(±)-1-[(1*R**,2*R**,8a*S**)-1,2,3,5,6,7,8,8a-Octahydro-1,2,8,8-tetramethylnaphthalen-2-yl]ethan-1-one: Isolation and Stereoselective Synthesis of a Powerful Minor Constituent of the Perfumery Synthetic *Iso E Super*®

by **Cornelius Nussbaumer**, **Georg Fráter***, and **Philip Kraft**

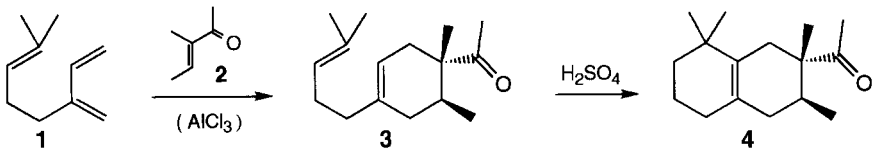
Givaudan Roure Fragrance R&D, Überlandstrasse 138, CH-8600 Dübendorf

(±)-1-[(1*R**,2*R**,8a*S**)-1,2,3,5,6,7,8,8a-Octahydro-1,2,8,8-tetramethylnaphthalen-2-yl]ethan-1-one (**5**) was identified as a minor (*ca.* 5%) but very powerful (5 pg/l (air)) constituent of the important perfumery synthetic *Iso E Super*®. Its structure was assigned by NMR spectroscopy and established by a stereoselective synthesis starting from α-ionone (**10**). Diastereoselective conjugate addition of Me_2CuLi to **10** was followed by a haloform reaction, esterification, and isomerization of the C=C bond by treatment with NaOCl (*Schemes 3* and *4*). The resulting allyl chloride **17** was ozonized and transformed into the trimethyl(vinyl)octahydrocoumarin **20** by diastereoselective *Grignard* reaction with ethynylmagnesium chloride, and subsequent *Lindlar* hydrogenation. *Ireland-Claisen* rearrangement of **20** followed by methylation with MeLi afforded the target molecule **5** that was identical with the material isolated from commercial *Iso E Super*®.

Introduction. – Only very few synthetic odorants really shaped the art of perfumery by creating new trends and new fragrance families [1–3]. *Iso E Super*® is certainly one of them, and 'Trésor' by Sophia Grojsman (*Lancôme*, 1990) can be considered the trendsetter. While 'Trésor' as well as 'Narcisse' (*Chloé*, 1992) contain already 18% of *Iso E Super*®, we can find it in 25% in 'Fahrenheit' (*Dior*, 1988) and 'Dolce Vita' (*Dior*, 1995), and even in 40% in 'Bill Blass' (*Blass*, 1978) and 43% in 'Feminité du Bois' (*Shiseido*, 1992).

Besides the odor characteristics, one condition for such a popularity of a perfumery synthetic is an easy and inexpensive synthetic access; that of *Iso E Super*® is outlined in *Scheme 1* [4]: Aluminum-trichloride-catalyzed *Diels-Alder* reaction of myrcene (**1**) with (3*E*)-3-methylpent-3-en-2-one (**2**) gives predominantly the regioisomer **3** that is cyclized in the presence of sulfuric acid to provide **4** as the major product. Today, the production scale of *Iso E Super*® is >500 t/a [5]. However, by GC-sniffing analysis it was found [6] that it is not the main component **4** but a *ca.* 5% constituent that determines the woody-ambery odor of commercial *Iso E Super*®.

Scheme 1. *Industrial Synthesis of* Iso E Super® (**4**) *from Myrcene* (**1**)



Results and Discussion. – This minor constituent was isolated from *Iso E Super*® in gram quantities of $>80\%$ purity by reaction of the commercial product with peracetic acid followed by repeated column chromatography on silica gel. While the isomers with tetrasubstituted double bonds were epoxydized, the desired compound did not react with peracetic acid as monitored by GC. INADEQUATE and NOEDIFF experiments on the isolated material led to the assignment of structure **5** (see Fig.).

