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Synthesis and Olfactory Properties of a 6'-Silasubstituted "Spiro[4.5]-δ-Damascone"

Martin A. Lovchik[a] and Philip Kraft*[a]

Dedicated to Christian Chapuis on the occasion of his 60th birthday

Abstract: The silicon analogue of the potent spirocyclic δ-damascone odorant **6** was synthesized from allyltrichlorosilane (**15**) and but-2-en-1-ol (**16**). The latter was transformed to 3-methylpen-4-enenitrile (**11**) by Saucy–Marbet reaction with ethoxyethane and subsequent treatment with $HONH_2 \cdot HCl$. The resulting γ,δ-unsaturated nitrile **11** was silylated with 1-allyl-1-chlorosilolane (**14**), which was prepared from allyltrichlorosilane (**15**) and the bis-Grignard reagent of 1,4-dichlorobutane. Metathetic ring closure employing the Grubbs I catalyst, followed by DIBAL reduction with non-aqueous work up, Grignard reaction with prop-1-en-1-ylmagnesium bromide, and Attenburrow MnO_2 oxidation concluded the synthesis. The target compound was found to be olfactorily related to the spiro[4.5]-δ-damascone lead, but ca. 900 times weaker. In a type of enol Brook rearrangement it thermally decomposes however to 3,6-dihydro-2*H*-1,2-oxasilocine (**20**), which surprisingly is a damascone odorant as well; yet, even 12'000 times weaker.

« *Stained glass syrup*
Serenades in damascone minor
Allegory obscured / pastel wound
A slurry of subtlety»
'Sådanne'[1] by Josh Lobb

Introduction

With some 5% of β-damascone (**2**, Fig. 1), 'Sådanne' (Slumberhouse, 2014)[1] by Josh Lobb is with some certainty the fine fragrance with the highest rose ketone dosage ever. Due to their price and IFRA regulations, the practical upper limit of rose ketones in fine fragrances is today rather in the 0.15% range. Recent examples for β-damascenone (**3**) dosages in that upper range are for instance 'Olympea' (Paco Rabanne, 2015) by Loc Dong, Anne Flipo and Dominique Ropion, and 'Invictus' (Paco Rabanne, 2013) by Veronique Nyberg, Anne Flipo, Olivier Polge and Dominique Ropion. All rose ketones possess floral-fruity odors,[2] but the nuances differ distinctly. With more pronounced woody, tobacco and camphoraceous facets, α-damascone (**1**, Fig. 1) is considered the most masculine rose ketone, while the plumy and sweeter odor of β-damascone (**2**) makes it typically feminine.

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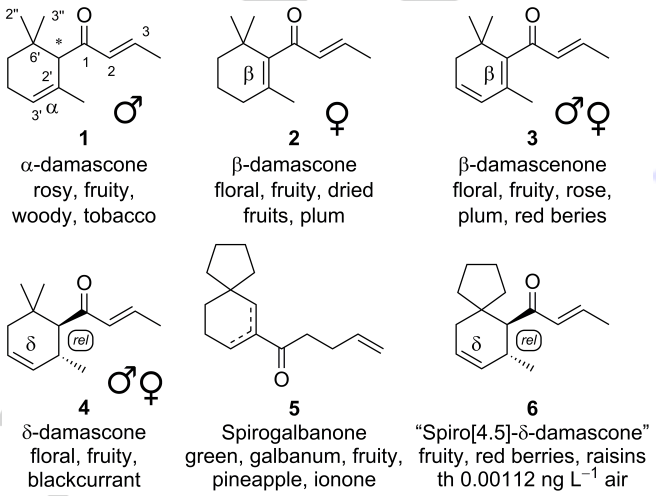


Fig. 1. The commercially important rose ketones **1**–**4**, as well as Spirogalbanone (**5**),[3] and the "Spiro[4.5]-δ-damascone" (**6**).[4]

In 'Sådanne', which translates from Danish into 'There you have it!', the 5% of β-damascone (**2**) in an accord with rose absolute, cinnamic alcohol and anisyl acetate, creates the image of a red fruits–rose petals jelly dressed up with raspberry syrup. Thus, 'Sådanne' demonstrates that there are very interesting effects beyond the skin sensitization limits of the IFRA norms. In laundry and detergent applications, the low odor threshold at a competitive cost makes δ-damascone (**4**) most popular to convey fruity freshness. With its blackcurrant and winy character δ-damascone (**4**) is like β-damascenone (**3**) truly unisex.

The only drawback of δ-damascone (**4**) in laundry and detergent applications is its lack of substantivity on fabric. Like the other rose ketones **1**–**3**, δ-damascone (**4**) is too volatile. In the related family of galbanum odorants, replacement of the geminal dimethyl group with a spiroannulated cyclopentyl ring led to Spirogalbanone (**5**),[3] which solved the lack in substantivity. Although the odorant receptors for galbanum odorants and damascones are unlikely related, the concept was nevertheless successfully transferred to the damascone family, and the corresponding "spiro[4.5]- δ-damascone" (**6**)[4] constitutes a very substantive fruity damascone odor reminiscent of red berries and raisins.

Substitution of quaternary carbon atoms by silicon is a way to further increase the molecular weight, thereby reducing the vapor pressure without overly affecting the electronic shape, and thus the receptor activity.[5] Generally, more substantive odorants result from such sila-substitutions, and in some cases such as for disila-Okoumal[6] and silicon-based patchouli

odorants,[7] the odor thresholds improved as well and compensated for the loss in volatility. In the case of Spirogalbanone (**5**), however, the odor detection threshold increased by a factor of about 170 from 0.023 ng L^{-1} air to 3.8 ng L^{-1} for the more potent α-isomer.[8]

