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Synthesis of β-damascone from 2,6-dimethylcyclohexanone

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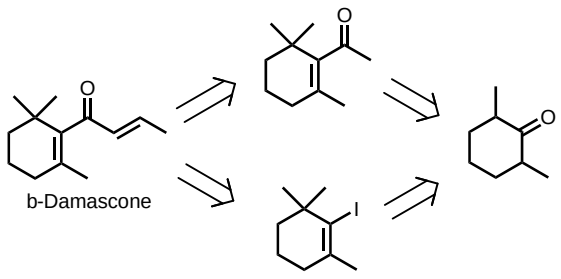
Abstract

The synthesis of β-damascone can be achieved from 2,6-dimethylcyclohexanone using a Rupe rearrangement or a Barton vinyl iodation as the key steps.



Keywords: β-Damascone, Rupe rearrangement, vinyl iodide, fragrance, organoleptics

Introduction

The essence of the Damask rose (*Rosa Damascena mill.*) contains a number of organoleptic compounds with a great diversity of flavors and fragrances.[1-10] This essence is used in the composition of fragrances, cosmetics, soaps and detergents.[11,12] Among the numerous constituents of the essential oil of the Bulgarian rose (more than 250 constituents), β-damascone possesses a strong floral/tobacco odor.[7] In addition, β-damascenone has been identified as 0.1% of the extract of the Damask rose and this product possesses a floral rose odor that can be detected at low concentration and represents 70% of the relative proportion of the rose oil in scent units. The structures of β-damascone and β-damascenone were established in 1970 by Demole *et al.* at Firmenich and Kováts of the *Chemical Laboratory*, ETH Zürich.[13,14] As β-damascenone was synthesized from β-damascone in two steps, using an allylic bromination followed by an elimination step,[15] it is important to have an efficient sequence of reactions that can produce β-damascone (Figure 1).

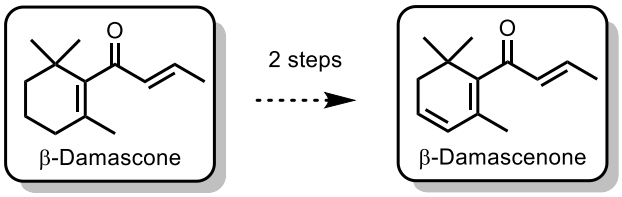
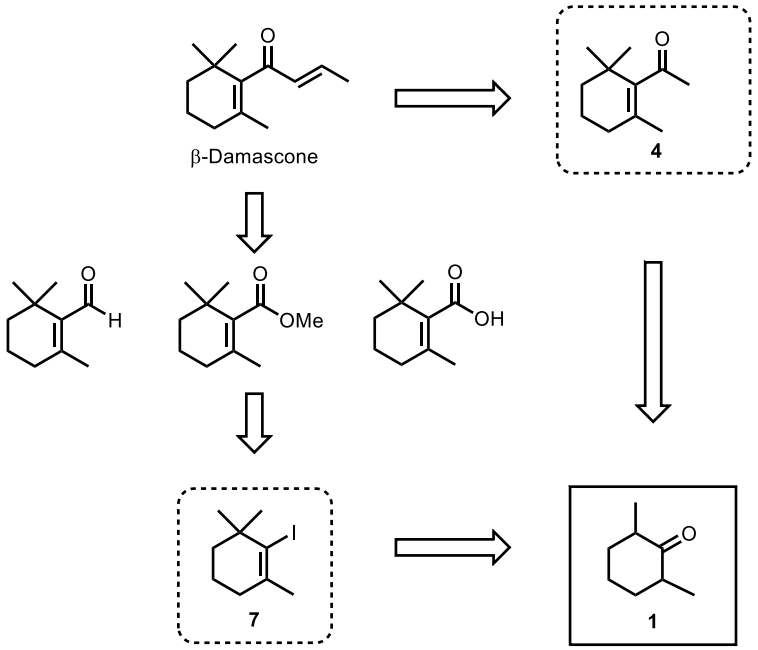


Figure 1. Structures of β-damascone and β-damascenone.

