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Silicon-Based Noncyclic Woody-Ambery Odorants: Synthesis and Olfactory Characterization of 4,4,6,6-Tetramethylheptan-2-one and Its Sila-Analogues

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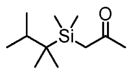
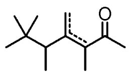
4,4,6,6-Tetramethylheptan-2-one ($Me_3C{-}CH_2{-}CMe_2{-}CH_2C(O)Me$, **7a**) and the three sila-analogues $Me_3Si{-}CH_2{-}CMe_2{-}CH_2C(O)Me$ (**7b**), $Me_3C{-}CH_2{-}SiMe_2{-}CH_2C(O)Me$ (**7c**), and $Me_3Si{-}CH_2{-}SiMe_2{-}CH_2C(O)Me$ (**7d**) were synthesized and studied for their olfactory properties and vapor pressures. While the parent carbon compound **7a** has a powerful woody-ambery odor reminiscent of Kohinool (**3**) with a camphoraceous-aromatic side, the 6-sila-analogue **7b** is similar in tonality with a fatty and more pronounced camphoraceous side. The camphor note increases even further for the intense 4-sila-analogue **7c** and dominates the odor profile of the 4,6-disila-analogue **7d**, which displays additional earthy and green-fruity facets. In terms of odor values and threshold values, compound **7d** is the most powerful, albeit the least woody-ambery compound. Concerning the vapor pressure, it constitutes the least volatile of the series studied; interestingly, the vapor pressure of **7b** is almost twice as high as that of **7c**.

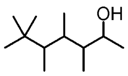
Introduction

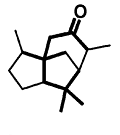
Upon chromatographic purification of the SAMP [(*S*)-1-amino-2-methoxymethylpyrrolidine] hydrazone of 3,3,4,4,5-pentamethyl-3-silahexan-1-al, prepared as a starting material for the synthesis of amino acid derivatives, a strong, woody-floral smell had been noticed, which was assigned to traces of 3,3,4,4,5-pentamethyl-3-silahexan-1-al formed by hydrolysis.[1] A few related analogues were prepared, for instance, 4,4,5,5,6-pentamethyl-4-silaheptan-2-one (**1**), which emanated an earthy, woody, floral, slightly minty, and green scent, which was somewhat reminiscent of patchouli, albeit more earthy.[1] Since woody odorants are usually characterized by bi- or even tricyclic structures, the odor of the noncyclic silicon compound **1** was quite surprising. Due to their low molecular mass and an accordingly high vapor pressure, such odorants could potentially be used as woody top notes in perfumery.

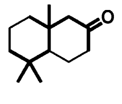
Koavone (**2**) and Kohinool (**3**), both of woody-ambery tonality with a violet, camphoraceous note in the former, and floral, earthy aspects in the latter case, are also noncyclic woody odorants. Structurally they can be seen as *seco*-derivatives of woody odorants such as Iso E Super/Arborone[2,3] and Georgywood,[2,3] retaining the methyl-substituted C1,C2,C7,C8,C8a-face of the octahydronaphthalene skeleton, the so-called “northern hemisphere”, which has been supposed to bind to an α-helical leu-gly-gly-leu motif.[2] However, this binding mode has recently been questioned by the synthesis of spirocyclic analogues[3] and probably also does not hold true for the odorants **2** and **3**. The aforementioned structure−odor relationships form the background of our interest in the olfactory properties of 4,4,6,6-tetramethylheptan-2-one (**7a**) and its silicon analogues **7b**−**7d**. In this context, it is interesting to note that partial structures of **7a** occur in the powdery cedarwood odorant Cedralone (**4**), in the woody-ambery, peppery perfumery material Jopsone (**5**), and even in the very trendy woody-musky smelling Cashmeran (**6**) with floral undertones. In each of these odorants, not only the woody tonalities but also the distances between the quaternary carbon atoms and the carbonyl osmophore as well as the conformations of the heptan-2-one backbone differ significantly.

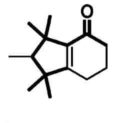

1 earthy, woody, floral,
sl. minty and green,
sl. reminiscent of patchouli

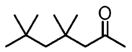

Koavone (**2**)
woody-ambery,
violet, camphor

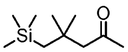

Kohinool (**3**)
woody-ambery,
floral, earthy

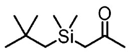

Cedralone (**4**)
cedarwood,
powdery

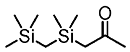

Jopsone (**5**)
woody-ambery,
pepper


Cashmeran (**6**)
woody-musky,
floral


7a


7b


7c


7d

We therefore found 4,4,6,6-tetramethylheptan-2-one (**7a**) a very promising structure to apply our carbon/silicon switch strategy, which has led to interesting insight into structure−odor relationships and to the discovery of new silicon-based fragrance materials.[4] We report here on the synthesis and olfactory characterization of the parent carbon compound **7a** and its three sila-analogues **7b**−**7d**.