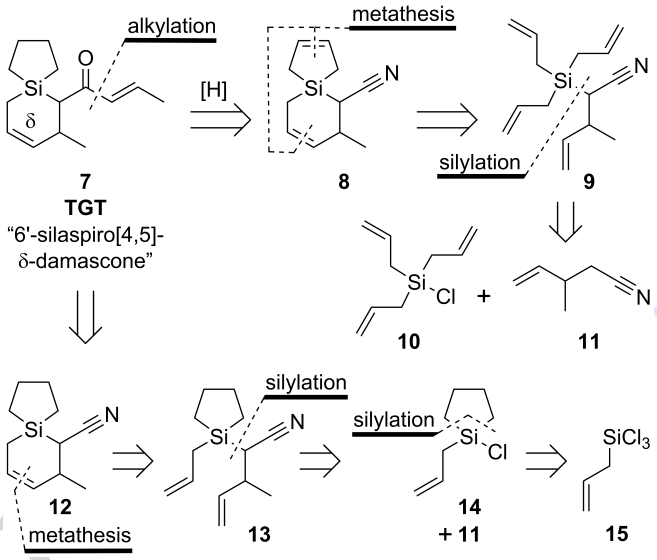
For the "spiro[4.5]- δ-damascone" (**6**) case, the outcome was completely open, and the prospect that a sila-substitution could lower the threshold and would in addition even further increase the substantivity, made "6'-silaspiro[4.5]- δ-damascone" (**7**) a highly attractive target (TGT). Furthermore, the sila-spiro atom potentially offered an easier synthetic access than the parent carbon compound **6**, since it could be constructed by simple Grignard-type alkylations on the central silicon atom. We had already made advantage of such a strategy in the synthesis of the silicon-based patchouli odorants,[7] and with a metathetic ring closure spirocyclic compounds should in principle be easily available as well.

Results and Discussion

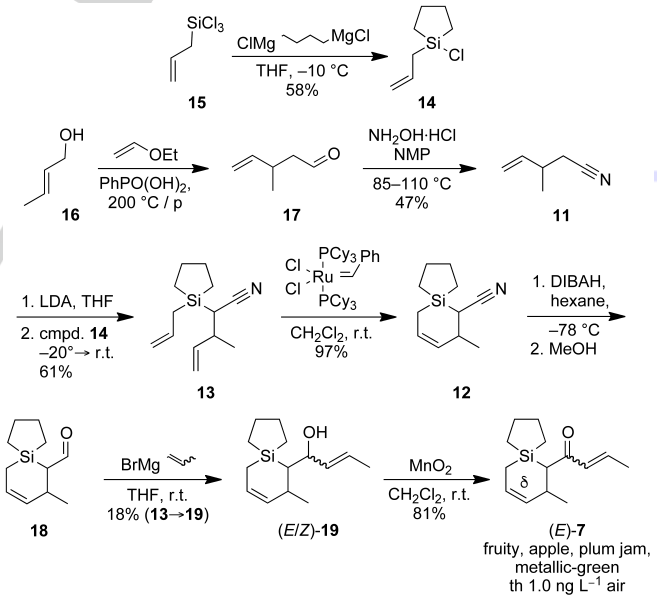
As delineated in Scheme 1, the retrosynthetic analysis of our silaspirocyclic TGT compound **7** suggested that a double metathesis strategy could in principle be used in the construction of the spirocyclic system. Introducing the but-2-en-1-one side chain by alkylation of the corresponding nitrile, and strategically placing a double bond in the five-membered ring in **8** which, due to its strain, could potentially be selectively reduced in a later stage. The two double bonds could be constructed metathetically from the triallylsilyl compound **9**, which itself should be accessible by silylation of 3-methylpent-4-enenitrile (**11**) with triallylsilyl chloride (**10**). While this strategy worked out well including the metathetic ring closure to compound **8** (83% yield with Grubbs I),[9] both in our hands and in the course of a collaborative PhD project,[9] all attempts to alkylate the nitrile **8** failed utterly, leading either to complete decomposition or no reaction at all. Preliminary DIBAL reduction of **8** furnished, in a mere 5% yield, the corresponding aldehyde, which proved so labile that Grignard reaction with prop-1-en-1-yl magnesium bromide or prop-1-en-1-yl lithium failed completely. The route was thus abandoned.

Leaving the silacyclopentane moiety intact, but still introducing the side chain by alkylation of the corresponding nitrile leads to 7-methyl-5-silaspiro[4.5]dec-8-ene-6-carbonitrile (**12**). Metathetical construction of the cyclohexenyl ring would require the 2-(1'-allylsilolan-1'-yl)-3-methylpent-4-enenitrile (**13**, Scheme 1). This should in turn be accessible by 2-silylation of 3-methylpent-4-enenitrile (**11**) with 1-allyl-1-chlorosilolane (**14**), which could be prepared by spiroannulation of allyltrichlorosilane (**15**).

As this route seemed promising, 1-allyl-1-chlorosilolane (**14**) was prepared following the general procedure of House, Hrabie and Narasimhan.[10] Allyltrichlorosilane (**15**) was reacted at –10 °C with the bis-Grignard reagent prepared from 1,4-dichlorobutane and magnesium. After leaving the reaction to warm to room temp. overnight, filtration under N_2, concentration and distillation over a 15 cm Vigreux column, chlorosilolane **14** was obtained in 58% yield as clear, colorless liquid.



Scheme 1. Retrosynthesis of our target structure, the 6'-sila-substituted "Spiro[4.5]-δ-damascone" (**7**).



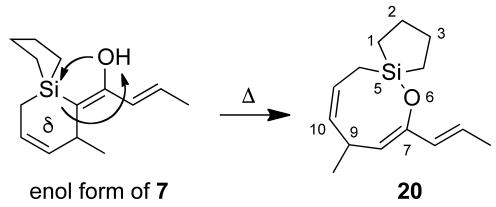
Scheme 2. Synthesis of the 6'-sila-substituted "Spiro[4.5]-δ-damascone" (**7**) from allyltrichlorosilane (**15**) and but-2-en-1-ol (**16**).

For the synthesis of the second building block, the nitrile **11** of the corresponding γ,δ-unsaturated aldehyde **17**, use was made of a Saucy–Marbet reaction,[11] a strategy we had successfully applied for a building block in the synthesis of a potential human pheromone.[12] Heating but-2-en-1-ol (**16**) and ethoxyethane in an autoclave to 200 °C for 1.5 h in the presence of

phenylphosphoric acid as catalyst afforded, after concentration under reduced pressure, crude 3-methylpen-4-enal (**17**). Without further purification this was added over the course of 4 h to a solution of hydroxylamine hydrochloride in NMP at 85° upon which the temp. rose to 100–110 °C. After quenching with water, extraction and distillation, the γ,δ-unsaturated nitrile **11** was isolated in an overall 47% yield.

