Aldols by *Michael* Addition: Application of the *retro-Michael* Addition to the Slow Release of Enones

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Dedicated to Dr. *Ferdinand Näf* on the occasion of his 65th birthday

The reversibility of *Michael* additions was exploited to create *Michael* adduct profragrances of several enones. Some of them proved to exhibit interesting properties. The synthesis of aldols (3-hydroxy ketones) by *Michael* addition also opens a ready access to 1,3-diketones.

Introduction. – Time-delayed fragrance-delivery systems have been developed to render possible the perception of a fragrance which, on its own, would be evanescent, over a long period of time. One distinguishes between physical delivery systems (*e.g.* micro-encapsulated perfumes [1]) and chemical delivery systems, in which an odorless 'profragrance' (or 'properfume') liberates the fragrance molecule by means of a chemical reaction [2–9]. The chemical approach is of course limited to compounds possessing an agreeable odor (fresh, clean) and having a low threshold value (cost, efficiency)[1])[2]). We herein report on a new chemical delivery system, based on *retro-Michael* reactions [8][3]) and on an alternative method for the formation of aldols (and 1,3-diketones) from enones [10][11].

In 1998, *Procter & Gamble* [6] submitted a patent covering the release properties of all possible aldehydic or ketonic fragrance compounds bound to an amine (or polyamine). Among all these '*Schiff* bases', the most efficient delivery systems were in fact those derived from enones (damascones, carvone). More recently, a similar patent has been published by *BASF* [7], indicating that this area represents a hot topic.

Based on earlier work in our laboratory, we hypothesized that the properfumes derived from enones were in fact not *Schiff* bases but β-amino ketones derived from *Michael* additions. We examined the possibility of other *Michael* adducts between the damascones and various O- and S-nucleophiles. The damascones were chosen as the first targets, because they represent good *Michael* acceptors, possess a fresh fruity-flowery odor which is perceived as agreeable even in the absence of other perfume components, and have very low threshold values [12].

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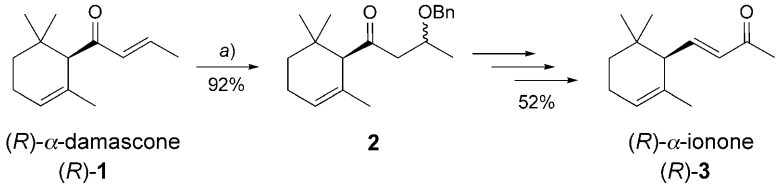
[1]) Digeranyl succinate represents the first commercialized *Firmenich* properfume (liberating geraniol); see [3].

[2]) Geranyl 2-phenyl-2-oxoacetate represents the first photolabile properfume (liberating citral); see [4].

[3]) For an extension of this work to polymer-bound *Michael* adducts, see the accompanying publication [9].

In addition, we knew from our earlier work [13] that benzyl alcohol (BnOH) readily adds to α-damascone (**1**) under basic conditions (*Scheme 1*; 1,1,3,3-tetramethylguanidine = TMG). The *Michael* adduct **2** served as intermediate for the conversion of (*R*)-α-damascone ((*R*)-**1**) into (*R*)-α-ionone ((*R*)-**3**) without any racemization.

Scheme 1



a) BnOH, TMG (0.2 equiv.), 20°.

From results of that same work, we could assume that hydrogenolysis of benzyl ether **2** should afford hydroxy ketone **4** (*Scheme 2*). The perspective of a simple protocol to access aldols (and 1,3-diketones) from enones, especially in cases where application of the aldol reaction would have been problematic (conservation of enantiomer purity, macrocyclic 3-hydroxy ketones, *etc.*), represented an interesting challenge[4])[5]). We expected that the corresponding esters, *e.g.*, benzoate **5**, would represent good candidates for the slow release of α-damascone (**1**) in typical applications of functional perfumery.

Results. – Following our own procedure [13], we treated (±)-**1** with excess BnOH in the presence of 20 mol-% of TMG and allowed the solution to stand for 24–48 h (*Scheme 2*). The volatile portion (**1**, TMG, and BnOH) of the equilibrium mixture (**2**/**1** *ca.* 70 : 30) was separated from **2** by bulb-to-bulb distillation and then equilibrated at r.t. for 24 h. Re-distillation and re-equilibration gave benzyloxy ketone **2** in 92% yield. Hydrogenolytic cleavage of the benzyl group with Pd/C and $TsOH \cdot H_2O$ as catalysts afforded hydroxy ketone **4**[6]) in 83% yield. Acylation with benzoyl chloride furnished benzoate **5** (Et_3N; cat. *N*,*N*-dimethylpyridin-4-amine (DMAP); 73%).

Whereas benzoate **5** proved to be an excellent properfume, releasing α-damascone (**1**) of intense odor strength over a period of at least one week [8], the benzyloxy ketone **2** was stable in the absence of base, and did not undergo the *retro-Michael* reaction. As we had found that the *Michael* addition of BnOH was reversible in the presence of TMG, we prepared ether **6** linked to an amine. Here, due to a lower conversion and an increased thermal instability, the yield was only 33%, but ether **6** indeed slowly released α-damascone over time.