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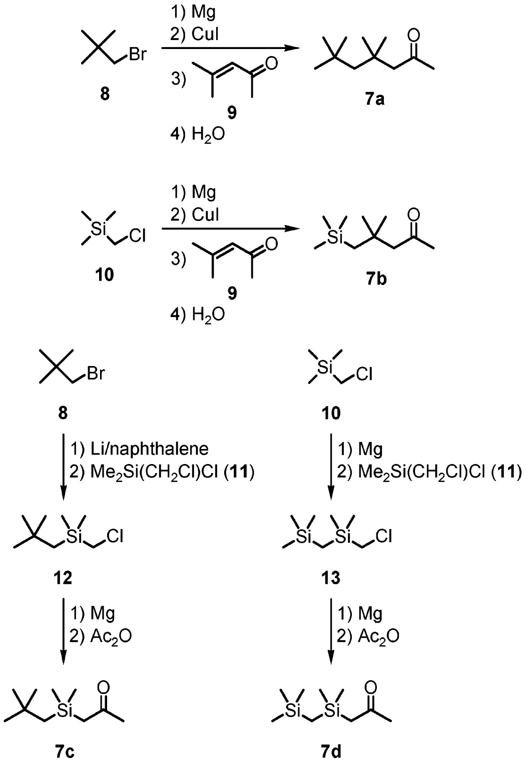
(1) Doszczak, L.; Gasperi, T.; Saint-Dizier, A.; Loreto, M. A.; Enders, D. In *Perspectives in Flavor and Fragrance Research*; Kraft, P., Swift, K. A. D., Eds.; Verlag Helvetica Chimica Acta. Zurich, 2005; Wiley-VCH: Weinheim, 2005; pp 89−103.

(2) Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 1346−1352.

(3) Kraft, P.; Frech, D.; Müller, U.; Fráter, G. *Synthesis* **2006**, 2215−2223.

10.1021/om700260q CCC: $37.00

Scheme 1



Results and Discussion

Syntheses. Compounds **7a**−**7d** were synthesized according to Scheme 1. 4,4,6,6-Tetramethylheptan-2-one (**7a**)[5] was obtained starting from 1-bromo-2,2-dimethylpropane (**8**). In the first step, a cuprate was formed by sequential treatment of **8** with magnesium and copper(I) iodide, which upon reaction with 4-methyl-3-penten-2-one (**9**), followed by hydrolysis, provided **7a** in 63% yield. 4,4,6,6-Tetramethyl-6-silaheptan-2-one (**7b**) was prepared in 65% yield analogously to the synthesis of **7a** by using (chloromethyl)trimethylsilane (**10**) as the starting material instead of **8**. 4,4,6,6-Tetramethyl-4-silaheptan-2-one (**7c**) was also synthesized starting from **8**. In the first step, compound **8** was treated with lithium/naphthalene, and the resulting lithium reagent was then allowed to react with chloro(chloromethyl)dimethylsilane (**11**) to afford 1-chloro-2,2,4,4-tetramethyl-2-silapentane (**12**) (48% yield). Reaction of **12** with magnesium gave the corresponding Grignard reagent, which upon treatment with acetic anhydride finally provided **7c** in 71% yield. 4,4,6,6-Tetramethyl-4,6-disilaheptan-2-one (**7d**) was synthesized starting from **10**. Reaction of **10** with magnesium and treatment of the resulting Grignard reagent with **11** provided 1-chloro-2,2,4,4-tetramethyl-2,4-disilapentane (**13**)[6] (82% yield), which upon reaction with magnesium and subsequent treatment of the resulting Grignard reagent with acetic anhydride afforded **7d** in 83% yield.

Table 1. Comparison of the Physical and Olfactory Data of Compounds 7a−7d

	7a	7b	7c	7d
IR stretching vibration ($\tilde{\nu}$) C═O [cm^{-1}]	1719	1718	1692	1692
NMR chemical shift (δ ^{13}C) C═O [ppm]	206.2	206.2	204.4	204.4
GC retention time (t_R) [min]	5.4	5.5	5.8	6.0
GC threshold (*GTH*) [ng L^{-1}]	65	25	10	5
headspace concentration at saturation (*HSS*) [mg L^{-1}]	3.2	2.8	1.6	1.1
relative molecular mass (M_r) [g mol^{-1}]	170.30	186.37	186.37	202.44
vapor pressure (*P*) [Pa]	47	37	21	13
odor value (*OV*)	49 230	112 000	160 000	220 000

While the synthesis of **13** was quite easy and straightforward, attempts to synthesize **12** analogously by reaction of **11** with a Grignard reagent (obtained by treatment of **8** with magnesium) gave complex product mixtures and were abandoned (solvent, THF: compound **12** could not be identified (GC/EI MS); solvent, Et_2O: compound **12** was obtained in only ca. 10% yield (GC)). To generate a more reactive species, compound **8** was therefore lithiated. Different methods for the formation of Me_3CCH_2Li by use of elemental lithium have been reported in the literature, but these required prolonged reaction times[7,8] or started from expensive 1-chloro-2,2-dimethylpropane.[8] Lithium/naphthalene has also been used in a two-step synthesis of Me_3CCH_2Li starting from 1-chloro-2,2-dimethylpropane.[9] In the present study, Me_3CCH_2Li was obtained by direct treatment of **8** with lithium/naphthalene. This method turned out to be the most appropriate, allowing mild reaction conditions and a short reaction time, resulting in the formation of **12** in pure form by treatment with **11**.

