An Efficient Enantioselective Synthesis of (+)-(*R*,*Z*)-5-Muscenone and (−)-(*R*)-Muscone − An Example of a Kinetic Resolution and Enantioconvergent Transformation

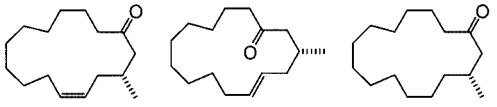
Charles Fehr,*[a] José Galindo,[a] and Olivier Etter[a]

Dedicated to Dr. Günther Ohloff on the occasion of his 80th birthday

Keywords: Enantioconvergence / Kinetic resolution / Macrocycles / Odorants / Reduction

An efficient catalytic kinetic resolution by CBS reduction and an original enantioconvergent transformation involving a Pd^{II}-catalyzed position-selective cyclization are the key steps for the synthesis of the exceptional musk odorant (*R*,*Z*)-5-muscenone [(*R*)-**1**] and (*R*)-muscone [(*R*)-**3**].

The most precious isomers of the perfume ingredient "Muscenone" (Firmenich SA) are the racemic (*Z*)- and (*E*)-5-muscenones [(±)-**1** and (±)-**2**].[1] The (*Z*) isomer (±)-**1** is particularly appreciated for its better top note and nitro-musk character.

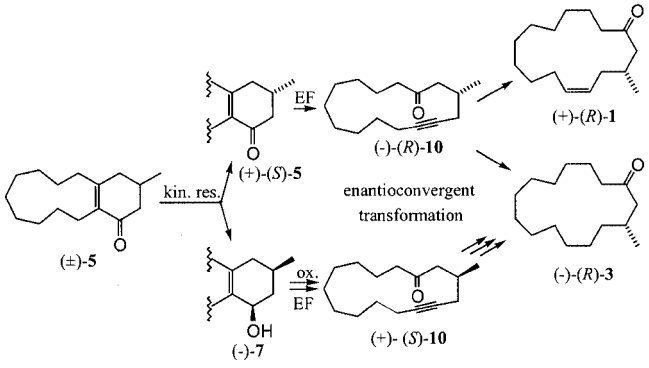


(+)-(*R*)-**1** (-)-(*R*)-**2** (-)-(*R*)-**3**

In view of the growing interest and research activities devoted to the natural (−)-(*R*)-muscone [(−)-(*R*)-**3**],[2] which exhibits a much more pronounced musk character than (+)-(*S*)-**3**, we decided to prepare the enantiomers of (*Z*)-5-muscenone (**1**) and (*E*)-5-muscenone (**2**).[3]

This led to the important finding that the target macrocyclic ketones with (*R*) configuration are much stronger musk odorants than the (*S*) enantiomers and that (+)-(*R*)-**1**, for the first time synthesized in a highly selective and efficient way, represents an outstanding musk odorant (musk character, power, tenacity, threshold value).[4]

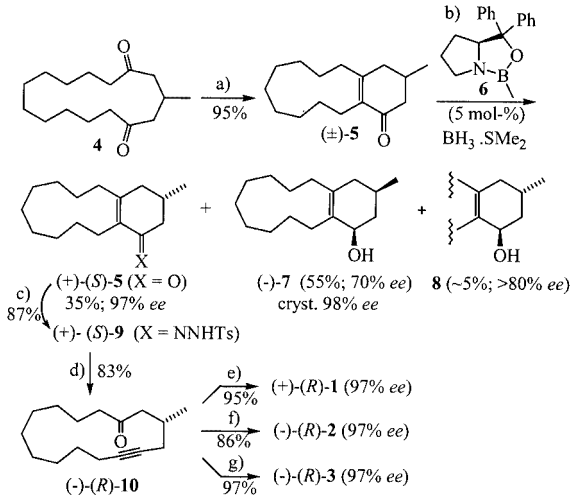
The key steps for the synthesis of (+)-(*R*)-**1** are a highly selective kinetic resolution (CBS reduction)[5] followed by an Eschenmoser fragmentation.[6] In addition, an original sequence of "interchange of functional groups" allowed us to convert the "wrong" enantiomer of the kinetic resolution process into the precious (−)-(*R*)-muscone [(−)-(*R*)-**3**] (enantioconvergent transformation; Scheme 1).



