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Unconventional Rose Odorants: Serendipitous Discovery and Unique Olfactory Properties of 2,2-Bis(prenyl)-3-oxobutyronitrile and Its Derivatives

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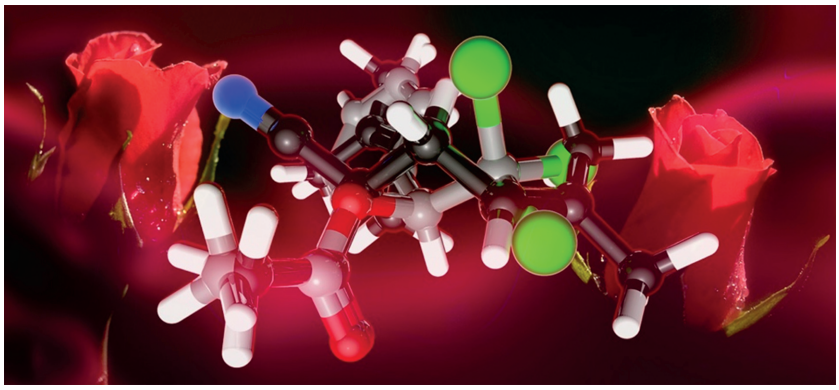

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Abstract 2,2-Bis(3-methylbut-2-enyl)-3-oxobutanenitrile [2,2-bis(prenyl)-3-oxobutyronitrile], an unusual bifunctional nitrile odorant with a fruity rosy, green odor was found to exhibit surprising differences in its detection thresholds (0.25 ng/L air for hyperosmics; 19 ng/L air for hyposmics) and perceived odor characters. To investigate this remarkable phenomenon, 13 derivatives of 2,2-bis(3-methylbut-2-enyl)-3-oxobutanenitrile were synthesized by either monoalkylation of 3-oxo-2-phenylbutanenitrile, or by dialkylation of sodium 1-cyano-2-oxopropan-1-ide or methyl or ethyl cyanoacetate, or by direct derivatization of 2,2-bis(3-methylbut-2-enyl)-3-oxobutanenitrile via its vinyl triflate and Negishi cross coupling. These systematic permutations of the substitution pattern allowed some insight to be gained into the underlying structure–odor relationships and the construction of a simple olfactophore model, albeit no final conclusion could be drawn as to whether the nitrile or carbonyl function acts as the prime osmophore of the bifunctional compounds. Depending on slight genetic variations and the corresponding differences in the receptor morphology both can engage in H-bond interactions with the olfactory receptors, which might explain the observed largely diverging sensitivities. Methyl 2-cyano-2,2-bis(3-methylbut-2-enyl)acetate with a uniform odor threshold of 0.38 ng/L air turned out to be the most interesting floral, rosy odorant of this study, followed by 3-methyl-2,2-bis(3-methylbut-2-enyl)but-3-enenitrile with only a nitrile function and varying odor thresholds (0.40 ng/L air vs. 125 ng/L air).

Key words bifunctional compounds, cross coupling, dialkylation, fragrance materials, molecular modeling, nitriles, rose odorants, structure–odor correlation

Serendipity has always been a significant factor behind innovations, especially those disruptive and surprising. The most pleasant and powdery floral-green rose odor of Rosacetol (**1**) was certainly completely unexpected for those who first synthesized it by chance at the end of the 19th century.[1] Neither is there any striking structural similarity with well-known rose odorants such as 2-phenylethanol that catches the eye, nor does the condensation product of benzaldehyde and chloroform in the presence of a base such as KOH possess any noteworthy olfactory properties. However, acetylation of the resulting 2,2,2-trichloro-1-phenylethan-1-ol changes everything, and the effect of **1**, especially in combination with 2-phenylethanol, is most impressive. Rosacetol (**1**) first appeared under the name of 'Rodindol' (Flora, Dübendorf/Th. Muhlethaler, Nyon) on the market around 1909, and due to its attractive price soon became very popular. Not protected by patents, it was widely produced and also sold as 'Rose Crystals', 'Rosone', 'Rosetone', 'Rosamen', 'Rodalin', 'Rosatol', 'Rosephenone', 'Trichlor-Rose Body', 'Trirosol', or 'Abracador', to name only the most popular.

Rosacetol (**1**) lends to perfumery compositions a deep and heavy powdery rose note of outstanding substantivity and excellent stability, especially in soaps, shampoos, and shower gels. However, despite its attractive olfactory properties it is obviously problematic to release such trichlorinated compounds into the environment, especially in aquatic systems, and insecticidal properties have been reported as well.[2] Therefore, an intense search for safe replacements with similar properties and performance started in the late 1990s, out of which Peonile (**2**)[3] and Petalia (**3**)[4] emerged as the most successful ones. In addition to the powdery rose note, the additional methyl group of Petalia (**3**) introduces an interesting lychee effect which has for instance been made use of in 'Hermann à mes Côtés me Paraissait une Ombre' (Etat Libre d'Orange, 2015) by Quentin

Bisch and 'Versace pour Femme Dylan Blue' (Versace, 2017) by Calice Becker. So additional facets are still in demand, especially if they attenuate some of the harshness generally associated with nitrile odorants.[5]

A nitrile function offers high stability in functional applications,[5] but besides Peonile (**2**) and Petalia (**3**), there are almost no nitrile rose odorants known. The only exception is Givrosia (**4**),[6] which with an odor threshold of 9.0 ng/L air is, however, rather weak and has a prominent woody-tobacco aspect that compromises the rosy floralcy. Citrowanil B (**5**)[7] is a nitrile odorant with a fresh, citrus note, however accompanied by some less appreciated spicy-herbal cuminic effect. We were, therefore, very surprised when by serendipity, the related structure **6**, which had been prepared in synthetic efforts towards a complex natural product, displayed a nice and substantive fruity rose odor with green-aromatic facets in front of a transparent freesia background (Figure 1). As a ketonitrile, compound **6** was bifunctional, and while bifunctional odorants are known in the lily-of-the-valley family, to the best of our knowledge none existed in the domain of rose odorants; all the more featuring a nitrile function.

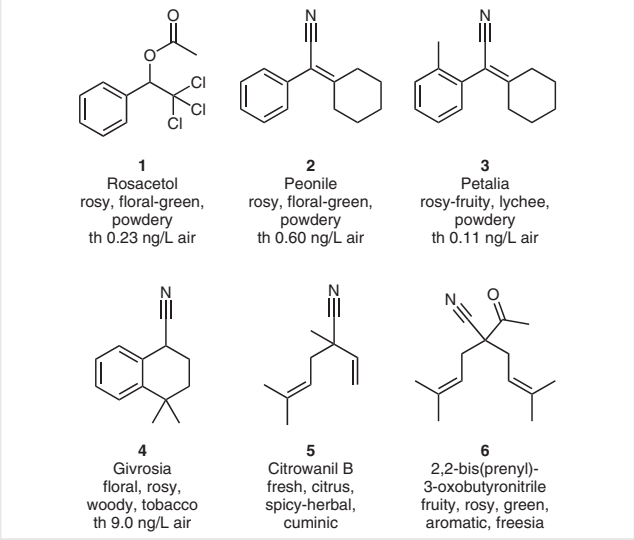
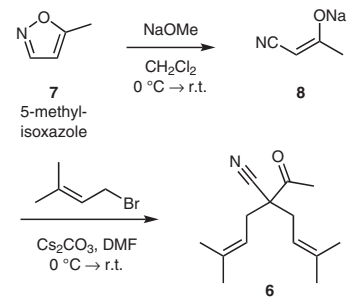


Figure 1 The trichlorinated powdery rose odorant Rosacetol with its halogen-free replacements Peonile[3] and Petalia,[4] the rosy nitrile Givrosia,[6] the citrus nitrile Citrowanil B,[7] and 2,2-bis(prenyl)-3-oxobutyronitrile, the serendipitous discovery of this paper

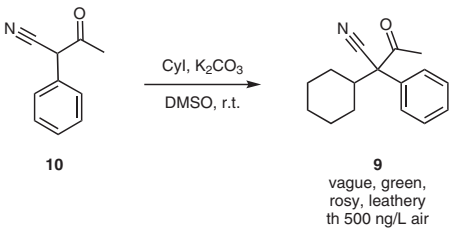
The synthesis of 2,2-bis(prenyl)-3-oxobutyronitrile (**6**) is delineated in Scheme 1 and commenced with the deprotonation of 5-methylisoxazole (**7**) with sodium methoxide in CH_2Cl_2 according to a procedure by Alexakis and coworkers.[8] The crude sodium salt of cyanoacetone **8** was obtained in quantitative yield and then bis-prenylated with prenyl bromide (2.2 equiv) in DMF in the presence of Cs_2CO_3 (1 equiv) as a base.[9] The corresponding target compound **6** was isolated in olfactory purity by flash chromatography in 74% yield.