A number of strategies involving different starting materials have been reported to synthesize β-damascone, such as β-ionone, β-cyclocitral (synthetized from citral), β-cyclogeranate as well as cyclohexanone and their derivatives.[16] Among the methods developed to synthesize β-damascone, different rearrangements were used such as a Wharton,[17,18] a Büchi–Vederas,[19,20] an Overman[21] rearrangement or epoxide rearrangements,[22] as well as a Rupe rearrangement which consist of the rearrangement of a propargylic alcohol to an α,β-unsaturated enone.[23,24] In 1981, it was reported that by using a Rupe rearrangement,[25] β-damascone could be prepared in six steps from 2,6,6-trimethylcyclohex-2-en-1-one, which was prepared by a Diels–Alder reaction. In this sequence of reactions, the intermediates were purified and, in addition, to synthesize the precursor of the Rupe rearrangement, acetylene gas and sodium were used, which would be avoided on large scale. Furthermore, for some steps the reported yields were above 100%.

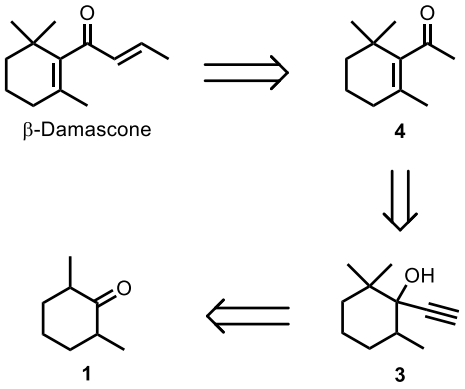
Results and Discussion

Here, we report the synthesis of β-damascone starting from a commercially available cheap starting material, 2,6-dimethylcyclohexanone (**1**), and by using a Rupe rearrangement affording the enone intermediate **4**. In the sequence of reactions, leading to β-damascone, the purification of the intermediates was not necessary except at the final stage where β-damascone was purified. Furthermore, the synthesis of three precursors of β-damascone, e.g. β-cyclocitral, β-cyclogeranate and β-cyclogeranic acid, were also obtained from the commercially available 2,6-dimethylcyclohexanone (**1**) *via* vinyl iodide **7** (Scheme 1).



Scheme 1. Retrosynthetic analysis of β-damascone from enone **4** and vinyl iodide **7**.

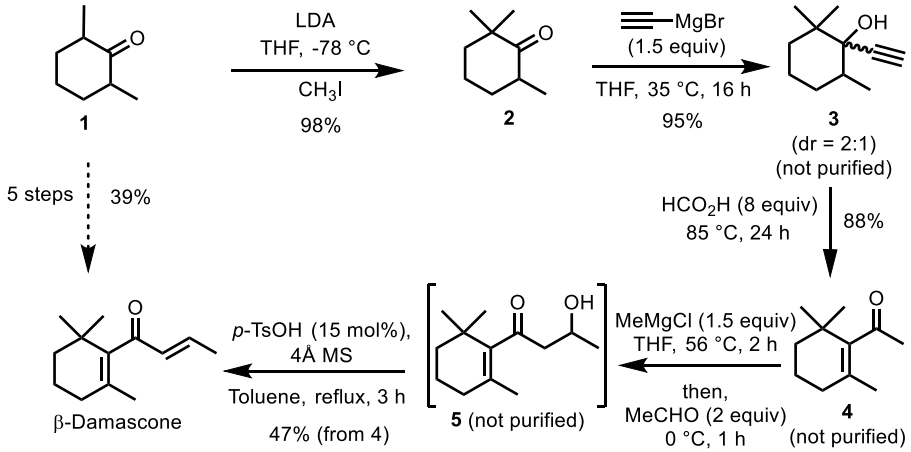
First of all, the synthesis of β-damascone was envisaged from enone **4**, resulting from a Rupe rearrangement applied to the propargylic alcohol **3**. This alcohol would be obtained from the commercially available 2,6-dimethylcyclohexanone (**1**) in two steps (Scheme 2).



Scheme 2. Retrosynthetic analysis of β-damascone using a Rupe rearrangement.

The synthesis of β-damascone started from the commercially available 2,6-dimethylcyclohexanone (**1**) which was transformed to 2,2,6-trimethylcyclohexanone (**2**) in 98% yield by treatment with methyl iodide under basic conditions (LDA, THF, -78 °C). Having 2,2,6-trimethylcyclohexanone (**2**) in hand, this compound was treated with ethynylmagnesium bromide (1.5 equiv) in THF (35 °C, 16 h), which is safer than the use of acetylene and sodium[26] to produce the desired propargylic alcohol **3**. This alcohol was isolated in 95% yield with a d.r. of 2:1. Propargylic alcohol **3** was then transformed into enone **4** under acid conditions (HCO_2H, 85 °C, 24 h) (88%) according to a Rupe rearrangement, and was engaged in the next step witout any purification. The final transformation of enone **4** into β-damascone was achieved in two steps. The first step was an aldol condensation which was performed under basic conditions (MeMgCl, THF, 56 °C, 2 h), followed by addition of

