Rose Ketones: Celebrating 30 Years of Success

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Can you remember life before the rose ketones? Can you remember what rose reconstitutions used to smell like before the rose ketones were available? Probably not. And if you can, you probably weren't too impressed with them.

Let me remind you. Firmenich's "Rosessence 17.600" was the first of a long series of Bulgarian rose essence reconstitutions containing rose ketones.[1] In this particular case, the formula contained 200 ppm of damascenone. We asked ourselves, "Does this low dosage really have any effect?" To test this hypothesis, we created a damascenone-free "Rosessence 17.600" and submitted the two to a traditional triangular smelling test amongst 10 perfumers.[2] We asked them if they could smell a difference between the three strips and, if yes, which they preferred. The results are presented in Table 1.

> O! How much more doth beauty beauteous seem
> By that sweet ornament which truth doth give!
> The rose looks fair, but fairer we it deem
> For that sweet odour, which doth in it live
> -William Shakespeare, 1609

The results are somewhat boring from a statistical viewpoint, but what a great victory for damascenone. We also asked the perfumers who took part to describe the difference between the "Rosessence 17.600" with damascenone and that without. As expected, we received 10 different answers, some of which we have summarized below:

- Damascenone adds more volume to the rose note.
- The one with damascenone has a stronger top note and more bouquet.
- Damascenone adds a modern touch to this fragrance.

And some more surprising remarks too: damascenone lends an artichoke, rose oxide, tobacco, leather, fibrous and even carrot note to the blend. Faced with such a clearly important molecule for perfumery it can only be right to trace its life story[3]… starting with its discovery.

History

At the beginning of the 1960s, the partnership between Firmenich, Professor Ruzicka and his newly appointed head of the terpenes group, Dr. Kovats (ETH Zürich), was given a new task: discover the signature chemical responsible for the characteristic smell of Bulgarian rose oil.

At the time, only 40 constituents were known; after five years of analysis, this rose to 80, but reconstitutions were still olfactively far away from that of the essential oil. In a final attempt, and by using a softer method of analysis, Kovats isolated over 200 fractions from 80 g of oil.[4] One of these fractions (Fraction D2.β = 0.076 g) had a honey-like note, which at the time was thought to be the odor of the chemical they were looking for. Incorporation of this fraction in reconstitutions based on the previously 80 identified constituents substantially increased its naturalness.

Further analysis of this 0.076 g fraction showed it to consist of six different chemicals, five of which were already known at the time. The sixth was thus deemed the key constituent whose structure was the unknown — **X**. The composition and odor description of damascenone containing distillation fraction D2.β is presented in Table 2.

Although the analysis was homing in on the honey-like note, it was only now evident that the chemical they were looking for was simply co-extracted with the honey-like

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Table 1. "Rosessence 17.600" panel results

Difference?	Freshly dipped strip		After 4 h on strip	
No. of panelists detecting a difference	10/10		10/10	
Preference?*	**Freshly dipped strip**		**After 4 h on strip**	
	With	Without	With	Without
Panelists' preference	10/10	0/10	10/10	0/10

*Preference for the sample with or without damascenone.

Table 2. Composition and odour description of the damascenone containing distillation fraction D2.β

Composition of fraction D2.β	Odour description
2-phenylethyl isobutyrate	Fruity-rosy, more fruity than rosy
trans-geranylacetone	Fresh-floral, sweet-rosy, slightly green, magnolia-like
2-tridecanone	Warm-oily, herbaceous, spicy, nut-like
2-phenylethyl 2-methylbutyrate	Cocoa, honey, slightly cinnamic
benzyl tiglate	Fungus, mushroom-like, rosy undertone
chemical **X**	Floral, fruity, rose, plum, grape, raspberry, sugary

substance (2-phenylethyl 2-methylbutyrate). Further work on fraction D2.β allowed the isolation of 0.0008 g of pure **X**. With such a small quantity of a chemical, a structural determination would cause no problem today. However, in 1967 the analytical equipment used was simply not powerful enough. Consequently, an incorrect structure **1** was first attributed to the unknown chemical **X** (Figure 1).