Compounds **7a** and **7b** were purified by column chromatography on silica gel and subsequent distillation in vacuo. However, compounds **7c** and **7d**, which both contain an $SiCH_2C(O)Me$ moiety, were found to be unstable on silica gel or aluminum oxide, but the syntheses developed for compounds **7c** and **7d** allowed their purification by simple vacuum distillation.[10] Although the syntheses of the low-molecular mass compounds **7a**−**7d** may look rather straightforward, they required a lot of optimization work in order to obtain olfactorily pure samples on a multigram scale, which was complicated by their high volatility.

Olfactory and Physical Properties. The high vapor pressure of the four C/Si analogues **7a**−**7d** was a prerequisite for the intended use as woody-ambery top notes in perfumery. The vapor pressures *P* were measured by quantitative headspace analysis,[11,12] and all were indeed determined to be greater than 10 Pa, with the corresponding headspace concentration at saturation (HSS) of >1 mg L^{-1} (Table 1). As expected, the parent carbon compound **7a** was found to be the most volatile odorant (*P*, 47 Pa) in the series **7a**−**7d**, possessing also the lowest molecular mass, and the disila-analogue **7d** with the

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(4) Recent publications: (a) Büttner, M. W.; Penka, M.; Doszczak, L.; Kraft, P.; Tacke, R. *Organometallics* **2007**, *26*, 1295−1298. (b) Doszczak, L.; Kraft, P.; Weber, H.-P.; Bertermann, R.; Triller, A.; Hatt, H.; Tacke, R. *Angew. Chem.* **2007**, *119*, 3431−3436; *Angew. Chem., Int. Ed.* **2007**, *46*, 3367−3371.

(5) For an alternative synthesis of **7a**, see also: Whitmore, F. C.; Wilson, C. D.; Capinjola, J. V.; Tongberg, C. O.; Fleming, G. H.; McGrew, R. V.; Cosby, J. N. *J. Am. Chem. Soc.* **1941**, *63*, 2035−2041.

(6) The synthesis of **13** has already been briefly reported, but in order to increase the yield, we improved the described procedure (see: Sommer, L. H.; Goldberg, G. M.; Gold, J.; Whitmore, F. C. *J. Am. Chem. Soc.* **1947**, *69*, 980) and characterized **13** by NMR spectroscopy. For an alternative synthesis of **13**, see also: Sommer, L. H.; Mitch, F. A.; Goldberg, G. M. *J. Am. Chem. Soc.* **1949**, *71*, 2746−2750.

(7) Chirik, P. J.; Dalleska, N. F.; Henling, L. M.; Bercaw, J. E. *Organometallics* **2005**, *24*, 2789−2794.

(8) Schrock, R. R.; Fellmann, J. D. *J. Am. Chem. Soc.* **1978**, *100*, 3359−3370.

(9) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713−719.

(10) To avoid high temperatures, which would cause a partial thermal decomposition of **7c** or **7d**, both compounds were distilled under mild conditions (0.02 mbar, ≤30 °C).

(11) Etzweiler, F.; Senn, E.; Neuner-Jehle, N. *Ber. Bunsen-Ges. Phys. Chem.* **1984**, *88*, 578−583.

(12) Neuner-Jehle, N.; Etzweiler, F. In *Perfumes: Art, Science, and Technology*; Müller, P. M., Lamparsky, D., Eds.; Elsevier Applied Science Publishers: London, 1991; pp 153−212.

highest molecular mass was the least volatile compound (*P*, 13 Pa). Astonishingly, the two monosila-analogues **7b** and **7c**, with identical molecular mass, differed significantly in their vapor pressures, the 6-sila-analogue **7b** displaying a vapor pressure (*P*, 37 Pa) almost twice as high as that of the 4-sila-analogue **7c** (*P*, 21 Pa). This effect could be explained by the different character of the carbonyl function of the 4-sila-analogue **7c**, which may also explain the high reactivity and the resulting difficulties with the chromatographic purification of **7c** and **7d**. The different character of the carbonyl functions of the $C-CH_2C(O)Me$ and $Si-CH_2C(O)Me$ groups is reflected in the bands of the C═O stretching vibrations in the IR spectra (**7a**, $\tilde{\nu}$ 1719 cm^{-1}; **7b**, $\tilde{\nu}$ 1718 cm^{-1}; **7c**, $\tilde{\nu}$ 1692 cm^{-1}; **7d**, $\tilde{\nu}$ 1692 cm^{-1}) and in the ^{13}C chemical shifts of the C═O group in the ^{13}C NMR spectra (**7a**, δ 206.2 ppm; **7b**, δ 206.2 ppm; **7c**, δ 204.4 ppm; **7d**, δ 204.4 ppm). The order of the vapor pressures of **7a**−**7d** is also in accord with the order of the GC retention times measured on a capillary column (**7a**, t_R 5.4 min; **7b**, t_R 5.5 min; **7c**, t_R 5.8 min; **7d**, t_R 6.0 min).