Although **2** was stable in the presence of weak bases (anilines, tertiary amines), it underwent rapid elimination in the presence of TMG or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Indeed, DBU also showed approximately the same catalytic activity

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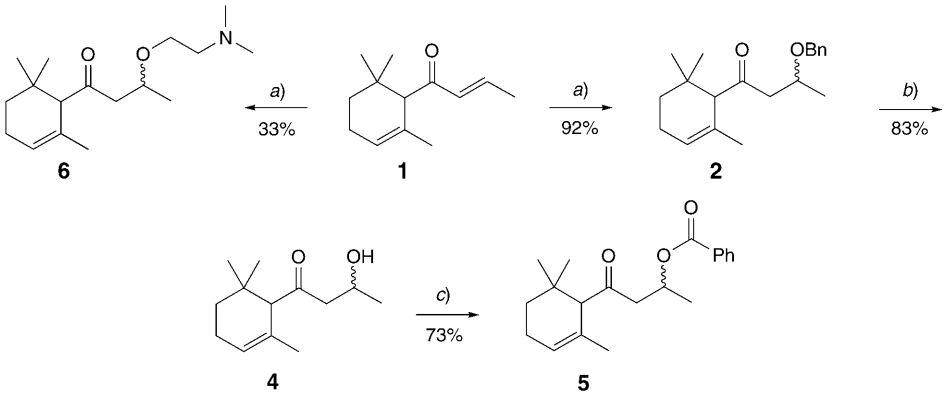
[4]) For other *Michael* additions of O-nucleophiles, see [10].

[5]) For aldols from epoxy alcohols, see [11a]; for aldols from epoxy ketones, see [11b].

[6]) For an alternative preparation by reduction of **8**, see [14]; the reported ^{1}H-NMR data are, however, not identical with ours.

Scheme 2

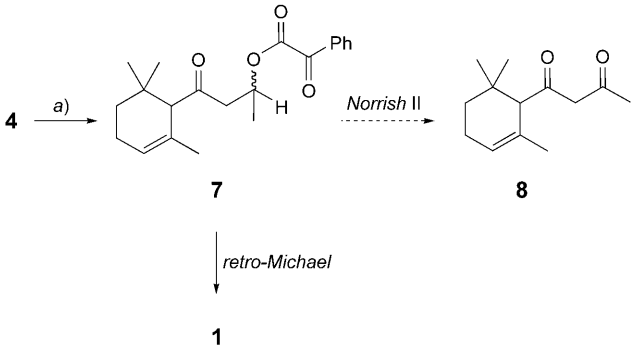


a) ROH, TMG (0.2 equiv.), 20°. *b*) H_2, 10% Pd/C, cat. $TsOH \cdot H_2O$, EtOH, 20°. *c*) PhCOCl (1.6 equiv.), Et_3N (1.4 equiv.), cat. DMAP, 0–20°.

for *Michael* additions as TMG. Very recently, an independent report on DBU-catalyzed *Michael* additions has been published [10b].

Oxo ester **7** is an interesting properfume, as it represents a *Michael* adduct capable of releasing α-damascone (**1**) but is also a photolabile system prone to undergo *Norrish*-II cleavage to generate the diketone **8** (*Scheme 3*) [4]. Under the usual conditions of application (softener at pH 3, weak light source), α-damascone (**1**) was formed, and the photolytic path could not be ascertained.

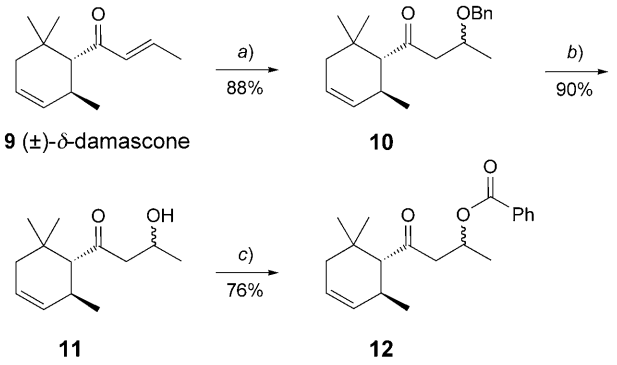
Scheme 3



a) PhCOCOCl (1.3 equiv.), Et_3N (1.83 equiv.), CH_2Cl_2, 0–20°.

The excellent releasing properties of benzoate **5**, derived from α-damascone (**1**), prompted us to prepare benzoate **12**, derived from δ-damascone (**9**; *Scheme 4*). The *Michael* addition worked very well, affording benzyl ether **10** as a mixture of two diasteroisomers (*ca.* 1:1) in 88% yield. However, hydrogenolysis of **10** in the presence of 10% Pd/C and catalytic amounts of $TsOH \cdot H_2O$ occurred with concomitant hydrogenation of the C=C bond. Omitting $TsOH \cdot H_2O$ even led to complete hydrogenation of

Scheme 4



a) BnOH, TMG (0.2 equiv.), 20°. *b*) DDQ (1.2 equiv.), CH_2Cl_2, H_2O, 20°. *c*) PhCOCl (1.6 equiv.), Et_3N (1.4 equiv.), cat. DMAP, 0–20°.

10 without any debenzylation[7]). However, debenzylation was readily achieved with 2,3-dichloro-5,6-dicyanoquinone (DDQ = 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile) [15], affording hydroxy ketone **11** in 90% yield[8]). Profragrance **12**, obtained by esterification of **11**, proved to be as efficient as benzoate **5**.

We next explored the thio-*Michael* adducts of α- and δ-damascone with the odorless dodecane-1-thiol (*Scheme 5*). These additions were very rapid in the presence of only 1 mol-% of DBU. *Michael* adducts **13** and **14** showed excellent releasing properties, were stable upon storage, and their preparations were straightforward. We also prepared the corresponding sulfoxide **15** and sulfone **16**. Whereas both **15** and **16** showed excellent releasing properties, sulfoxide **15** was too unstable for application in a softener[9]).