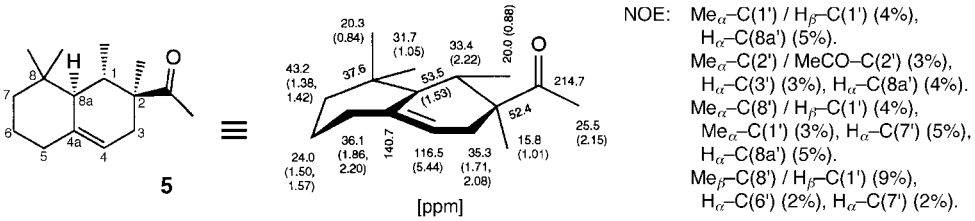
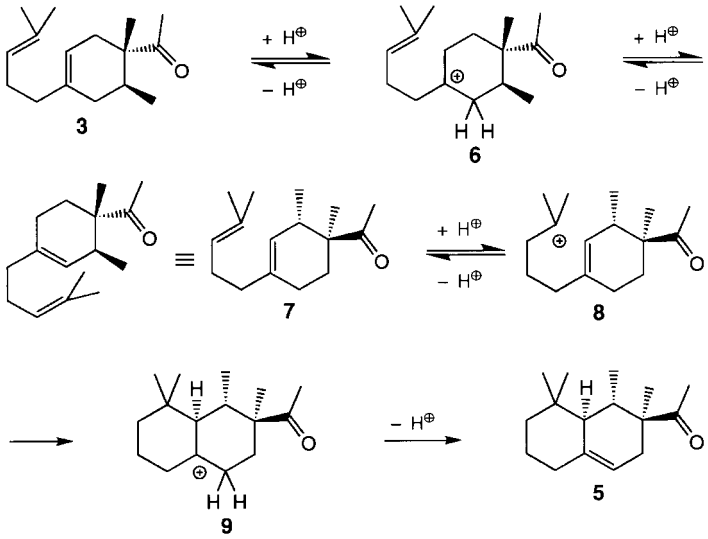


Fig. 1. *Structure of the powerful trace constituent* **5** *as established by INADEQUATE and NOEDIFF experiments.*

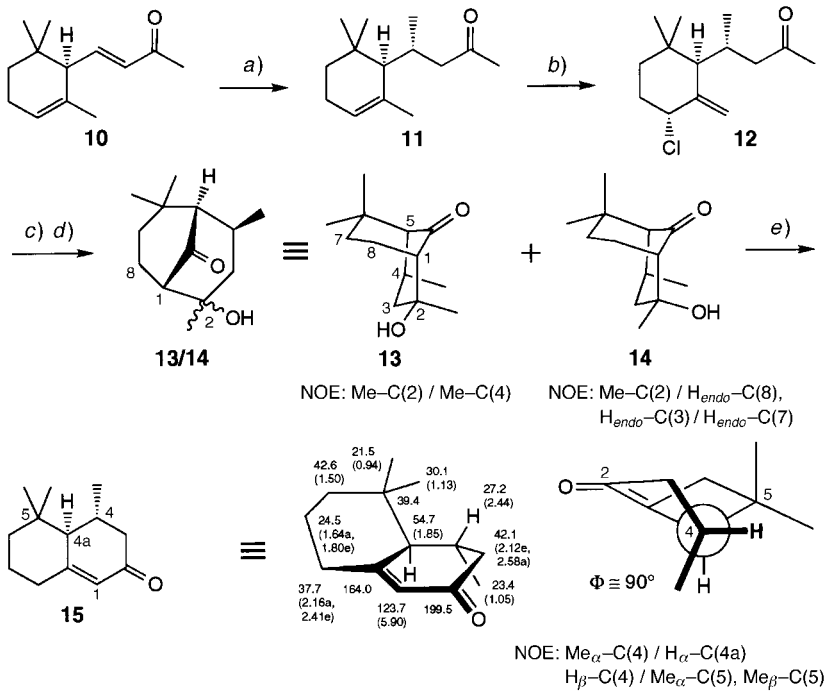
The formation of **5** as a by-product of the industrial synthesis of **4** could be rationalized by acid-catalyzed rearrangement of the endocyclic C=C bond of **3** *via* **6** and **7** (*Scheme 2*). That only one diastereoisomer of **5** was found in the commercial sample of *Iso E Super*® is probably due to steric interactions of Me–C(1) with the $Me_2C(8)$ groups (numbering of **5**) in the subsequent cyclization reaction **8** → **9**. However, the proposed structure, as well as the assumed configuration of the minor component **5**, required proof by a directed synthesis.