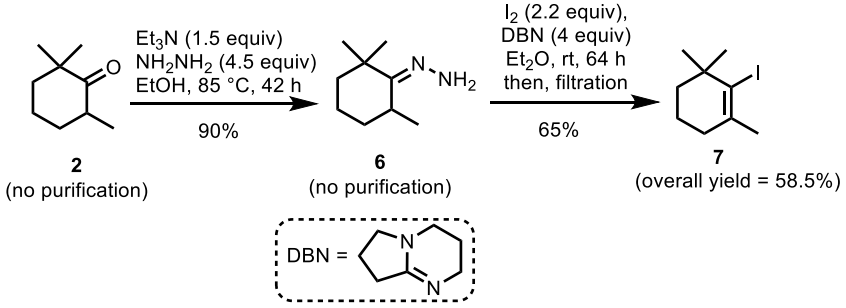
acetaldehyde. Even though aldol reactions involving acetaldehyde are challenging, the resulting aldol product **5** was isolated in 56% yield.[25,27] The second step is a crotonization (*p*-TsOH, 3Å MS, toluene, reflux), which led to β-damascone in 84% yield. By using a Rupe rearrangement, β-damascone was obtained in five steps from 2,6-dimethylclohexanone (**1**) (Scheme 3), without any purification of the intermediates, which is an advantage compared to the previously described synthesis.[25]



Scheme 3. Synthesis of β-damascone from 2,6-dimethylcyclohexanone using a Rupe rearrangement.

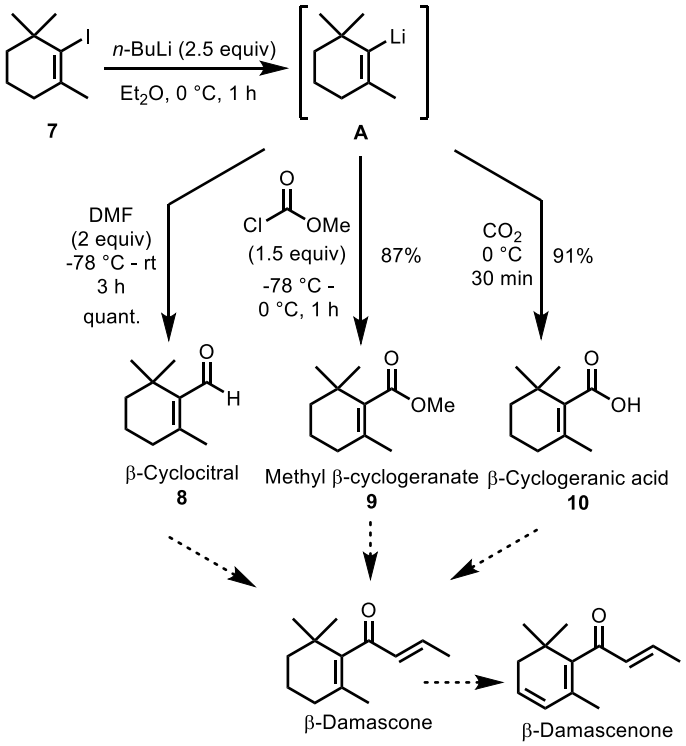
As previously mentioned, β-damascone was synthesized from β-ionone. Initially, ozonolysis of β-ionone was used to produce β-cyclocitral **8**.[28] However, on large scale, the use of ozone can be problematic due to its toxicity and explosiveness. Having 2,2,6-trimethylcyclohexanone (**2**) in hand, we preferred to transform this ketone into β-cyclocitral **8** *via* vinyl iodide **7** which can be prepared by using a Barton vinyl iodation.[29] A simple procedure involving hydrazine instead of *tert*-butyl-1,1,3,3-tetramethylguanidine, which has to be prepared, was envisaged.[30]

Thus, 2,2,6-trimethylcyclohexanone (**2**) was transformed to hydrazone **6** (NH_2NH_2, EtOH, 85 °C, 42 h, 90% yield) which was then treated with I_2 in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in diethyl ether (Et_2O). After optimization of the reaction conditions, we found that by using of 2.2 equiv of I_2, 4 equiv of DBN in Et_2O at rt for 64 h and, after a simple filtration, vinyl iodide **7** was isolated in 65% yield.[31] Vinyl iodide **7** was prepared in 3 steps with an overall yield of 53% from cheap and commercially available materials, e.g. 2,6-dimethylcyclohexanone (**1**) and hydrazine. Here also, only one purification was required: the purification of the vinyl iodide **7** (Scheme 4).