Scheme 1. Synthetic strategy for the synthesis of (+)-(*R*)-**1** and (−)-(*R*)-**3**; EF: Eschenmoser fragmentation

In the event, readily available dione **4**[7] was transformed almost quantitatively into the 11/6-membered bicyclic enone **5** upon prolonged heating in KOH/EtOH (Scheme 2). Partial reduction of (±)-**5** using Corey's oxazaborolidine **6** (5 mol %) and $BH_3{\cdot}SMe_2$ (CBS reduction) afforded the *cis*-alcohol (−)-**7** (55%; 70% *ee*), the *trans*-alcohol **8** (ca. 5%; > 80% *ee*) and unchanged (+)-(*S*)-**5** (35%; 97% *ee*). Pure (*S*)-**5** could be recovered by derivatization of the alcohols (−)-**7** and **8** as their succinic acid esters (see Exp. Sect.) or by chromatography. Upon crystallization, the *ee* of (−)-**7** could be increased to 98%. This represents one of the rare examples of an efficient catalytic kinetic resolution process for a CBS reduction[8] (Scheme 2).

[a] Firmenich SA, Corporate R&D Division
P. O. Box 239, 1211 Geneva 8, Switzerland
Fax: (internat.) + 41-22-780-3334
E-mail: charles.fehr@firmenich.com



Scheme 2. Synthesis of (+)-(*R*)-**1**, (−)-(*R*)-**2** and (−)-(*R*)-**3**: a) KOH (0.95 equiv.), EtOH, reflux; b) BH_3·SMe_2 (0.40 equiv.), **6** (5 mol %), THF, then 5% aq. NaOH; c) H_2NNHTs (1.1 equiv.), cat. AcOH, MeOH, reflux; d) AcO_2H (3 equiv.), toluene/H_2O (25:1), 30 °C, 6 h, then room temp., 15 h; e) H_2, Lindlar catalyst, EtOH; f) Li (8 equiv.), $H_2N(CH_2)_3NH_2$ (8 equiv.), THF, then Jones oxidation; g) H_2, Raney-Ni, EtOAc

Surprisingly, it was found that the enantioselectivity for the formed alcohol (−)-**7** increased at low conversion (10% conv.: 75% *ee*; 25% conv.: 80% *ee*) and then gradually decreased in the expected way.[9] Apparently, the initially formed oxazaborolidine-complexed alkoxyborane is a more selective catalyst than **6**·BH_3.[10] We could demonstrate that the selectivity (*S*),[11] increases from about 13 to 17 when the reduction is performed in the presence of 10% of (−)-**7** [54% conv.: (+)-**5**: 85% *ee*] and that it decreases to about 5 when using (+)-**7** [61% conv.: (+)-**5**: 70% *ee*].

Tosylhydrazone (*S*)-**9**, derived from (*S*)-**5**, underwent smooth Eschenmoser fragmentation to afford the ring-enlarged acetylenic ketone (*R*)-**10**, which was transformed in high yield and without any loss of *ee* (97%) into (*R*)-**1** (Lindlar hydrogenation), (*R*)-**2** (Li reduction[12]) and (*R*)-**3** (hydrogenation). Likewise, the enantiomeric series [(*S*)-**1**, (*S*)-**2** and (*S*)-**3**] was accessed from (*R*)-**5**, itself obtained from (*S*)-**7** (Jones oxidation, 91%).

(*R*,*Z*)-5-Muscenone [(*R*)-**1**], for the first time synthesized in a highly selective and efficient way, was found to be an excellent and very powerful musk odorant.[4,13]

Whereas (*R*)-**10** is the direct precursor of (*R*)-muscone, the conversion of (*S*)-**10** into (*R*)-muscone would require a position-selective transfer of the carbonyl group to the acetylenic triple bond. This unprecedented enantioconvergent transformation was achieved by a Pd^{II}-catalyzed transannular ring closure/isomerization of the acetylenic alcohol **11** as the key step (Scheme 3).[14]