Scheme 2. *Proposed Mechanism for the Formation of the By-product* **5** *in the Industrial Synthesis of* Iso E Super®



Our synthesis of (±)-1-[(1*R**,2*R**,8a*S**)-1,2,3,5,6,7,8,8a-octahydro-1,2,8,8-tetramethylnaphthalen-2-yl]ethan-1-one (**5**) [7] [8] commenced with the addition of Me_2CuLi to *rac*-α-ionone (**10**) furnishing **11** diastereoselectively in 81% isolated yield (*Scheme 3*). This reaction had already been described [9], but the relative configuration of the product **11** had not been determined. We assigned the *like* configuration to **11** by its transformation to the corresponding octahydronaphthalenone **15** (*Scheme 3*). By an addition-elimination reaction, found by *Wolinsky* and coworkers [10] to be operative for highly substituted olefins, the allylic chloride **12** was obtained in 60% yield upon treatment of **11** with sodium hypochlorite. Ozonolysis of **12**, followed by reductive workup, provided a mixture of diastereoisomeric aldol adducts **13**/**14**. The corresponding aldol-condensation products would violate *Bredt*'s rule [11][12]. Refluxing the mixture **13**/**14** in methanolic KOH furnished in 83% yield the octahydronaphthalenone **15** with the two stereocenters C(4) and C(4a) effectively locked in a + *anti*- or *syn*-clinal conformation (with respect to the H-atoms at C(4) and C(4a)). A slightly broadened *s* of H–C(4a) at δ 1.85, *i.e.*, a vicinal H–C(4a)/H–C(4) coupling constant near zero corresponding to a torsion angle $\Phi \approx 90°$ in the *Karplus* equation, clearly indicated the relative (4*R**,4a*R**) configuration (*Scheme 3*). This was further substantiated by the intense NOE cross-peaks between δ 1.05 (Me_α–C(4); pseudo-axial) and 1.85 (H_α–C(4a); pseudo-axial), and between δ 2.44 (H_β–C(4);

Scheme 3. *Assignment of the Relative Configuration of* **11**

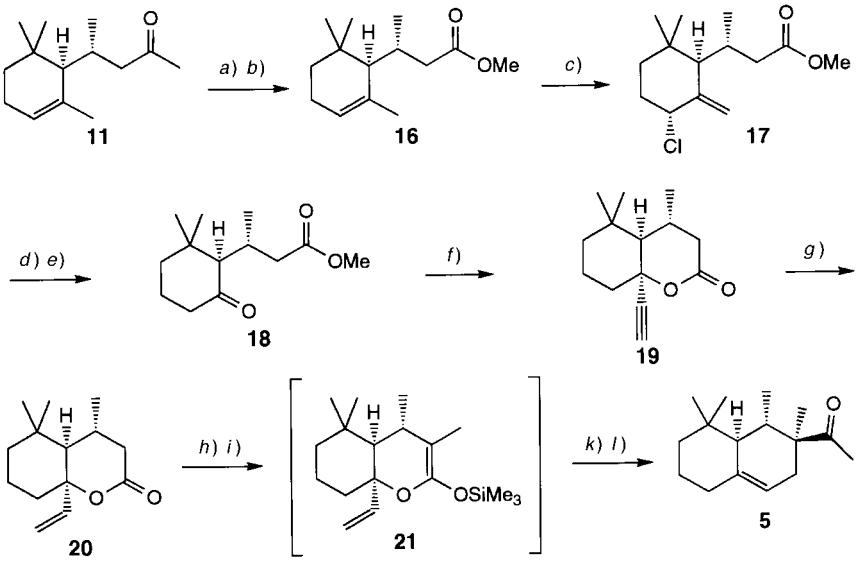


a) Me_2CuLi, Et_2O, $-10° \rightarrow$ r.t.; 71%. *b*) NaOCl, H_3PO_4, C_6H_{14}, 0°; 68%. *c*) O_3, MeOH, $-70°$. *d*) Zn, H_2O, H_3PO_4; 57% (**13**), 27% (**14**). *e*) KOH, MeOH/H_2O (9:1), $\uparrow\downarrow$, 83%.

pseudo-equatorial) and 1.13 (Me_α–C(5); pseudo-equatorial) as well as 0.94 (Me_β–C(5); pseudo-axial). Thus, the (4*R**,1′*R**)-configuration of **11** was established.