Scheme 4. Synthesis of vinyl iodide **7**.

Having vinyl iodide **7** in hand, different precursors of β-damascone, were prepared. After a halogen/metal exchange, using *n*-BuLi (2.1 equiv) in Et_2O (0 °C), the vinyl lithium intermediate **A** was produced and quenched with different electrophiles.[28,32] When DMF was utilized, β-cyclocitral **8** was produced in quantitative yield. By using methyl chloroformate, methyl β-cyclogeranate **9** was obtained in 87% isolated yield and, when intermediate **A** was quenched with solid CO_2,[33] β-cyclogeranic acid **10** was obtained in 91% yield (Scheme 5). Compounds **8**-**10** could then be transformed into β-damascone,[14,16,34,35] and eventually to β-damascenone.[15]



Scheme 5. Synthesis of β-damascone and β-damascenone precursors from vinyl iodide **7**.

Conclusions

We have developed efficient synthetic pathways to access β-damascone and three of its precursors. These compounds were obtained in good yields from the cheap and commercially available compound, 2,6-dimethylcyclohexanone (**1**). It is worth mentioning that to access β-damascone either from enone **4** or vinyl iodide **7**, no purification of the intermediates was needed, thus the purification factor is very low,[36] which is an important factor in respect of the green chemistry rules.

We are currently investigating the development of a continuous flow process to increase the efficiency and the overall yield of the process to produce β-damascone and β-damascenone.

Experimental Section

General. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica plates, visualized by irradiation with UV light or by stain visualisation (specified for each experiment). Commercially available

reagents were purchased from Sigma-Aldrich and used without further purification. Grignard reagents and *n*-BuLi were twice titrated before use by a standard titration method (titration with menthol dissolved in dry THF at 0 °C, using 2,2'-bipyridyl as a color indicator). ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz for ^{1}H and 101 MHz for ^{13}C. Chemical shifts are reported in δ unit parts per million (ppm); signals are referenced to TMS as an internal standard. Coupling constants (*J*) are given in Hz and multiplicity is abbreviated as: s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet or massif). Gas Chromatography coupled to Mass Spectrometry (GC/MS) analyses were performed on a Shimadzu GC/MS-QP2010S using an electron impact (EI) spectrometer. The abundance indicated for each mass number (*m/z* values) is given in percentage relative to the strongest peak of 100% abundance (base peak). Infrared (IR) spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer and are reported as wavenumbers in cm^{-1}.

Synthesis of compounds 2-10 and β-damascone

2,2,6-Trimethylcyclohexan-1-one (2).[37] *n*-BuLi (14.7 mL of 2.3 M solution in hexanes, 33.7 mmol, 1.06 equiv) was added dropwise to a solution of freshly distilled diisopropylamine (5.51 mL, 39.3 mmol, 1.24 equiv) in THF (dry, 40 mL) at -78 °C. After the addition of *n*-BuLi, the reaction mixture was warmed up to 0 °C and stirred for 40 min. The solution was cooled again to -78 °C and at this temperature a solution of 2,6-dimethyl cyclohexanone (**1**) (4.0 g, 4.32 mL, 31.7 mmol, 1 equiv) in THF (dry, 8 mL) was added over 30 min using a syringe pump. The solution was stirred at -78 °C. After 1.5 h, MeI (6.76 g, 2.96 mL, 47.5 mmol, 1.5 equiv) was added dropwise to the reaction mixture which was stirred for 1 h at -78 °C. The reaction was allowed to warm up to rt (by removing the cooling bath) and after 16 h the solution was added to a heterogeneous mixture of saturated aqueous NH_4Cl solution (80 mL), H_2O (8 mL) and Et_2O (40 mL) with vigorous stirring. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 40 mL). The collected organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. 2,2,6-Trimethylcyclohexan-1-one (**2**) was obtained as a yellowish liquid (4.0 g, 90%) contaminated by traces of 2,6-dimethylcyclohexanone (**1**). As the product was isolated in satisfactory purity, it was used in the next reaction without further purification. The spectral data were identical to those reported in the literature.[37] R_f = 0.57 (SiO_2, petroleum ether/Et_2O = 95:5). IR (ATR): 2964, 2929, 2853, 1704, 1455, 1365, 1126, 991 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (m, 1H), 2.04 (m, 1H), 1.87 (m, 1H), 1.76 (dq, *J* 13.4, 2.9 Hz, 1H), 1.64 (m, 1H), 1.54 (td, *J* 13.4, 4.2 Hz, 1H), 1.31 (qd, *J* 13.1, 3.9 Hz, 1H), 1.17 (s, 3H), 1.03 (s, 3H), 0.98 (d, *J* 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 217.5, 45.3, 41.9, 40.9, 36.9, 25.7, 25.4, 21.6, 15.1. MS (EI) *m/z*: 140 (M^+, 21), 83 (11), 82 (100), 72 (6), 70 (13), 69 (37), 67 (10), 57 (9), 56 (44), 55 (32).