Kovats was not in a position to tackle the synthesis of the cyclopentadiene **1** so it was decided to prepare the six membered constitutional isomer instead (Figure 2) which, due to its structural relationship with the ionones, would be certainly easier to prepare. The preparation of this iso-ionone was undertaken by Firmenich R&D using the approach from β-cyclocitral **3** presented in Figure 3.[5]

The intermediate β-iso-ionone **5** already had a powerful "rose" odor which in itself was an encouraging sign and gave the impetus to move on with

Figure 1. Incorrect structure attributed to chemical X

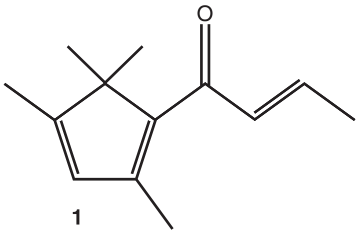

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Figure 2. Six-membered constitutional isomer of 1

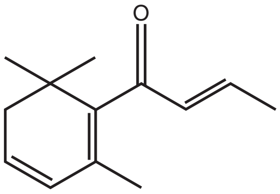

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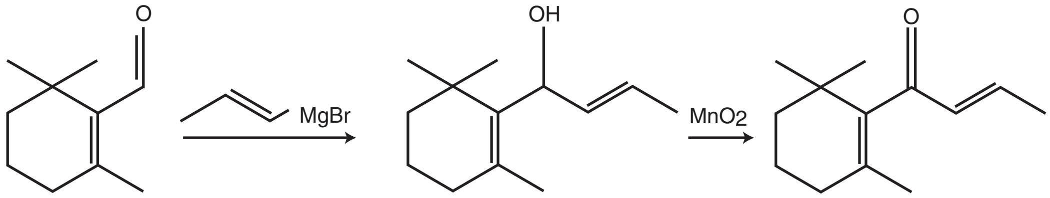
Figure 3. The first synthesis of β-iso-ionone 5 (β-damascone)



3 4 5

the preparation of **2**. In the meantime, reinterpretation of the analytical data gathered for substance **X** led to a new structural proposition, namely the iso-ionone **6** (Figure 4). This structure was favored over **1** from a biogenetic standpoint simply because of its much closer resemblance to the ionones that are found abundantly in nature.

Dehydrogenation of **5** gave the expected target molecule **2**.[6] What was to happen next was incredible. When the analytical data of **2** was compared to that of unknown **X,** an exact match was established (i.e. **X**=**2**); the analogue molecule that they had chosen to prepare was in fact **X**. What's even more fascinating is that **2** was selected simply because of its ease of synthesis.

The unknown **X** was quickly baptized “damascenone,” the root “damasc” taken from the botanical name of the essential oil Kovats had worked on (*Rosa damascena* Mill.), and the suffix “enone” taken from the chemical functionality of **X**. Using a similar nomenclature the intermediate β-iso-ionone **5**, which had already attracted the perfumers attention due to its intense rose odor, became β-damascone.

Shortly after the discovery of damascenone, the decision was taken to concentrate efforts on finding a technical synthesis of β-damascone because it represented a more realistic target from a synthetic perspective. This decision was rapidly vetoed by the perfumers who demanded both molecules; but above all damascenone, whose olfactive description was first recorded as simply “magnificent.”

With damascenone and β-damascone in their pocket, Firmenich R&D saw these chemicals as interesting “leads”

Figure 4. Iso-ionone

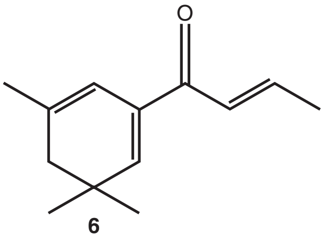


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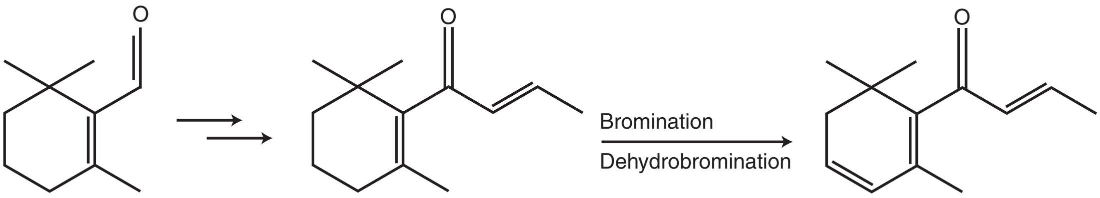
Table 3. Discovery chronology of rose ketones at Firmenich

Rose Ketone	1st Synthesis	Added to perfumers palette	Commercially available since
damascenone	1967	1971	1982
β-damascone	1967	1973	1979
α-damascone	1968*	1972	1978
γ-damascone	1969	1989	2002
ε-damascone	1981	-	-