In the next step of our synthesis of the minor *Iso-E-Super*® component **5**, the methyl ketone **11** [(4*R**,1′*R**)] was subjected to a haloform reaction employing NaOBr (*Scheme 4*). The resulting crude acid was transformed into the corresponding methyl ester **16** in 91% overall yield. Analogously to the reaction **11** → **12**, the methyl ester **16** was treated with NaOCl [10][13] to furnish the allylic chloride **17**. Ozonization followed by reductive workup led to the 2′-oxo ester **18**, which diastereoselectively reacted in a *Grignard* reaction with ethynylmagnesium bromide to provide the ethynyl lactone **19**. This was hydrogenated to the corresponding vinyl lactone **20** with the *Lindlar* catalyst. Due to appreciable enolization of **18**, an attempt on the direct transformation of **18** → **20** with vinylmagnesium bromide or vinylmagnesium chloride failed, and 4,6,6-trimethylbicyclo[3.3.1]nonane-2,9-dione, the diketone corresponding to **13**/**14**, was isolated as the main product.

Scheme 4. *Stereoselective Synthesis of the Target Molecule* **5**

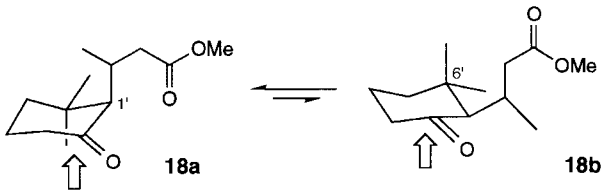


a) NaOBr, NaOH, H_2O, 15° → r.t. *b*) MeOH, PhH, TsOH; 91%. *c*) NaOCl, H_3PO_4, C_6H_{14}, 0°. *d*) O_3, MeOH, −70 °. *e*) Zn, H_2O, H_3PO_4; 51%. *f*) HC≡CMgBr, THF, 0° → r.t. *g*) H_2, EtOH, 5% Pd/$CaCO_3$/Pb, r.t.; 75%. *h*) LDA, MeI, THF/3,4,5,6-tetrahydro-1,3-dimethylpyrimidin-2(1*H*)-one (DMPU), −70° → 0°. *i*) BuLi, Me_3SiCl, −70°. *k*) PhMe, Δ. *l*) MeLi, Et_2O, 0° → 35°; 32%.

The observed high diastereoselectivity (> 98%) of the ethynyl *Grignard* reaction on **18** – crucial for the stereoselective synthesis of our target molecule **5** – is due to the steric effect of either the butanoate chain at C(1′) in the axial conformer **18a** or the axial Me group at C(6′) in the equatorial conformer **18b** (see *Scheme 5*). The selectivity, however, is expected to be higher in the case of a nucleophilic attack on **18a**, and this is the preferred conformation by *ca.* 1.4 kcal/mol, as was calculated by a conformational

analysis with the computer program MOLOC [14]. The main reason for this '2-alkylcyclohexanone effect' [15] seems to be that there are two butane-*gauche* interactions in **18b** *vs.* one such interaction in **18a**. By analogy, the unsaturated side chain of α-ionone is preferentially in the pseudo-axial conformation [16].

Scheme 5. *Conformational Analysis of* **18**



With **20** in hand, the stage was set for the γ-lactone-enolate rearrangement [17]. Alkylation of the lactone enolate of **20** – generated by action of lithium diisopropylamide (LDA) – with MeI furnished the corresponding α-methyl lactone. Without isolation, this was treated at $-20°$ with BuLi, followed by addition of excess Me_3SiCl. The resulting trimethylsilyl enol ether **21** was then heated in toluene to provide the trimethylsilyl ester, which finally was converted to **5** by means of MeLi. The one-pot reaction sequence **20** → **21** → **5** provided the target molecule in 32% overall yield. By GC co-injection and NMR spectra, the synthetic material **5** proved to be identical with the sample isolated from commercial *Iso E Super*®.