The parent carbon compound **7a** emanates a natural and powerful sweet, woody-ambery odor that is closer in tonality to Kohinool (**3**) than to Koavone (**2**), albeit camphoraceous-aromatic aspects are present, accompanied by fruity nuances in the direction of apricots. The 6-sila-analogue **7b** is quite close in odor to **7a**, displaying also a sweet, woody-ambery note reminiscent of Kohinool (**3**) with a slightly fatty undertone and a somewhat more pronounced camphoraceous facet. Shifting the silicon atom to the 4-position of the heptan-2-one skeleton increases the odor intensity, but also makes the odor somewhat harsher and shifts the tonality more toward the camphoraceous-earthy side. However, the main character of the 4-sila-analogue **7c** is still sweet, woody-ambery, and Kohinool-like, and besides the distinct camphoraceous-earthy character, agrestic-aromatic and animalic facets accompany its odor. In the case of the 4,6-disila-analogue **7d**, however, the camphoraceous-earthy note dominates the odor profile, in addition to which only green-fruity facets and an acidic, sweaty, butyric but no woody-ambery undertone are detectable.

With regard to the vapor pressure, the following order was observed: **7a** > **7b** > **7c** > **7d**. However, this tells only something about the gas-phase concentration offered to the olfactory receptors, but nothing about their affinity to the receptors. The latter is characterized by the odor threshold values, which were determined by GC-olfactometry.[12] The lowest GC threshold (*GTH*, 5 ng L^{-1}) was found for the camphoraceous-earthy 4,6-disila-analogue **7d**, which, however, has no woody-ambery character. If one considers only woody-ambery odorants, the 4-sila-analogue **7c** possesses the lowest odor threshold value (*GTH*, 10 ng L^{-1}). For compounds **7b** and **7a**, values of 25 and 65 ng L^{-1} were measured, respectively (Table 1). Thus, the order **7a** > **7b** > **7c** > **7d** is also valid for the odor thresholds, which means the most volatile carbon compound **7a** displays the lowest affinity toward the olfactory receptors.

The effective odor intensity is a function of both vapor pressure and odor threshold, which in this particular case have opposite effects. The odor intensities can be best compared by means of the odor values (*OV*), also known as "aroma values" or "odor unit numbers",[12] which are defined as the quotient of the headspace concentration at saturation (*HSS*) and the threshold concentration (*GTH*). The odor values are compiled in Table 1 and show the threshold values to have the decisive influence on the resulting odor intensity, overturning the vapor pressures to give the following rank order of intensity: **7d** > **7c** > **7b** > **7a**. The most intense woody-ambery compound of the series thus is **7c** (*OV*, 160 000).

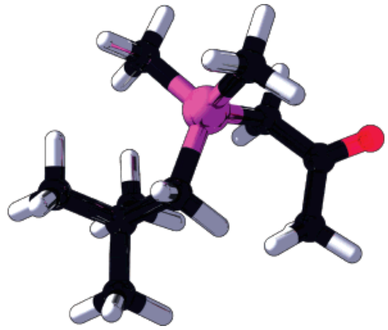

Figure 1. Minimum-energy conformation (PM3 method)[13] of 4,4,6,6-tetramethyl-4-silaheptan-2-one (**7c**), the most intense woody-ambery odorant of the series **7a**−**7d**, structurally resembling the 4,4,6,6-tetramethylheptan-2-one backbone highlighted in the formula of Jopsone (**5**).

In summary, within the series **7a** → **7b** → **7c** → **7d** the woody-ambery character decreases and is gradually replaced by a camphoraceous-earthy tonality, with the 4-sila-substitution of **7a** (→ **7c**) marking the turning point. Compound **7c** is also the most powerful woody-ambery odorant of the series (*OV*, 160 000). The order of the vapor pressures (**7a** > **7b** > **7c** > **7d**) is inverted by the influence of the odor thresholds, resulting in the ranking of the overall intensity: **7d** > **7c** > **7b** > **7a**.

In an attempt to rationalize the olfactory properties of the compounds studied, the minimum-energy conformations (PM3 method)[13] of **7a**−**7d** were calculated. With the exception of **7d**, all these compounds resemble the 4,4,6,6-tetramethylheptan-2-one motif indicated in bold in the structural formula of Jopsone (**5**). This is in accord with the olfactory properties: of the three polycyclic odorants **4**−**6**, only Jopsone (**5**) is woody-ambery in smell; compound **7d** does not smell woody-ambery but is only camphoraceous-earthy. Exemplarily for **7a**−**7c**, the minimum-energy conformer of **7c** is delineated in Figure 1. Since olfactory receptor proteins can, however, stabilize conformations by a few kcal mol^{-1}, the results of these calculations should be taken only as an indication. Nevertheless, the 3D resemblance to Jopsone (**5**) seems a more likely rational for the olfactory properties of **7a**−**7c** (and probably as well for those of Koavone (**2**) and Kohinool (**3**)) than the docking to an α-helical leu-gly-gly-leu motif.[2] As the 6-sila-analogue **7b** and the 4-sila-analogue **7c** differ distinctly in their odor character and intensity, sila-substitution indeed can be regarded as a powerful tool for fine-tuning olfactory properties. Balancing woody, camphoraceous, and earthy elements would for instance be very useful for the discovery of new patchouli odorants.[14] Thus, the carbon/silicon exchange can be an important strategy in odorant design, not only in the woody domain.[4]