In the next step, nitrile **11** was deprotonated with lithium diisopropylamide at –20°C, and then reacted with the first building block **14**. After 15 min. of stirring, the cooling bath was removed, and after further 1 h at room temp. the reaction was quenched with water. Extraction and bulb-to-bulb distillation provided the diene nitrile **13** in 61% yield ready for the central metathesis step. The metathesis of **13** went smoothly employing Grubbs' first generation catalyst[13, 14] in dichloromethane, and after 48 h GC monitoring indicated complete conversion. After work up and Kugelrohr distillation the 5-silaspiro[4.5]dec-8-ene (**12**) was obtained in 97% yield, and subjected to DIBAH reduction in hexane at –78 °C. However, all aqueous quenching and work up attempts, e.g. with satd. aq. NH_4Cl or potassium sodium tartrate, led to unsatisfactory yields of **18** in the range of 1%. As was suspected from the GC monitoring of the work up, the 7-methyl-5-silaspiro[4.5]dec-8-ene-6-carbaldehyde (**18**) seemed unstable and highly reactive towards water. In order to avoid the decomposition of the carbaldehyde **18**, the non-aqueous quenching procedure of Stoltz, Kano and Corey was therefore tried.[15] Accordingly, the DIBAH reduction of **12** was quenched at –78 °C by addition of methanol followed by sodium sulfate decahydrate and Celite. The coagulated solid material was removed by filtration, and the filtrate containing the crude aldehyde **18** was concentrated to half of its volume, and treated as such with excess Grignard reagent prepared from (2*E*/*Z*)-1-bromoprop-2-ene in THF. The Grignard reaction was quenched with satd. aq. NH_4Cl, and the product (*E*/*Z*)-**19** isolated by flash chromatography as a 3:2 mixture of (*E*/*Z*)-diastereoisomers, already enrichted in the desired (*E*) isomer. The (*E*) enricherd mixture of the alcohol (*E*/*Z*)-**19** was isolated in 18% yield over two steps, based on nitrile **12**.

The concluding Attenburrow MnO_2 oxidation[16] of (*E*/*Z*)-**19** was straightforward, and the odoriferous pure (*E*)-configured target compound **7** was isolated by chromatography in 61% yield. The (*E*)-configuration of the double bond in the side chain is apparent from the respective ^3J coupling of 16.0 Hz in the ^{1}H NMR spectrum.



enol form of **7** **20**

Scheme 3. Thermal ring enlargement of the "spiro[4.5]-δ-damascone" (**7**) target by intramolecular nucleophilic attack of the carbonyl oxygen on the silolane silicon.

However, upon GC experiments to determine the odor threshold of target compound (*E*)-**7**, its high thermal instability became evident. It was only possible to determine the threshold of the main decomposition product **20** as 13.7 ng/L air; the target structure (*E*)-**7** itself was not detectable. To investigate the course of the thermal decomposition, 10 μg of **20** was isolated for structure elucidation by preparative GC. Its enol ether substructure was immediately apparent from the strong downfield shift of the double bond singlet at 148.1 ppm, and the missing carbonyl signal in the ^{13}C NMR spectrum. HSQC and HMBC experiments then unambiguously corroborated the 3,6-dihydro-2*H*-1,2-oxasilocine ring and allowed for the full structural assignment of decomposition product **20**. As delineated in Scheme 3, especially in the enol form of **7**, the silicon atom becomes highly susceptible to nucleophilic attack by the hydroxy group in α-position, and the associated flattening of the 6-membered ring in the strained 5-silaspiro[4.5]dec-8-en-6-ylidene system increases the reactivity even further. Basically, this is a Brook rearrangement of a ketone via its enol form that does not require the presence of an acid or base. Matsuda et al.[17] as well as Larson et al.[18] made use of this type of thermal rearrangement in the regio- and stereodefined synthesis of (*E*)- or (*Z*)-configured silyl enol ethers, which they carried out at 140 °C and 175 °C, respectively. Target compound **7** seemed In our hands thermally instabile even at lower temperatures, which makes silaspirocyclic damascones unsuitable for fragrance applications; yet, the olfactory properties of (*E*)-**7** and **20** were still highly interesting for structure–odor correlations.

A possible reason for the high thermal reactivity could be the electron-donating properties of the spirocyclic sila atom, a strong electron releasing group (ERG) especially on its own and even more so in a strained ring system. This also would explain why the more strained system **8** could not be alkylated to a carbonyl system at all. A similar silicon hyperconjugation of the σ orbital (β-silicon effect) with the partially positively charged carbonyl carbon led to the instability of 4,4,6,6-tetramethyl-4-silaheptan-2-one and its 4,6-disila analogue, even without any ring strain involved.[19] In these systems the IR stretching vibration (ν) was shifted from 1719 cm^{-1} to 1692 cm^{-1}, while the C=O vibration of (*E*)-**7** was even observed as a finger band at 1672 cm^{-1} and 1652 cm^{-1}.

Olfactory Properties and Conclusions

Most interestingly, on GC–olfactometry even the 3,6-dihydro-2*H*-1,2-oxasilocine decomposition product **20** possesses a fruity, damascone-like odor, albeit with distinct woody and green inflections. Yet, with a GC detection odor threshold of 13.7 ng/L air it is 12'000 times weaker in threshold than the "Spiro[4.5]-δ-damascone" (**6**) lead. Due to its thermal instability it was impossible to determine the detection odor threshold of the target sila-analogue (*E*)-**7** directly by GC–olfactometry, so we

determined it by a classical dilution series against the parent carba structure with its outstanding value of 0.00112 ng/L air. Thereby an odor detection threshold of 1.0 ng/L air was designated to the target compound (*E*)-**7**, which means in terms of threshold (*E*)-**7** is about 900 times weaker than the parent carba lead structure **6**. In its qualitative olfactory properties, (*E*)-**7** is however a typical rose ketone, directly related to β-damascenone (**3**). It was characterized as fruity in the direction of apple and plum, more specifically stewed apple and plum jam, with reminiscence to β-damascenone (**3**) with some additional metallic-green nuances. So (*E*)-**7** definitely addresses the olfactory rose ketone receptors; yet, with a significantly lower affinity than the parent carba lead **6**. With its even lower affinity but still damascone-like odor, the thermal rearrangement product **20** can be considered to outline the maximum dimensions of damascone odorants.