Olfactory Evaluation. – (±)-1-[(1*R**,2*R**,8a*S**)-1,2,3,5,6,7,8,8a-Octahydro-1,2,8,8-tetramethylnaphthalen-2-yl]ethan-1-one (**5**) is a very potent odorant with an intense warm, woody, ambery character and an odor threshold as low as 5 pg/l (air). Accordingly, **5** is the most powerful compound in the commercial product *Iso E Super*®, and thus determines its odor characteristics to a great extent.

Experimental Part

General. Reagents and solvents: *Fluka (puriss.* or *purum)*, used without further purification, except Et_2O, which was distilled from $LiAlH_4$. Moisture-sensitive reactions were conducted in oven-dried (130°) glassware under inert atmosphere. The given temp. refer to the heating or cooling baths. FC = flash chromatography. GC: *Carlo-Erba-GC-6000-Vega* gas chromatograph; *SE-30* glass-cap. column (28 m × 0.3 mm) with He (70 kPa) as carrier gas; temp. program: 2 min at 90°, then 8°/min → 200°, then 20°/min → 240°. IR: *Perkin-Elmer-681* and *Nicolet-510-FT-IR* spectrometer, $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR: *Bruker-AVANCE-DPX-400* or *Bruker-AM-400*, and *Bruker-AC-F-200* spectrometer, resp.; δ in ppm rel. to $SiMe_4$, J in Hz; the configurations of compounds **13**–**15**, **20**, and **5** were assigned by INADEQUATE, NOESY, and NOEDIFF experiments. MS: *Finnigan-MAT-212* and *Varian-MAT-CH-5* instrument; rel. int. in % of the base peak.

*Isolation of (±)-1-[(1*R**,2*R**,8a*S**)-1,2,3,5,6,7,8,8a-Octahydro-1,2,8,8-tetramethylnaphthalen-2-yl]ethan-1-one* (**5**) *from* Iso E Super®. At 0°, 40% aq. peracetic acid (190 g, 1.00 mol) was added during 20 min to a stirred soln. of commercial-grade *Iso E Super*® (234 g, 1.00 mol) in $CHCl_3$ (2.5 l). The mixture was allowed to warm to r.t. within 2 h, and stirring was continued at r.t. for 16 h prior to the introduction in an ice-cold mixture of 1M aq. Na_2SO_3 (300 ml) and 30% aq. NaOH soln. (300 ml). The org. layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The yellow oil obtained (271 g) was purified by two successive FC (silica gel (2.5 and 0.6 kg, resp.), hexane/^{t}BuOMe 19 : 1) providing **5** (9.0 g, 60% (GC) pure, 2.3%). A third FC (silica gel (500 g), pentane: Et_2O, 49 : 1), finally afforded a 83% (GC) pure sample of **5** (3.8 g, 1.4%). Spectroscopic data: identical to those of the synthesized material **5**, see below.