But not only was the synthesized 2,2-bis(prenyl)-3-oxobutyronitrile (**6**) exceptional in being a bifunctional rose odorant, upon measuring its odor threshold it was observed that there were two distinctly different groups of panelists in the ratio of 1:2, hyperosmics/hyposmics. While an odor threshold of 0.25 ng/L air, so very close to Roseacetol (**1**, th 0.23 ng/L air), was determined for the more sensitive group of hyperosmics, the threshold for the hyposmics was at 19 ng/L air almost two orders of magnitude higher. The significant quantitative difference in the odor perception was accompanied by a qualitative one: green, aromatic, freesia, ivy-type aspects dominate for the hyperosmics, while the fruity-rosy note prevails for the hyposmics.



Scheme 1 Synthesis of 2,2-bis(prenyl)-3-oxobutyronitrile from 5-methylisoxazole

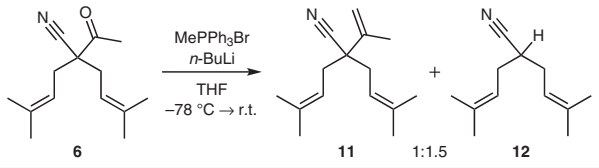
Due to the olfactory reminiscence of **6** to Peonile (**2**), ketonitrile **9** was synthesized by alkylation of 3-oxo-2-phenylbutanenitrile (**10**) with iodocyclohexane (4 equiv) in the presence of K_2CO_3 (4 equiv) in DMSO at r.t. (Scheme 2).[10] After stirring at r.t. for 4.5 days, the target compound **9** was obtained in a mere 31% yield due to the incomplete conversion of the starting material and the formation of minor amounts of *O*-alkylated product. However, much to our disappointment, the Peonile analogue **9** turned out to be very weak to odorless (th 500 ng/L air) with only a vague, green, rosy, leathery odor.



Scheme 2 Synthesis of a Peonile-related ketonitrile from 3-oxo-2-phenylbutanenitrile by α-alkylation

To investigate the structural parameters of both the olfactory characteristics and the strongly diverging sensitivities towards the unconventional bifunctional rose odorant **6**, a detailed structure–odor relationship study was thus undertaken. First, the importance of the carbonyl function

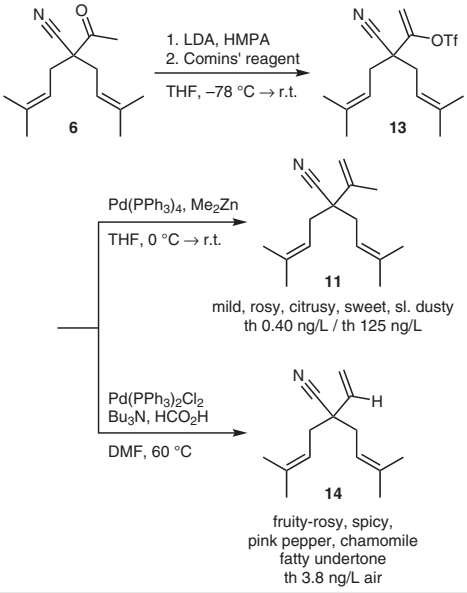
of **6** as the principal osmophore was challenged by replacing it with a hydrophobic methylene unit. To this end, a standard Wittig methylenation with methyltriphenylphosphonium bromide (1.3 equiv) and *n*-BuLi in THF/hexane was first performed on **6**;[11] yet, as delineated in Scheme 3 this led to the formation of significant amounts of an undesired byproduct along with the desired compound **11**. The byproduct was identified as the known[12] bis(prenyl)acetonitrile **12**, the formation of which can be explained by a retro-Claisen reaction[13] following the attack of the phosphorous ylide on the carbonyl group.



Scheme 3 Attempted Wittig methylenation of 2,2-bis(prenyl)-3-oxobutanenitrile (^{1}H NMR ratio)

Hence, a two-step sequence relying on a Pd-catalyzed Negishi coupling[14] was employed to construct the propen-2-yl moiety via methylation of the corresponding vinyl triflate **13** (Scheme 4).[15] The latter was obtained from ketonitrile **6** in 90% yield by treatment with LDA (1.3 equiv) in the presence of HMPA (4.2 equiv), followed by the addition of Comins' reagent [*N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide), 1.3 equiv].[16] The Negishi coupling of **13** with dimethylzinc (2 equiv) in the presence of 5 mol% $Pd(PPh_3)_4$ smoothly afforded the bis-prenylated nitrile **11** in 74% yield after chromatographic purification. While the main rose character of **6** remained present in the odor profile of **11**, its green facets were replaced by citrusy aspects. Overall **11** was, however, weaker than **6**, but again, there were marked differences amongst the panelists. The hyperosmics (5 panelists) found **11** at 0.40 ng/L air about as strong as **6** (0.25 ng/L air), while for the smaller group of hyposmics (3 panelists) **11** was at 125 ng/L air over six times weaker than the lead structure **6**. But since for both panelist groups **11** smelled similar in character, the nitrile function seems to be the main osmophore that binds to the olfactory receptor, certainly so for hyperosmics.

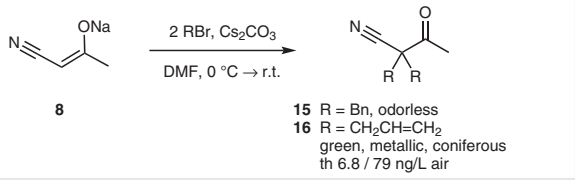
To investigate if the spatial requirement of the propen-2-yl moieties hampered the interaction of the osmophore with the receptor, it was then decided to replace it by a vinyl group. To that end, vinyl triflate **13** was reacted with formic acid (1.8 equiv) as the hydride source in the presence of Bu_3N (2.8 equiv) and 5 mol% $Pd(PPh_3)_2Cl_2$ as catalyst in DMF at 60 °C.[17] After purification by flash chromatography, 2,2-bis-prenylated but-3-enenitrile **14** was obtained in 65% yield. The main odor note of **14** was again rosy, though



Scheme 4 Synthesis of the bis-prenylated but-3-enenitriles from 2,2-bis(prenyl)-3-oxobutyronitrile

in a fruity direction, and with a spicy chamomile–pink pepper character above a fatty undertone. The sensitivities of the panelists towards **14** did not differ, and the threshold for **14** was concordantly determined at 3.8 ng/L air, so about 10 times weaker as compared to **11** for hyperosmics and over 30 times more intense for the hyposmics.

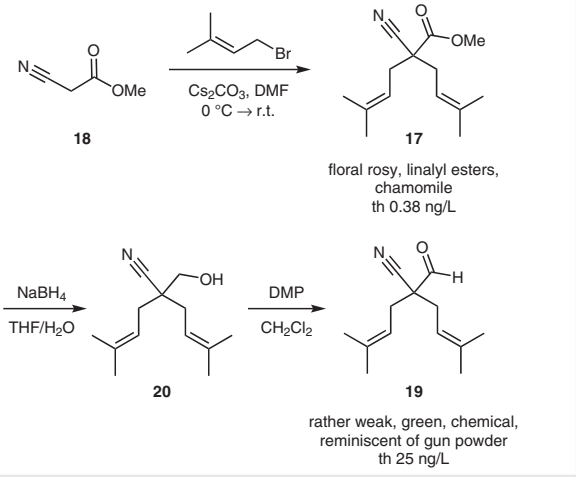
Therefore, there did not seem to be much of a steric component at this position involved in the receptor interaction regarding the hyperosmics. It thus seemed sensible to keep the ketonitrile functionality and modify the side chains instead. We first set out to synthesize dibenzylated ketonitrile **15**. As delineated in Scheme 5, the crude cyanoacetone enolate **8** was treated with benzyl bromide (2 equiv) in DMF in the presence of Cs_2CO_3 (1 equiv) as a base.[9] After purification by flash chromatography, the corresponding target compound **15** was obtained as a colorless solid in 67% yield over two steps. Unfortunately, **15** turned out to be completely odorless, perhaps due to its relatively high molecular weight ($C_{18}H_{17}ON$, 263.34 u) compared to **6**, though Rosacetol (**1**, $C_{10}H_9O_2Cl_3$ 267.54 u) has about the same. We next synthesized the diallylated ketonitrile **16** analogously from crude **8** and allyl bromide (2.2 equiv) as the electrophile. The diallylated compound **16** was isolated in 63% yield over two steps, and lacked the rosy floralcy of our lead structure **6**. There were, however, significant differences in sensitivity towards **16** among the panelists with odor thresholds of 6.8 ng/L air for hyperosmics (4 panelists) and 79 ng/L air for the smaller group of hyposmics (3 panelists).