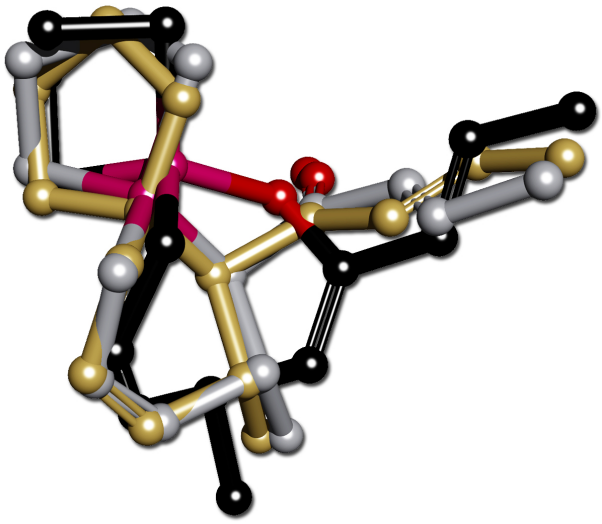


Fig. 2. Flexible superposition of the "Spiro[4.5]-δ-damascone" (**6**, in gold), the target sila-analogue (2*E*)-**7** (in silver) and its thermal decomposition product **20** (in black) employing the MOE2015.10 software package. Selection criterion was the lowest *F* value (–99.0535889), which is the negative value of the *P*-density overlap function as a similarity measure. The lower the *F* value, the greater the similarity.[20]

To get an impression of the binding site dimensions for damascone odorants, the structures of the "Spiro[4.5]-δ-damascone" (**6**) lead, the molecular target (*E*)-**7** and its thermal decomposition product **20** were flexibly superimposed employing the MOE2015.10 software package with an Amber10:EHT forcefield.[20] As (*E*)-**7** was obtained as a mixture of *syn*/*anti* isomers, which due to its instability was impossible to isomerize to the *all-anti* derivatives, and since it was already significantly weaker in intensity, only the better superimposing *anti*-isomer has been selected for the structural analysis assuming the same stereoisomeric preferences. The overlay with the lowest *F* value (–99.0535889) as measure of the configurational similarity is depicted in Fig. 2. As expected, the sila substitution leads to an enlargement of the ring systems and the overall shape with an effect even on the conformation of the but-2-en-1-one side chain; the factor of 900 of difference in detection threshold is still impressive, and indicates a high complementarity of **6** to the rose ketone receptors. It is not surprising that the overlay of the 3,6-dihydro-2*H*-1,2-oxasilocine decomposition product **20** on both **6** and (*E*)-**7** is less good, but explaines why it still bears some olfactory reminiscence to the damascone family. The shape of **20** therefore marks the maximum dimensions of the binding site(s) for rose ketone odorants. So despite the synthetic difficulties en route to the (2*E*)-1-(7'-methyl-5'-silaspiro[4.5]dec-8'-en-6'-yl)but-2-en-1-one [(*E*)-**7**] target, the thermal instability as well as the rather disappointing olfactory properties, it was still very useful for gaining insight into the structural requirements for damascone odorants. Since the asymmetric synthesis of building block **17** by Evans alkylation[21],[22] has been reported, it would be possible to fix the stereochemistry of C-7' in target compound (*E*)-**7;** yet, at maximum the threshold would be halved in case of only one enantiomer smelling. The thermal instability of **7** and considerable synthetic efforts would therefore not make up for this gain in insight as it is evident that **7** will never be a potent and commercially viable odorant. All related sila damascones will likely suffer from the same shortcomings if the sila atom is situated in α-position to an oxygen functionality.

Experimental Section

General Details. – Column Chromatography was performed on silica gel 60 Merck, particle size 40–63 μm and aluminum oxide, basic, Brockmann V, particle size 50-200 μm, 60 A. Mixtures of hexane (hex) and ethyl acetate (EtOAc) were used as eluent. Thin layer chromatography was performed on commercial 60-mesh silica gel plates, visualization was effected with short wavelength UV light (254 nm) and $KMnO_4$ or $Ce(SO_4)_2$ as staining reagents. For Al_2O_3-coated TLC plates Macherey-Nagel Polygram precoated polyester sheets (0.2 mm) were used. Standard GC analysis was performed with an Agilent 5890/Chemstation employing a ZB1 column (15 m, 0.53 mm), H_2 as carrier gas (3.0 ml/min), and 1 μl injection volume. IR spectra were recorded on Spectrum One FT-IR- and Bruker Vector 22 FT-IR-spectrometers. The relative intensities of the absorption bands are indicated as vs = very strong (> 90%), s = strong (70–90%), m = medium (40–70%), w = weak (<40%). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance IIIHD (400 MHz, 5mm BBFO probe head) or a Bruker Avance III (600 MHz, 1.7 mm micro cyo-probe TCI) spectrometer; δ in ppm, J in Hz, $CDCl_3$ and C_6D_6 were used as solvents. Chemical shifts are given in ppm relative to internal TMS. Multiplicities are specified as s (singlet), d (doublet), t (triplet), and m (multiplet). In ^{13}C-NMR spectra the solvent served as internal standard, e.g. $CDCl_3$ (δ = 77.00 ppm, t, J_{CD} = 31.5 Hz). The multiplicity is designated as q (quartet), t (triplet), d (doublet) and s (singlet). Mass spectra were measured in electron impact (EI) mode at 70 eV, with

230 °C ion-source temp. GC-MS was measured routinely on a HP MSD 5975C instrument with a 12 m BPX5 column from SGE. HPLC high resolution mass spectra (LC-HRMS) were recorded on a Q-Exactive Orbitrap (Thermo Scientific) instrument. Most products were purified by fractionated distillation or short path Kugelrohr distillation. The vacuum was provided either by a rotary slide pump (0.05 mbar) or a membrane vacuum pump (10 mbar). Dichloromethane was purchased from Fisher Chemical (D/1852/15), all other chemicals were purchased from Sigma–Aldrich and Chemie Brunschwig, and were used without further purification.