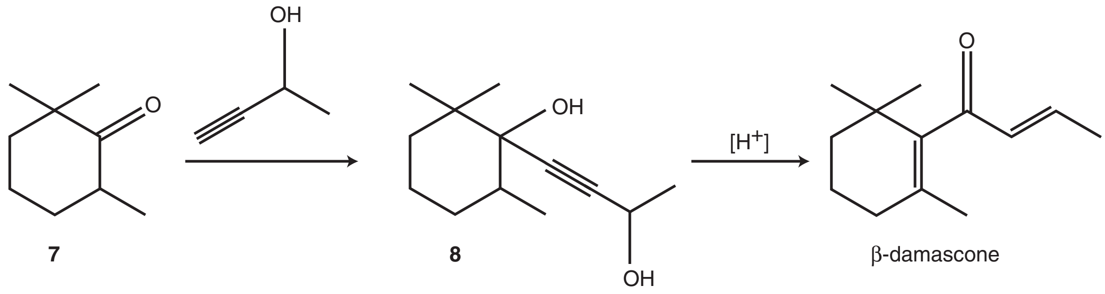
*a few milligrams had been prepared in 1966[7] but not olfactively evaluated.

Figure 5. Production of damascenone in 1971



3 β-damascone damascenone

Figure 6. β-Damascone synthesis from trimethylcyclohexane[9]

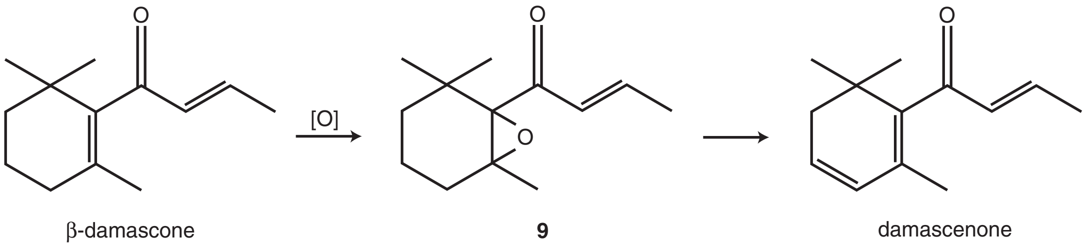


7

8

β-damascone

Figure 7. Damascenone from β-damascone via epoxidation and dehydration[10]



β-damascone

9

damascenone

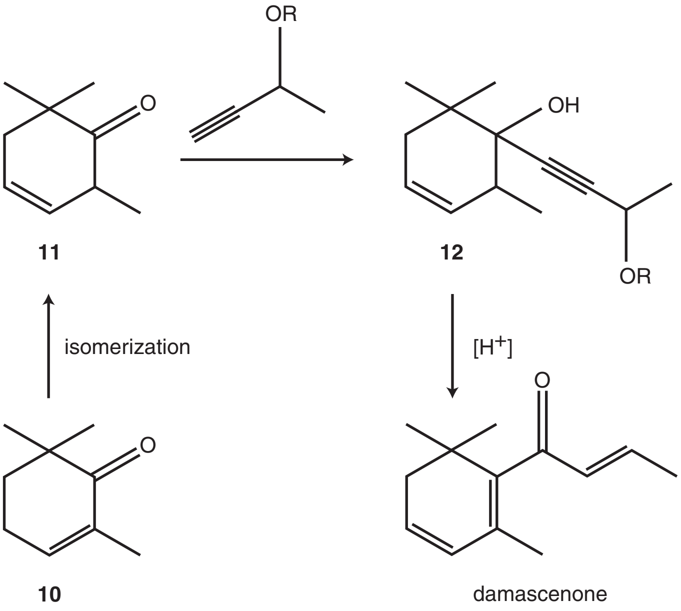
and rapidly synthesised the α- and γ- analogues for olfactive evaluation, but more about these later. The timeline of rose ketone discovery is presented in Table 3.

From the Lab Bench to Production

Much has already been published about the chemical development of the rose ketones.[8] What is particularly worth remembering from the first 10 years of work is the enormous challenge that perfumers, chemists and marketing personnel faced to master the original olfactive character and manufacture of these key compounds.

Damascenone: In the early 1970s the production of damascenone was none other than a scale up of the first lab synthesis presented in Figure 5. The major drawbacks in this approach, the new chromate based oxidation of **4**, the bromination-dehydrobromination step required to transform β-damascone into damascenone and the scarcity of β-cyclocitral **3**, were all solved towards the end of the 1970s. The chromate and β-cyclocitral problems were solved simultaneously when a synthesis of β-damascone starting from trimethylcyclohexanone **7** was developed (Figure 6).