Scheme 5 Synthesis of the dibenzylated and the diallylated ketonitriles from sodium 1-cyano-2-oxopropan-1-ide

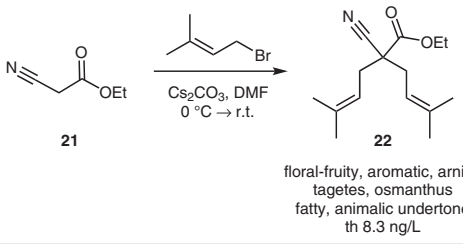
With these results in hand, we decided to rather modify the polarity and H-bond acceptor properties of **6**.[18] One of the easiest ways to do so was a simple alkylation of cyanoacetates. In order to be sterically comparable to the methyl ketone lead **6**, the methyl ester **17** was prepared. Methyl cyanoacetate (**18**) was bis-prenylated by treatment with Cs_2CO_3 (2.2 equiv) and prenyl bromide (2.2 equiv) in DMF (Scheme 6),[19] and cyanoacetate **17** was isolated in 92% yield by chromatographic purification. As for the vinyl nitrile **14**, neither quantitative nor qualitative perception differences were observed, and with an odor threshold of 0.38 ng/L air, cyanoacetate **17** smelled intensely floral-rosy with some additional reminiscence of linalyl esters and chamomile.

Next, the bis-prenylated aldehyde **19** was prepared by hydride reduction with $NaBH_4$ in THF/H_2O (14:1, 86% yield, Scheme 6)[20] and subsequent oxidation of the resulting alcohol **20** with Dess–Martin periodinane[21] in CH_2Cl_2. Aldehyde **19** was isolated in 71% yield and found to smell rather weak (th 25 ng/L air) in a green, chemical direction with some reminiscence to gun powder. The rosy floralcy of **6** and its fruity character were lost.



Scheme 6 Bis-prenylation of methyl cyanoacetate affording a methyl ester, and synthesis of an aldehyde via the corresponding alcohol

This made us return to cyanoacetates, and to synthesize the homologous ethyl ester **22** by employing our standard bis-prenylation conditions[19] on **21** (Scheme 7). The desired product **22** was obtained olfactorily pure in 90% yield and possessed the floral-fruity, aromatic odor note of **6** and **17** with additional accents of arnica, tagetes, and osmanthus in front of a fatty, animalic background. While all panelists perceived **22** equally well, the odor threshold (th 8.3 ng/L air) dropped by one order of magnitude compared to **17** (th 0.38 ng/L air).

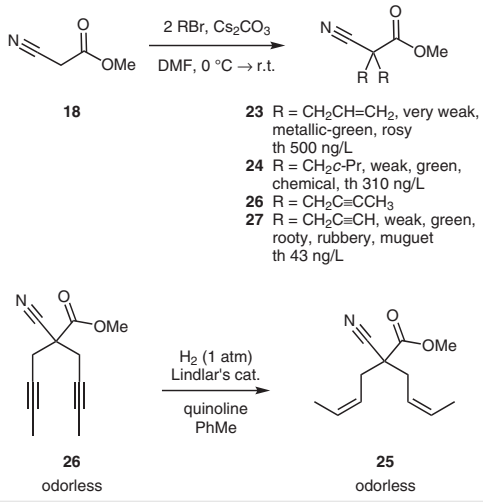


Scheme 7 Bis-prenylation of ethyl cyanoacetate affording the ethyl ester

Since the C-2 substituents exert a significant impact both on the qualitative and the quantitative olfactory properties, further analogues were synthesized from methyl cyanoacetate (**18**) by treatment with the respective bromides, as summarized in Scheme 8. Diallylated methyl cyanoacetate **23** was obtained in 89% yield in olfactory purity after flash chromatography. The smell of **23** was very weak (th 500 ng/L air) with only faint metallic green, rosy, fruity, pear-type aspects.

Due to the increased sp^2-character of their carbons,[22] cyclopropane rings can mimic double bonds. Thus, the 2,2-bis(cyclopropropylmethyl) derivative **24** was synthesized as bioisostere[23] to **23**, employing cyclopropylmethyl bromide (2.1 equiv). The bis-cyclopropylmethylated cyanoacetate **24** was obtained in 60% yield as a yellowish oil with a weak green, chemical odor, though its threshold was with 310 ng/L air slightly lower than that of **23**.

As a bis-demethyl *seco*-structure to **17**, the bis-(*Z*)-crotylated methyl cyanoacetate **25** was our next target. Dibutynylation of **18** in the presence of Cs_2CO_3 in DMF afforded the dibut-2-ynylcyanoacetate **26** in 63% after chromatographic purification. Hydrogenation of **26** in toluene under 1 atm H_2 in the presence of 2 mol% Lindlar's catalyst[24] and 30 mol% quinoline[25] yielded **25** as a colorless and, unexpectedly, completely odorless liquid (Scheme 8). To finalize the series, the known[26] dipropargylated methyl cyanoacetate **27** was synthesized from methyl cyanoacetate (**18**) with propargyl bromide using our standard conditions. Methyl 2-cyano-2,2-di(prop-2-ynyl)acetate (**27**) was isolated in 77% yield by chromatography as a colorless liquid (Scheme 8). As in **26**, we expected the side chains to lack the rotational barriers that were observed by ^1H NMR with the other products investigated so far. Compound **27** smelled, however, only weak and vague in a green, rooty direction with a rubbery lily-of-the-valley connotation for the hyperosmic (43 ng/L air), while it was completely odorless for the hyposmic panelists.



Scheme 8 Difunctionalization of methyl cyanoacetate with allyl bromide, cyclopropylmethyl bromide, and but-2-ynyl and propargyl bromide, and synthesis of the bis-(*Z*)-crotylated methyl ester

Besides our original lead structure, the 2,2-bis(prenyl)-3-oxobutyronitrile (**6**, 0.25 ng/L air), of the 14 nitriles synthesized and investigated in this study (Table 1) only the corresponding methylene derivative **11** (0.4 ng/L air) and the analogous methyl ester **17** (0.38 ng/L air) possessed rosy, floral-green odor characteristics and threshold intensities in the range of Rosacetol (**1**), Peonile (**2**), and Petalia (**3**). Only the methyl ester **17** was perceived equally strong by all panelists. Even the ethyl ester **22** was already 20× weaker in terms of odor threshold. Abstraction of both terminal methyl groups (compound **23**) or even the (*Z*)-configured methyl only (compound **25**) of ester **17** led to weak and vague odors or even complete odorlessness, while the abstraction of both terminal methyl groups of our lead **6** resulted in an almost 30× higher odor threshold (for compound **16**) considering hyperosmics only. Most surprising was that even Sturm's isobutenyl–phenyl analogy[27] does not work for ketonitrile **6**, as the dibenzyl analogue **15** is completely odorless. So, the molecular space for this unusual odorant family seems exceptionally narrow.

While the uncommon and pronounced sensitivity differences towards compounds **6**, **16**, and **27** as well as the broad qualitative perceptive range of the compounds, varying between rosy, floral-fruity, green-metallic, and aromatic make it extremely challenging to conclude anything about the interactions with the olfactory receptors involved in this odorant family, it was nevertheless very interesting to gain some insight if the osmophore, i.e. the group engaging in H-bonding with the odorant receptors, was the nitrile or the carbonyl function. Perhaps this bifunctionality even was the very reason for the sensitivity differences of the different panelists groups. Taking the low odor threshold of the methylene derivative **11** (0.4 ng/L air) for hyperosmics as well as the dipole moments of the synthesized ketonitriles into account, one would of course expect the nitrile function of the synthesized odorants to interact mainly with the olfactory receptor(s), but would this also be reflected in an olfactophore model?