Experimental Section

General Procedures. All syntheses were carried out under dry nitrogen. The organic solvents used were dried and purified according to standard procedures and stored under dry nitrogen. A Büchi GKR 50 apparatus was used for the bulb-to-bulb distillations. The ^{1}H, ^{13}C, and ^{29}Si NMR spectra were recorded at 23 °C on a

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(13) The PM3 minimum-energy conformers were calculated with the *Spartan'04 Macintosh program system*; Wavefunction, Inc.: Irvine, CA, 2005. In this context, see also: Hehre, W. J. *A Guide to Molecular Mechanics and Quantum Chemical Calculations*; Wavefunction, Inc.: Irvine, CA, 2003.

(14) Kraft, P.; Bruneau, A. *Eur. J. Org. Chem.* **2007**, 2257−2267.

Bruker Avance 500 NMR spectrometer (^{1}H, 500.1 MHz; ^{13}C, 125.8 MHz; ^{29}Si, 99.4 MHz), and C_6D_6 was used as the solvent. Chemical shifts were determined relative to internal C_6HD_5 (^{1}H, δ 7.28), internal C_6D_6 (^{13}C, δ 128.0), or external TMS (^{29}Si, δ 0). Assignment of the ^{1}H NMR data was supported by ^{1}H,^{1}H gradient-selected COSY, ^{13}C,^{1}H gradient-selected HMQC and gradient-selected HMBC, and ^{29}Si,^{1}H gradient-selected HMQC experiments (optimized for $^{2}J_{\mathrm{SiH}} = 7$ Hz). Assignment of the ^{13}C NMR data was supported by DEPT 135 and the aforementioned ^{13}C,^{1}H correlation experiments. The GC analyses were performed with a Shimadzu GC-14B gas chromatograph (Phenomenex Zebron ZB-1 capillary column, 15 m, i.d. 0.32 mm; flow rate, 0.67 mL min^{-1}; injector, split (30 mL min^{-1}), split ratio (1:10), 220 °C; detector (FID), 320 °C; carrier gas, nitrogen; temperature program, 40 °C (2 min) with 20 °C/min). The GC/EI-MS studies were performed with a Thermo MS-8060 gas chromatograph (Phenomenex Zebron ZB-1 capillary column, 15 m, i.d. 0.32 mm; flow rate, 0.73 mL min^{-1}; injector, split (36.6 mL min^{-1}), split ratio (1:25), 220 °C; carrier gas, helium; temperature program, 40 °C (2 min) with 20 °C/min) and a Thermo TRIO 1000 mass spectrometer (EI MS, 70 eV). The IR spectra (neat, NaCl plates) were recorded on a Bruker IFS 55 EQUINOX spectrometer.

Preparation of 4,4,6,6-Tetramethylheptan-2-one (7a). A solution of **8** (10.0 g, 66.2 mmol) in diethyl ether (60 mL) was added dropwise within 1 h to a stirred suspension of magnesium turnings (1.61 g, 66.2 mmol) in diethyl ether (10 mL), causing the reaction mixture to boil under reflux. The mixture was heated under reflux for a further 30 min, cooled to 20 °C, and then added dropwise at −45 °C over a period of 1 h to a stirred suspension of copper(I) iodide (6.30 g, 33.1 mmol) in diethyl ether (50 mL). The reaction mixture was then stirred for 1 h at −45 °C, and a solution of **9** (2.17 g, 22.1 mmol) in diethyl ether (50 mL) was added dropwise at −45 °C within 45 min. The resulting mixture was stirred for 2 h at −45 °C and then allowed to warm to 20 °C within 2 h. The mixture was stirred for 16 h at 20 °C and then added to a mixture consisting of a 25% aqueous ammonia solution (25 mL) and a saturated aqueous ammonium chloride solution (250 mL). The resulting mixture was stirred for 1 h at 20 °C, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The organic solutions were combined, washed with a saturated aqueous sodium chloride solution (100 mL), and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (column dimensions, 50 × 2.5 cm; silica gel (32−63 μm, ICN 02826), 80 g; eluent, *n*-hexane/ethyl acetate (85:15 (v/v))). The relevant fractions (GC control) were combined, the solvent was removed under reduced pressure, and the residue was then purified by bulb-to-bulb distillation (20−30 °C/0.02 mbar) to afford compound **7a** in 63% yield as a colorless, odoriferous liquid (2.36 g, 13.9 mmol). ^{1}H NMR: δ 1.06 (s, 9 H, $C(CH_3)_3$), 1.17 (s, 6 H, $C(CH_3)_2$), 1.52 (s, 2 H, CCH_2C), 1.81 (s, 3 H, $CH_2C(O)CH_3$), 2.17 (s, 2 H, $CH_2C(O)CH_3$). ^{13}C NMR: δ 29.5 ($C(CH_3)_2$), 31.8 ($CH_2C(O)CH_3$), 32.0 ($C(CH_3)_3$), 32.3 ($C(CH_3)_2$), 35.1 ($C(CH_3)_3$), 53.9 (CCH_2C), 55.5 ($CH_2C(O)CH_3$), 206.2 ($C{=}O$). IR: $\tilde{\nu}$ 1719 cm^{-1}. Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.3; H, 13.2. Odor description: Sweet, woody-ambery, Kohinool-like, camphoraceous-aromatic, and fruity odor, with some reminiscence to apricots, natural and powerful. Odor threshold: *GTH*, 65 ng L^{-1}. Headspace concentration at saturation: *HSS*, 3.2 mg L^{-1}. Relative molecular mass: M_r, 170.30 g mol^{-1}. Vapor pressure: *P*, 47 Pa. Odor value: *OV*, 49 230.