Figure 8. Damascenone from trimethylcyclohexenone



11

12

10

damascenone

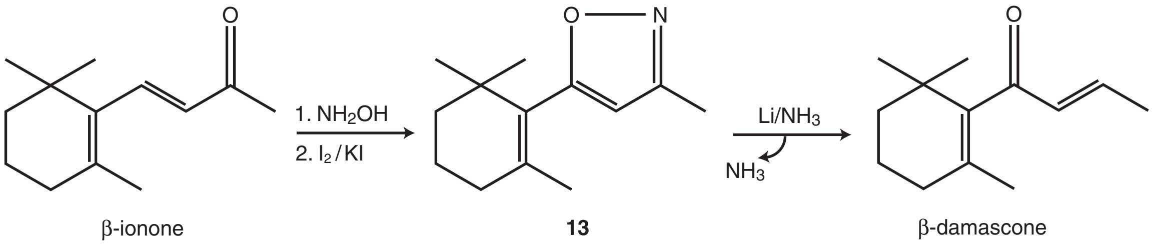
The bromination-dehydrobromination step was avoided by epoxidation of β-damascone and subsequent base treatment (Figure 7).

These new processes were introduced in stages over a 10-year period which saw the internal consumption of damascenone rise from a few grams in 1971, to 2 kg in 1975, to just over 100 kg in 1979. Although all the problems facing the early production of damascenone had been solved, the entire process still remained somewhat folkloric. Batches were of varying chemical purity and olfactive quality and had to be mixed and cut to obtain a consistent quality, and even this quality was not acceptable to all the perfumers at the time.

The desire to commercialize damascenone at the beginning of the 1980s once again focused research efforts on providing a cheaper synthesis, a higher chemical yield and an improved olfactive profile. Significant cost reductions were obtained using **10** as a starting material.[11] Isomerization of the double bond into the δ-position gave the correct isomer **11** to proceed directly to damascenone using essen–tially the same chemistry as that for the synthesis of β-damascone (Figure 8).

Unfortunately, the damascenone obtained was con–stantly plagued with problems of olfactive quality, a situation that was eventually overcome through the use of

Figure 9. β-Damascone from β-ionone via its isoxazole[13]



a special final conditioning sequence. This purification method gave such a vastly improved damascenone quality that it was virtually rediscovered as a new chemical. The difference was such that older creations containing the previous damascenone quality had to be olfactively reworked. This paved the way to a commercial release, which took place in 1982.

β-Damascone: The early syntheses of β-damascone are described above. It was only when the more recent damascenone syntheses circumvented β-damascone as an intermediate product that the synthesis of β-damascone was reinvestigated. In the early 1970s, an elegant synthesis starting from β-ionone was developed.[12] β-Damascone obtained by the formation of the isoxazole **13** of β-ionone and subsequent elimination of ammonia (Figure 9).

A later development saw the replacing the iodine/potassium iodide-based oxidation of the intermediate oxime into the isoxasole **13** with an electrochemical oxidation. However, although this offered a cleaner reaction, this route could not compete with the cyclohexanone-based route, which was already in production.

α-Damascone: Whereas β-damascone was originally synthesized as an intermediate in the route towards damascenone, α-damascone was the first rose ketone "analogue" to be synthesized. The first synthesis used the cyclocitral route, which provided enough material for an olfactive evaluation. Strangely enough, α-damascone received "bad reviews" from the perfumers at the time (1968) and was not added to their palette of chemicals for creation until a year later. It would appear that the real olfactive value of this compound was not fully realized in the early days.