(±)-(4R)-4-[(1R*)-2,6,6-Trimethylcyclohex-2-en-1-yl]pentan-2-one* (**11**). At $-10°$ under N_2, 1.6M MeLi in Et_2O (600 ml, 0.96 mol) was added during 20 min to a stirred suspension of CuI (91.1 g, 478 mmol) in Et_2O (3 l). Stirring was continued at 0° for 1 h prior to recooling the mixture to $-10°$ and addition of a soln. of α-ionone (**10**; 84.5 g, 439 mmol) in Et_2O (100 ml) within 30 min. The mixture was then allowed to warm to r.t. and, under N_2, slowly poured into ice/H_2O. The org. layer was washed with brine, dried ($MgSO_4$), and evaporated. Distillation at 92°/0.4 Torr afforded **11** (74.0 g, 88% (GC) pure; 71%). Colorless liquid consisting of a single diastereoisomer with 6% of the starting material and 6% of the corresponding *tert*-alcohol. IR (film): 1717*s* (C=O), 1361*s* (Me), 1163*s* (C–O). ^{1}H-NMR ($CDCl_3$): 0.87, 0.99 (2*s*, 2 Me–C(6′)); 1.03 (*d*, *J* = 7.0, 3 H–C(5)); 1.09–1.14 (*m*, H–C(4)); 1.35–1.42 (*m*, 2 H–C(5′)); 1.70 (*q*, *J* = 2.0, Me–C(2′)); 1.95–1.99 (*m*, 2 H–C(4′)); 2.11 (*s*, 3 H–C(1)); 2.20 (*dd*, *J* = 16.5, 10.5, H_b–C(3)); 2.40 (*m*, H–C(1′)); 2.51 (*dd*, *J* = 16.5, 3.0, H_a–C(3)); 5.38 (*s*, H–C(3′)). ^{13}C-NMR ($CDCl_3$): 23.1 (*t*, C(4′)); 23.9 (*q*, C(5)); 26.0 (*q*, Me–C(2′)); 28.0, 28.1 (2*q*, 2 Me–C(6′)); 28.2 (*d*, C(4)); 30.5 (*q*, C(1)); 30.6 (*t*, C(5′)); 33.4 (*s*, C(6′)); 49.1 (*t*, C(3)); 55.0 (*d*, C(1′)); 121.8 (*d*, C(3′)); 134.8 (*s*, C(2′)); 209.2 (*s*, C(2)). MS (70 eV): 208 (1, M^+), 190 (4, $[M-H_2O]^+$), 175 (5, $[M-H_2O-Me]^+$), 150 (69, $[M-C_3H_6O]^+$), 135 (28, $[M-C_4H_9O]^+$), 123 (100, $C_9H_{15}^+$), 109 (37, $C_8H_{13}^+$), 85 (56, $C_6H_{13}^+$), 81 (66, $C_6H_9^+$), 43 (47, $C_2H_3O^+$).

(±)-(4R)-4-[(1R*,5R*)-5-Chloro-2,2-dimethyl-6-methylidenecyclohexyl]pentan-2-one* (**12**). During 20 min, 40% aq. H_3PO_4 soln. (20 ml) was added with cooling in an ice-water bath to a stirred soln. of **11** (33.1 g, 140 mmol) in hexane (85 ml) and 14% aq. NaOCl soln. (165 ml). After complete addition, the neutral (pH 6.5) mixture was diluted with H_2O, and extracted with Et_2O. The combined org. extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a red, viscous oil (38.7 g) which was purified by FC (silica gel, hexane/^{t}BuOMe 9:1): **12** (23.1 g, 68%). IR ($CHCl_3$): 1715*s* (C=O), 1358*s* (Me), 757*m* and 700*w* (C–Cl), 1645*w* (C=C). ^{1}H-NMR ($CDCl_3$): 0.96, 1.04 (2*s*, 2 Me–C(2′)); 1.05 (*d*, *J* = 7.5, 3 H–C(5)); 1.15–1.26 (*m*, 2 H–C(3′)); 1.81–1.92 (*m*, 2 H–C(4′)); 2.06–2.14 (*m*, H–C(4)), overlapped by 2.08 (*s*, 3 H–C(1)); 2.24 (*dd*, *J* = 16.5, 10.0, H_b–C(3)); 2.53 (*m*, H–C(1′)); 2.85 (*dd*, *J* = 16.5, 2.0, H_a–C(3)); 4.58 (*t*, *J* = 4.5, H–C(5′)); 4.90 (*t*, *J* = 1.0, 1 H, CH_2=C); 5.32 (*t*, *J* = 1.0, 1 H, CH_2=C). MS (70 eV): 242 (1, M^+), 207 (6, $[M-Cl]^+$), 149 (12, $[M-Cl-H_2O]^+$), 121 (19)/107 (57)/93 (32)/79 (22) ($[C_nH_{(2n-5)}]^+$ series), 69 (32, $C_5H_9^+$), 43 (100, $C_2H_3O^+$).