The herein described synthesis of aldols was extended to the synthesis of 1,3-diketones. 'Ketodamascone' **8** (*Scheme 6*), in solution predominantly enolized according to NMR, possesses interesting odor properties [14]. As we were interested in the odor of its enantiomers and have ready access to the enantiomers of α-damascone by enantioselective protonation [13][17], we decided to convert both (−)-(*S*)- and (+)-(*R*)-**1** into the target compounds (−)-(*S*)-**8** and (+)-(*R*)-**8**. This was accomplished in three straightforward steps (*Michael* addition, hydrogenolysis, *Jones* oxidation [18]) without any racemization. The olfactive evaluation showed that (−)-(*S*)-**8** contributes almost exclusively to the appreciated character of racemic 'ketodamascone' **8**.

Finally, we applied the herein outlined reaction sequence to the synthesis of cyclododecane-1,3-dione **20** (*Scheme 7*), which we required in another project. The known syntheses of diketone **20** are either less efficient [19a,b] or give rise to a mixture of the isomeric 1,2- and 1,3-diones [19c]. The *Michael* addition of BnOH to enone **17**

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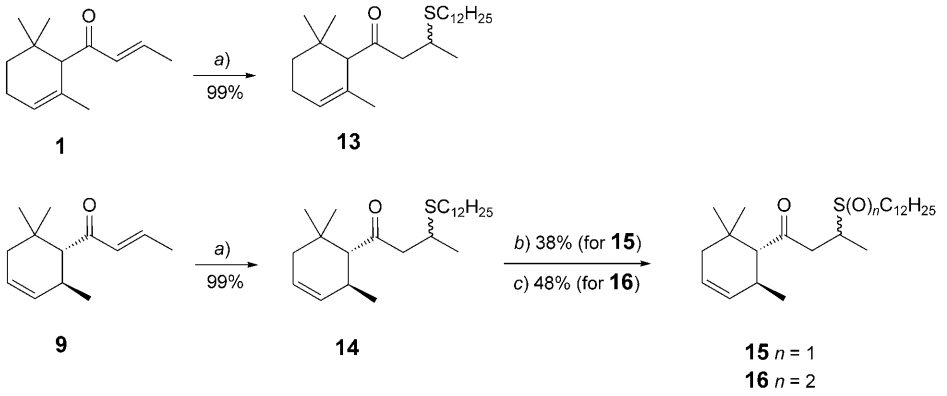
[7]) We thank Dr. *M. Marty*, *Firmenich SA*, for performing this study.

[8]) For an alternative synthesis of crude **11** (no spectral data were given), see [16].

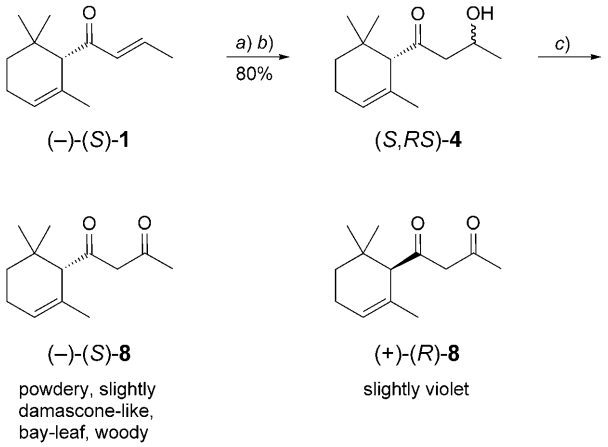
[9]) Possibly, the thioethers were oxidized to the sulfoxides in air (*e.g.*, **14** to **15**) and the sulfoxides then underwent elimination (*via* an enol or by E_i elimination). It should be noted that all *Michael* adducts eliminate rapidly under basic conditions (*e.g.*, in detergents) but are inappropriate for slow release. We have not tried to quantify this release process.

Scheme 5



a) Dodecane-1-thiol (1.0 equiv.), DBU (1 mol-%), THF, 25°. *b*) $NaIO_4$ (1.04 equiv.), MeOH, EtOH, 20°. *c*) $KHSO_5$ (4.9 equiv.), MeOH, H_2O, 0–40°.

Scheme 6

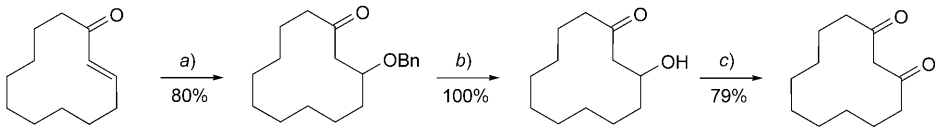


a) BnOH, TMG (0.2 equiv.), 20°. *b*) H_2, 10% Pd/C, cat. $TsOH \cdot H_2O$, EtOH, 20°. *c*) *Jones* oxidation.

worked as expected, affording crude benzyloxy ketone **18** in 80% yield (in addition to recovered **17**). Hydrogenolysis of **18** and oxidation of the resultant hydroxy ketone **19** furnished diketone **20** (in part enolized) in 79% yield. It should be noted that the preparation of macrocyclic hydroxy ketone **19** by intramolecular aldolization would certainly be more difficult.

Conclusions. – The preparation of aldols (3-hydroxy ketones) from enones by BnOH *Michael* addition/debenzylation was applied to the synthesis of properfumes, *e.g.*, **5** and **12**, and to 1,3-diketones, *e.g.*, (–)-(*S*)-**8** and **20**. On the other hand, *Michael* adducts derived from thiols are readily accessible and also represent excellent properfumes for applications in functional perfumery, as exemplified by dodecylthioketones **13** and **14**.

Scheme 7



a) BnOH, TMG (0.2 equiv.), 20°. *b*) H_2, 10% Pd/C, EtOH, 20°. *c*) *Jones* oxidation.