Figure 10. The first production synthesis of α-damascone

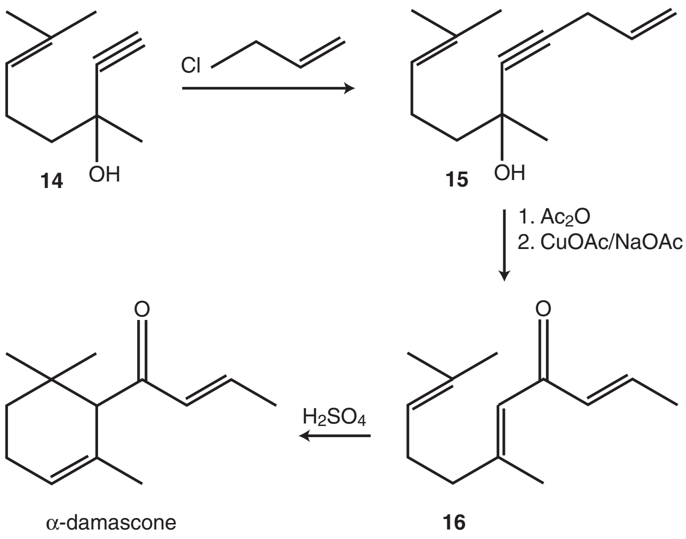


Figure 11. The formation of Dynascone in the early α-damascone synthesis

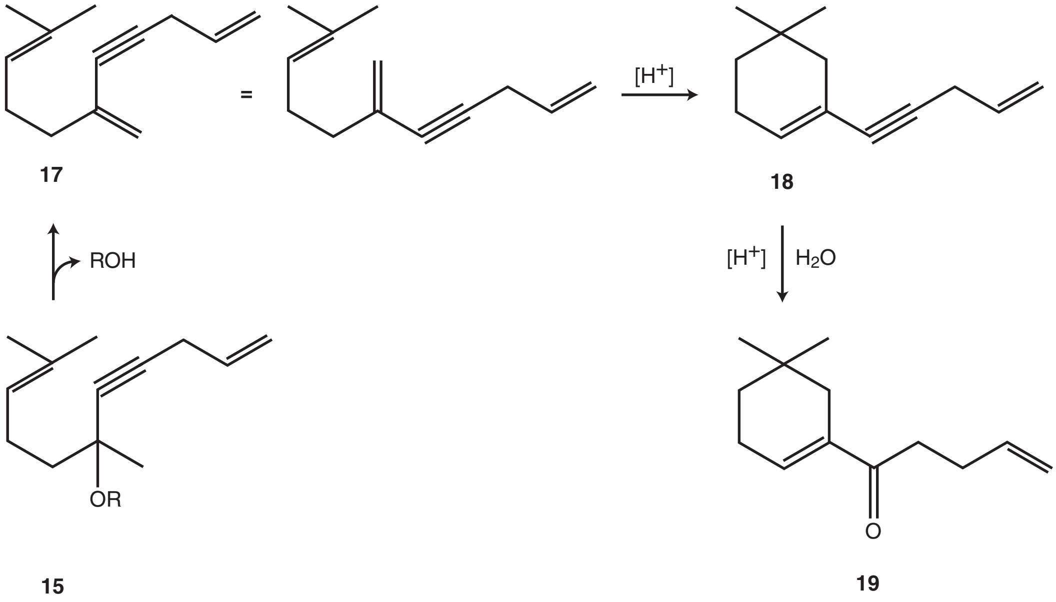


Figure 12. α- and β-Methyl cyclogeranate 20 from methylheptanone 21

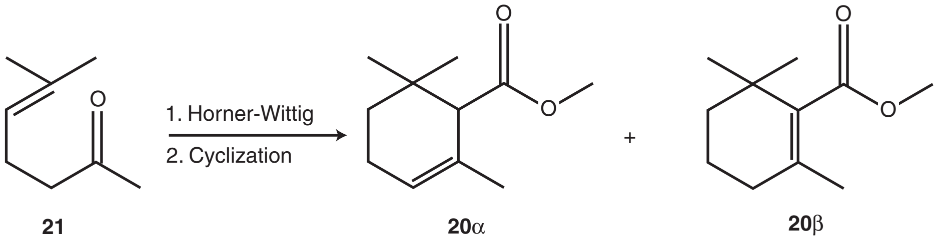


Table 4. Gaseous detection thresholds of some commercially available rose ketones[15]

Rose Ketone	μg/dm³ of air at 25°C
damascenone	1.3×10^{-5}
α-damascone	1.4×10^{-4}
β-damascone	1.9×10^{-4}
δ-damascone	2.1×10^{-5}
γ-damascone	4.5×10^{-3}

Here again routes via the isoxazole of α-ionone were investigated as possible production routes but abandoned for the same reasons as given for the analogous β-damascone synthesis. A synthesis that did make it to production is shown below and was used between 1972 and 1975.

The route illustrated in Figure 10 was based on the cyclization of the pseudo-damascone **16**, which was obtained from dehydrolinalool **14**, as shown. Unfortunately, here again, problems of olfactive quality surfaced. A green-galbanum note, whose intensity varied from batch to batch, routinely accompanied the typical floral-fruity apple note characteristic of α-damascone. This problem initiated an in-depth analytical investigation to identify the molecule(s) responsible for this off-note with a view at eliminating their formation during the process.

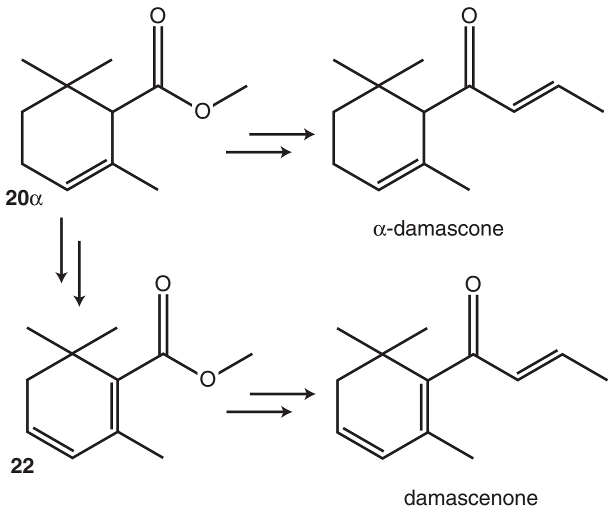
The molecule responsible for the green-galbanum note was found thanks to a gas chromatography-sniffing exercise. It was subsequently isolated, and its structure determined as the now well-known and important aroma chemical Dynascone **19**.[14] Its formation in the α-damascone synthesis was rationalized as shown in Figure 11.