An olfactophore is basically a 'super pharmacophore' comprising the different receptor sites involved in the combinatorial coding of a given odor impression, such that the broad receptive range might not be too much in the way to gain at least some rudimentary idea about the required geometry for nitrile rose odorants. Using the activity data calculated from the measured odor thresholds in Table 1 for hyperosmics, an olfactophore model was generated with the Discovery Studio 18.1.100.18065 software package.[28] In order not to overemphasize weak to odorless materials in the construction of the model, compounds with thresholds >500 ng/L air (**15**, **25**, and **26**) were not considered. Also excluded were compound **16** with only green-metallic, but no

Figure 2 Olfactophore model for nitrile rose odorants with Petalia (**3**, black), Rosacetol (**1**, dark grey), the ketonitrile lead **6** (light grey), and the corresponding methyl ester **17** (white) docked into, featuring: 1 hydrogen-bond acceptor (HBA) colored green, 2 hydrophobes depicted in cyan, and 1 double-bond feature in orange. The model has a correlation of 77.1% (max. fit 7.97, total cost 68.9, RMS 1.87) and was generated with the Discovery Studio 18.1.100.18065 software package,[28] using a training set comprising of Rosacetol (**1**), Peonile (**2**), and Petalia (**3**) as well as compounds **6**, **9**, **11**, **14**, **17**, **19**, **22**, **23**, and **24** (uncert = 3, conformational space = 20 kcal/mol).

floral odor character, and **27** for its weak and vague odor without any rosy aspects. This gave a small training set of only 12 compounds, consisting of 6 active, 3 moderately active, and 3 inactive structures, that did not allow splitting into test sets. The resulting olfactophore model is depicted in Figure 2 and has a correlation value of 77.1%, featuring no excluded volumes. The inactive compounds (**9**, **23**, **24**) thus are not penalized sterically and are still predicted moderately active; yet, enforcing excluded volumes did not improve on the overall correlation. The model should therefore be seen in a more illustrating way, though the calculated picomolar activities are nevertheless given in Table 1.

Table 1 Overview of the Threshold Data (Hyperosmics in the Case of Different Sensitivity Groups)[a]

Compound	Odor threshold [ng/L]	Experimental activity [pM]	Calculated activity [pM]
Rosacetol (**1**)	0.23 (rosy)	0.86 (active)	68 (moderate)
Peonile (**2**)	0.60 (rosy)	0.52 (active)	0.96 (active)
Petalia (**3**)	0.11 (rosy)	0.51 (active)	0.63 (active)
6	0.25 (freesia)	1.1 (active)	3.6 (active)
9	500 (vague)	2100 (inactive)	41 (moderate)
11	0.40 (rosy)	1.8 (active)	12 (active)
14	3.8 (rosy)	19 (moderate)	13 (active)
15	>500 (odorless)	not considered	not considered
16	6.8 (green)	not considered	not considered
17	0.38 (rosy)	1.6 (active)	3.3 (active)
19	25 (green)	120 (moderate)	2.7 (active)
22	8.3 (floral)	33 (moderate)	1.4 (active)
23	500 (vague)	2800 (inactive)	32 (moderate)
24	310 (green)	1500 (inactive)	33 (moderate)
25	>500 (odorless)	not considered	not considered
26	>500 (odorless)	not considered	not considered
27	43 (vague)	not considered	not considered

[a] For the compounds synthesized and considered in the generation of the model as well as a comparison of the measured experimental activities [pM] with the activities calculated by the Discovery Studio software[28] for the olfactophore model in Figure 2.

Interestingly, the nitrile function is not always bound by the hydrogen-bond acceptor (HBA, green) feature; in fact, the cyano and carbonyl function compete for the hydrogen bond, depending on the overall complementarity to the binding pocket. Thus, the osmophore of the ketonitrile lead **6** (light grey) is the carbonyl function with the nitrile function pointing towards the double-bond feature (orange), while the methyl ester **17** (white) binds via its nitrile function with the ester methyl group situated in a hydrophobe (cyan). Whether this explains why there was no sensitivity difference for the methyl ester **17** is highly speculative. But in any case, the bifunctional compounds investigated have in this model competing binding poses of similar energy. Generally, however, the benzene, cyclohexyl, or prenyl moieties are preferentially situated in the two hydrophobic volumes (depicted in cyan). Decisive for the docking pose is rather the fit into the double-bond feature (orange), which is situated more closely towards the hydrophobe binding the trichloromethyl group, thereby indicating a certain polarizability of this hydrophobic group. The overall idea of a triangular constellation of one HBA and two hydrophobes, one of which flanked by a double-bond feature, is however quite plausible for these rosy, floral-green odorants, even though the hydrophobes are not perfectly addressed by Roseacetol (**1**, dark grey).

In the superposition analysis (Figure 3) of Petalia (**3**, black), Peonile (**2**, dark grey), Rosacetol (**1**, grey), lead structure **6** (light grey), and its methyl ester analogue **17** (white) with the MOE 2016.08.02 software[29] using an Amber10: Extended Hückel Theory (EHT) forcefield, the nitrile functions of both **6** and **17** however point away from those of Petalia (**3**) and Peonile (**2**), each pair of compounds **6**/**17** and **2**/**3** overlying almost perfectly. Here, the cyano nitrogens of the pair **2**/**3** map with the carbonyl oxygens of compound **1**, **6**, and **7**, which would indicate the carbonyl group to be the osmophoric group of the lead structure **6** and methyl ester **17**.

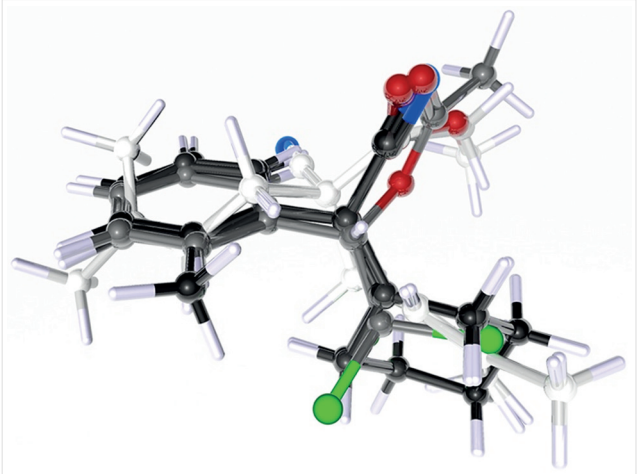


Figure 3 Multiflexible alignment of Petalia (**3**, black), Peonile (**2**, dark grey), Rosacetol (**1**, grey), lead structure **6** (light grey), and the corresponding methyl ester **17** (white) with the MOE 2016.08.02 software package.[29] The strain energy induced by this superposition has a value U = 16.4 kcal/mol, its feature overlap as a measure of configurational similarity is F = –95.0, while the resulting alignment score of the probability-density overlap is S = –78.6.

In conclusion, it is not clear whether or not the ketonitrile lead **6** and the analogous methyl ester **17** bind via the nitrile function, which the methylene derivative **11** (0.4 ng/L air) certainly must. This can be the reason for the observed sensitivity differences if only the olfactory receptors responsible for these rose odorants vary very subtly subject

to the respective genome. This could be interesting for future receptor studies, but the sensitivity differences of **6** and **17** hamper any commercial utilization of these compounds. So methyl 2-cyano-2,2-bis(3-methylbut-2-enyl)-acetate (**17**) is the only viable new floral rosy odorant emerging from this study. It is available from methyl cyanoacetate in one step at an attractive cost, but is with an odor threshold of 0.38 ng/L air only on a par with Rosacetol (**1**) and its halogen-free replacer Peonile (**2**), while slightly inferior to Petalia (**3**, 0.11 ng/L air). As seen in **23** and **25**, both methyl groups of the isobutenyl tail are important, and since even the ethyl ester **22** is one order of magnitude weaker (8.3 ng/L air), the room for improvements seems largely exhausted. Nevertheless, the unique olfactory properties of the derivatives of 2,2-bis(prenyl)-3-oxobutyronitrile have already demonstrated that there is still ample opportunity for surprise in Fragrance Chemistry.

Analytical TLC was performed on Merck silica gel 60 F254 TLC glass plates and visualized with 254 nm light and $KMnO_4$ staining solution, followed by heating. Purification of reaction products was carried out by flash chromatography using silica gel from SigmaAldrich (60752, 230–400 mesh particle size) or SiliaFlash P60 from Silicycle (230–400 mesh particle size) under 0.3–0.5 bar pressure. Analytical data were in accordance with previously reported values. Sodium 1-cyano-2-oxopropan-1-ide (**8**) was prepared following literature precedence.[9] ^{1}H NMR spectra were recorded on a Bruker AV 400 MHz spectrometer with the solvent resonance as the reference ($CDCl_3$ δ = 7.26). ^{13}C NMR spectra were recorded with ^{1}H-decoupling on a Bruker AV 100 MHz spectrometer with the solvent resonance as the reference ($CDCl_3$ δ = 77.0). Infrared spectra were recorded neat on a Perkin-Elmer Spectrum Two FT-IR spectrometer. HRMS data were obtained from the mass spectrometry service operated by the Laboratory of Organic Chemistry at the ETHZ on a Micromass (Waters) AutoSpec Ultima for EI or on a Bruker maXis–ESI-Qq-TOF-MS for ESI, respectively.

