78. Efficient Synthesis of Enantiomerically Pure α-Ionone from (*R*)- and (*S*)-α-Damascone

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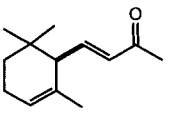
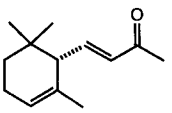
(*R*)- and (*S*)-α-ionone ((*R*)- and (*S*)-**1**, resp.) were prepared from (*R*)- and (*S*)-α-damascone ((*R*)- and (*S*)-**3**, resp.) without racemization in 48% yield employing a new enone transposition. The described transposition is complementary to existing methods whose application is often prohibited by the structural requirements of the substrate. The now easily accessible α-ionones of desired absolute configuration are useful as chiral building blocks for terpenoid synthesis.

The (*R*)- and (*S*)-α-ionones ((*R*)- and (*S*)-**1**, resp.) have often been used or proposed as chiral building blocks for the synthesis of carotenes [1] or drimanes (*e.g.* forskolin [2]). Unfortunately, enantiomerically pure (*R*)- and (*S*)-**1** have been, up to now, only accessible through laborious separation of the racemate [3], whereas the conversion of (*S*)-α-cyclogeranic acid [4] into (*S*)-α-ionone was reported to proceed with *ca.* 5% global yield and partial racemization (→ 60% ee) [5].



(*R*)-**1**



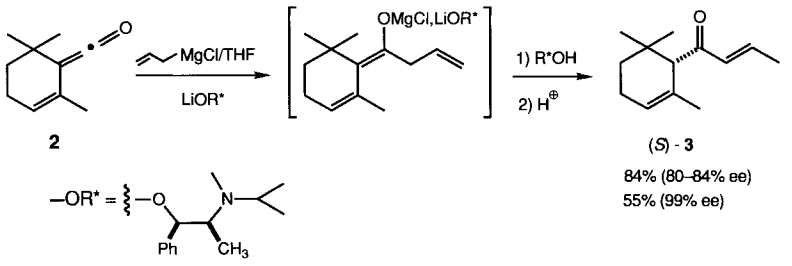
(*S*)-**1**

As we required the pure enantiomers of α-ionone for organoleptic evaluation[1]) and as precursors for enantiomerically pure odorants, we envisaged their preparation from enantiomerically pure (*R*)- and (*S*)-α-damascone ((*R*)- and (*S*)-**3**, resp.) which are now readily accessible from ketene **2** [7], with an improved yield of 55%, by allyl *Grignard* reaction and enantioselective protonation of the intermediate enolate [8] (*cf. Scheme 1* and *Exper. Part*).

Despite the propensity of published methods for enone transposition [9–11], exploratory experiments quickly revealed that the sterically hindered carbonyl group of **3**

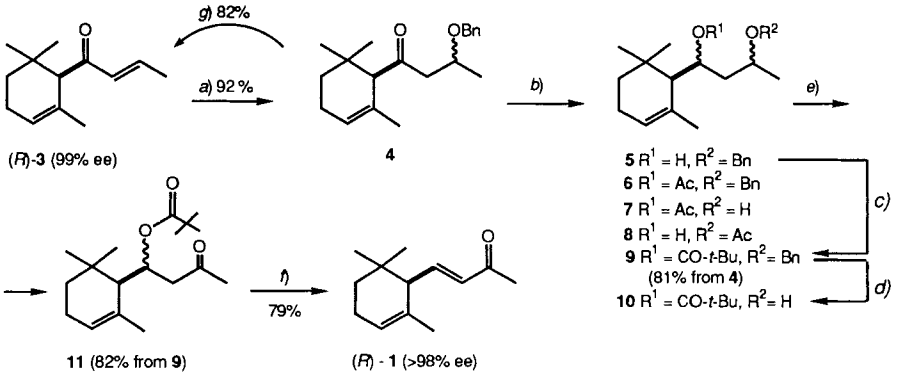
[1]) Most people show a pronounced aptitude to perceive either one or the other enantiomer of α-ionone [6a]; *M. Lindström* (*Firmenich SA*) noticed similar odor responses; see also [6b].