Elimination of water (R=H) and/or acetic acid (R=Ac) from the intermediate **15** can give the intermediate trienyne **17**, which can cyclize and hydrate under the acidic reaction conditions to give Dynascone.

Production Today: Four Rose Ketones, One Process

As described above, at one point in time, the three original rose ketones, damascenone, β-damascone and α-damascone were all obtained using different production methods, which, considering their close structural similarity, was disappointing. From the mid 1980s, a new process was finally ready which would provide a common intermediate for all the rose ketones: methyl cyclogeranate **20** (Figure 12).

Figure 13. α-Damascone and damascenone production from α-methyl cyclogeranate



This ester can be easily obtained from methylheptenone **21** after the appropriate Horner-Wittig and cyclization reactions have been carried out. The cyclization step leads to a mixture of α- and β-methyl cyclogeranate, which can be separated by distillation. The α-methyl cyclogeranate **20α** is then used as a raw material for the production of α-damascone and damascenone and the β-isomer **20β** for the production of β-damascone and γ-damascone (Figures 13 and 14).

This new concerted approach further solved new problems which had surfaced in the meantime. First, the starting material for damascenone, trimethyl cyclohexenone **10**, had ceased to be commercially available. This did away with the costly in-house synthesis that had to be carried out for several years to satisfy the ever-growing demand of damascenone. Second, this route provided a Dynasconefree and consistent quality of α-damascone and thirdly a route to γ-damascone was made available.

Rose Ketone Analogues

The first rose ketone to be olfactively evaluated was β-damascone, which at the time was merely a synthetic intermediate on the way to damascenone. From the very early days, chemists and perfumers were intrigued by the olfactive difference a single extra double bond could have when comparing β-damascone with damascenone. This naturally lead to "analogue bashing," an exercise in which research chemists prepare a structurally similar molecule in the hope that the over-all olfactive note is retained (in this case, floral-fruity), but that the small difference given to the new molecule will give either an enhanced, more natural or original olfactive note.

The first such analogue was α-damascone, a double bond isomer of β-damascone. Whereas β-damascone has more of a blackcurrant-plum note, α-damascone is more rose-apple. Both α- and β-damascone have similar detection thresholds (see Table 4), and are about 10 times higher than that of damascenone. γ-Damascone is fruitier than α- and β-damascone, with a dominant floral rosy green note. Surprisingly γ-damascone detection threshold is 10 times higher than those of α- and β-damascone. *trans*-δ-Damascone has a distinctive blackcurrant-floral woody note and shows exceptional diffusion with a detection threshold similar to that of damascenone.[16] All of the above-mentioned rose ketones (Figure 15) are now commercially available. Also available on the market is isodamascone, which, as its name implies, is a side chain isomer of β-damascone.[17] Although this molecule retains the floral-fruity aspect of the damascones, it is less diffusive and long lasting.

ε-Damascone (Figure 16) was first prepared in 1981, and although it possesses typical damascone character, it is weaker than both the α- and β- isomers. When the ring double bond is removed, a predominantly camphoraceous-celluloid olfactive character is obtained with some moldy-corky facets, the strength of which depends on the *cis/trans* ratio of the ring substituents. When all double bonds are removed, the olfactive note changes back to a more woody-rosy one with varying degrees of celluloid — camphoraceousness again depending on the *cis/trans* ratio of the methyl and butanone side chains. Damascenone ana–logues have also been prepared. The ε,α-damascenone still retains some damascone character; the de-conjugated