Olfactory evaluations were performed by an expert perfumer with a 10% soln of the sample substances in dipropylene glycol (DPG) and EtOH on smelling blotters. Odor thresholds were determined by GC–olfactometry: Different dilutions of the sample substance were injected into a gas chromatograph in descending order of concentration until the panelist failed to detect the respective substance at the sniffing port. The reported threshold values are the geometric means of the individual odor thresholds of 4–5 trained panelists.

Sodium 1-Cyano-2-oxopropan-1-ide (8)[8]

5-Methylisoxazole (**7**; 1.00 mL, 23.3 mmol, 1 equiv) was dissolved in CH_2Cl_2 (14 mL), and the resulting soln was immersed in a cooling bath. At 0 °C, NaOMe (2.20 mL, 5.4 M, 23.2 mmol, 1 equiv) was added in one portion. A colorless precipitate started to form, and the mixture was allowed to spontaneously warm to r.t., and stirred overnight. The solvent was removed in vacuo; the crude residue was washed with anhyd Et_2O and filtered to give a colorless solid (1.20 g, 99%), which was used without further purification.

2,2-Bis(3-methylbut-2-enyl)-3-oxobutanenitrile (6)

Sodium 1-cyano-2-oxopropan-1-ide (**8**; 950 mg, 9.04 mmol, 1 equiv) was dissolved in DMF (40 mL). The resulting soln was placed in a cooling bath and at 0 °C, Cs_2CO_3 (3.00 g, 9.49 mmol, 1.1 equiv) and 1-bromo-3-methylbut-2-ene (2.3 mL, 20 mmol, 2.2 equiv) were added. The mixture was stirred at r.t. for 2.5 h, and then it was quenched by the addition of sat. aq NH_4Cl soln (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, hexane/EtOAc, 40:1, R_f = 0.2) afforded **6** (1.50 g, 74%) as a colorless liquid.

IR (neat): 2986, 2920, 2857, 2236, 1723, 1443, 1379, 1357, 1168, 1018, 841, 799 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.14 (m, 2 H, 2′-H), 2.55 (dd, *J* = 14.3, 7.7 Hz, 2 H, 1′-H), 2.42 (dd, *J* = 14.3, 7.5 Hz, 2 H, 1′-H), 2.35 (s, 3 H, 3-Me), 1.75–1.72 (m, 6 H, 3′-$Me_{(E)}$), 1.64 (br, s, 6 H, 3′-$Me_{(Z)}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.0 (s, C-3), 137.8 (2 s, C-3′), 121.0 (s, C-1), 116.6 (2 d, C-2′), 54.6 (s, C-2), 34.8 (t, C-1′), 29.4 (q, 3-Me), 25.9 (2 q, 3′-$Me_{(E)}$), 18.1 (2 q, 3′-$Me_{(Z)}$).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{21}NO$: 219.1618; found: 219.1621.

Odor description (10% DPG, blotter): green, aromatic, freesia, ivy leaves (hyperosmics); floral, fruity-rosy (hyposmics).

Odor threshold (GC): 0.25 ng/L air (hyperosmics); 19 ng/L air (hyposmics).

2-Cyclohexyl-3-oxo-2-phenylbutanenitrile (9)

An oven-dried Schlenk flask was charged with K_2CO_3 (1.70 g, 12.3 mmol, 4 equiv). DMSO (1.80 mL) was added, and the resulting colorless slurry was vigorously stirred prior to the addition of solid 3-oxo-2-phenylbutanenitrile (**10**; 500 mg, 3.08 mmol, 1 equiv) with rinsing of the vessel walls with additional DMSO (1.80 mL). Iodocyclohexane (1.60 mL, 12.4 mmol, 4 equiv) was added in one portion via syringe. The mixture was stirred for 4.5 d at r.t., and then it was transferred to a separatory funnel and diluted with EtOAc (10 mL) and water (5 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ soln (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography (silica gel, hexanes/EtOAc, 19:1, R_f = 0.3) afforded **9** (230 mg, 31%) as a colorless and odorless oil that solidified upon storage in the freezer.

IR (neat): 2931, 2855, 2238, 1725, 1495, 1449, 1357, 1182, 1166, 754, 698, 595 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.45 (m, 2 H, 2′-H), 7.43–7.33 (m, 3 H, 3′-H, 4′-H), 2.45 (tt, *J* = 10.9, 3.6 Hz, 1 H, 1″-H), 2.30 (s, 3 H, 3-Me), 1.86–1.73 (m, 2 H, 2″-H, 2″-H or 3″-H), 1.73–1.61 (m, 2 H, 2″-H and/or 3″-H), 1.46–1.28 (m, 2 H, 2″-H, 2″-H or 3″-H), 1.26–0.97 (m, 4 H, 2″-H or 3″-H, 4″-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.2 (s, C-3), 132.7 (s, C-1′), 129.3 (2 d, C-2′), 128.7 (d, C-4′), 126.7 (2 d, C-3′), 118.9 (s, C-1), 65.9 (s, C-2), 43.4 (d, C-1″), 29.8 (t, C-2″), 28.3 (q, 3-Me), 27.5 (t, C-4″), 26.1 (t, C-2″ or C-3″), 26.0 (t, C-2″ or C-3″), 25.8 (t, C-2″ or C-3″).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{19}NO$: 241.1462; found: 241.1475.

Odor description (10% DPG, blotter): vague, green, rosy, leathery.

Odor threshold (GC): 500 ng/L air.

3-Methyl-2,2-bis(3-methylbut-2-enyl)but-3-enenitrile (11)

In a cooling bath at 0 °C, $Pd(PPh_3)_4$ (7.9 mg, 6.86 µmol, 5 mol%) was added to a soln of 3-cyano-6-methyl-3-(3-methylbut-2-enyl)hepta-1,5-dien-2-yl trifluoromethanesulfonate (**13**; 48 mg, 0.14 mmol, 1 equiv) in degassed THF (1 mL). The mixture was stirred at this temperature for 5 min, and then Me_2Zn (0.14 mL, 0.28 mmol, 2 equiv)

was added dropwise, which resulted in complete discoloration of the yellow mixture. Upon stirring overnight at r.t. the mixture slowly turned back yellow again. It was then diluted with EtOAc (3 mL) and quenched by the addition of sat. aq $NaHCO_3$ (2 mL). The aqueous layer was extracted with EtOAc (3 × 3 mL), and the combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, hexane/EtOAc, 39:1, R_f = 0.1) afforded **11** (22 mg, 74%) as a colorless liquid.

IR (neat): 2973, 2917, 2237, 1674, 1645, 1446, 1379, 1233, 1112, 1065, 904, 839, 777 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.20–5.18 (m, 1 H, 4-H), 5.16–5.09 (m, 2 H, 2′-H), 5.05–5.03 (m, 1 H, 4-H), 2.46 (dd, *J* = 14.8, 7.5 Hz, 2 H, 1′-H), 2.35–2.27 (m, 2 H, 1′-H), 1.73 (m, 9 H, 3-Me, 3′-$Me_{(E)}$), 1.64 (br. s, 6 H, 3′-$Me_{(Z)}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.7 (s, C-3), 135.8 (2 s, C-3′), 122.4 (s, C-1), 117.9 (2 s, C-2′), 115.1 (t, C-4), 48.8 (s, C-2), 35.1 (2 t, C-1′), 25.9 (2 q, 3′-$Me_{(E)}$), 18.2 (3 q, 3′-$Me_{(Z)}$), 18.1 (3 q, 3-Me).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{24}N$: 218.1903; found: 218.1906.

Odor description (10% DPG, blotter): mild, rosy, citrusy, sweet, sl. dusty.

Odor threshold (GC): 0.40 ng/L air (hyperosmics); 125 ng/L air (hyposmics).