Scheme 1



strongly limits the available pathways. *E.g.*, the *Wharton* rearrangement [9] could not be applied, and the first step in the *Büchi* procedure (**3** + NH_2OH [10]) or the enone transposition recently applied by us starting with a carbonyl reduction [11] led predominantly to undesired 1,4-addition products. Among several tested reduction conditions ($LiAlH_4$, *Vitride*, $LiAlH_4/AlCl_3$ [12], $LiAlH_4/CeCl_3$, or $NaBH_4/CeCl_3$ [13]), only $LiAlH_4/CeCl_3$ in THF gave substantial amounts of 1,2 reduction (1,2/1,4 reduction *ca.* 1:1). We, therefore, decided to take advantage of the inherent capacity of **3** to undergo 1,4 addition, and we thus present here an efficient new enone-transposition sequence initiated by a *Michael* reaction of benzyl alcohol (BnOH) to **3** (*cf. Scheme 2*).

Scheme 2



a) BnOH, 1,1,3,3-tetramethylguanidine (0.20 equiv.), 20°. *b*) $LiAlH_4$ (0.55 mol-equiv.), Et_2O, 35°. *c*) LDA (1.40 equiv.), THF; *t*-BuCOCl (2.80 equiv.), 30°. *d*) H_2, 10% Pd/C, cat. TsOH, EtOH, 20°. *e*) *Jones* reagent (1.2 equiv.), acetone, 0→20°. *f*) K_2CO_3 (2.0 equiv.), 140°/*ca.* 10 Torr. *g*) $N(C_2H_4OH)_3$, 150°, 3 h.

Treatment of (*R*)-**3** at 20° with excess BnOH in the presence of 20 mol-% of 1,1,3,3-tetramethylguanidine[2]) resulted in conversion to **4**/**3** (*ca.* 70:30), assumed to represent an equilibrium mixture. The overall conversion could be improved by distillation of the volatile components ((*R*)-**3**, BnOH, tetramethylguanidine) which on standing at 20° for 15 h re-afforded the equilibrium mixture **4**/**3**. We had thus succeeded to introduce the

[2]) See [14a]. $BF_3 \cdot Et_2O$-Catalyzed benzyloxylation of **3** led to partially racemized **4** (*ca.* 70%) [14b]. For other recent benzyloxylations of α,β-unsaturated carbonyl compounds, see [14c].

required, appropriately protected, O-functionality which would resist the subsequent $LiAlH_4$ reduction (**4**→**5**). In order to ensure that no racemization had occurred, ether **4** was heated in $N(C_2H_4OH)_3$ at 150° to afford, *via* elimination of BnOH, (*R*)-α-damascone ((*R*)-**3**) of unchanged optical activity. The described methodology demonstrates also the potential general value of the benzyloxy group for the protection of α,β-unsaturated enone C=C bonds.

In a first approach, **5** was converted without purification into acetate **6** (Ac_2O/pyridine, cat. 4-(dimethylamino)pyridine; 76% from **4**) and the latter submitted to hydrogenolytic cleavage of the benzyl group (H_2, 10% Pd/C, EtOH; 93%). To our surprise, a 9:1 mixture of the two isomeric hydroxyacetates **7**/**8** was formed, as evidenced by their conversion into the respective regioisomeric oxoacetates (*Jones* oxidation) and ultimately into (*R*)-**1**/(*R*)-**3** 9:1.

This undesired 1,3-acyl transposition could be completely suppressed by use of a bulkier and less electrophilic acyl protecting group. Accordingly, reaction of **5** with lithium diisopropylamide (LDA) and *t*-BuCOCl afforded pivalate **9** (81% yield from **4**) which could easily be debenzylated to **10** (H_2, Pd/C, TsOH (cat.), abs. EtOH; 91% yield)[3]). Finally, *Jones* oxidation (**10**→**11**; 88% yield) and base-catalyzed thermal elimination ($N(C_2H_4OH)_3$, 140°) afforded (*R*)-α-ionone ((*R*)-**1**; 84% yield, *ca.* 99% ee; see *Fig.*), which represents the naturally preponderant antipode [6b][4]).

Likewise, repetition of the sequence starting from (*S*)-α-damascone ((*S*)-**3**) furnished (*S*)-α-ionone ((*S*)-**1**) of high enantiomeric purity (*ca.* 99% ee; see *Fig.*). The olfactive