Experimental Part

General. Bulb-to-bulb distillation: *Büchi-GKR-51* glass-oven; b.p. correspond to the oven temp. TLC: silica gel *F-254* plates (*Merck*); detection with EtOH/anisaldehyde/H_2SO_4 18:1:1. Column chromatography: silica gel *60* (*Merck*; 0.063–0.2 mm, 70–230 mesh, ASTM); FC = flash chromatography. GC: *Varian* instrument, model *3500*; capillary columns: *DB1 30 W* (15 m × 0.319 mm), *DB-WAX 15W* (15 m × 0.32 mm); chiral capillary column: *CP-Chirasil-DEX CB* (25 m × 0.25 mm; *Chrompack*), carrier gas He at 0.63 bar. Optical rotations: 1-ml cell, *Perkin-Elmer-241* polarimeter. ^{1}H- and ^{13}C-NMR: *Bruker WH 400* (400 and 100 MHz, resp.). MS: *Hewlett Packard MSD 5972* automated GC/MS instrument, electron energy 70 eV.

(±)-3-Hydroxy-1-(2,6,6-trimethylcyclohex-2-en-1-yl)butan-1-one ((±)-**4**; diast. *ca.* 1:1). A suspension of benzyl ether **2** [13] (69.0 g, 230 mmol), TsOH·H_2O (3.3 g), and 10% Pd/C (1.5 g) in EtOH (250 ml) was shaken in an H_2 atmosphere. After uptake of 5.75 l (90 min), the mixture was filtered over *Celite*, treated with 10% aq. K_2CO_3 soln. (100 ml), and evaporated. The residue was extracted with Et_2O, and the extract washed with H_2O and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated: 43.8 g (92% pure; 83% of (±)-**4**). ^{1}H-NMR (2 diast.; 1:1): 0.92, 0.92, 0.93 (3*s*, 6 H); 1.12–1.23 (*m*, 1 H); 1.17–1.19 (*d*, *J* = 6, 3 H); 1.60 (split *s*, 3 H); 1.64–1.77 (*m*, 1 H); 1.96–2.20 (*m*, 2 H); 2.42–2.80 (*m*, 2 H); 2.72 (br. *s*, 1 H); 3.25–3.43 (br. *d*, 1 H, OH); 4.20 (*m*, 1 H); 5.62 (br. *m*, 1 H). ^{13}C-NMR (2 diast.; 1:1): 215.8, 215.3 (2*s*); 129.9, 129.7 (2*s*); 123.9, 123.8 (2*d*); 63.9 (*d*); 63.8, 63.5 (2*d*); 53.3 (*t*); 32.5 (*s*); 30.8, 30.7 (2*t*); 28.0 (*q*); 27.8, 27.7 (2*q*); 23.4 (*q*); 22.6 (*t*); 22.2 (*q*). MS (both diast.): 210 (33), 123 (100), 109 (30), 87 (84), 81 (52), 43 (57).

(±)-1-Methyl-3-oxo-3-(2,6,6-trimethylcyclohex-2-en-1-yl)propyl Benzoate ((±)-**5**; diast. *ca.* 1:1). A soln. of **4** (4.00 g, 92% pure, 17.5 mmol), Et_3N (2.30 g (3.20 ml), 22.85 mmol), and DMAP (400 mg) in CH_2Cl_2 (100 ml) was treated at r.t. with benzoyl chloride (2.94 g, 2.43 ml, 20.94 mmol). The soln. was stirred for 65 h, treated with 5% HCl soln., and extracted with Et_2O (2×). The extract was washed with H_2O, sat. aq. $NaHCO_3$ soln., and sat. aq. NaCl soln., dried (Na_2SO_4), and concentrated at 50–60°/0.03 mbar. The oil (5.84 g) was purified by FC, (SiO_2 (90 g), cyclohexane/AcOEt 97:3). 4.25 g (73%) of (±)-**5**. ^{1}H-NMR (2 diast.; 1:1): 0.92, 0.93, 0.94 (3*s*, 6 H); 1.12–1.23 (*m*, 1 H); 1.39–1.42 (2*d*, *J* = 6, 3 H); 1.59 (*s*, 3 H); 1.65–1.80 (*m*, 1 H); 1.95–2.20 (*m*, 2 H); 2.60–2.83 (*m*, 1 H); 2.72–2.74 (2*s*, 1 H); 3.02–3.20 (*m*, 1 H); 5.50–5.63 (*m*, 2 H), 7.36–7.45 (*m*, 2 H), 7.48–7.57 (*m*, 1 H), 7.96–8.04 (*m*, 2 H). ^{13}C-NMR (2 diast.; 1:1): 210.1 (*s*); 165.7 (*s*); 132.8 (*d*); 130.5 (*s*); 129.9 (*s*); 129.5 (2*d*); 128.2 (2*d*); 123.8 (*d*); 67.4, 67.6 (2*d*); 63.6, 63.8 (2*d*); 51.1 (*t*); 32.5 (*s*); 30.7, 30.8 (2*t*); 27.9 (*q*); 27.8 (*q*); 23.5 (*q*); 22.6 (*t*); 20.1, 20.1 (2*q*). MS: 192 (52), 123 (22), 105 (100), 81 (13), 77 (20), 69 (45).