5-Methyl-2-(3-methylbut-2-enyl)hex-4-enenitrile (12)

To a soln of methyltriphenylphosphonium bromide (221 mg, 0.606 mmol, 1.3 equiv) in THF (0.93 mL) at –78 °C was added dropwise 1.6 M *n*-BuLi (0.38 mL, 0.608 mmol, 1.3 equiv). The mixture was stirred at –78 °C for 10 min and then it was warmed to 0 °C and stirred for a further 20 min. Then, 2,2-bis(3-methylbut-2-enyl)-3-oxobutanenitrile (**6**; 105 mg, 0.477 mmol, 1 equiv) in THF (0.30 mL) was added and the mixture was allowed to spontaneously warm to r.t. and stirred overnight. It was diluted with Et_2O (5 mL) and quenched with brine (5 mL). The aqueous layer was extracted with Et_2O (2 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude ^1H NMR revealed the formation of **12** together with the desired product **11**, in ca. 1.5:1 ratio. Purification by flash chromatography (silica gel, hexanes/EtOAc, 39:1) afforded clean fractions of both compounds **11** and **12** for structure assignment.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.24–5.12 (m, 2 H, 2′-H), 2.55–2.46 (m, 1 H, 2-H), 2.40–2.20 (m, 4 H, 1′-H), 1.76–1.71 (m, 6 H, 3′-$Me_{(E)}$), 1.64 (br. s, 6 H, 3′-$Me_{(Z)}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.8 (2 s, C-3′), 122.3 (s, C-1), 119.2 (2 d, C-2′), 32.4 (d, C-2), 30.2 (2 t, C-1′), 25.8 (2 q, 3′-$Me_{(E)}$), 17.9 (2 q, 3′-$Me_{(Z)}$).

The spectroscopic data of **12** were identical to those reported in the literature.[12]

3-Cyano-6-methyl-3-(3-methylbut-2-enyl)hepta-1,5-dien-2-yl Trifluoromethanesulfonate (13)

2,2-Bis(3-methylbut-2-enyl)-3-oxobutanenitrile (**6**; 300 mg, 1.37 mmol, 1 equiv) and HMPA (1.00 mL, 5.71 mmol, 4.2 equiv) were dissolved in THF (8.40 mL). The resulting soln was cooled to –78 °C and 0.2 M LDA (8.70 mL, 1.74 mmol, 1.3 equiv) was added dropwise. The mixture was stirred for 40 min at –78 °C, prior to the dropwise addition of *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide) (Comins' reagent) (700 mg, 96%, 1.71 mmol, 1.3 equiv) in THF (1.5 mL) and the removal of the cooling bath. When the reaction had warmed up to r.t., sat. aq $NaHCO_3$ (10 mL) was added, the phases were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, hexanes/EtOAc, 39:1, R_f = 0.2) furnished **13** (0.43 g, 90%) as a colorless liquid.

IR (neat): 2975, 2919, 2864, 1656, 1422, 1211, 1138, 940, 794, 724, 602 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.45 (d, *J* = 5.0 Hz, 1 H, 4-H), 5.38 (d, *J* = 5.0 Hz, 1 H, 4-H), 5.20–5.14 (m, 2 H, 2′-H), 2.54 (dd, *J* = 14.7, 7.6 Hz, 2 H, 1′-H), 2.44 (dd, *J* = 14.7, 7.2 Hz, 2 H, 1′-H), 1.79–1.74 (m, 6 H, 3′-$Me_{(E)}$), 1.69–1.65 (br. s, 6 H, 3′-$Me_{(Z)}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.2 (s, C-3), 138.2 (2 s, C-3′), 119.2 (s, C-1), 118.2 (q, *J* = 319.8 Hz, C-5), 116.0 (2 d, C-2′), 105.5 (t, C-4), 48.4 (s, C-2), 34.1 (2 t, C-1′), 25.9 (2 q, 3′-$Me_{(E)}$), 18.2 (2 q, 3′-$Me_{(Z)}$).

^{19}F NMR (377 MHz, $CDCl_3$): δ = –74.19.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{20}F_3NO_3S$: 351.1111; found: 351.1097.

2,2-Bis(3-methylbut-2-enyl)but-3-enenitrile (14)

$Pd(PPh_3)_2Cl_2$ (530 mg, 0.754 mmol, 50 mol%) and formic acid (0.10 mL, 2.65 mmol, 1.8 equiv) were added to a soln of 3-cyano-6-methyl-3-(3-methylbut-2-enyl)hepta-1,5-dien-2-yl trifluoromethanesulfonate (**13**; 0.53 g, 1.51 mmol, 1 equiv) and Bu_3N (1.0 mL, 4.21 mmol, 2.8 equiv) in DMF (12 mL). The mixture was stirred at 60 °C for 3 h, and then it was allowed to cool to r.t., prior to the addition of Et_2O (10 mL) and water (5 mL). The organic layer was separated, the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, 100:0 to 99:1 pentane/Et_2O, R_f = 0.20) afforded **14** (0.20 mg, 65%) as a colorless liquid.

IR (neat): 2971, 2916, 2238, 1673, 1640, 1448, 1379, 1111, 986, 926, 843, 778 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.55 (dd, *J* = 17.1, 10.0 Hz, 1 H, 3-H), 5.43 (dd, *J* = 17.1, 0.8 Hz, 1 H, 4-H), 5.24 (dd, *J* = 10.0, 0.8 Hz, 1 H, 4-H), 5.21–5.14 (m, 2 H, 2′-H), 2.43 (dd, *J* = 14.4, 7.8 Hz, 2 H, 1′-H), 2.25 (dd, *J* = 14.4, 7.0 Hz, 2 H, 1′-H), 1.76–1.73 (m, 6 H, 3′-$Me_{(E)}$), 1.64 (br, s, 6 H, 3′-$Me_{(Z)}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.8 (d, C-3), 136.3 (2 s, C-3′), 121.6 (s, C-1), 117.6 (2 d, C-2′), 116.7 (t, C-4), 46.2 (s, C-2), 36.5 (2 t, C-1′), 25.9 (2 q, 3′-$Me_{(E)}$), 18.2 (2 q, 3′-$Me_{(Z)}$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{22}N$: 204.1747; found: 204.1743.

Odor description (10% DPG, blotter): fruity-rosy, spicy, pink pepper, chamomile, fatty undertone.

Odor threshold (GC): 3.8 ng/L air.

2,2-Dibenzyl-3-oxobutanenitrile (15)

At 0 °C in a cooling bath, Cs_2CO_3 (650 mg, 2.00 mmol, 1.1 equiv) and BnBr (0.46 mL, 2.00 mmol, 2 equiv) were added to a soln of sodium 1-cyano-2-oxopropan-1-ide (**8**; 200 mg, 1.90 mmol, 1 equiv) in DMF (10 mL). The mixture was stirred for 3 h at r.t., and then it was quenched by the addition of sat. aq NH_4Cl soln (15 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with water (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, hexane/EtOAc, 9:1, R_f = 0.3) afforded **15** (0.34 g, 67%) as a crystalline, colorless and odorless solid; mp 93.3–93.8 °C.

IR (neat): 3033, 2930, 2238, 1721, 1497, 1456, 1358, 1183, 756, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 10 H, Ph-H), 3.27 (d, *J* = 13.3 Hz, 2 H, 1′-H), 3.00 (d, *J* = 13.3 Hz, 2 H, 1′-H), 1.84 (s, 3 H, 3-Me).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 203.5 (s, C-3), 134.1 (2 s, C-2′), 130.1 (4 d, C-3′), 128.7 (4 d, C-4′), 127.8 (2 d, C-5′), 120.5 (s, C-1), 57.3 (s, C-2), 43.2 (2 t, C-1′), 31.4 (q, 3-Me).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{17}NNaO$: 286.1202; found: 286.1204.

2,2-Diallyl-3-oxobutanenitrile (16)

At 0 °C in a cooling bath, Cs_2CO_3 (1.00 g, 3.06 mmol, 1.1 equiv) and allyl bromide (0.50 mL, 5.78 mmol, 2.2 equiv) were added to a soln of sodium 1-cyano-2-oxopropan-1-ide (**8**; 300 mg, 2.86 mmol, 1 equiv) in DMF (14 mL). The mixture was stirred at r.t. for 2.5 h, and then it was quenched by the addition of sat. aq NH_4Cl soln (15 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with water (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, hexane/EtOAc, 9:1, R_f = 0.3) afforded **16** (0.29 g, 63%) as a colorless oil.

IR (neat): 3084, 2985, 2922, 2238, 1724, 1643, 1442, 1419, 1361, 1186, 995, 929, 600 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.83–5.71 (m, 2 H, 2′-H), 5.29–5.17 (m, 4 H, 3′-H), 2.59 (ddt, *J* = 13.8, 7.4, 1.1 Hz, 2 H, 1′-H), 2.45 (ddt, *J* = 13.8, 7.3, 1.1 Hz, 2 H, 1′-H), 2.38 (s, 3 H, 3-Me).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 201.8 (s, C-3), 130.4 (2 d, C-2′), 121.2 (2 t, C-3′), 120.0 (s, C-1), 54.0 (s, C-2), 40.1 (2 t, C-1′), 29.4 (q, 3-Me).