1-Allyl-1-chlorosilolane (14). Mg turnings (7.27 g, 299 mmol) were placed in a 500 ml sulfonation flask and covered with THF (10 mL). A crystal of I_2 was added, followed by a soln. of 1,4-dichlorobutane (18.1 g, 142 mmol) in THF (150 mL) while heating the mixture gently with a hot air gun. When the reaction set in, the remaining 1,4-dichlorobutane soln. was added at such a rate as to maintain a gentle reflux. A soln. of allyltrichlorosilane (**15**, 25.0 g, 142 mmol) and Et_2O (355 mL) was placed in a 1000 mL sulfonation flask under inert conditions. At –10 °C, the soln. of the bis-Grignard reagent was transferred into a dropping funnel, and added dropwise to the well-stirred soln. of allyltrichlorosilane (**15**) over the period of 1 h while maintaining the temp. at –10 °C. The reaction mixture was then left to warm to room temp. and stirred over night. The resulting thick, opaque suspension was filtered rapidly under an atmosphere of N_2. The filtrate was partially concentrated on a rotary evaporator under reduced pressure to remove most of the Et_2O. The residual THF soln. was transferred to a distillation apparatus with a 15 cm Vigreux column. The THF was removed at 100 mbar, and the resulting residue distilled to afford at 40–45 °C/1 mbar compound **14** (13.3 g, 58% yield) as a clear, colorless liquid that fumes in contact with air. IR (neat): 3081vw, 2936m, 2862m, 1632m. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (m_c, 1 H, 2'-H), 5.06–4.94 (m, 2 H, 3'-H_2), 1.96 (dt, *J* = 8.0, 1.0 Hz, 2 H, 1'-H_2), 1.79–1.67 (m, 2 H, 3-, 4-H_b), 1.64–1.53 (m, 2 H, 3-, 4-H_a), 0.95–0.81 (m, 4 H, 2-, 5-H_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.8 (d, C-2'), 115.6 (t, C-3'), 26.0 (2t, C-3, -4), 24.7 (t, C-1'), 13.8 (2t, C-2, -5). GC-MS (EI, tR 3.93 min): m/z (%) = 160 (12, [M^+]), 121 (34), 120 (11), 119 (100), 117 (22), 93 (81), 91 (18), 83 (15), 65 (11), 63 (25). Anal. calc. for $C_7H_{13}SiCl$ (160.72): C 52.31, H 8.15; found: C 52.07, H 8.25.

3-Methylpent-4-enenitrile (11). A mixture of but-2-en-1-ol (**16**, 120.0 g, 1664 mmol) and ethoxyethene (300.0 g, 4161 mmol) was placed in an autoclave. Phenylposphonic acid (300 mg, 1.90 mmol) was added and the reactor was sealed. The mixture was heated with stirring to 200 °C for 1.5 h (**Caution**: Upon heating the pressure rises to 130 bar, which the equipment needs to sustain). The autoclave was then allowed to cool to room temp., and the reaction mixture concentrated in vacuo to afford crude 3-methylpent-4-enal (**17**). A soln. of hydroxylamine hydrochloride (160.0 g, 2318 mmol) in NMP (660 mL) was heated to 85 °C, the heating source was removed and the crude 3-methylpent-4-enal (**17**) was added over the period of 4 h, during which the temp. rose to 100–110 °C. The mixture was stirred at 85 °C for an additional 10 min., and then poured into water (2.5 L). The aq. layer was extracted with pentane (2 × 500 mL), and the organic extracts were combined, washed with water (3 × 100 mL) and brine (200 mL), and then dried ($MgSO_4$). Distillation over a 15 cm Vigreux column afforded **11** as a colorless liquid (75.0 g, 47% yield; bp 80 °C/100 mbar). IR (neat): 3085w, 2970m, 2934w, 2248m, 1644m, 921vs. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78 (ddd, *J* = 18.0, 10.5, 7.0 Hz, 1 H, 4-H), 5.17–5.08 (m, 2 H, 5-H_2), 2.57 (m_c, 1 H, 3-H), 2.37 (dd, *J* = 6.5, 4.5 Hz, 2 H, 2-H_2), 1.18 (d, *J* = 7.0 Hz, 3 H, 3-Me). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.9 (d, C-4), 118.3 (s, C-1), 115.1 (t, C-5), 34.2 (d, C-3), 24.2 (t, C-2), 19.0 (q, 3-Me). GC-MS (EI, tR 3.03 min): m/z (%)= 95 (6, [M^+]), 94 (11), 68 (22), 67 (11), 55 (100), 53 (23), 41 (111), 40 (7), 39 (22), 29 (14), 27 (17). Anal. calc. for C_6H_9N (95.14): C 75.74, H 9.53, N 14.72; found: C 75.58, H 9.77, N 14.65.