(±)-3-[2-(Dimethylamino)ethoxy]-1-(2,6,6-trimethylcyclohex-2-en-1-yl)butan-1-one ((±)-**6**; diast. *ca.* 1:1). A soln. of α-damascone (**1**; 6.44 g; 33.5 mmol), 2-(dimethylamino)ethanol (26.83 g, 30.25 ml, 301 mmol), and TMG (0.77 g, 6.70 mmol) was stirred at r.t. for 15 h (GC control: 4% conversion). Heating at 70° for 15 h gave a 70% conversion. The flask was equipped with a distillation still, and excess 2-(dimethylamino)ethanol was distilled at *ca.* 60°/10 to 2 mbar. Unreacted **1** (3.74 g, 58%), due to some *retro-Michael* reaction during workup, was recovered by extraction (Et_2O, 5% HCl soln.) and washing (H_2O, then sat. aq. NaCl soln.). The aq. phases were basified (aq. NaOH) and extracted with Et_2O (2×), the combined org. phases were washed with H_2O and sat. aq. NaCl soln.), dried (Na_2SO_4), and evaporated. Bulb-to-bulb distillation (100–125°/0.05 mbar) afforded 3.14 g (33%) of **7**. ^{1}H-NMR: 0.90, 0.92, 0.93 (3*s*, 6 H); 1.10–1.20 (*m*, 1 H); 1.15–1.18 (2*d*, *J* = 6, 3 H); 1.58 (*s*, 3 H); 1.65–1.77 (*m*, 1 H); 1.95–2.20 (*m*, 2 H); 2.23 (*s*, 6 H); 2.37–2.56 (*m*, 3 H); 2.70–2.75 (br. *m*, 1 H); 2.82–3.00 (*m*, 1 H); 3.40–3.50 (*m*, 1 H); 3.55–3.64 (*m*, 1 H); 3.86–3.99 (*m*, 1 H); 5.58 (br. *m*, 1 H). ^{13}C-NMR: 211.7–212.0 (*s*); 130.2 (*s*); 123.6 (*d*); 71.8, 71.4 (2*d*); 66.9, 66.8 (2*t*); 64.1, 64.0 (2*d*); 59.2 (*t*); 52.6, 52.4 (2*t*); 45.9 (2*q*); 32.4 (*s*); 30.9, 30.7 (2*t*); 28.0 (*q*); 27.9 (*q*); 23.5, 23.4 (2*q*); 22.7 (*t*); 19.8, 19.6 (2*q*). MS: 281 (3, M^+), 192 (2), 123 (7), 73 (17), 72 (17), 58 (100).

(±)-1-Methyl-3-oxo-3-(2,6,6-trimethylcyclohex-2-en-1-yl)propyl Oxophenylacetate ((±)-**7**; diast. *ca.* 1:1). A soln. of phenylglyoxylic acid (= oxophenylacetic acid; 2.57 g, 17.1 mmol) and DMF (5 drops) in CH_2Cl_2 (40 ml) was treated at 35° with oxalyl chloride (3.47 g, 2.35 ml, 27.4 mmol) in CH_2Cl_2 (6 ml). After the exothermic reaction and gas evolution, the yellow soln. was evaporated under N_2 (removal of excess oxalyl chloride), the residue dissolved in CH_2Cl_2 (10 ml), and the soln. added at 0° to a soln. of **4** (3.00 g, 92% pure, 13.1 mmol) and Et_3N (2.43 g, 3.40 ml, 24.0 mmol) in CH_2Cl_2 (15 ml). The mixture was allowed to reach r.t. (15 min), treated with 5% HCl soln., and extracted with Et_2O (2×), the extract washed with H_2O, 5% NaOH soln., and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated, and the residue (4.95 g) purified by FC (SiO_2 (50 g), cyclohexane/AcOEt 95:5): 3.93 g (88%) of (±)-**7**. ^{1}H-NMR: 0.82, 0.85, 0.90, 0.91 (4*s*, 6 H); 1.08–1.20 (*m*, 1 H); 1.42–1.43 (2*d*, *J* = 6, 3 H); 1.51–1.54 (2 split *s*, 3 H); 1.59–1.78 (*m*, 1 H); 1.96–2.18 (*m*, 2 H); 2.56–2.81 (*m*, 1 H); 2.70 (*s*, 1 H); 2.96–3.19 (*m*, 1 H); 5.53–5.62 (*m*, 1 H); 5.62–5.75 (*m*, 1 H); 7.45–7.54 (*m*, 2 H); 7.60–7.68 (*m*, 1 H); 7.96–8.04 (*m*, 2 H). ^{13}C-NMR: 209.8 (*s*); 186.8, 186.6 (2*s*); 163.4, 163.3 (2*s*); 134.8 (*d*); 132.4 (*s*); 129.8 (2*d*); 129.8, 129.7 (2*s*); 128.9 (2*d*); 123.9 (*d*); 68.3–69.2 (*d*); 63.8, 63.6 (2*d*); 50.6, 50.5 (2*t*); 32.5, 32.4 (2*s*); 30.7 (*t*); 27.9, 27.8 (2*q*); 27.7 (*q*); 23.4, 23.3 (2*q*); 22.6 (*t*); 19.8 (*q*). MS: 191 (49), 135 (15), 123 (72), 105 (100), 81 (23), 77 (28), 69 (62).

(±)-trans-*3-(Benzyloxy)-1-(2,6,6-trimethylcyclohex-3-en-1-yl)butan-1-one* ((±)-**10**; diast. *ca.* 1:1). A soln. of (±)-δ-damascone (**9**; 500 g, 2.46 mol), BnOH (798.1 g, 7.39 mol), and TMG (57.4 g, 0.49 mol) was stirred at 40° for 21 h (GC control: 78% conversion). The volatiles were separated from **10** by distillation (bath temp. 50–70°/0.2 mbar) furnishing 867 g of distillate (containing at least 150 g (30%) of **9**) and 480 g of residue. Bulb-to-bulb distillation of a sample (10.6 g) at 125°/0.05 mbar afforded 10.1 g of pure **10** (58%). ^{1}H-NMR: 0.87 (split *d*, *J* = 6, 3 H); 0.91–1.03 (4*s*, 6 H); 1.24 (*d*, *J* = 6, 3 H); 1.69 (*dd*, *J* = 16, 4, 1 H); 1.97 (br. *d*, *J* = 16, 1 H); 2.23–2.26 (2*d*, *J* = 9, 1 H); 2.52 (*m*, 1 H); 2.38–3.03 (*m*, 2 H); 4.12 (*m*, 1 H); 4.49 (*m*, 1 H); 4.55 (*m*, 1 H); 5.45 (br. *d*, *J* = 9, 1 H); 5.53 (*m*, 1 H); 7.21–7.35 (*m*, 5 H). ^{13}C-NMR: 212.9–213.2 (*s*); 138.7 (*s*); 124.0–131.9 (5*d*); 71.1, 71.0 (2*t*); 70.7 (*d*); 63.3, 63.2 (2*d*); 54.9, 54.8 (2*t*); 41.8, 41.7 (2*t*); 33.2, 33.0 (2*s*); 31.6, 31.5 (2*d*); 29.8 (*q*); 20.8 (*q*); 19.9 (2*q*). MS: 300 (2, M^+), 209 (11), 194 (21), 123 (53), 91 (100), 87 (22).