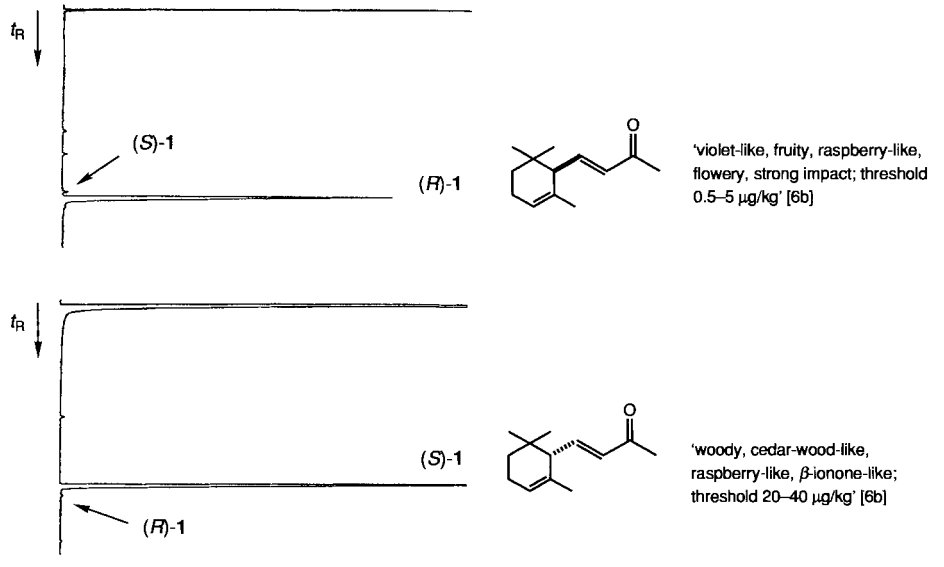


Figure. *Enantiomer separation of* (R)- *and* (S)-**1** *by GC using permethylated β-cyclodextrin in* OV-1701 *as chiral stationary phase*

[3]) In the absence of TsOH, concurrent hydrogenation of the C=C bond (*ca.* 4%) was observed.

[4]) See also [15], where inadvertently the assignment of the absolute configurations on chiral GC was interchanged.

differences between the two enantiomers of α-ionone (**1**) [6b] were confirmed by our perfumers, and the use of (*R*)- and (*S*)-**1** as chiral building blocks for the synthesis of enantiomerically pure odorants is in progress.

We thank Dr. *K. H. Schulte-Elte* for bringing to our attention the ready accessibility of (±)-**4** from (±)-**3** [14b].

Experimental Part

General. TLC: silica gel *F 254* plates (*Merck*); detection with EtOH/anisaldelyde/H_2SO_4 18:1:1. Column chromatography: silica gel *60* (*Merck*, 0.063–0.2 mm, 70–230 mesh, ASTM). GC: *Varian* instrument, model *3500*; capillary columns: *DB1 30W* (15 m × 0.319 mm), *DB-WAX 15W* (15 m × 0.32 mm); chiral capillary column (12 m × 0.25 mm): permethylated β-cyclodextrin in *OV-1701* (program: 95° (10 min)→120° (2°/min)), carrier gas He at 0.63 bar. Optical rotations: 1-ml cell, *Perkin-Elmer-241* polarimeter. IR: *Hewlett-Packard-GC-FTIR-5965B* spectrometer, vapor phase. ^{1}H- and ^{13}C-NMR: *Bruker WH 360* (360 MHz). MS: *Finnigan 1020* automated GC/MS instrument, electron energy 70 eV.

(−)-(S)-α-Damascone (= *(−)-(S,E)-1-(2,6,6-Trimethylcyclohex-2-enyl)but-2-en-1-one; (S)*-**3**). A soln. of (−)-*N*-isopropylephedrine (= (−)-(1*R*,2*S*)-2-[(isopropyl)methylamino]-1-phenylpropan-1-ol; 27.6 g, 133.3 mmol) in THF (160 ml) at −10° was treated with 1.7M BuLi in hexane (78.4 ml, 133.2 mmol). At the end of the addition (5 min), the temp. had attained 25–30°. The temp. was maintained at 20°, and 1.85M allylmagnesium chloride in THF (82.8 ml, 153.2 mmol) was added *via* canula (1 min). The soln. was cooled to −10°, and ketene **2** (20.0 g, 133.2 mmol) in THF (20 ml) was introduced at such a rate that the temp. did not exceed 20° (*ca.* 20 min)[5]). The mixture was then cooled to −50°, treated rapidly (3 min) with (−)-*N*-isopropylephedrine (41.4 g, 199.8 mmol), and brought to −5° (1 min). The mixture was then immediately poured into a vigorously stirred ice-cold 5% aq. HCl soln. (500 ml) and extracted (Et_2O), the org. phase treated with 5% aq. HCl soln., and the combined aq. phase washed (Et_2O), basified (aq. 20% KOH), and extracted (Et_2O). The extract of the basic aq. phase was distilled *i.v.* to afford recovered (−)-*N*-isopropylephedrine (40.5 g, 98%; b.p. 90°/2 Torr). The combined org. phase (containing **3** and double-bond isomers) was washed with H_2O, sat. aq. $NaHCO_3$ soln., and sat. aq. NaCl soln., evaporated (→24.2 g), and distilled (60–70°/0.05 Torr). A soln. of the distillate (22.0 g) and TsOH (400 mg) in toluene (25 ml) was stirred at 20° for 15 h, poured into 10% aq. Na_2CO_3 soln., and the product was extracted (Et_2O). Distillation (60–70°/0.05 Torr) afforded (−)-(*S*)-**3** (21.0 g, 82%; 80–84% ee). After 8 consecutive recrystallizations (pentane, −70°), almost enantiomerically pure (−)-(*S*)-**3** was obtained (14.0 g, 55%[6]); 99% ee, $[\alpha]_D^{20} = -490$ ($CHCl_3$, $c = 0.04$)).