(±)-(1R,2R*,4S*,5R*)-2-Hydroxy-2,4,6,6-tetramethylbicyclo[3.3.1]nonan-9-one* (**13**) and *(±)-(1R*,2S*,4S*,5R*)-2-Hydroxy-2,4,6,6-tetramethylbicyclo[3.3.1]nonan-9-one* (**14**). At $-70°$, a soln. of **12** (16.5 g, 68.0 mmol) in MeOH (450 ml) was ozonized until the blue color persisted. Excess O_3 was removed by passing N_2 through the soln. until the blue color disappeared. The mixture was poured into a stirred suspension of Zn powder (50 g, 765 mmol) in H_2O (100 ml). By dropwise addition of H_3PO_4, the soln. was adjusted to pH 3, and stirring was continued at 60° for 7 h. After filtration and evaporation, the residue was partitioned between Et_2O and H_2O. The aq. phase was extracted with Et_2O, and the combined org. extracts were dried ($MgSO_4$) and evaporated. The crude amorphous material was purified by FC (silica gel (350 g), hexane/^{t}BuOMe 3:1): less polar **13** (8.15 g, 57%) and more polar **14** (3.80 g, 27%).

Data of **13**: M.p. (neat) 137°. IR (KBr): 1691*s* (C=O), 3411*s* (O–H), 1371*m* (Me), 1111*m* and 1217*m* (C–O). ^{1}H-NMR ($CDCl_3$): 0.93 (*s*, Me_{exo}–C(6)); 1.00 (*d*, *J* = 3.5, Me–C(4)); 1.04 (*s*, Me_{endo}–C(6)); 1.22 (*dd*, *J* = 14.0, 6.0, H_b–C(7)); 1.30 (*s*, Me–C(2)); 1.47 (*dd*, *J* = 14.5, 5.0, H_b–C(3)); 1.66 (br. *s*, OH, H–C(5)); 1.79–1.87 (*m*, H_b–C(8)); 2.00 (*td*, *J* = 14.0, 5.5, H_a–C(7)); 2.11 (*dd*, *J* = 14.5, 7.0, H_a–C(3)); 2.21–2.27 (*m*, H–C(1), H_a–C(8)); 2.45 (*m*, H–C(4)). NOEDIFF ($CDCl_3$): 1.00 (Me–C(4)) → 1.30 (Me–C(2), 1.3%); 1.30 (Me–C(2)) → 1.00 (Me–C(4), 1.0%). ^{13}C-NMR ($CDCl_3$): 23.3 (*q*, *Me*–C(4)); 25.1 (*t*, C(8)); 27.6 (*q*, Me_{exo}–C(6)); 28.3 (*q*, Me_{endo}–C(6)); 29.3 (*d*, C(4)); 32.3 (*t*, C(7)); 33.3 (*q*, *Me*–C(2)); 40.2 (*s*, C(6)); 43.6 (*t*, C(3)); 57.1 (*d*, C(1)); 64.0 (*d*, C(5)); 75.4 (*s*, C(2)); 218.5 (*s*, C(9)). MS (70 eV): 210 (13, M^+), 195 (5, $[M-Me]^+$), 177 (3, $[M-Me-H_2O]^+$), 152 (72, $[M-C_3H_6O]^+$), 111 (50, $C_8H_{15}^+$), 85 (100, $C_6H_{13}^+$), 69 (27, $C_5H_9^+$), 55 (35, $C_4H_7^+$), 43 (71, $C_2H_3O^+$).