Figure 14. β- and γ-Damascone production from β-methyl cyclogeranate

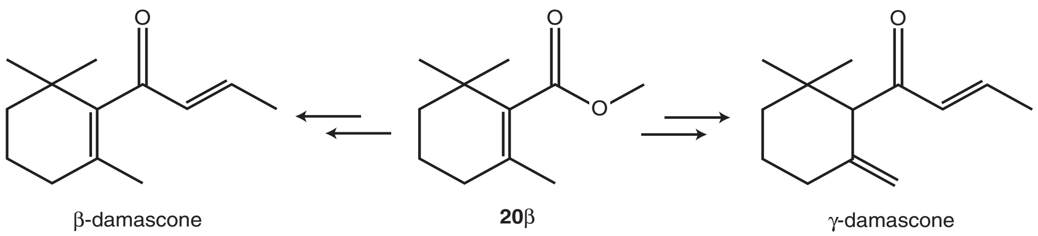
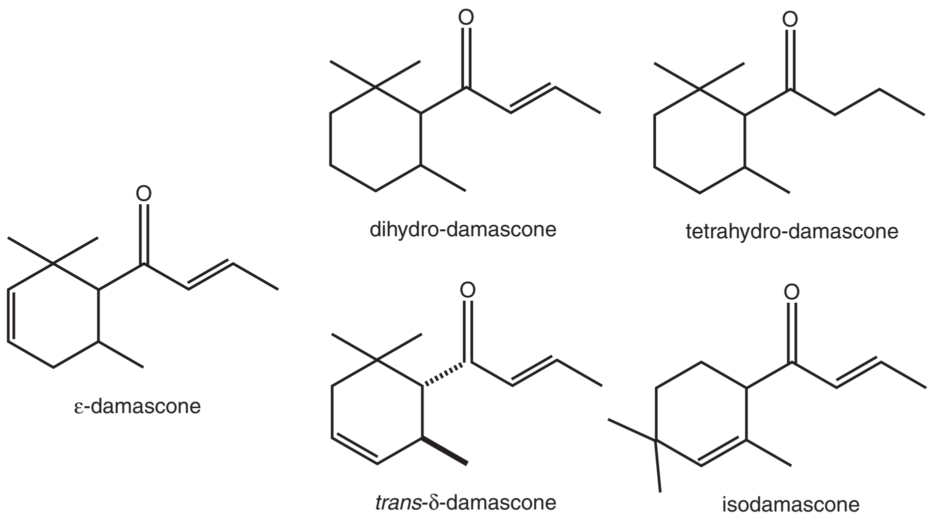


Fig. 15. Some rose ketone analogues



ε,β-analogue, however, is fatty, minty, leathery and woody. To our knowledge, none of these di- and tetra-hydro rose ketones or damascenone analogues are commercially available.[18] A plethora of other analogues are described in the literature, a detailed description of which is outside the scope of this article. [19]

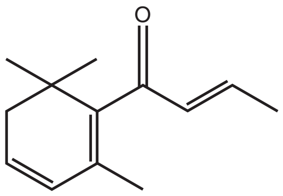
Classic Bases, New Products and New Ideas for Perfumery Creation

Rosessence 17.600 was the first perfumery creation to make use of a rose ketone, in this case damascenone. This rose reconstitution found immediate success because it delivered synthetic Bulgarian rose oil with increased top note, volume, "bouquet" and naturalness, compared to anything that had been blended before.

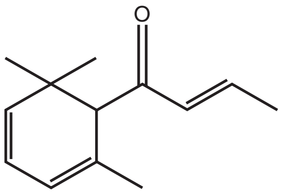
But using such strong and powerful chemicals was far from easy and it took years before our most talented perfumers managed to understand and appreciate all the facets that the rose ketones possessed. Naturally, this led to the creation of many specialties, allowing perfumers to more easily "harness" the desired aspect of a particular rose ketone. Some of these bases are still commercially available today (Table 5).

The newly launched γ-damascone was formally only available in Florascone and Rhodascone bases, to which it lends its specific green-rose character. [20,21] Perfumers will now be able to test for themselves this new rose ketone, which differentiates itself from the others due to its uniquely

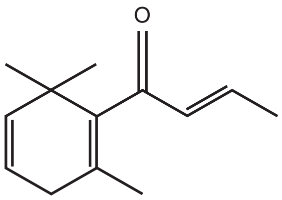
Fig. 16. Damascenone and its ring double bond isomers



damascenone
Rose, plum, grape



ε, α-damascenone
Rose, plum, grape



ε, β-damascenone
Fat, mint, leather wood

green-pine-terpenic and slightly safranic overtures.

γ-Damascone is particularly effective at adding a fresh-green fruity touch to woody blends and rendering rose blends greener and leafier than α-damascone. Spicy notes can be easily rounded and softened with a touch of γ-damascone.

Also new to the market is Romascone.[21] Although chemically not a rose ketone, Romascone has an aromatic and damascone-like character. On a smelling strip its aromatic, rosemary and thuyonic aspects are dominant with a fruity-damascone undertone. Typical of the rose ketones, this ester's damascone character is especially evident in composition. At low levels of use, its floral-fruity (blackberry) side dominates which, as dosage is increased, changes to a more aromatic note. With citrus, and in particular mandarin notes, the material may add freshness.