1-Ethynyl-2,2,6-trimethylcyclohexan-1-ol (3).[38] Ethynylmagnesium bromide (13.4 mL of 0.4 M solution in THF, 5.34 mmol, 1.5 equiv) was added dropwise to a solution of ketone **2** (500 mg, 3.56 mmol, 1 equiv) in THF (dry, 3.5 mL) at rt. The yellow solution was then heated at 30 °C for 16 h. The reaction mixture was then cooled to 0 °C and quenched with a saturated aqueous NH_4Cl solution (6 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvents were evaporated under reduced pressure. 1-Ethynyl-2,2,6-tri-methylcyclohexan-1-ol (**3**) was isolated as a yellowish liquid (565 mg, 95%, d.r. = 2:1). The diastereomers were not separated and the mixture was used in the next reaction without further purification. Compound **3** has an olfactive property of wet earth. *Major diastereomer:* $\mathbf{R_f}$ = 0.50 (SiO_2, petroleum ether/Et_2O = 90:10, visualization with $KMnO_4$). IR (ATR): 2930, 2103, 1649, 1259, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.48 (s, 1H), 1.95-1.84 (m, 1H + OH), 1.66-1.55 (m, 2H), 1.51-1.40 (m, 2H), 1.36-1.28 (m, 2H), 1.12 (s, 3H), 1.04 (d, *J* 6.5 Hz, 3H), 1.00 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 84.2, 78.7, 75.3, 38.8, 38.0, 36.7, 32.7, 26.7, 21.2, 19.8, 16.4. MS (EI) *m/z*: 166 (M^+, 1), 151 (13), 133 (10), 125 (29), 124 (10), 123 (18), 110

(35), 109 (33), 105 (8), 97 (14), 96 (14), 95 (67), 93 (11), 91 (12), 83 (15), 82 (100), 81 (36), 77 (9), 69 (25), 67 (27), 56 (12), 55 (36), 54 (14), 53 (28). *Minor diastereomer:* R_f = 0.61 (SiO_2, petroleum ether/Et_2O = 90:10, visualization with $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 1H), 1.95-1.84 (m, 1H + OH), 1.66-1.55 (m, 2H), 1.51-1.40 (m, 2H), 1.36-1.28 (m, 2H), 1.10 (s, 3H), 1.09 (s, 3H), 1.07 (d, *J* 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 86.3, 76.1, 73.1, 38.3, 36.1, 33.7, 28.8, 26.2, 23.7, 21.2, 17.1.

1-(2,2,6-Trimethylcyclohex-1-en-1-yl)ethan-1-one (4).[37] Formic acid (0.94 mL, 24.9 mmol, 8 equiv) was added at rt to tertiary alcohol **3** (518 mg, 3.11 mmol, 1 equiv). The reaction mixture was heated to 85 °C and after 24 h the reaction was cooled to rt and H_2O (4 mL) and Et_2O (4 mL) were added. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (2 x 10 mL), brine (2 x 10 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. 1-(2,2,6-Trimethylcyclohex-1-en-1-yl)ethan-1-one (**4**) was isolated as an orange oil (456 mg, 88%). The product was isolated in satisfactory purity and used in the next step without further purification. The spectral data were identical to those reported in the literature.[37] Compound **4** has an olfactive property of sweet and fruity smell. R_f = 0.56 (SiO_2, petroleum ether/Et_2O = 90:10). IR (ATR): 2971, 2901, 1691, 1406, 1393, 1381, 1066, 1056 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 1.95 (t, *J* 6.3 Hz, 2H), 1.69 – 1.61 (m, 2H), 1.58 (s, 3H), 1.48 – 1.40 (m, 2H), 1.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 210.1, 143.5, 128.4, 38.7, 33.4, 33.1, 31.0, 28.5 (2C), 20.7, 18.8. MS (EI) *m/z*: 166 (M^+, 31), 151 (63), 124 (10), 123 (100), 109 (35), 107 (18), 95 (13), 93 (9), 91 (12), 81 (61), 79 (14), 77 (10), 67 (20), 57 (9), 55 (12), 53 (9).