HRMS (EI): *m*/*z* $[M - C_2H_3O]^+$ calcd for $C_8H_{11}N$: 120.0808; found: 120.0813.

Odor description (10% DPG, blotter): green, metallic, coniferous, hay.

Odor threshold (GC): 6.8 ng/L air (hyperosmics); 79 ng/L air (hyposmics).

Methyl 2-Cyano-2,2-bis(3-methylbut-2-enyl)acetate (17)

At 0 °C in a cooling bath, 1-bromo-3-methylbut-2-ene (5.80 mL, 50.0 mmol, 2.2 equiv) and Cs_2CO_3 (16.3 g, 50.0 mmol, 2.2 equiv) were added to a soln of methyl 2-cyanoacetate (**18**; 2.00 mL, 22.8 mmol, 1 equiv) in DMF (100 mL). The mixture was stirred at r.t. for 1.5 h, and then the solvent was removed in vacuo. The resulting residue was partitioned between sat. aq $NaHCO_3$ (50 mL) and EtOAc (200 mL), and the aqueous phase was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (3 × 200 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the resulting residue by flash chromatography (silica gel, hexane/EtOAc, 95:5, R_f = 0.2) afforded **17** (4.93 g, 92%) as a colorless liquid.

IR (neat): 2917, 1747, 1438, 1379, 1310, 1231, 1068, 840, 795 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.20–5.13 (m, 2 H, 2′-H), 3.78 (s, 3 H, 4-H), 2.64 (dd, *J* = 14.3, 7.6 Hz, 2 H, 1′-H), 2.55 (dd, *J* = 14.3, 7.5 Hz, 2 H, 1′-H), 1.76–1.72 (m, 6 H, 3′-$Me_{(E)}$), 1.65 (br, s, 6 H, 3′-$Me_{(Z)}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.3 (s, C-1), 137.8 (2 s, C-3′), 119.3 (s, C-3), 116.5 (2 d, C-2′), 53.2 (q, C-4), 50.0 (s, C-2), 35.2 (2 t, C-1′), 26.0 (2 q, 3′-$Me_{(E)}$), 18.1 (2 q, 3′-$Me_{(Z)}$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{22}NO_2$: 236.1645; found: 236.1642.

Odor description (10% DPG, blotter): floral, rosy, linalyl esters, chamomile.

Odor threshold (GC): 0.38 ng/L air.

2-Formyl-2,2-bis(3-methylbut-2-enyl)acetonitrile (19)

To a soln of 3-hydroxy-2,2-bis(3-methylbut-2-enyl)propanenitrile (**20**; 440 mg, 2.12 mmol, 1 equiv) in CH_2Cl_2 (14 mL) was added Dess–Martin periodinane (1.80 g, 4.24 mmol, 2 equiv). The mixture was stirred at r.t. for 2 h, and then it was quenched by the addition of sat. $NaHCO_3$/10% $NaHSO_4$ soln (1:1, 15 mL). Phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with sat. $NaHCO_3$ soln (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, hexane/EtOAc, 10:1, R_f = 0.3) afforded **19** (311 mg, 71%) as a colorless liquid.

IR (neat): 2972, 2917, 2860, 2244, 1735, 1673, 1444, 1379, 839, 776, 713 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.42 (s, 1 H, 3-H), 5.19–5.12 (m, 2 H, 2′-H), 2.60–2.44 (m, 4 H, 1′-H), 1.75 (m, 6 H, 3′-$Me_{(E)}$), 1.65 (br, s, 6 H, 3′-$Me_{(Z)}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.8 (d, C-3), 138.2 (2 s, C-3′), 118.7 (s, C-1), 115.7 (2 d, C-2′), 54.2 (s, C-2), 32.1 (2 t, C-1′), 25.9 (2 q, 3′-$Me_{(E)}$), 18.2 (2 q, 3′-$Me_{(Z)}$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{19}NO$: 205.1462; found: 205.1462.

Odor description (10% DPG, blotter): rather weak, green, chemical, reminiscent of gun powder.

Odor threshold (GC): 25 ng/L air.

3-Hydroxy-2,2-bis(3-methylbut-2-enyl)propanenitrile (20)

$NaBH_4$ (849 mg, 22.44 mmol, 8 equiv) was added to a soln of methyl 2-cyano-2,2-bis(3-methylbut-2-enyl)acetate (**17**; 660 mg, 2.80 mmol, 1 equiv) in THF/H_2O (14:1, 9 mL). The mixture was stirred at r.t. for 9.5 h, and then it was quenched by the addition of sat. aq NH_4Cl (8 mL) and diluted with EtOAc (4 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the resulting residue by flash chromatography (silica gel, hexane/EtOAc, 9:1, R_f = 0.1) afforded **20** (500 mg, 86%) as a colorless liquid which solidified upon storage in the freezer.

IR (neat): 3470, 2970, 2916, 2237, 1673, 1444, 1379, 1078, 1050, 842, 779 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.29–5.19 (m, 2 H, 2′-H), 3.64 (d, *J* = 6.4 Hz, 2 H, 3-H), 2.35–2.30 (m, 4 H, 1′-H), 1.76 (m, 6 H, 3′-$Me_{(E)}$), 1.72 (br. t, *J* = 6.4 Hz, 1 H, OH), 1.66 (br. s, 6 H, 3′-$Me_{(Z)}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.9 (2 s, C-3′), 122.5 (s, C-1), 117.4 (2 d, C-2′), 65.4 (t, C-3), 44.5 (s, C-2), 32.0 (2 t, C-1′), 26.0 (2 q, 3′-$Me_{(E)}$), 18.1 (2 q, 3′-$Me_{(Z)}$).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{21}NO$: 207.1618; found: 207.1623.

Ethyl 2-Cyano-2,2-bis(3-methylbut-2-enyl)acetate (22)

At 0 °C in a cooling bath, 1-bromo-3-methylbut-2-ene (0.72 mL, 6.19 mmol, 2.2 equiv) and Cs_2CO_3 (2.02 g, 6.20 mmol, 2.2 equiv) were added to a soln of ethyl 2-cyanoacetate (**21**; 0.30 mL, 2.82 mmol, 1 equiv) in DMF (15 mL). The mixture was stirred at r.t. for 1.5 h, and then it was diluted with Et_2O (15 mL), prior to quenching by the addition of sat. aq $NaHCO_3$ (10 mL) and water (10 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with water (2 × 15 mL) and brine (15 mL), dried ($MgSO_4$), and

concentrated in vacuo. Purification of the resulting residue by flash chromatography (silica gel, hexane/EtOAc, 25:2, R_f = 0.2) afforded **22** (630 mg, 90%) as a colorless liquid.

IR (neat): 2979, 2917, 2243, 1742, 1446, 1379, 1227, 1068 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.24–5.17 (m, 2 H, 2′-H), 4.25 (q, J = 7.1 Hz, 2 H, 4-H), 2.61 (dd, J = 14.2, 7.7 Hz, 2 H, 2′-H), 2.51 (dd, J = 14.2, 7.3 Hz, 2 H, 2′-H), 1.74 (br, s, 6 H, 3′-$Me_{(E)}$), 1.67 (br, s, 6 H, 3′-$Me_{(Z)}$), 1.31 (t, J = 7.1 Hz, 3 H, 5-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.8 (s, C-1), 137.6 (2 s, C-3′), 119.4 (s, C-3), 116.6 (2 d, C-2′), 62.4 (t, C-4), 50.0 (s, C-2), 35.3 (2 t, C-1′), 25.9 (2 q, 3′-$Me_{(E)}$), 18.1 (2 q, 3′-$Me_{(Z)}$), 14.1 (q, C-5).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{24}NO_2$: 250.1802; found: 250.1806.

Odor description (10% DPG, blotter): floral-fruity, aromatic, arnica, tagetes, osmanthus, with fatty, animalic undertone.

Odor threshold (GC): 8.3 ng/L air.