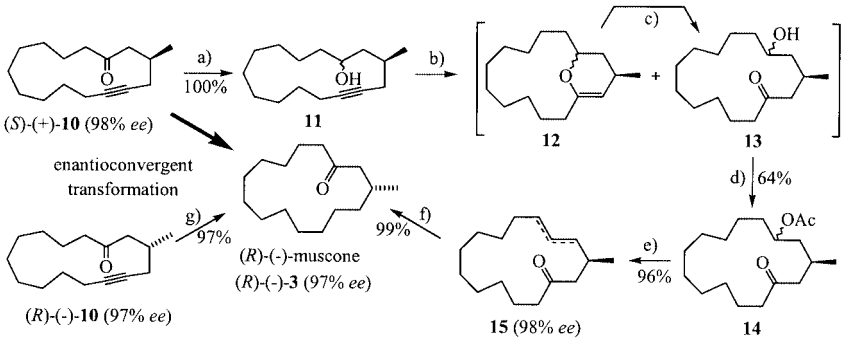
The perfectly position-selective 6-*exo*-*dig* cyclization/isomerization afforded a mixture of dihydropyran **12**[15] and hydroxy ketone **13**. In the presence of dilute aqueous HCl remaining **12** was converted into **13**, followed by acetylation. Acetate **14** was pyrolyzed at 400 °C and the resulting four muscenone isomers [(*E*)-4-/(*E*)-5-/(*Z*)-4-/(*Z*)-5-muscenone, 46:35:10:9; 98% *ee*) were hydrogenated with $[Ir(COD)(py)(PCy_3)]^+(PF_6)^-$ (Crabtree's catalyst) (99% yield) or with Raney-Ni/cat. MsOH in EtOH (81%; 12% of over-reduction was observed) to afford (*R*)-muscone [(*R*)-**1**] without noticeable loss of enantiomeric purity (97−98% *ee*).[16] The global yield from (*S*)-**10** (using the Ir catalyst) is 61%.

In conclusion, we have devised an efficient and original synthesis for the exceptional musk odorant (*R*,*Z*)-5-muscenone [(*R*)-**1**] and (*R*)-muscone [(*R*)-**3**].

Experimental Section

General: Bulb-to-bulb distillation: Büchi GKR-51 glass-oven, b.p. corresponds 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). GC: Varian instrument, model 3500; cap. columns: DB1 30 W (15 m × 0.319 mm), DB-WAX 15 W (15 m × 0.32 mm); chiral cap. 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. ^1H and ^{13}C NMR: Bruker WH 400 (400 MHz). MS: Hewlett Packard MSD 5972 automated GC/MS instrument, electron energy 70 eV.

(±)-14-Methylbicyclo[9.4.0]pentadec-1(11)-en-12-one [(±)-5]: A mixture of the diketone **4**[7] (240 g of 50% solution in toluene, 0.48



Scheme 3. Enantioconvergent transformation of (*R*)- and (*S*)-**10** into (*R*)-muscone: a) $NaBH_4$, MeOH/H_2O (6:1), cat. aq. NaOH (ca. 1 mol %); b) $PdCl_2$ (5 mol %), CH_3CN/H_2O (60:1), reflux, 30 min; c) 5% HCl, THF; then org. phase + NEt_3, extraction; d) Ac_2O (2.2 equiv.), NEt_3 (2.6 equiv.), cat. DMAP, CH_2Cl_2; e) 400 °C, N_2 stream; f) H_2, cat. $[Ir(COD)(py)(PCy_3)]^+(PF_6)^-$ (Crabtree's catalyst), CH_2Cl_2 (or: H_2, Raney-Ni, cat. MsOH, EtOH); g) H_2, Raney-Ni, EtOAc

mol), KOH (25.3 g, 0.45 mol, 0.95 equiv.) and EtOH (1 l) was heated at reflux for 16 h. The reaction mixture was cooled to room temperature, poured into 5% HCl, extracted with pentane, washed (2 × H_2O, then satd. NaCl), dried (Na_2SO_4), concentrated (115.8 g) and distilled (100 °C/ 0.07 Torr) to afford (±)-**5** (104.9 g, 95%) as a colorless viscous oil which crystallizes upon standing. M.p. 39−42 °C. ^{1}H NMR: δ = 1.05 (d, *J* = 7 Hz, 3 H), 1.10−1.80 (m, 14 H), 1.95−2.20 (m, 3 H), 2.30−2.60 (m, 6 H) ppm. ^{13}C NMR: δ = 197.8 (s), 157.1 (s), 136.9 (s), 47.2 (t), 38.8 (t), 32.8 (t), 30.7 (d), 27.4 (t), 27.2 (t), 26.9 (t), 26.3 (t), 26.0 (t), 25.9 (t), 25.4 (t), 24.4 (t), 21.6 (q) ppm. MS: *m*/*z* (%) = 234 (31) [M^+], 219 (8), 191 (37), 177 (100), 163 (28), 121 (16), 107 (23), 91 (20), 79 (25), 67 (22), 55 (26), 41 (40).