3-Hydroxy-1-(2,6,6-trimethylcyclohex-1-en-1-yl)butan-1-one (5).[39] Methylmagnesium chloride (1.47 mL of 3 M solution in Et_2O, 4.43 mmol, 1.5 equiv) was added dropwise to a solution of methyl ketone **4** (490 mg, 2.95 mmol, 1 equiv) in THF (dry, 10 mL) at rt. The obtained orange solution was stirred for 2 h at 56 °C. The mixture was then cooled to 0 °C and a solution of acetaldehyde (0.33 mL, 5.90 mmol, 2 equiv) in THF (dry, 2 mL) was added dropwise. The resulting solution was stirred at 0 °C and after 1 h, the reaction mixture was quenched by addition of H_2O (15 mL). The solution was allowed to warm up to rt and a 10% aqueous H_2SO_4 solution (9 mL) was added to the mixture. After stirring for 30 min, the layers were separated and the organic layer was washed with H_2O (2 x 10 mL), a saturated aqueous $NaHCO_3$ solution (2 x 10 mL) and brine (2 x 10 mL). The resulting organic phase was dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The crude product (346 mg, 56%) was used in the next step without further purification and characterization.

β-Damascone.[22] *p*-TsOH (23 mg, 0.12 mmol, 0.15 equiv) and 3Å molecular sieves (1 g) were added to a solution of crude alcohol **5** (170 mg, 0.80 mmol) in toluene (15 mL). The reaction mixture was stirred under reflux with a Dean–Stark apparatus. After 3 h, the reaction mixture was allowed to cool down to rt. Molecular sieves were removed by filtration and washed with Et_2O. The filtrate was washed with H_2O (10 mL), a saturated aqueous $NaHCO_3$ solution (2 x 10 mL) and brine (2 x 10 mL). The obtained organic layer was dried over $MgSO_4$, filtrated and the solvents were removed under reduced pressure. β-Damascone was isolated as an orange yellow oil (131 mg, 84%). The spectral data were identical to those reported in the literature.[22] β-Damascone has an olfactive property of sweet, fruity and rose floral. R_f = 0.32 (SiO_2, petroleum ether/Et_2O = 95:5). IR (ATR): 1647, 1442, 1378, 1290, 1238, 973 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (dq, *J* 15.6, 6.9 Hz, 1H), 6.17 (dq, *J* 15.6, 1.7 Hz, 1H), 1.99 (t, *J* 6.6 Hz, 2H), 1.92 (dd, *J* 6.9, 1.6 Hz, 3H), 1.73 – 1.65 (m, 2H), 1.51 (s, 3H), 1.49 – 1.44 (m, 2H), 1.02 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.4, 146.0, 140.3, 134.8, 130.6, 38.9, 33.5, 31.3, 29.0 (2C), 21.4, 19.0, 18.5. MS (EI) *m/z*: 192 (M^+, 39), 178 (13), 177 (100), 159 (8), 149 (13), 135 (18), 123 (48), 121 (32), 109 (13), 107 (39), 105 (9), 95 (17), 93 (19), 91 (17), 81 (50), 79 (19), 77 (14), 69 (75), 67 (16), 65 (8), 57 (8), 55 (19), 53 (11).

2,2,6-trimethylcyclohexanone hydrazone (6).[37] Hydrazine hydrate (6 mL of 50% solution in H_2O, 96.2 mmol, 4.5 equiv) was added to solution of ketone **2** (3.0 g, 21.3 mmol, 1 equiv) and Et_3N (4.5 mL, 32.1 mmol, 1.5 equiv) in EtOH (15 mL) at rt. The yellow solution was then heated at 85 °C for 42 h. The reaction mixture was then cooled to rt and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvents were evaporated under reduced pressure. 2,2,6-Trimethylcyclohexanone hydrazone (**6**) was isolated as a white crystalline solid (2.97 g, 90%). The product was isolated in satisfactory purity and used in the next reaction without further purification. The spectral data were identical to those reported in the literature.[37] mp 60-62 °C. R_f = 0.45 (SiO_2, petroleum ether/Et_2O = 95:5). IR (ATR): 3362, 2927, 1459, 1381, 986, 808, 750, 692, 653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.97 (br s, 2H), 3.03-2.95 (m, 1H), 1.85-1.73 (m, 1H), 1.67-1.54 (m, 3H), 1.51-1.39 (m, 2H), 1.17 (d, *J* 7.5 Hz, 3H), 1.13 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.7, 40.5, 37.7, 31.8, 29.6, 29.0, 26.6, 17.5, 17.3. MS (EI) *m/z*: 155 (M+1, 13), 154 (M^+, 100), 139 (43), 138 (17), 137 (15), 136 (10), 126 (15), 125 (8), 124 (9), 123 (41), 122 (61), 112 (24), 111 (28), 110 (10), 109 (34), 108 (14), 107 (14), 105 (9), 99 (16), 98 (10), 97 (27), 96 (24), 95 (39), 94 (28), 93 (11), 86 (20), 85 (40), 84 (13), 83 (30), 82 (23), 81 (67), 80 (15), 79 (16), 77 (8), 72 (51), 71 (10), 70 (38), 69 (53), 68 (38), 67 (46), 65 (7), 58 (32), 57 (24), 56 (42), 55 (94), 54 (17), 53 (23).