Methyl 2,2-Diallyl-2-cyanoacetate (23)

At 0 °C in a cooling bath, allyl bromide (0.60 mL, 6.93 mmol, 2.0 equiv) and Cs_2CO_3 (2.24 g, 6.86 mmol, 2.0 equiv) were added to a soln of methyl 2-cyanoacetate (**18**; 0.30 mL, 3.41 mmol, 1 equiv) in DMF (15 mL). The mixture was stirred at r.t. for 1 h, and then it was diluted with Et_2O (15 mL) and quenched by the addition of sat. aq $NaHCO_3$ (10 mL) and water (10 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with water (2 × 15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the resulting residue by flash chromatography (silica gel, hexane/EtOAc, 25:2, R_f = 0.2) afforded **23** (0.54 g, 89%) as a colorless liquid.

IR (neat): 3085, 2985, 2958, 2247, 1748, 1644, 1440, 1229, 994, 930 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.88–5.75 (m, 2 H, 2′-H), 5.27–5.25 (m, 2 H, 3′-H), 5.25–5.21 (m, 2 H, 3′-H), 3.80 (s, 3 H, 4-H), 2.65 (ddt, J = 13.8, 7.4, 1.1 Hz, 2 H, 1′-H), 2.55 (ddt, J = 13.8, 7.2, 1.1 Hz, 2 H, 1′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.5 (s, C-1), 130.4 (2 d, C-2′), 121.1 (2 t, C-3′), 118.4 (s, C-3), 53.3 (q, C-4), 49.4 (s, C-2), 40.7 (2 t, C-1′).

HRMS (EI): m/z [M – C_3H_5]$^+$ calcd for $C_7H_8NO_2$: 138.0550; found: 138.0551.

Odor description (10% DPG, blotter): very weak, metallic-green, rosy.

Odor threshold (GC): 500 ng/L air.

Methyl 2-Cyano-2,2-bis(cyclopropylmethyl)acetate (24)

At 0 °C in a cooling bath, Cs_2CO_3 (2.3 g, 6.99 mmol, 2.1 equiv) and cyclopropylmethyl bromide (0.68 mL, 7.01 mmol, 2.1 equiv) were added to a soln of methyl 2-cyanoacetate (**18**; 0.30 mL, 3.41 mmol, 1 equiv) in DMF (15 mL). The mixture was stirred for 1.25 h at r.t., and then it was poured into sat. aq $NaHCO_3$ soln (20 mL). The aqueous phase was extracted with Et_2O (2 × 70 mL), and the combined organic layers were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, hexane/EtOAc, 19:1, R_f = 0.3) afforded **24** (0.42 g, 60%) as a colorless liquid.

IR (neat): 3084, 3007, 2955, 1770, 1746, 1435, 1239 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, 4-H), 1.89 (dd, J = 14.0, 6.3 Hz, 2 H, 1′-H), 1.73 (dd, J = 14.0, 7.7 Hz, 2 H, 1′-H), 0.93–0.82 (m, 2 H, 2′-H), 0.62–0.54, (m, 2 H, 3′a-H), 0.54–0.45 (m, 2 H, 3′b-H), 0.24 (dddd, J = 9.6, 5.0, 5.0, 5.0, 5.0, Hz, 2 H, 3′a-Ha), 0.11 (dddd, J = 9.6, 4.9, 4.9, 4.9 Hz, 2 H, 3′b-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.0 (s, C-1), 119.7 (s, C-3), 53.2 (q, C-4), 50.4 (s, C-2), 42.2 (2 t, C-1′), 7.1 (2 d, C-2′), 4.3 (2 t, C-3′a), 4.1 (2 t, C-3′b).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{18}NO_2$: 208.1332; found: 208.1328.

Odor description (10% DPG, blotter): weak, green, chemical.

Odor threshold (GC): 310 ng/L air.

Methyl 2,2-Di[(2*Z*)-but-2-enyl]-2-cyanoacetate (25)

Methyl 2,2-di(but-2-ynyl)-2-cyanoacetate (**26**; 0.32 g, 1.58 mmol, 1 equiv) was dissolved in toluene (16 mL). Lindlar's catalyst (0.13 g, 0.031 mmol, 5% Pd, 2 mol%) and quinoline (0.05 mL, 0.424 mmol, 0.3 equiv) were added. The flask was evacuated until the solvents started to bubble and flushed with N_2 (3 ×) prior to the evacuation and the installation of a H_2 balloon. The mixture was stirred at r.t. for 2.5 h. Then, the mixture was filtered through a plug of wet Celite and concentrated in vacuo. Purification by flash chromatography (silica gel, hexane/EtOAc, 15:1, R_f = 0.3) afforded **25** (0.25 g, 1.221 mmol, 78%) as a colorless and odorless liquid.

IR (neat): 3023, 2957, 2923, 2245, 1745, 1437, 1233, 1211, 711 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.75 (dqt, J = 11.1, 6.9, 1.4 Hz, 2 H, 3′-H), 5.44 (dtq, J = 11.1, 7.6, 1.8 Hz, 2 H, 2′-H), 3.79 (s, 3 H, 4-Me), 2.73–2.66 (m, 2 H, 1′-H), 2.64–2.57 (m, 2 H, 1′-H), 1.69–1.63 (m, 6 H, 4′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.1 (s, C-1), 129.9 (2 d, C-3′), 122.2 (2 d, C-2′), 118.9 (s, C-3), 53.3 (q, C-4), 49.4 (s, C-2), 33.9 (2 t, C-1′), 13.1 (2 q, C-4′).

HRMS (ESI): m/z [M]$^+$ calcd for $C_{12}H_{17}NO_2$: 207.1254; found: 207.1248.

Methyl 2,2-Di(but-2-ynyl)-2-cyanoacetate (26)

At 0 °C in a cooling bath, 1-bromobut-2-yne (900 mg, 6.77 mmol, 2.1 equiv) and Cs_2CO_3 (2.26 g, 6.93 mmol, 2.1 equiv) were added to a soln of methyl 2-cyanoacetate (0.29 mL, 3.30 mmol, 1 equiv) in DMF (15 mL). The mixture was stirred at r.t. for 45 min, and then it was diluted with Et_2O (10 mL), prior to quenching the reaction by the addition of sat. aq $NaHCO_3$ (8 mL) and water (5 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the resulting residue by flash chromatography (silica gel, hexane/EtOAc, 9:1, R_f = 0.3) afforded **26** (420 mg, 63%) as a colorless and odorless liquid.

IR (neat): 2958, 2924, 2856, 2243, 1750, 1437, 1244, 1217, 1071 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, 4-H), 2.84 (q, J = 2.5 Hz, 4 H, 1′-H), 1.81 (t, J = 2.5 Hz, 6 H, 4′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.3 (s, C-1), 117.9 (s, C-3), 81.1 (2 s, C-2′), 71.2 (2 s, C-3′), 53.9 (q, C-4), 48.4 (s, C-2), 26.3 (2 t, C-1′), 3.6 (2 q, C-4′).

HRMS (EI): m/z [M – CH_3]$^+$ calcd for $C_{11}H_{10}NO_2$: 188.0706; found: 188.0710.

Methyl 2-Cyano-2,2-di(prop-2-ynyl)acetate (27)

At 0 °C in a cooling bath, propargyl bromide (0.75 mL, 80% in toluene, 6.96 mmol, 2.0 equiv) and Cs_2CO_3 (2.24 g, 6.86 mmol, 2.0 equiv) were added to a soln of methyl 2-cyanoacetate (**18**; 0.30 mL, 3.41 mmol, 1 equiv) in DMF (15 mL). The mixture was stirred at r.t. for 1 h, then it was diluted with Et_2O (15 mL), prior to quenching the reaction by the addition of sat. aq $NaHCO_3$ (10 mL) and water (10 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic lay-

ers were washed with water (2 × 15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the resulting residue by flash chromatography (silica gel, hexane/EtOAc, 4:1, R_f = 0.3) afforded **27** (0.46 g, 77%) as a colorless liquid.

IR (neat): 3293, 2960, 2254, 2129, 1751, 1438, 1246, 1221, 660 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3 H, 4-H), 2.95 (d, *J* = 2.7 Hz, 4 H, 1′-H), 2.24 (t, *J* = 2.7 Hz, 2 H, 3′-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.5 (s, C-1), 117.0 (s, C-3), 76.0 (2 s, C-2′), 73.7 (2 d, C-3′), 54.2 (s, C-4), 47.2 (s, C-2), 25.7 (2 t, C-1′).

HRMS (EI): *m*/*z* [M – CH_3]$^+$ calcd for $C_9H_6NO_2$: 160.0393; found: 160.0393.

The spectroscopic data of **27** were identical to those reported in the literature.[26]

Odor description (10% DPG, blotter): weak and vague, green, rooty, rubbery, muguet.

Odor threshold (GC): 43 ng/L air (hyperosmics); odorless (hyposmics).

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