(±)-trans-*3-Hydroxy-1-(2,6,6-trimethylcyclohex-3-en-1-yl)butan-1-one* ((±)-**11**; diast. *ca.* 1:1). A soln. of **10** (10.0 g, 33.3 mmol) in CH_2Cl_2 (180 ml) was treated under stirring at r.t. with H_2O (20 ml) and DDQ (9.10 g, 40.0 mmol). The mixture turned red, and gradually an orange precipitate formed. After 6 h, the mixture was filtered over *Celite*, the filtrate washed with sat. aq. $NaHCO_3$ soln. and sat. aq. NaCl soln. (2×), dried (Na_2SO_4), and evaporated, and the residue (9.75 g) purified by FC (SiO_2 (300 g), cyclohexane/AcOEt 95:5): 6.29 g (90%) of (±)-**11**. ^{1}H-NMR: 0.89–0.92 (2*d*, *J* = 6, 3 H); 0.95 (*s*, 3 H); 0.97–1.00 (2*s*, 3 H); 1.18–1.20 (2*d*, *J* = 6, 3 H); 1.71 (*dd*, *J* = 16, 4, 1 H); 1.96 (br. *d*, *J* = 16, 1 H); 2.24–2.25 (2*d*, *J* = 9, 1 H); 2.52 (*m*, 1 H); 2.41–2.80 (*m*, 2 H); 3.10–3.80 (br. *m*, 1 H); 4.24 (*m*, 1 H); 5.46 (br. *d*, *J* = 9, 1 H); 5.55 (*m*, 1 H). ^{13}C-NMR: 216.7–217.1 (*s*); 131.6, 131.7 (2*d*); 124.2, 124.3 (2*d*); 63.3–63.6 (2*d*); 55.6, 55.4 (2*t*); 41.7 (*t*); 33.2 (*s*); 31.7, 31.6 (2*d*); 29.8 (*q*); 22.2, 22.1 (2*q*); 20.7 (*q*); 19.9, 19.8 (*q*). MS: 210 (15, M^+), 192 (11), 166 (9), 135 (9), 123 (100), 109 (27), 107 (48), 87 (60), 81 (56), 69 (63), 43 (60).

(±)-trans-*1-Methyl-3-oxo-3-(2,6,6-trimethylcyclohex-3-en-1-yl)propyl Benzoate* ((±)-**12**; diast. *ca.* 1:1). A soln. of **11** (25.9 g, 124 mmol), Et_3N (16.26 g, 22.40 ml, 161 mmol), and DMAP (2 g) in CH_2Cl_2 (200 ml) was treated at r.t. with benzoyl chloride (19.04 g, 15.7 ml, 136 mmol). The mixture was stirred for 15 h, treated with 5% HCl soln., and extracted with Et_2O (2×). The extract was washed with H_2O, sat. aq. $NaHCO_3$ soln., and sat. aq. NaCl soln., dried (Na_2SO_4), and concentrated at 65–75°/0.01 mbar, and the oil (32.0 g) purified by FC (SiO_2 (500 g), cyclohexane/AcOEt 95:5): 29.6 g (76%) of (±)-**12**. ^{1}H-NMR: 0.88–0.92 (2*d*, 3 H); 0.93–1.05 (4*s*, 6 H); 1.40–1.44 (2*d*, 3 H); 1.65–1.75 (*m*, 1 H); 1.95–2.02 (2 br. *m*, 1 H); 2.22–2.30 (*m*, 1 H); 2.52 (*m*, 1 H); 2.60–2.83 (*m*, 1 H); 2.95–3.20 (*m*, 1 H); 5.40–5.61 (*m*, 3 H), 7.38–7.45 (*m*, 2 H); 7.50–7.56 (*m*, 1 H); 7.96–8.04 (*m*, 2 H). ^{13}C-NMR: 211.5, 211.3 (2*s*); 165.7 (*s*); 132.8 (*d*); 131.8, 131.7 (2*d*); 130.6, 130.5 (2*s*); 129.5 (2*d*); 128.3 (2*d*); 124.2, 124.1 (2*d*); 67.4, 67.2 (2*d*); 62.9–63.1 (*d*); 53.3 (*t*); 41.7 (*t*); 33.1 (*s*); 31.6 (*d*); 29.8 (*q*); 20.7 (*q*); 20.1 (*q*); 19.9 (*q*). MS: 192 (42), 122 (33), 105 (90), 77 (45), 69 (100).