2-Iodo-1,3,3-trimethylcyclohex-1-ene (7).[37]A solution of I_2 (7.2 g, 28.5 mmol, 2.2 equiv) in Et_2O (dry, 40 mL) was added dropwise to a solution of 2,2,6-trimethylcyclohexanone hydrazone (**6**) (2 g, 12.9 mmol, 1 equiv) and DBN (6.4 mL, 51.6 mmol, 4 equiv) in Et_2O (dry, 40 mL). The brownish turbid solution was stirred at rt for 64 h (conversion was followed by TLC). The reaction mixture was then filtered through short pad of Celite and the filtrate was concentrated under reduced pressure. The crude product was filtered through silica gel (petroleum ether = 100%) and the solvent was removed under reduced pressure. 2-Iodo-1,3,3-trimethylcyclohex-1-ene (**7**) was obtained as a slightly yellow liquid (2.1 g, 65%). The spectral data were identical to those reported in the literature.[37] R_f = 0.94 (SiO_2, petroleum ether). IR (ATR): 1467, 1360, 1124, 921, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.12 (t, *J* 7.5 Hz, 2H), 1.87 (s, 3H), 1.70-1.59 (m, 4H), 1.09 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.9, 117.5, 39.7, 38.0, 33.8, 31.7 (2C), 31.2, 19.5. MS (EI) *m/z*: 251 (M+1, 7), 250 (M^+, 76), 234 (34), 124 (10), 123 (100), 108 (62), 107 (25), 95 (14), 93 (59), 91 (23), 81 (84), 79 (32), 77 (19), 69 (9), 67 (23), 65 (12), 57 (11), 55 (20), 53 (17), 51 (8).

2,6,6-Trimethylcyclohex-1-ene-1-carbaldehyde (8).[40] *n*-BuLi (0.67 mL of 2.5 M solution in hexanes, 1.68 mmol, 2.1 equiv) was added dropwise to a solution of vinyl iodide **7** (200 mg, 0.79 mmol, 1 equiv) in Et_2O (dry, 4 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h (full consumption of vinyl iodide was checked by GC/MS analysis of quenched aliquots of the crude reaction mixture). The colorless solution was then cooled to -78 °C (acetone/dry ice bath) and DMF (dry, 0.12 mL, 1.60 mmol, 2 equiv) was added dropwise. After addition, the cooling bath was removed and the reaction mixture was stirred at rt. After 3 h, the reaction was quenched at rt by slow addition of H_2O (5 mL) and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over $MgSO_4$, filtered and the solvents were distilled at 40 °C under atmospheric pressure. 2,6,6-Trimethylcyclohex-1-ene-1-carbaldehyde (**8**) was isolated as a colorless liquid (120 mg, quantitative yield). Compound **8** has an olfactive property of fruity smell. The spectral data were identical to those reported in the literature.[40] R_f = 0.36 (SiO_2, pentane/Et_2O = 90:10). IR (ATR): 2928, 1671, 1611, 1457, 1377, 1359, 1120, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 10.31 (s, 1H), 2.19 (t, *J* 6.3 Hz, 2H), 1.66 – 1.58 (m, 2H), 2.10 (s, 3H), 1.47 – 1.41 (m, 2H), 1.20 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.2, 156.0, 140.6, 40.5, 35.6, 32.9, 27.7 (2C), 19.3, 18.5. MS (EI) *m/z*: 153 (M+1, 10), 152 (M^+, 95), 138 (9), 137 (100), 123 (80), 119 (17), 109 (79), 107 (18), 95 (33), 93 (25), 91 (32), 82 (73), 79 (32), 77 (25), 69 (9), 67 (82), 65 (15), 55 (31), 53 (22), 51 (11),