2-(1'-Allylsilolan-1'-yl)-3-methylpent-4-enenitrile (13). At –40 °C, a 3 M soln. of BuLi in hexane (112 mL, 336 mmol) was added portionwise to a stirred soln. of diisopropylamine (18.1 g, 179 mmol) in THF (240 mL). At –20 °C, nitrile **11** (15.6 g, 164 mmol) was added dropwise, and the resulting mixture was stirred for 30 min prior to the portionwise addition of silylchloride **14** (24.0 g, 149 mmol). After 15 min of stirring at –20 °C, the mixture was allowed to warm to room temp., and after further stirring for 1 h, the mixture was quenched with water (500 mL). The aqueous layer was extracted with *t*-BuOMe (2 × 200 mL). The organic extracts were combined, washed with water (2 × 100 ml) and brine (100 ml), dried ($MgSO_4$), and concentrated in vacuo to afford crude **13** as a slightly yellowish oil, which was purified by bulb-to-bulb distillation (140 °C/0.05 mbar) to provide the silylated nitrile **13** as a colorless liquid (20.0 g, 61% yield). IR (neat): 3079w, 2931s, 2859m, 2219m, 1630m. ^{1}H NMR (400 MHz, $CDCl_3$), mixture of diastereomers: δ = 5.92–5.68 (m, 2 H, 4-, 2''-H), 5.20–4.90 (m, 4 H, 5-, 3''-H_2), 2.55 (m_c, 1 H, 3-H), 2.11 (d, *J* = 5.5 Hz)/2.09 (d, *J* = 4.5, 1 H, 2-H), 1.84–1.76 (m, 2 H, 1''-H_2), 1.76–1.50 (m, 4 H, 3'-, 4'-H_2), 1.24 (d, *J* = 7.0, 3 H, 3-Me), 0.89–0.67 (m, 4 H, 2'-, 5'-H_2). ^{13}C NMR (100 MHz, $CDCl_3$), mixture of diastereomers: δ = 141.6/139.9/132.6/132.5 (4d, C-4, -2''), 120.3/120.2 (2s, C-1), 115.7/115.1/115.0/114.6 (4t, C-5, -3''), 36.4/36.1 (2d, C-3), 26.9/26.9/26.8/26.7 (4t, C-3', -4'), 24.0/23.5 (2d, C-2), 21.7/19.2 (2q, 3-Me), 20.1/20.0 (2t, C-1''), 10.2/9.9/9.8/9.8 (4t, C-2', -5'). GC-MS (EI, tR 7.92 min): m/z (%) = 219 (1, [M^+]), 179 (18), 178 (100), 125 (37), 124 (18), 122 (16), 98 (15), 97 (32), 83 (27), 55 (14), 43 (12). Anal. calc. for $C_{13}H_{21}NSi$ (219.40): C 71.17, H 9.65, N 6.38; found: C 70.91, H 9.94, N 6.16.

7-Methyl-5-silaspiro[4.5]dec-8-ene-6-carbonitrile (12). 2-(1-Allylsilolan-1'-yl)-3-methylpent-4-enenitrile (**13**, 4.00 g, 18.2 mmol) was added directly into a freshly opened bottle of CH_2Cl_2

together with a magnetic stir bar. At room temp., with a gentle flow of nitrogen passing over the bottle neck bis(tricyclohexylphosphine)benzylidine ruthenium(IV) (Grubbs I catalyst, 150 mg, 180 μmol) was added and the mixture was stirred at room temp. with monitoring by GC. After 48 h, the GC trace indicated complete conversion, and the mixture was filtered over a pad of silica gel and concentrated on a rotatory evaporator. The resulting residue was Kugelrohr distilled (140 °C/0.05 mbar) to furnish **12** (3.40 g, 97% yield) as a colorless liquid mixture of *syn*- and *anti*-isomers in a ratio of 45:55, which turned out to be inseparable by preparative chromatographic methods. IR (neat): 3009w, 2930s, 2856m, 2220m. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87–5.75 (m, 2 H, 9-H), 5.50 (ddt, *J* = 10.5, 4.0, 2.0 Hz)/5.44 (ddt, *J* = 10.5, 3.0, 2.0 Hz, 2 H, 8-H), 2.67–2.52 (m, 2 H, 7-H), 2.12 (d, *J* = 4.5, 1 H, 6-$H_{(Z)}$), 1.83–1.58 (m, 9 H, 3-, 4-H_2,10-H_a), 1.78 (d, *J* = 11.0, 1 H, 6-$H_{(E)}$),1.50 (dddd, *J* = 18.0, 5.0, 3.0, 2.0, 1 H, 10-H_b), 1.42–1.33 (m, 2 H, 10-$H_{c/d}$), 1.32/1.30 (2d, *J* = 7.0, 6 H, 7-Me), 1.08–0.97/0.91–0.81/0.80–0.64 (3m, 8 H, 2-, 5-H_2). NMR (100 MHz, $CDCl_3$): δ = 133.8/133.1 (2d, C-8), 125.9/125.4 (2d, C-9), 121.7/120.9 (2s, C≡N), 32.9/30.9 (2d, C-7), 26.9/26.8/26.7/26.6 (4t, C-3, -4), 23.0/21.3 (2q, 7-Me), 20.8/19.9 (2d, C-6), 11.2/10.7/10.6/10.5/10.0/9.5 (6t, C-2, -5, -10). GC-MS (EI, tR 7.70, 7.93 min): m/z (%) = 191 (16, [M^+]), 190 (17), 176 (100), 164 (28), 124 (31), 122 (18), 120 (17), 96 (39), 83 (26), 81 (17), 67 (19) Anal. calc. for $C_{11}H_{17}NSi$ (191.35): C 69.05, H 8.95, N 7.32; found: C 68.92, H 9.13, N 7.29.