Preparation of 4,4,6,6-Tetramethyl-6-silaheptan-2-one (7b). A solution of **10** (25.0 g, 204 mmol) in diethyl ether (100 mL) was added dropwise within 1 h to a stirred suspension of magnesium turnings (4.95 g, 204 mmol) in diethyl ether (5 mL), causing the reaction mixture to boil under reflux. The mixture was heated under reflux for a further 30 min, cooled to 20 °C, and then added dropwise at −45 °C within 1 h to a stirred suspension of copper(I) iodide (19.4 g, 102 mmol) in diethyl ether (50 mL). The reaction mixture was then stirred for 1 h at −45 °C, and a solution of **9** (5.00 g, 50.9 mmol) in diethyl ether (20 mL) was added dropwise at −45 °C over a period of 45 min. The resulting mixture was stirred for 2 h at −45 °C and then allowed to warm to 20 °C within 2 h. After stirring for a further 16 h at this temperature, the reaction mixture was poured into a mixture consisting of a 25% aqueous ammonia solution (100 mL) and a saturated aqueous ammonium chloride solution (300 mL). After stirring for 1 h at 20 °C, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic solutions were washed with a saturated aqueous sodium chloride solution (100 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (column dimensions, 50 × 3.5 cm; silica gel (15−40 μm, Merck 1.1511), 190 g; eluent, *n*-hexane/ethyl acetate (90:10 (v/v))). The relevant fractions (GC control) were combined, the solvent was removed under reduced pressure, and the residue was then purified by bulb-to-bulb distillation (20−30 °C/0.02 mbar) to furnish compound **7b** in 65% yield as a colorless, odoriferous liquid (6.17 g, 33.1 mmol). ^{1}H NMR: δ 0.15 (s, 9 H, $Si(CH_3)_3$), 0.92 (s, 2 H, $SiCH_2C$), 1.16 (s, 6 H, $C(CH_3)_2$), 1.83 (s, 3 H, $CH_2C(O)CH_3$), 2.15 (s, 2 H, $CH_2C(O)CH_3$). ^{13}C NMR: δ 0.9 ($Si(CH_3)_3$), 30.6 ($C(CH_3)_2$), 31.8 ($CH_2C(O)CH_3$), 31.9 ($SiCH_2C$), 33.6 ($C(CH_3)_2$), 56.8 ($CH_2C(O)CH_3$), 206.2 ($C{=}O$). ^{29}Si NMR: δ −1.4. IR: $\tilde{\nu}$ 1718 cm^{-1}. Anal. Calcd for $C_{10}H_{22}OSi$: C, 64.45; H, 11.90. Found: C, 64.1; H, 11.5. Odor description: Sweet, woody-ambery, and Kohinool-like odor, with a fatty undertone and a camphoraceous facet, stronger than **7a**. Odor threshold: *GTH*, 25 ng L^{-1}. Headspace concentration at saturation: *HSS*, 2.8 mg L^{-1}. Relative molecular mass: M_r, 186.37 g mol^{-1}. Vapor pressure: *P*, 37 Pa. Odor value: *OV*, 112 000.