(±)-3-(Dodecylthio)-1-(2,6,6-trimethylcyclohex-2-en-1-yl)butan-1-one ((±)-**13**). A mixture of α-damascone (**1**, 12.00 g, 62.5 mmol) and DBU (95 mg, 0.625 mmol) was treated under water cooling at 25–35° with dodecane-1-thiol (12.63 g, 14.95 ml, 62.5 mmol). After 45 min at 25°, the mixture was treated with aq. H_2SO_4 soln. (from conc. H_2SO_4 (34 mg, 0.35 mmol) and H_2O (12 ml)) and extracted with AcOEt (12 ml) and the extract washed with H_2O, sat. aq. $NaHCO_3$ soln., and 10% aq. NaCl soln., and concentrated at 75°/0.01 mbar: 24.35 g (99%) of crude **13**. ^{1}H-NMR: 0.88 (*t*, *J* = 7, 3 H); 0.91 (*s*, 3 H); 0.93 (*s*, 3 H); 1.17 (*m*, 1 H); 1.20–1.33 (*m*, 19 H); 1.36 (*m*, 2 H); 1.57 (*m*, 2 H); 1.60 (br. *s*, 3 H); 1.73 (*m*, 1 H); 1.96–2.18 (*m*, 2 H); 2.52 (*m*, 2 H); 2.53–2.94 (*m*, 2 H); 2.71 (br. *s*, 1 H); 3.27 (*m*, 1 H); 5.58 (*m*, 1 H). ^{13}C-NMR: 211.2, 211.1 (2*s*); 130.0 (*s*); 123.7 (*d*); 63.7, 63.6 (2*d*); 53.4, 53.1 (2*t*); 34.3, 34.2 (2*d*); 32.5, 32.4 (2*s*); 31.9–29.0 (several *t*); 27.9 (*q*); 27.8 (*q*); 23.5 (*q*); 22.7 (*t*); 21.6 (*q*); 14.1 (*q*).

(±)-trans-*3-(Dodecylthio)-1-(2,6,6-trimethylcyclohex-3-en-1-yl)butan-1-one* ((±)-**14**; diast. *ca.* 1:1). As described for (±)-**13**, with *δ*-damascone (**9**; 12.00 g, 62.5 mmol), DBU (95 mg, 0.625 mmol) and dodecane-1-thiol (12.63 g, 14.95 ml, 62.5 mmol): 23.83 g (97%) of crude **14**. ^{1}H-NMR: 0.84–0.92 (*m*, 6 H); 0.93–1.02 (4*s*, 6 H); 1.26 (*m*, 16 H); 1.29 (*m*, 3 H); 1.36 (*m*, 2 H); 1.58 (*m*, 2 H); 1.69 (*m*, 1 H); 1.96 (2 br. *m*, 1 H); 2.22 (*m*, 1 H); 2.50 (*m*, 3.5 H); 2.70 (*m*, 1 H); 2.90 (*m*, 0.5 H); 3.30 (*m*, 1 H); 5.43 (*m*, 1 H); 5.53 (*m*, 1 H). ^{13}C-NMR: 212.5, 212.4 (2*s*); 131.9, 131.8 (2*d*); 124.2, 124.1 (2*d*); 62.9–63.0 (*d*); 55.3, 55.2 (2*t*); 41.7 (*t*); 34.1 (*d*); 33.2, 33.0 (2*s*); 31.9 (*t*); 31.8, 31.6 (2*d*); 30.9 (*t*); 29.8 (*q*); 29.0–29.8 (several *t*); 22.7 (*t*); 21.8, 21.6 (2*q*); 20.7 (*q*); 19.9 (*q*); 14.1 (*q*).

(±)-trans-*3-(Dodecylsulfinyl)-1-(2,6,6-trimethylcyclohex-3-en-1-yl)butan-1-one* ((±)-**15**; diast. *ca.* 1:1). A soln. of **11** (2.00 g, 5.10 mmol) in MeOH (20 ml) was added at 0° to a soln. of $NaIO_4$ (1.14 g, 5.30 mmol) in H_2O (11 ml). For solubility reasons, the temperature was brought to r.t., and EtOH (30 ml) was added. The suspension was stirred for 15 h and then extracted (Et_2O/sat. aq. NaCl soln.). The org. phase was washed with aq. $NaHSO_3$ soln., H_2O, sat. aq. $NaHCO_3$ soln., and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated, and the residue (16.2 g) subjected to FC (SiO_2 (40 g), cyclohexane/AcOEt 7:3, then 1:1): 803 mg (38%) of **15**.

In another experiment, oxidation with H_2O_2/AcOH was less satisfactory, and one diastereoisomer decomposed during purification. ^{1}H-NMR: 0.85–0.94 (*m*, 6 H); 0.95–1.03 (4*s*, 6 H); 1.25 (*m*, 19 H); 1.45 (*m*, 2 H); 1.65–1.83 (*m*, 3H); 1.97 (2 br. *m*, 1 H); 2.28 (*m*, 1 H); 2.46–2.62 (*m*, 2.5 H); 2.67 (*m*, 1 H); 2.78 (*m*, 0.5 H); 2.98 (*m*, 0.5 H); 3.15–3.27 (*m*, 1.5 H); 5.45 (*m*, 1 H); 5.54 (*m*, 1 H). ^{13}C-NMR: 211.9, 211.8 (2*s*); 131.6, 131.5 (2*d*); 124.4, 124.2 (2*d*); 62.9–63.0 (*d*); 49.0–49.3 (*t*); 48.0 (*d*); 41.6 (*t*); 33.2 (*s*); 31.9 (*t*); 31. 8 (*d*); 29.8 (*q*); 29.0–29.8 (several *t*); 23.2 (*t*); 22.7 (*t*); 21.8, 21.6 (2*q*); 20.7 (*q*); 19.9 (*q*); 14.1 (*q*); 10.4, 10.3 (2*q*).