(2*E*/*Z*)-1-(7'-Methyl-5'-silaspiro[4.5]dec-8'-en-6'-yl)but-2-en-1-ol [(2*E*/*Z*)-19]. Mg turnings (0.45 g, 18.3 mmol) were placed in a reaction flask and covered with a soln. of (2*E*/*Z*)-1-bromoprop-1-ene (1.90 g, 15.7 mmol) in THF (20 mL). The reaction was started by addition of an I_2 crystal with gentle heating with a hot air gun. When the reaction started the remaining (2*E*/*Z*)-1-bromoprop-1-ene was added at such a rate as to keep the solution at gentle reflux. In a second reactor, a soln. of **12** (1.00 g, 5.23 mmol) in hexane (20.0 ml) was cooled to –78 °C and a 1 M DIBAH soln. in hexane (7.84 ml, 7.84 mmol) was added over a period of 15 min, keeping the temp. below –65 °C at all times. The reaction was stirred at –78 °C for 30 min, before quenching with MeOH (170 mg, 5.23 mmol). The mixture was stirred for 5 min, then $Na_2SO_4 \cdot 10\ H_2O$ (5.00 g) and Celite (2.00 g) were added at once. The cooling bath was removed, and the stirred mixture left to reach room temp. Upon reaching 25 °C, a slight evolution of gas was observed. After the gas evolution had seized, the solids were removed by filtration. The filtrate was passed through a plug of anhydrous Na_2SO_4 and concentrated to half its volume. This hexane soln. was added as such to the Grignard soln. at room temp. The reaction mixture was stirred at room temp. for 4 h. The reaction mixture was quenched with satd. aq. NH_4Cl and extracted with *t*-BuOMe. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The product was purified by silica-gel chromatography (hexane/*t*-BuOMe, 8:2, R_f **3.5**) with enrichment in the (2*E*) isomer to afford (2*E*/*Z*)-**19** (220 mg, 18% yield) as a diastereomeric mixture of (*E*/*Z*)-isomers in a ratio of 3:2. IR (neat): 3385m, 2999w, 2932m, 2851m, 1638w. ^{1}H NMR (400 MHz, $CDCl_3$), for the sake of simplicity only the major (*E*/*Z*)-diastereomers are described: δ = 5.79–5.50 (m, 4 H, 2-, 3-, 8'-, 9'-H), 4.79–4.69/4.37–4.29 (m, 1 H, 1-H), 2.67–2.47 (m, 1 H, 7'-H), 1.74–1.50 (m, 8 H, 4-H_3, 3'-, 4'-H_2, OH), 1.28–1.23 (m, 2 H, 10'-H_2), 1.15–1.07 (m, 4 H, 6'-H, 7'-Me), 0.93–0.48 (m, 4 H, 2'-, 5'-H_2). ^{13}C NMR (100 MHz, $CDCl_3$), mixture of (*E*)-and (*Z*)-isomer: δ = 135.9 (d, C-8' [*E*]), 135.9 (d, C-8' [*Z*]), 134.4 (d, C-2 [*E*]), 133.5 (d, C-2 [*Z*]), 126.6 (d, C-3 [*E*]), 126.4 (d, C-3 [*Z*]), 125.3 (d, C-9' [*E*]), 125.3 (d, C-9' [*Z*]), 75.0 (d, C-1 [*E*]), 68.8 (d, C-1 [*Z*]), 36.6 (d, C-6' [*Z*]), 36.1 (d, C-6' [*E*]), 31.9/31.9 (2d, C-7' [*E*, *Z*]), 26.9/26.8 (2t, C-3'/4' [*Z*]), 27.0/26.7 (2t, C-3'/4' [*E*]), 23.0 (q, 7'-Me [*Z*]), 22.9 (q, 7'-Me [*E*]), 17.7 (q, C-4 [*E*]), 13.3 (q, C-4 [*Z*]), 13.6/12.4/11.6 (3t, C-2', -5', -10' [*Z*]), 13.5/12.3/11.5 (3t, C-2', -5', -10' [*E*]). GC-MS (EI, tR 8.84 min, 8.89 min): m/z (%) = 236 (1, [M^+]), 113 (15), 112 (21), 101 (100), 99 (43), 97 (14), 95 (23), 83 (18), 73 (17), 55 (19), 45 (40). Anal. calc. for $C_{14}H_{24}OSi$ (236.43): C 71.12, H 10.23; found: C 71.04, H 10.19.

(2*E*)-1-(7'-Methyl-5'-silaspiro[4.5]dec-8'-en-6'-yl)but-2-en-1-one [(2*E*)-7]. MnO_2 (368 mg, 4.23 mmol) was suspended in a soln. of **19** (100 mg, 0.42 mmol) in CH_2Cl_2 (3.0 mL), and the resulting reaction mixture was stirred at room temp. for 48 h, prior to filtration and removal of the solvent under reduced pressure. By silica-gel chromatography (hexane/*t*-BuOMe, 9:1, R_f 4.5) the pure (2*E*)-**7** isomer (60 mg, 61% yield) was isolated as a colorless odoriferous liquid. IR (neat): 3004w, 2927m, 2855w, 1727w, 1672m, 1652m, 1624m. (2*E*) isomer: ^{1}H NMR (400 MHz, C_6D_6): δ((2*E*)-**7**) = 6.62 (dq, *J* = 16.0, 7.0, 1 H, 3-H), 5.96 (dq, *J* = 16.0, 1.5 Hz, 1 H, 2-H), 5.73 (dddd, *J* = 10.5, 5.5, 5.0, 2.5, 1 H, 9'-H), 5.49 (ddt *J* = 10.5, 3.0, 2.0, 1 H, 8'-H), 3.26 (m_c, 1 H, 7'-H), 2.51 (d, *J* = 10.5 Hz, 1 H, 6'-H), 1.56–1.37 (m, 4 H, 3'/4'-H_2), 1.39 (dd, *J* = 6.5, 2.0 Hz, 3 H, 4-H_3), 1.30 (dddd, *J* = 17.5, 4.5, 2.5, 1.5, 1 H, 10'-H_b), 1.16 (ddt, *J* = 17.5, 5.5, 2.0, 1.5, 1 H, 10'-H_a), 1.11 (d, *J* = 7.0, 3 H, 7'-Me), 1.00/0.67 (2m_c, 2 H, 2'/5'-H_2), 0.54–0.39 (m, 2 H, 2'/5'-H_2). (2*E*) isomer: ^{13}C NMR (100 MHz, C_6D_6): δ((2*E*)-**7**) = 198.2 (s, C-1), 139.5 (d, C-3), 136.4 (d, C-8'), 133.3 (d, C-2), 123.6 (d, C-9'), 48.9 (d, C-6'), 31.9 (d, C-7'), 26.8/26.7 (2t, C-2', -3'), 22.9 (q, 7'-Me), 17.3 (q, 4'-Me), 11.8/11.1 (2t, C-1', -4'), 8.6 (t, C-10'). HRMS (EI): m/z [M + H]$^+$ calcd. for $C_{14}H_{23}OSi$: 235.1513; found: 235.1515. Odor description (blotter): fruity, apple, plum, metallic-green, stewed apple, plum jam, β-damascenone (**3**). Odor threshold (by dilution series against the carba analogue **6**): 1.0 ng/L air.