Preparation of 4,4,6,6-Tetramethyl-4-silaheptan-2-one (7c). A solution of **12** (2.70 g, 15.1 mmol) in tetrahydrofuran (THF) (13 mL) was added dropwise within 10 min to a stirred suspension of magnesium turnings (440 mg, 18.1 mmol) in THF (2 mL), causing the reaction mixture to boil under reflux. The mixture was heated under reflux for a further 1 h, cooled to 20 °C, and then added dropwise at −75 °C within 25 min to a stirred solution of acetic anhydride (1.62 g, 15.9 mmol) in THF (5 mL). The reaction mixture was allowed to warm to −40 °C within 4 h, the cooling bath was replaced by an ice bath, and a saturated aqueous ammonium chloride solution (40 mL), water (10 mL), and diethyl ether (40 mL) were added sequentially. The organic layer was separated, the aqueous layer was extracted with diethyl ether (2 × 40 mL), and the combined organic solutions were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by distillation in vacuo to provide **7c** in 71% yield as a colorless, odoriferous liquid (2.01 g, 10.8 mmol); bp 27 °C/0.02 mbar. ^{1}H NMR: δ 0.17 (s, 6 H, $Si(CH_3)_2$), 0.74 (s, 2 H, $(CH_3)_3CCH_2Si$), 1.03 (s, 9 H, $C(CH_3)_3$), 1.90 (t, $^{4}J_{\mathrm{H,H}} = 0.6$ Hz, 3 H, $CH_2C(O)CH_3$), 2.04 (q, $^{4}J_{\mathrm{H,H}} = 0.6$ Hz, 2 H, $CH_2C(O)CH_3$). ^{13}C NMR: δ −0.4 ($Si(CH_3)_2$), 30.9 ($CH_2C(O)CH_3$), 31.7 ($(CH_3)_3CCH_2$-Si), 32.6 ($C(CH_3)_3$), 33.0 ($C(CH_3)_3$), 38.7 ($CH_2C(O)CH_3$), 204.4 ($C{=}O$). ^{29}Si NMR: δ −1.0. IR: $\tilde{\nu}$ 1692 cm^{-1}. Anal. Calcd for $C_{10}H_{22}OSi$: C, 64.45; H, 11.90. Found: C, 64.4; H, 12.2. Odor description: Sweet, woody-ambery, Kohinool-like, and camphoraceous-earthy odor, with agrestic-aromatic and animalic facets, stronger than **7a**, but also more camphoraceous and harsher. Odor threshold: *GTH*, 10 ng L^{-1}. Headspace concentration at saturation: *HSS*, 1.6 mg L^{-1}. Relative molecular mass: M_r, 186.37 g mol^{-1}. Vapor pressure: *P*, 21 Pa. Odor value: *OV*, 160 000.

Preparation of 4,4,6,6-Tetramethyl-4,6-disilaheptan-2-one (7d). A solution of **13** (7.00 g, 35.9 mmol) in diethyl ether (50 mL) was added dropwise within 30 min to a stirred suspension of magnesium turnings (873 mg, 35.9 mmol) in diethyl ether (5 mL), causing the reaction mixture to boil under reflux. The mixture was heated under reflux for a further 2 h, cooled to 20 °C, and then added dropwise at −75 °C within 90 min to a stirred solution of acetic anhydride (3.49 g, 34.2 mmol) in diethyl ether (40 mL). The reaction mixture was allowed to warm to −40 °C within 5 h, the cooling bath was replaced by an ice bath, and a saturated aqueous ammonium chloride solution (120 mL) and water (20 mL) were added sequentially. The organic layer was separated, the aqueous layer was extracted with diethyl ether (3 × 75 mL), and the combined organic solutions were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation (20−30 °C/0.02 mbar) with subsequent distillation in vacuo to furnish **7d** in 83% yield as a colorless odoriferous liquid (5.73 g, 28.3 mmol); bp 29−30 °C/0.02 mbar. ^{1}H NMR: δ −0.24 (s, 2 H, SiCH_2Si), 0.12 (s, 9 H, Si(CH_3)$_3$), 0.15 (s, 6 H, Si(CH_3)$_2$), 1.91 (s, 3 H, CH$_2$C(O)CH_3), 2.08 (s, 2 H, CH_2C(O)CH$_3$). ^{13}C NMR: δ −0.1 (Si(CH$_3$)$_2$), 1.3 (Si(CH$_3$)$_3$), 2.8 (SiCH$_2$Si), 31.7 (CH$_2$C(O)CH$_3$), 39.7 (CH$_2$C(O)-CH$_3$), 204.4 (C=O). ^{29}Si NMR: δ 0.0, 0.6. IR: $\tilde{\nu}$ 1692 cm^{-1}. Anal. Calcd for $C_9H_{22}OSi_2$: C, 53.40; H, 10.95. Found: C, 53.4; H, 10.8. Odor description: Camphoraceous-earthy odor, with green-fruity facets and acidic, sweaty, and butyric aspects, more earthy than **7c**. Odor threshold: *GTH*, 5 ng L^{-1}. Headspace concentration at saturation: *HSS*, 1.1 mg L^{-1}. Relative molecular mass: M_r, 202.44 g mol^{-1}. Vapor pressure: *P*, 13 Pa. Odor value: *OV*, 220 000.

1-Bromo-2,2-dimethylpropane (8). This compound was commercially available.

4-Methyl-3-penten-2-one (9). This compound was commercially available.

(Chloromethyl)trimethylsilane (10). This compound was commercially available.

Chloro(chloromethyl)dimethylsilane (11). This compound was commercially available.