(+)-(R)-α-Damascone ((*R*)-**3**; 99% ee, $[\alpha]_D^{20} = +501$ ($CHCl_3$, $c = 0.036$)) was obtained accordingly when (+)-*N*-isopropylephedrine was used.

3-(Benzyloxy)-1-(2,6,6-trimethylcyclohex-2-enyl)butan-2-one (**4**). A soln. of (+)-(*R*)-**3** (3.50 g, 18.2 mmol; 99% ee) in BnOH (17.5 g, 162 mmol) was treated with 1,1,3,3-tetramethylguanidine (0.42 g, 3.64 mmol) and stirred at 25° for 48 h. The volatiles were separated from **4** by bulb-to-bulb distillation (oven temp. 80°/0.05 Torr) and stirred at 25° for 24 h. This process was repeated once more, the non-volatiles were combined (5.00 g, 92%), and a sample was bulb-to-bulb distilled (oven temp. 130°/0.05 Torr): **4** as a *ca.* 1:1 mixture of diastereoisomers. IR: 3034, 2926, 1713, 1455, 1360, 1204, 1079. ^{1}H-NMR (360 MHz): 0.90 (split *s*, 3H); 0.92 (*s*, 3H); 1.16 (*m*, 1H); 1.22, 1.24 (*dd*, *J* = 6, together 3H); 1.57 (split *s*, 3H); 1.72 (*m*, 1H); 1.96–2.16 (*m*, 2H); 2.47, 2.57 (*dd*, *J* = 18, 6.5, 1H); 2.72, 2.74 (br. *s*, 1H); 2.89, 3.00 (*dd*, *J* = 18, 6.5, 1H); 4.08 (*m*, 1H); 4.48, 4.49 (*d*, *J* = 12, together 1H); 4.55 (*d*, *J* = 12, 1H); 5.58 (br. *s*, 1H); 7.22–7.34 (*m*, 5H). MS: 300 (trace, M^+), 209 (2), 123 (25), 107 (7), 91 (100), 81 (17), 69 (19); identical MS for both diastereoisomers.

Regeneration of (+)-(R)-3 from **4**. A soln. of distilled **4** (200 mg, 0.67 mmol) in $N(C_2H_4OH)_3$ (0.6 ml) was heated in a bulb-to-bulb distillation apparatus at 150°/*ca.* 10 Torr. Within 1 h, (+)-(*R*)-**3** and BnOH were collected in the distillation bulb. Chromatography (SiO_2, cyclohexane/AcOEt 99:1) afforded (+)-(*R*)-**3** (103 mg, 82%) of *ca.* 99% ee.

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[5]) The herein described sequence of operations allows to perform the entire reaction in one flask.

[6]) In principle, the yield could be improved by recrystallization of the mother liquors.