(±)-trans-*3-(Dodecylsulfonyl)-1-(2,6,6-trimethylcyclohex-3-en-1-yl)butan-1-one* ((±)-**16**; diast. *ca.* 1:1). A soln. of $KHSO_5$ (10.9 g, 86.5% pure, 62.1 mmol) in H_2O (50 ml) was added under ice cooling to a soln. of **14** (5.00 g, 12.7 mmol) in MeOH (100 ml). The temp. was allowed to attain 40°. The suspension was stirred for 2 h, and sulfone **16** was extracted (Et_2O/aq. NaCl soln.). The org. phase was washed with H_2O, sat. aq. $NaHCO_3$ soln., and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated, and the residue (4.32 g) subjected to FC (SiO_2 (130 g), cyclohexane/AcOEt 95:5): 2.59 g (48%) of **16**. ^{1}H-NMR: 0.84–0.92 (*m*, 6 H); 0.95–1.02 (3*s*, 6 H); 1.26 (*m*, 16 H); 1.38 (*m*, 3 H); 1.43 (*m*, 2 H); 1.72 (*m*, 1 H); 1.85 (*m*, 2 H); 1.98 (2 br. *m*, 1 H); 2.29 (*m*, 1 H); 2.52 (*m*, 1 H); 2.60 (*m*, 0.5 H); 2.83 (*m*, 0.5 H); 2.95 (*t*, *J* = 8, 2 H); 3.12 (*m*, 0.5 H); 3.35 (*m*, 0.5 H); 3.63 (*m*, 1 H); 5.46 (*m*, 1 H); 5.55 (*m*, 1 H). ^{13}C-NMR: 210.8, 210.6 (2*s*); 131.5, 131.4 (2*d*); 124.5, 124.2 (2*d*); 63.3, 63.0 (2*d*); 52.1 (*d*); 50.2 (*t*); 45.9, 45.7 (2*t*); 41.6 (*t*); 33.4, 33.1 (2*s*); 28.6–32.1 (several signals); 22.7 (*t*); 21.6 (*t*); 20.7 (*q*); 19.9 (*q*); 14.6, 14.5 (2*q*); 14.1 (*q*).

*(−)-1-[(1*S*)-(2,6,6-Trimethylcyclohex-2-en-1-yl)-butane-1,3-dione* ((−)-(*S*)-**8**). An ice-cooled soln. of crude (*S*,*RS*)-**4** (1.43 g, max. 6.33 mmol; obtained from (*S*,*RS*)-**2** (1.90 g, 6.33 mmol)) in acetone (60 ml) was treated dropwise under vigorous stirring with 0.5M *Jones* reagent (15 ml) in acetone. After 20 min, the green suspension was treated with sat. aq. NaCl soln. and pentane, the org. phase washed with H_2O + trace of aq. $NaHCO_3$ soln. (pH *ca.* 7), H_2O, and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated, and the residue (1.32 g) subjected to FC (SiO_2 (15 g), cyclohexane/AcOEt 98:2): 840 mg (64% from (*S*,*RS*)-**2**) of (−)-(*S*)-**8**. $[\alpha]_D^{20} = -408$ (EtOH, *c* = 0.024). ^{1}H-NMR ((*Z*)-enol form): 0.91 (*s*, 3 H); 0.96 (*s*, 3 H); 1.18 (*m*, 1 H); 1.63 (*d*, *J* = 2, 3 H); 1.68 (*m*, 1 H); 2.07 (*s*, 3 H); 2.08 (*m*, 2 H); 2.34 (br. *s*, 1 H); 5.53 (*s*, 1 H); 5.61 (br., 1 H); 10.17 (br., 1 H). ^{13}C-NMR ((*Z*)-enol form): 194.2 (*s*); 192.6 (*s*); 130.6 (*s*); 123.6 (*d*); 101.4 (*d*); 59.5 (*d*); 32.5 (*s*); 31.1 (*t*); 28.0 (*q*); 27.7 (*q*); 25.5 (*q*); 23.2 (*q*); 22.7 (*t*). MS: [14].

*(+)-1-[(1*R*)-2,6,6-Trimethylcyclohex-2-en-1-yl)butane-1,3-dione* ((+)-(*R*)-**8**). As described above, from (*R*, *RS*)-**4**). $[\alpha]_D^{20} = +404$ (EtOH, *c* = 0.035).

3-Hydroxycyclododecanone (**19**). As described for **2** [13], **17** (10.80 g, 60.0 mmol) was converted into crude benzyl ether **18** (13.75 g, 80%). A suspension of **18** (13.75 g, max. 47.7 mmol) and 10% Pd/C (1.37 g) in EtOH (150 ml) was shaken in an H_2 atmosphere. After uptake of 1.30 l (13 h), the mixture was filtered over *Celite* and the filtrate evaporated: 9.61 g (100%) of crude, solid **19**. ^{1}H-NMR: 1.15–1.48 (*m*, 13 H); 1.50–1.85 (*m*, 4 H); 2.28 (*m*, 1 H); 2.61 (*m*, 1H); 2.65 (*m*, 1 H); 2.90 (*dd*, *J* = 16, 4, 1 H); 3.96 (*m*, 1 H). ^{13}C-NMR: 214.0 (*s*); 68.9 (*d*); 44.9 (*t*); 43.2 (*t*); 33.4 (*t*); 25.8 (*t*); 25.6 (*t*); 24.2 (*t*); 23.9 (*t*); 22.8 (*t*); 22.3 (*t*); 21.8 (*t*). MS: 198 (2), 180 (12), 137 (15), 122 (33), 111 (33), 98 (61), 95 (47), 81 (76), 71 (62), 58 (100), 55 (62), 43 (88).

Cyclododecane-1,3-dione (**20**). As described for (−)-(*S*)-**8**, with **19** (9.61 g, max. 47.7 mmol): **20** (8.90 g). Bulb-to-bulb distillation afforded 8.19 g (79%) of pure solid **20** (in soln., *ca.* 36% as (*Z*)-enol according to NMR). M.p. 55–57° ([19b]: 57–59°).

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