(+)-(*S*)-14-Methylbicyclo[9.4.0]pentadec-1(11)-en-12-one [(+)-(*S*)-5] and (−)-(12*R*,14*R*)-14-Methylbicyclo[9.4.0]pentadec-1(11)-en-12-ol [(−)-7]: Over a period of 5 h, BH_3·SMe_2 (11.94 g (14.93 mL), 157.2 mmol) in THF (200 mL) was added at 25−27 °C to a stirred solution of (±)-**5** (92.6 g, 396 mmol) and the (*S*)-oxazaborolidine **6** (50 mL, 0.396 M, 19.8 mmol) in THF (700 mL).[17] The reaction was quenched by addition of 5% NaOH (40 mL). After stirring for 1 h, the product was extracted (2 × Et_2O), washed (2 × satd. NaCl), dried (Na_2SO_4), concentrated (98.3 g) and distilled (simple distillation; 120 °C/0.15 Torr): 90.0 g of distillate [**7** (+ **8**)/**5**, 64:36; 383 mmol). A solution of the distillate in CH_2Cl_2 (800 mL) was treated with diisopropylethylamine (96.2 g (126.5 mL), 750 mmol), succinic anhydride (48.5 g, 485 mmol) and 4-dimethylaminopyridine (DMAP; 4.4 g, 36.1 mmol). The resulting solution was stirred at room temperature for 20 h [disappearance of **7** (+ **8**)], cooled to 0 °C and treated with an excess of 5% aq. NaOH. The organic phase was separated and the aqueous phase was extracted with EtOAc (2 ×). The combined organic phases were washed with satd. $NaHCO_3$, H_2O (2 ×) and satd. NaCl, dried (Na_2SO_4) and the solvents evaporated (35.8 g). Bulb-to-bulb distillation (100 °C/ 0.06 Torr) afforded 33.85 g of (*S*)-**5** (GC: 92% pure; 35% yield; 97% *ee*). The aqueous phase was acidified (concd. HCl, ice), and the acidic parts extracted (2 × Et_2O), washed (satd. aq. NaCl), dried (Na_2SO_4) and the solvents evaporated (77.4 g). The alcohols (−)-**7** **+8** could be liberated by hydride reduction ($LiAlH_4$, Et_2O). Alternatively, pure (*S*)-**5** (31%) and (−)-**7** (45%; 70% *ee*) could be isolated by column chromatography (SiO_2; cyclohexane/EtOAc, 97:3). Yield of (−)-**7** after crystallization (heptane, 0 °C): 26% (98% *ee*) (chiral GC).

(+)-(*S*)-5: $[\alpha]_D^{20}$ (98% *ee* from another experiment) = +90.1 (*c* = 2.7, MeOH). M.p. 51−52 °C.

(−)-7 (98% *ee*): $[\alpha]_D^{20}$ = −77.2 (*c* = 1.4, $CHCl_3$). M.p. 75−76 °C. ^{1}H NMR: δ = 0.97 (d, *J* = 7 Hz, 3 H), 1.10−1.80 (m, 18 H), 1.88 (m, 1 H), 2.05−2.20 (m, 2 H), 2.29 (m, 1 H), 2.40−2.55 (m, 2 H), 4.30 (broad m, 1 H) ppm. ^{13}C NMR: δ = 135.5 (s), 132.7 (s), 69.3 (d), 42.3 (t), 37.6 (t), 32.0 (t), 27.4 (d), 26.9−24.9 (6t), 24.1 (t), 23.3 (t), 21.9 (q) ppm. MS: *m*/*z* (5) = 236 (100) [M^+], 221 (78), 218 (35), 137 (81), 124 (69), 109 (60), 105 (66), 91 (65), 55 (51), 41 (66).