Just as important to the perfumer as new materials for creation, is insight and inspiration on how to make new use of the classic rose ketones (α-, β-, δ-damascone and damascenone). We have now successfully opened new olfactive doors by using many of these rose ketones in rice, chocolate, honey, tomato, olive, verveine and yuzu fragrances. In many cases, a carefully selected and dosed rose ketone can add radiance, bloom and a touch of naturalness to these mainly culinary notes.[22]

The Future

Rose ketones have become important and routinely used perfumery raw materials since their discovery more than 30 years ago.[23] Although it doesn't seem likely that a new, more performant, structural analogue is yet to be found, work to "improve" the existing rose ketones has never ceased—nor is it expected to.

Such improvements encompass the quest to find a cost-effective synthesis of (S)-(-)-α-damascone which, besides being the actual enantiomer found in nature (tea), it is approximately 100 times stronger than its antipode.[24,25] From an olfactive perspective, it is also less corky-earthy than the currently available commercial grade, as this sometimes-undesirable note stems from the (R)-(+)-isomer.

Many other improvements/projects are currently being worked on in this industry's labs—some will see the light of day, most won't. In any case, what is sure is that the rose ketones are here to stay.

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1. Date of creation 10.02.1970.
2. Firmenich perfumers based in Geneva, Switzerland representing all segments of perfumery.
3. See also: D. Kastner, *Parfüm. Kosmetik*, 1994, 75, 170.
4. For a report on the complete analysis see: E. Kovats, *J. Chromatogr.*, 1987, *406*, 185.

Table 5. Rose ketone specialty bases[20]

Base	Rose Ketone	Odor
Rosessence 17.600	damascenone	A synthetic reconstitution of Bulgarian rose oil
Rosessence 193	damascenone β-damascone	A synthetic reconstitution of Bulgarian rose oil
Damascenia 185	damascenone β-damascone	Possesses the characteristic top note of Bulgarian rose Very powerful, warm and fresh. In use, it develops the beautiful freshness of the rose fragrance
Dorinia	β-damascone	A diffusive floral speciality that possesses the total rose fragrance with its dewy petal character and green leafy freshness
Cetylia Base	α-damascone β-damascone	Very natural diffusive rose floral base with fresh green, somewhat fruity and petal character
Wardia	α-damascone β-damascone	Wardia possesses the power and the homogeneity of the natural rose of May absolute

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12. G. Büchi, J. C. Vederas, *J. Am. Chem. Soc.*, 1972, *94*, 9128. K. H. Schulte-Elte, B. L. Miiller, G. Ohloff, *Helv. Chim. Acta*, 1973, *56*, 310.
13. Firmenich Patent CH 553207, 30.03.1972.
14. A. F. Morris, F. Näf, R. L. Snowden, *Perfum. Flavor.*, 1991, *16*, 33.
15. The values given are averages. The detection threshold is a subjective measurement and as such can vary widely between individuals.
16. IFF Patent US 4211242. d-Damascone was first commercialised by IFF and is now commercially available from both Firmenich and IFF.
17. Dragoco Patent DE 2120413, 24.04.1971. Commercialised by Dragoco.
18. The Damascone/Damascenone analogues mentioned in this paragraph have been prepared and evaluated by Firmenich SA, Geneva. Tetrahydro-Damascone has also been prepared by IFF. IFF Patent EP 12436, 15.12.1978.
19. See G. Frater, J. A. Bajgrowicz, P. Kraft, *Tetrahedron*, 1998, *54*, 7633 and references cited therein.
20. These bases were created by Firmenich.
21. Firmenich Patent US 5015625, 18.01.1989.
22. These blends have been specially created for the "Rose Ketones 2002" presentation by Firmenich.
23. Our statistics show that over 30% of all fragrances contain one or more rose ketone.
24. C. Fehr, J. Galindo, *J. Am. Chem. Soc.*, 1988, *110*, 6909. Firmenich Patent EP 326 869, 05.02.1988. C. Fehr, *Angew. Chem.*, 1996, 108, 2726; *Angew. Chem. Int. Ed. Engl.*, 1996, 35, 2566. C. Fehr, "Enantioselective Protonation in Fragrance Synthesis," In *Chirality in Industry II*; Editors A. N. Collins, G. N. Sheldrake, J. Crosby; Wiley: Chichester, 1997, 335. C. Fehr, J. Galindo, *Angew. Chem.*, 1994, *106*, 1967; *Angew. Chem. Int. Ed. Engl.*, 1994, *33*, 1888. C. Fehr, J. Galindo, *Helv. Chim. Acta*, 1995, 78, 539.
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