Preparation of 1-Chloro-2,2,4,4-tetramethyl-2-silapentane (12). Naphthalene (15.9 g, 124 mmol) was added to a mechanically stirred suspension of a 30 wt-% lithium dispersion in mineral oil (2.86 g, 124 mmol of lithium) in THF (250 mL), and the resulting mixture was stirred for 3 h at 20 °C. The suspension was cooled to −60 °C, and a solution of **8** (14.0 g, 92.7 mmol) in THF (15 mL) was added dropwise within 15 min. The reaction mixture was stirred for a further 30 min at −60 °C, and then a solution of **11** (13.3 g, 93.0 mmol) in THF (15 mL) was added dropwise within 15 min. After stirring for a further 10 min at −60 °C, the reaction mixture was poured into water (250 mL). Diethyl ether (200 mL) was added, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 150 mL). The combined organic solutions were washed with a saturated aqueous sodium chloride solution (100 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (column dimensions, 70 × 5 cm; silica gel (32−63 μm, ICN 02826), 450 g; eluent, *n*-pentane). The relevant fractions (GC control) were combined, the solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation (70−100 °C/12 mbar) to give **12** in 48% yield[15] as a colorless liquid (5.30 g, 29.6 mmol). ^{1}H NMR: δ 0.18 (s, 6 H, Si(CH_3)$_2$), 0.75 (s, 2 H, CCH_2Si), 1.01 (s, 9 H, C(CH_3)$_3$), 2.64 (s, 2 H, SiCH_2Cl). ^{13}C NMR: δ −2.3 (Si-(CH$_3$)$_2$), 30.7 (C(CH$_3$)$_3$), 30.9 (CCH$_2$Si), 31.6 (SiCH$_2$Cl), 32.9 (C(CH$_3$)$_3$). ^{29}Si NMR: δ 1.2. Anal. Calcd for $C_8H_{19}ClSi$: C, 53.75; H, 10.71. Found: C, 53.3; H, 10.6.

Preparation of 1-Chloro-2,2,4,4-tetramethyl-2,4-disilapentane (13). A solution of **10** (50.0 g, 408 mmol) in THF (100 mL) was added dropwise within 30 min to a stirred suspension of magnesium turnings (11.9 g, 490 mmol) in THF (10 mL), causing the reaction mixture to boil under reflux. The mixture was heated under reflux for a further 2 h, cooled to 20 °C, and then added dropwise within 20 min to a stirred solution of **11** (58.4 g, 408 mmol) in THF (100 mL), causing the reaction mixture to boil under reflux. The mixture was heated under reflux for a further 15 min, cooled to 20 °C, and then stirred for 16 h at 20 °C, prior to pouring it into a half-saturated aqueous ammonium chloride solution (150 mL), which was cooled in an ice bath. The resulting mixture was allowed to warm to 20 °C, the organic layer was separated, the aqueous layer was extracted with diethyl ether (3 × 150 mL), and the combined organic solutions were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by distillation in vacuo to furnish compound **13** in 82% yield as a colorless liquid (65.1 g, 334 mmol); bp 68−70 °C/13 mbar. ^{1}H NMR: δ −0.24 (s, 2 H, SiCH_2Si), 0.10 (s, 9 H, Si-(CH_3)$_3$), 0.16 (s, 6 H, Si(CH_3)$_2$), 2.64 (s, 2 H, SiCH_2Cl). ^{13}C NMR: δ −2.1 (Si(CH$_3$)$_2$), 1.0 (SiCH$_2$Si), 1.2 (Si(CH$_3$)$_3$), 32.1 (SiCH$_2$Cl). ^{29}Si NMR: δ 0.1, 2.6. Anal. Calcd for $C_7H_{19}ClSi_2$: C, 43.15; H, 9.83. Found: C, 43.2; H, 9.6.

Determination of Odor Thresholds. The odor threshold values were determined by GC-olfactometry. Different dilutions of the sample substances were injected into a gas chromatograph in descending order of concentration. Without seeing the recorded trace, the panelist smelled in blind and pressed a button whenever he detected an olfactory impression. The experiment was continued until the panelist failed to detect an odor at the right retention time. The lowest concentration correctly detected defines the respective GC odor threshold (*GTH* [ng L^{-1}]).

Determination of Vapor Pressures. The vapor pressures (*P*) were determined by quantitative headspace analysis.[11,12] The sample substance (250 mg) was transferred into a 100 mL Erlenmeyer flask, which was closed with a two-inlet cone joint. One inlet was connected via a headspace microfilter (Porapak Super Q) to a battery-operated pump, the other one to an air filter. The device was kept at 25 °C to ensure phase distribution equilibrium, and under quasi-static conditions an exactly defined volume (19.6 mL) was sucked through the adsorption trap. The headspace components were then desorbed from the filter and quantified by GC. The reported headspace concentration at saturation (*HSS* [mg L^{-1}]) was calculated as the geometrical mean of two independent measurements each. Since the test compounds are ideal-diluted in air, the vapor pressure P [Pa = kg m^{-1} s^{-2}] is given via the perfect gas law as $P = \mathrm{R}Tn/V$, with the gas constant $\mathrm{R} = 8.314$ kg m^2 s^{-2} K^{-1} mol^{-1}, the temperature $T = 298.15$ K, and the concentration $n/V = HSS/M_r$ of the respective substance with a relative molecular mass M_r.

Determination of Odor Values. While the odor threshold tells something about the receptor affinity, the potency of an odorant is best described by its odor value (*OV*), which takes into account the vapor pressure. Also known as "aroma value" or "odor unit number",[12] the odor value (*OV*) of a substance is defined as the quotient of its headspace concentration at saturation (*HSS*) and its odor threshold concentration (*GTH*). Thus, the odor value is given by the equation $OV = HSS/GTH$.

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[15] The yield is related to the half-molar equivalent of lithium (62 mmol).