3-Oxo-1-(2,6,6-trimethylcyclohex-2-enyl)butyl 2,2-Dimethylpropanoate (**11**). A soln. of **4** (5.00 g, 16.7 mmol) in Et_2O (20 ml) was added within 2 min to a stirred slurry of $LiAlH_4$ (0.348 g, 9.15 mmol) in Et_2O (30 ml). The mixture, which had attained 35°, was cooled to 10° and carefully treated under stirring with H_2O (0.4 ml), then 15% aq. NaOH soln. (0.4 ml) and H_2O (1.2 ml). Filtration of the white cake and evaporation of the filtrate afforded **5** (4.95 g) as a mixture of 4 diastereoisomers (37:33:20:10). Without purification, **5** (4.95 g, max. 16.4 mmol) in THF (10 ml) was added at −20° to a soln. of LDA (22.95 mmol) in THF (30 ml)/hexane (from 1.7M BuLi (13.5 ml)). The soln. was warmed up and stirred at 20° for 15 min and at 30° for 15 min. Pivaloyl chloride (5.94 g (6.03 ml), 49.2 mmol) was then added at 25° within 2 min. After 5 min, the mixture was poured into ice/H_2O and extracted with Et_2O. The org. phase was vigorously shaken with 10% NaOH soln., washed successively with H_2O, 10% aq. HCl soln., H_2O, and sat. aq. NaCl soln., dried (Na_2SO_4), filtered (*Hyflo*), and evaporated. Bulb-to-bulb distillation (oven temp. 130°/0.03 Torr) and flash chromatography (SiO_2, cyclohexane/AcOEt 98:2) afforded **9** (5.20 g, 81% from **4**) as a mixture of 4 diastereoisomers (37:32:20:11; ^{1}H-NMR (360 MHz): 0.82–1.26 (21H); 1.30–2.30 (*m*, 7H); 3.44 (*m*, 1H); 4.32–4.57 (*m*, 2H); 5.17–5.62 (*m*, 2H); 7.22–7.40 (*m*, 5H)). Pivalate **9** (5.20 g, 13.5 mmol) in abs. EtOH (50 ml) was treated with TsOH (200 mg) and hydrogenated with 5% Pd/C (0.52 g) at 1 atm. After uptake of 340 ml of H_2 (45 min), the mixture was filtered (*Hyflo*) and extracted (pentane/sat. aq. $NaHCO_3$ soln.). The org. phase was washed with sat. aq. $NaHCO_3$ soln. and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated. The crude diastereoisomer mixture **10** (37:31:21:11; 3.90 g, max. 13.2 mmol) in acetone (150 ml) was treated at 0° with 2.5M *Jones* reagent (6.32 ml, 15.8 mmol). After complete addition (10 min), the green mixture was stirred at 25° for 30 min and extracted (pentane/sat. aq. $NaHCO_3$ soln.). The org. phase was washed with sat. aq. $NaHCO_3$ soln. (2 ×) and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated (3.46 g, 87% from **9**) and a sample (200 mg) bulb-to-bulb distilled (oven temp. 110°/0.05 Torr) to afford **11** (190 mg, 82% from **9**) as a *ca.* 55:45 mixture of diastereoisomers. IR: 2967, 1735, 1480, 1366, 1278, 1146. ^{1}H-NMR (360 MHz): 0.89, 0.93, 1.03, 1.23 (4*s*, together 6H); 1.15, 1.17 (2*s*, together 9H); 1.20–1.60 (*m*, 2H); 1.77, 1.80 (split *s*, together 3H); 1.84 (*m*, 1H); 1.99 (*m*, 2H); 2.15, 2.17 (2*s*, together 3H); 2.47, 2.71 (*dd*, J = 16, 3, together 1H); 2.64, 2.85 (*dd*, J = 16, 9, together 1H); 5.40–5.70 (*m*, 2H). MS: 192 (12), 177 (7), 159 (6), 149 (15), 136 (34), 121 (63), 109 (12), 107 (14), 93 (40), 85 (21), 77 (16), 57 (100), 43 (43); other diastereoisomer: almost identical fragment distribution.

(+)-(R)-α-Ionone (= *(+)-(R,E)-4-(2,6,6-Trimethylcyclohex-2-enyl)but-3-en-2-one*; (*R*)-**1**). A mixture of crude **11** (3.26 g, *ca.* 95% pure, *ca.* 10.5 mmol) and K_2CO_3 (2.90 g, 21.0 mmol) was heated in a bulb-to-bulb distillation apparatus at 140°/*ca.* 10 Torr for 30 min. The distillate was extracted (Et_2O/sat. aq. $NaHCO_3$ soln.) and the org. phase washed with sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated. Bulb-to-bulb distillation (oven temp. 80°/0.03 Torr) afforded (*R*)-**1** (94% pure; > 98% ee; 1.79 g, 79%). A second distillation bulb contained 82% pure (*R*)-**1** (141 mg, 5%). (*R*)-**1** of higher purity (≥ 97%; > 98% ee, $[\alpha]_D^{20}$ = +407 ($CHCl_3$, c = 0.04)) was obtained by column chromatography (SiO_2, cyclohexane/AcOEt 99.5:0.5).

(−)-(S)-Ionone ((*S*)-**1**; > 99% pure; > 99% ee, $[\alpha]_D^{20}$ = −431 ($CHCl_3$, c = 0.035)) was obtained accordingly from (−)-(*S*)-α-damascone ((*S*)-**3**).

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