(+)-(*S*)-14-Methylbicyclo[9.4.0]pentadec-1(11)-en-12-one *p*-Toluenesulfonylhydrazone [(+)-(*S*)-9]: A mixture of (*S*)-**5** (23.4 g, 100 mmol), tosylhydrazine (20.5 g, 110 mmol), MeOH (200 mL) and AcOH (3 drops) was heated at reflux for 5 h, stored at 25 °C overnight (formation of a precipitate), heated again at reflux for 3 h, cooled to 0 °C and filtered. Yield of (*S*)-**9**: 35.1 g (87%). $[\alpha]_D^{20}$ (99% *ee* from another experiment) = +79.9 (*c* = 2.1, $CHCl_3$). M.p. (dec.) 157−159 °C (other sample with 80% *ee*). ^{1}H NMR: δ = 0.97 (d, *J* = 7 Hz, 3 H), 1.13−1.85 (m, 19 H), 2.15 (d, *J* = 14 Hz, 1 H), 2.25−2.60 (m, 4 H), 2.41 (s, 3 H), 7.28 (d, *J* = 14 Hz, 2 H), 7.85 (d, *J* = 14 Hz, 2 H) ppm. ^{13}C NMR: δ = 143.8 (s), 135.5 (s), 131.9 (s) (2 s are not visible), 129.3 (2 d), 128.4 (2 d), 36.9 (t), 32.8 (t), 31.8 (t), 27.7 (d), 26.7 (t), 26.1−25.2 (5 t), 24.7 (t), 23.9 (t), 21.6 (q), 21.3 (q) ppm.

(−)-(*R*)-3-Methyl-5-cyclopentadecyn-1-one [(−)-(*R*)-10]: Peracetic acid (40%; 5.07 mL, 5.70 g, 30.1 mmol) and water (3.8 mL) were added whilst stirring to a solution of (*S*)-**9** (4.02 g, 10.0 mmol) in toluene (102 mL). The two-phase system was warmed to 30 °C and vigorously stirred for 6 h. Stirring was continued at 25 °C for 15 h. The phases were separated and the aqueous phase was extracted with diethyl ether. The organic phases were successively washed with 10% aq. Na_2SO_3, water and satd. NaCl, dried (Na_2SO_4), concentrated (2.49 g) and bulb-to-bulb distilled from $CaCO_3$ (1%) at 100 °C/0.06 Torr to afford 1.98 g of (*R*)-**10** (83%, 97% *ee*) containing 1% of (*S*)-**5**. The *ee* was determined by reduction of (*R*)-**10** to the corresponding alcohol diastereomers ($LiAlH_4$, diethyl ether) and injection onto the chiral GC column (good separation of the minor diastereomer). $[\alpha]_D^{20}$ = −29.6 (*c* = 0.05, MeOH). M.p. 38−39 °C. ^{1}H NMR: δ = 0.94 (d, *J* = 7 Hz, 3 H), 1.15−1.55 (m, 12 H), 1.62 (m, 1 H), 1.80 (m, 1 H), 1.97 (m, 1 H), 2.15−2.50 (m, 7 H), 2.93 (dd, *J* = 17, 4 Hz, 1 H) ppm. ^{13}C NMR: δ = 211.7 (s), 81.8 (s), 78.6 (s), 49.2 (t), 41.6 (t), 28.2 (d), 28.0 (t), 27.3 (t), 26.8 (t), 26.5 (t), 26.3 (t), 26.1 (t), 25.7 (t), 24.7 (t), 20.1 (q), 18.4 (t) ppm. MS: 234 *m*/*z* =(16) [M^+], 219 (20), 177 (20), 149 (17), 135 (32), 121 (39), 107 (41), 93 (61), 79 (94), 55 (68), 41 (100).

(+)-(*R*,*Z*)-3-Methyl-5-cyclopentadecen-1-one [(*R*,*Z*)-5-Muscenone, (*R*)-1]: A solution of (*R*)-**10** (3.38 g, 14.4 mmol) in EtOH (30 mL) was hydrogenated using 600 mg of Lindlar's catalyst. After 1 h, the reaction was complete and the hydrogenation stopped immediately (sometimes additional catalyst was necessary). Filtration through Celite, concentration and bulb-to-bulb distillation (80 °C/0.06 Torr) afforded 3.23 g (95%, 97% *ee*) of (*R*)-**1** containing 2% of muscone. $[\alpha]_D^{20}$ (99 *ee* from another experiment) = +11.7 (*c* = 2.45, MeOH). The *ee* was determined by reduction of (*R*)-**1** to the corresponding alcohol diastereomers ($LiAlH_4$, ether) and injection onto the chiral GC column (excellent separation of the major diastereomer).The spectroscopic data are in agreement with those reported for (±)-**1**.[1]