(7*Z*,10*Z*,1'*E*)-9-Methyl-7-(prop-1'-en-1'-yl)-6-oxa-5-silaspiro[4.7]do-deca-7,10-diene (20). To prove that the (2*E*/*Z*)-1-(7'-methyl-5'-silaspiro[4.5]dec-8'-en-6'-yl)but-2-en-1-one [(2*E*/*Z*)-**7**] rearranges under GC conditions ca. 10 μg of compound **20** was isolated by preparative gas chromatography and elucidated by 2D NMR spectroscopy (HSQC/HMBC

experiments). ^{1}H NMR (600 MHz, C_6D_6): 5.98 (dq, *J* = 15.0, 7.0 Hz, 1 H, 2'-H), 5.85 (dq, *J* = 15.0, 2.0 Hz, 1 H, 1'-H), 5.46–5.37 (m, 2 H, 10-, 11-H), 4.73 (d, *J* = 8.0 Hz, 1 H, 8-H), 3.63 (sxt, *J* = 7.0 Hz, 1 H, 9-H), 2.13 (dd, *J* = 15.0, 5.0 Hz, 1 H, 12-H_b), 1.83–1.75 (m, 1 H, 2-/3-H_b), 1.63 (dd, *J* = 7.0, 1.5 Hz, 3 H, 3'-H_3), 1.61 (m_c, 1 H, 2-/3-H_b), 1.48–1.40 (m, 2 H, 2-, 3-H_a), 1.15 (dd, *J* = 15.0, 8.0 Hz, 1 H, 12-H_a), 1.04 (d, *J* = 7.0 Hz, 3 H, 9-Me), 0.91–0.84 (m, 1 H, 1-/4-H_b), 0.83–0.77 (m, 1 H, 1-/4-H_b), 0.60 (dt, *J* = 14.5, 7.0 Hz, 1 H, 1-/4-H_a), 0.32–0.26 (m, 1 H, 1-/4-H_a). ^{13}C NMR (extracted from HSQC/HMBC, 600 MHz, C_6D_6): 148.1 (s, C-7), 136.5/130.0/124.1/121.6/120.0 (5d, C-8, -10, -11, -1', -2'), 29.6 (d, C-9), 26.6/26.4 (2t, C-2, -3), 20.6 (q, 9-Me), 18.3 (t, C-12), 17.7 (q, C-3'), 12.9/11.0 (2t, C-1, -4). Odor description (GC): fruity, damascone, woody, green. Odor threshold (GC, 5 panelists): 13.7 ng/L air.

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Keywords: Brook rearrangement • Fragrances • Metathesis • Rose ketones • Silicon • Spiro compounds

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FULL PAPER

Sila-Sonata in δ-Damascone Spiro: The sila derivative of a potent spirocyclic δ-damascone was prepared by metathesis, and characterized in its insightful olfactory properties. Thermally highly instable, the target compound rearranges by an enol Brook rearrangement to give a 3,6-dihydro-2*H*-1,2-oxasilocine; yet, surprisingly during this thermal decomposition the damascone note remains partially intact.

*Martin A. Lovchik, Philip Kraft**

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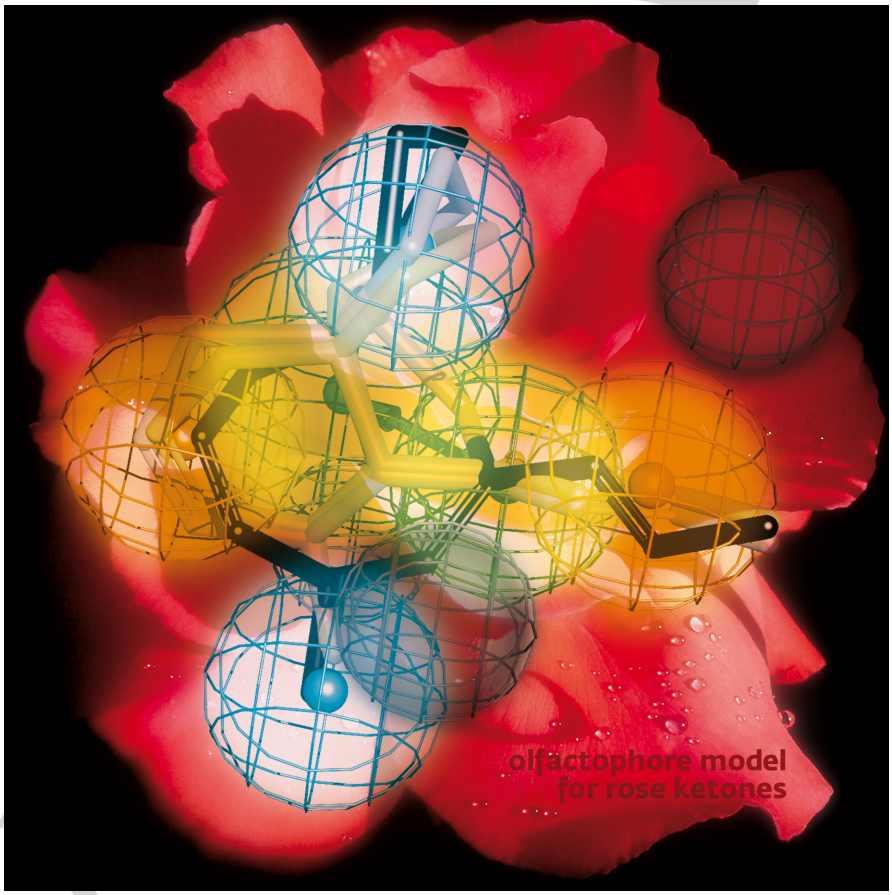
Synthesis and Olfactory Properties of a 6'-Silasubstituted "Spiro[4.5]-δ-Damascone"

A Small Thorn's Difference on the Rose Olfactophore…



…yet, with giant consequences for olfaction! The odor threshold of a thermal enol Brook rearrangement product (black), which only slightly extends the upmost hydrophobe (cyan) is already 12'000 times weaker than the "Spiro[4.5]-δ-damascone" lead (gold). Its precursor, the highly instable 6'-silasubstituted target structure (silver) is only 900 times weaker, and as reported by M. A. Lovchik and P. Kraft on page ■ ff offers a fine-tuned insight into the structural requirements of rose ketones.