Methyl 2,6,6-trimethylcyclohex-1-ene-1-carboxylate (9).[41] *n*-BuLi (0.33 mL of 2.5 M solution in hexanes, 0.83 mmol, 2.1 equiv) was added dropwise to a solution of vinyl iodide **7** (100 mg, 0.39 mmol, 1 equiv) in Et_2O (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h (full consumption of the vinyl iodide was checked by GC/MS analysis). The colorless solution was then cooled to -78 °C (acetone/dry ice bath) and neat methyl chloroformate (50 µL, 0.58 mmol, 1.5 equiv) was added dropwise to the solution. After addition, the cooling bath was changed for an ice bath and the reaction mixture was stirred for 1 h at 0 °C. The solution turned to a white color and after 1 h, the reaction mixture was quenched at 0 °C with a saturated aqueous NH_4Cl solution (4 mL). The aqueous layer was extracted with Et_2O (2 x 5 mL) and the combined organic layers were washed with brine (2 x 10 mL), dried over $MgSO_4$, filtrated and the solvents were distilled off at 40 °C under atmospheric pressure. Methyl 2,6,6-trimethylcyclohex-1-ene-1-carboxylate (**9**) was isolated as a slightly yellow liquid (63 mg, 87%). The product was isolated in satisfactory purity and involved in the next reaction without further purification. The spectral data were identical to those reported in the literature.[41] Compound **9** has an olfactive property of sweet smell. R_f = 0.74 (SiO_2, pentane/Et_2O = 90:10). IR (ATR): 2932, 1720, 1272, 1229, 1065, 1037 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 3H), 1.99 (t, *J* 7.5 Hz, 2H), 1.70 – 1.63 (m, 2H), 1.66 (s, 3H), 1.48 – 1.41 (m, 2H), 1.09 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 135.0, 134.2, 51.0, 38.3, 33.0, 31.1, 28.3 (2C), 21.3, 18.7. MS (EI) *m/z*: 182 (M^+, 13), 167 (35), 151 (13), 140 (5), 136 (9), 135 (100), 123 (56), 108 (5), 107 (52), 93 (8), 91 (19), 81 (20), 79 (23), 77 (11), 67 (9), 59 (6), 55 (9), 53 (8).

2,6,6-Trimethylcyclohex-1-ene-1-carboxylic acid (10).[41] *n*-BuLi (2.8 mL of 2.4 M solution in hexanes, 6.71 mmol, 2.1 equiv) was added drpwise to a solution of vinyl iodide **7** (800 mg, 3.19 mmol, 1 equiv) in Et_2O (dry, 16 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h (full consumption of the vinyl iodide was checked by GC/MS analysis). Solid CO_2 was added to the colorless solution by pieces. After 30 min, CO_2 was fully consumed and H_2O (10 mL) was slowly added to the solution followed by dropwise addition of concentrated HCl (2 mL). The formed yellow-orange solution was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with 5% aqueous NaOH solution (3 x 16 mL) and the combined aqueous layers were acidified with concentrated HCl until pH ~ 2. The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvents were evaporated under reduced pressure. 2,6,6-Trimethylcyclohex-1-ene-1-carboxylic acid (**10**) was isolated as a white solid (488 mg, 91%). The spectral data were identical to those reported in the literature.[41] mp 76 -77 °C. R_f = 0.67 (SiO_2, hexanes/EtOAc = 70:30). IR (ATR): 2933, 1683, 1295, 1280, 1257, 874, 727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 11.24 (br s, 1H), 2.03 (t, *J* 6.4 Hz, 2H), 1.79 (s, 3H), 1.71 – 1.63 (m, 2H), 1.49 – 1.44 (m, 2H), 1.16 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.8, 136.6, 133.9, 38.5, 33.0, 31.6, 28.3 (2C), 21.6, 18.6. MS (EI) *m/z*: 168 (M^+, 18), 154 (9), 153 (100), 135 (37), 126 (10), 125 (20), 123 (44), 109 (11), 108 (6), 107 (66), 105 (7), 95 (6), 93 (9), 91 (23), 81 (25), 79 (27), 77 (15), 68 (6), 67 (22), 65 (9), 59 (6), 57 (4), 55 (16), 53 (12), 51 (6).

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Supplementary Material

Supplementary material containing the ^1H and ^{13}C NMR spectra is available online.

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