(−)-(*R*,*E*)-3-Methyl-5-cyclopentadecen-1-one [(*R*,*E*)-5-Muscenone, (*R*)-2]: Under argon, a vigorously stirred, cooled (−30 °C) solution of (−)-**10** (1.20 g, 5.10 mmol), 1,3-diaminopropane (3.04 g, 3.40 mL, 41.0 mmol) and THF (10 mL) was treated with small pieces of lithium (287 mg, 41.0 mmol). Stirring was continued for 2.5 h. The reaction mixture became progressively dark blue. The liquid was decanted from the remaining lithium and poured into ice/10% HCl whilst the lithium was decomposed with EtOH. The muscenones [(*E*)/(*Z*) = 11:1] and corresponding alcohols (29% by GC) were isolated by extraction with diethyl ether (2 ×), followed by washing (satd. $NaHCO_3$, then H_2O, then satd. NaCl), drying (Na_2SO_4) and concentration (1.20 g). The oil was dissolved in acetone (15 mL) and treated at 0 °C with Jones reagent (2.5 M; 0.61 mL). The green reaction mixture was poured onto ice and extracted as above. The crude oil (1.12 g) was bulb-to-bulb-distilled (80 °C/0.08 Torr). Yield: 1.04 g (86%) of (*R*)-**2**, containing 5% of (+)-**1**. $[\alpha]_D^{20}$ (97 *ee*) = −3.3 (*c* = 0.06, MeOH). The spectroscopic data are in agreement with those reported for (±)-**2**.[1]

(−)-(*R*)-Muscone [(−)-(*R*)-3] from (−)-(*R*)-10: (−)-(*R*)-**10** (250 mg, 1.07 mmol) was dissolved in EtOAc (5 mL) and hydrogenated with Raney-Ni [500 mg of suspension (not optimized), washed successively with H_2O, EtOH and EtOAc] (1 h). Filtration, concentration and bulb-to-bulb distillation (80 °C/0.08 Torr) afforded (−)-(*R*)-**3**

(246 mg, 97%, 97% *ee*). The *ee* was determined by reduction of (*R*)-**3** to the corresponding alcohol diastereomers ($LiAlH_4$, Et_2O) and injection onto the chiral GC column (excellent separation of the major diast.). The use of 10% Pd/C/EtOH led to 3% racemization. $[\alpha]_D^{20}$ (97 % *ee*) = −12.7 (*c* = 0.09, MeOH).

(−)-(*R*)-Muscone [(−)-(*R*)-3] from (±)-(*R*)-10 (Scheme 3)

(1*RS*,3*R*)-3-Methyl-5-cyclopentadecyn-1-ol:[11] A solution of $NaBH_4$ (382 mg, 10.0 mmol) in H_2O (5 mL) and 5% NaOH (0.1 mL) was added whilst stirring to a solution of (*R*)-**10** (1.96 g, 8.38 mmol) in MeOH (30 mL). After 2 h, the reaction mixture was partially concentrated, treated with diethyl ether (50 mL) and poured into 5% HCl (50 mL). After separation of the phases, the alcohol **11** (70:30 mixture of diastereomers) was isolated by extraction with diethyl ether, followed by washing (satd. $NaHCO_3$, then water, then satd. NaCl), drying (Na_2SO_4) and concentration (1.97 g, 100%). This product was used without further purification. Characteristic signals: ^{1}H NMR: δ = 1.00 (d, *J* = 7 Hz, 3 H), 3.83 (m, 1 H) ppm. ^{13}C NMR: δ = 81.9 (s), 78.5 (s), 69.2 (d) (major diastereomer), 81.6 (s), 78.0 (s), 68.4 (d) (minor diastereomer) ppm. MS: *m*/*z* (%) = 236 (10) [M^+], 221 (22).

