odor thresholds in olfactory studies did not activate recombinant hOR17-4 in the tested concentrations. Because the classical expression systems lack specifically conserved molecular mechanisms required for the functional expression of ORs,[16] heterologously expressed ORs are typically less sensitive to the odorant ligands than the same ORs endogenously expressed in OSNs.[11] We can therefore only conclude that *rac*-**1a**, **2a**, and **2b** are potent agonists of hOR17-4, whereas *rac*-**1b**–**d** and **2c**–**d** exhibit significantly decreased activation potencies at hOR17-4. However, we cannot yet define whether *rac*-**1b**–**d** and **2c**–**d** are weak agonists or inactive at the receptor. Experimental details of the studies described in this paragraph are given in the Supporting Information.

Conclusion

Compounds *rac*-**1c**, *rac*-**1d**, **2c**, and **2d** were synthesized in multistep syntheses. The carbon/silicon/germanium/tin analogues *rac*-**1a**–**d** and **2a**–**d** were characterized for their olfactory properties, including GC–olfactometry studies. Compounds *rac*-**1a**, *rac*-**1b**, *rac*-**1c**, **2a**, **2b**, and **2c** possess a typical lily-of-the-valley odor, whereas the stanna-analogues *rac*-**1d** and **2d**, despite some floral aspects, clearly no longer belong to the lily-of-the-valley family. In both series of the carbon/silicon/germanium/tin analogues studied, the lily-of-the-valley odor decreased in the order of carbon < silicon < germanium < tin; this increase was more pronounced for the lilial series.

To analyze recombinant hOR17-4 activation by compounds *rac*-**1a**–**d** and **2a**–**d**, a HEK293 cell line with stable tetracycline-regulated expression of hOR17-4 was generated. In functional characterization by Ca^{2+} imaging experiments, compound **2a** showed the highest activation potency, whereas *rac*-**1a** and **2b** exhibited lower activation potencies. Compounds *rac*-**1b**, *rac*-**1c**, and *rac*-**1d**, as well as **2c** and **2d**, did not activate heterologously expressed hOR17-4 at the concentrations tested.

With the silicon/germanium/tin analogues of the lily-of-the-valley odorants *rac*-**1a** and **2a**, the presumed hydrophobic bulk binding pocket of the hOR17-4 receptor could be characterized in more detail; this could be useful for the generation of olfactophore models, and thus, for the design of novel lily-of-the-valley odorants. The carbon/silicon/germanium/tin switch strategy[16] used for these studies proved to be a powerful tool to extend our knowledge about the structure–odor correlation in the family of lily-of-the-valley perfumery materials.

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Keywords: bioisosterism · germanium · lily of the valley · odorants · silicon · structure–activity relationships · tin

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