(1*RS*,3*R*)-3-Methyl-5-oxocyclopentadecyl Acetate (14): $PdCl_2$ (37.4 mg, 0.21 mmol) was added to a solution of **11** (2 diastereomers, 70:30; 98% *ee*) (986 mg, 4.18 mmol) in acetonitrile (20 mL). The stirred mixture was then treated with water (0.32 mL) and heated at reflux. After stirring for 30 min, the product was poured into 5% NaOH (40 mL) and extracted (2 × Et_2O), washed (H_2O, then satd. NaCl), dried (Na_2SO_4) and concentrated. The resulting oil (**13** + remaining **12**) was dissolved in THF (6 mL) and 5% HCl (0.6 mL) and stirred at room temp. for 2 h. The aqueous phase was removed by pipette and discarded and the organic phase was quenched with NEt_3 (84.4 μL, 0.84 mmol). After 3 min, the solution was poured into satd. $NaHCO_3$, extracted (2 × Et_2O), washed (H_2O, then satd. NaCl), dried (Na_2SO_4) and concentrated. Hydroxy ketone **13** (1.20 g) was dissolved in CH_2Cl_2 (7 mL, to which 3 drops of NEt_3 had been added) and treated with NEt_3 (1.24 g, 1.71 mL, 12.2 mmol), Ac_2O (1.03 g, 0.96 mL, 10.2 mmol) and 4-dimethylaminopyridine (DMAP; 50 mg). After stirring for 3 h, the solution was poured into 5% HCl, extracted (2 × Et_2O), washed (H_2O, satd. $NaHCO_3$, then satd. NaCl), dried (Na_2SO_4), concentrated and bulb-to-bulb-distilled (150 °C/0.01 Torr). The acetoxy ketone **14** (980 mg, 87% pure by GC, 69%) was further purified by chromatography (SiO_2), using cyclohexane/EtOAc (95:5). Yield: 796 mg of **14** (2:1 mixture of diastereomers; 64% from **10**). ^{1}H NMR: δ = 0.95 (major diastereomer), 1.02 (minor diastereomer) (d, *J* = 7 Hz, 3 H), 1.15−2.70 (m, 25 H), 2.04 (s, 3 H), 4.89 (m, 1 H) ppm. ^{13}C NMR (characteristic signals major diastereomer): δ = 211.4 (s), 170.9 (s), 71.4 (d), 49.6 (t), 42.0 (t), 40.4 (t), 31.4 (t), 27.7 (t), 25.7 (d) ppm. MS: *m*/*z* (%) = 236 (47) [M^+ − 60].

(4*S*)- and (5*R*)-Muscenone Isomers 15: The acetoxy ketone **14** (2.24 mmol) in toluene (14 mL) was added dropwise (in 10 min) under an N_2 stream into a quartz tube (4 m) heated at 400 °C. The product was concentrated and bulb-to-bulb-distilled (125−150 °C/0.05 Torr) to afford **15** as a mixture of four isomers [(*E*)-4-/(*E*)-5-/(*Z*)-4-/(*Z*)-5-, 46:35:10:9]; 508 mg, 96%, 98% *ee*. The GC retention times correspond to those of racemic "Muscenone" (Firmenich SA). The *ee* could be determined by injection onto the chiral GC column, as the (*E*)-4-enantiomers show different retention times.

(−)-(*R*)-Muscone [(−)-(*R*)-3]: The muscenone isomeric mixture **15** (500 mg, 2.12 mmol) was dissolved in CH_2Cl_2 (20 mL) and the system was purged with Ar (2 min) and H_2 (2 min). $[Ir(COD)(py)(PCy_3)]^+(PF_6)^-$ (Crabtree's catalyst from Aldrich; 9.5 mg), was added and the colorless solution was hydrogenated (4 h). Concentration and bulb-to-bulb distillation (100 °C/0.08 Torr) afforded (−)-(*R*)-**3** (497 mg, 99%, 97% *ee*). The *ee* was determined by reduction of (*R*)-**3** to the corresponding alcohol diastereomers ($LiAlH_4$, ether) and injection onto the chiral GC column (excellent separation of the major diast.). Alternatively, **15** (250 mg, 1.06 mmol) was dissolved in EtOH (20 mL) containing 150 mg of a 2.5% solution of MsOH in EtOH and hydrogenated with Raney-Ni [500 mg of suspension (not optimized); washed successively with H_2O and EtOH]. The reaction was complete after 2 h. Filtration, concentration and bulb-to-bulb distillation (100 °C/0.08 Torr) afforded (−)-(*R*)-**3** (232 mg, 88% pure, containing 12% of the corresponding alcohol diastereomers; 81%, 97% *ee*).

Acknowledgments

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