Data of **14**: M.p. (AcOEt/hexane) 65°. IR (KBr): 3373*s* (O–H), 1697*s* (C=O), 1122*m* and 1234*m* (C–O), 1373 (Me). ^{1}H-NMR ($CDCl_3$): 0.93 (*s*, Me_{exo}–C(6)); 1.06 (*s*, Me_{endo}–C(6)); 1.14 (*d*, *J* = 7.5, Me–C(4)); 1.23–1.28 (*m*, H_b–C(7)); 1.31 (*s*, Me–C(2)); 1.59 (*d*, *J* = 15.0, H_b–C(3)); 1.62 (br. *s*, OH); 1.77 (br. *s*, H–C(5)); 1.88–1.99 (*m*, H_a–C(7), 2 H–C(8)); 2.16 (*t*, *J* = 3.0, H–C(1)); 2.20 (*dd*, *J* = 15.5, 7.0, H_a–C(3)); 2.50 (*m*, H–C(4)). NOESY ($CDCl_3$): 1.31 (Me–C(2)) ↔ 1.91 (H_a–C(8)); 1.89 (H–C(7)) ↔ 2.20 (H_a–C(3)). ^{13}C-NMR ($CDCl_3$): 23.6 (*q*, Me–C(4)); 26.0 (*t*, C(8)); 28.3 (*q*, Me_{exo}–C(6)); 28.7 (*q*, Me_{endo}–C(6)); 29.2 (*q*, *Me*–C(2)); 32.3 (*d*, C(4)); 32.4 (*t*, C(7)); 39.9 (*s*, C(6)); 40.5 (*t*, C(3)); 58.1 (*d*, C(1)); 64.1 (*d*, C(5)); 80.0 (*s*, C(2)); 218.5 (*s*, C(9)). MS (70 eV): 210 (15, M^+), 195 (5, $[M-Me]^+$), 177 (3, $[M-CH_3-H_2O]^+$), 152 (88, $[M-C_3H_6O]^+$), 111 (61, $C_8H_{15}^+$), 85 (100, $C_6H_{13}^+$), 69 (40, $C_5H_9^+$), 55 (23, $C_4H_7^+$), 43 (50, $C_2H_3O^+$).

(±)-2,3,4,4a,5,6,7,8-Octahydro-4,5,5-trimethylnaphthalen-2-one (**15**). A mixture of **13**/**14** (0.50 g, 2.38 mmol) was added to a soln. of KOH (0.56 g, 10 mmol) in MeOH/H_2O 9:1 (10 ml), and the resulting

mixture was heated under reflux for 30 min. After the mixture had cooled to r.t., it was poured onto ice, acidified with citric acid, and extracted with *t*BuOMe. The combined org. extracts were dried ($MgSO_4$) and evaporated, and the residue purified by bulb-to-bulb distillation: **15** (0.38 g, 83%). Colorless oil. IR ($CHCl_3$): 1672*s* (C=C–C=O), 1628*m* (C=C). ^{1}H-NMR ($CDCl_3$): 0.94 (*s*, ax. Me_β–C(5)); 1.05 (*d*, *J* = 8.0, ax. Me_α–C(4)); 1.13 (*s*, eq. Me_α–C(5)); 1.50 (*m*, 2 H–C(6)); 1.64 (*m*, H_{ax}–C(7)); 1.80 (*m*, H_{eq}–C(7)); 1.85 (br. *s*, H_α–C(4a)); 2.12 (*m*, H_{eq}–C(3)); 2.16 (*m*, H_{ax}–C(8)); 2.41 (*m*, H_{eq}–C(8)); 2.44 (*m*, H_β–C(4)); 2.58 (*dd*, *J* = 6.0, H_{ax}–C(3)); 5.90 (br. *s*, H–C(1)). ^{13}C-NMR ($CDCl_3$): 21.5 (*q*, ax. Me_β–C(5)); 23.4 (*q*, ax. Me_α–C(4)); 24.5 (*t*, C(7)); 27.2 (*s*, C(4)); 30.1 (*q*, eq. Me_α–C(5)); 37.7 (*t*, C(8)); 39.4 (*s*, C(5)); 42.1 (*t*, C(3)); 42.6 (*t*, C(6)); 54.7 (*d*, C(4a)); 123.7 (*d*, C(1)); 164.0 (*s*, C(8a)); 199.5 (*s*, C(2)). MS (70 eV): 192 (24, M^+), 150 (19, $[M - C_2H_2O]^+$), 135 (34, $[M - C_3H_5O]^+$), 124 (100, $C_9H_{16}^+$), 107 (28, $C_8H_{11}^+$), 69 (78, $C_5H_9^+$).

*(±)-Methyl (3*R*)-3-[(1*R*)-2,6,6-Trimethylcyclohex-2-en-1-yl]butanoate* (**16**). At 15°, a soln. of **11** (37.0 g, 178 mmol) in dioxane (700 ml) was added within 15 min to an aq. NaOBr soln. (freshly prepared by addition of Br_2 (40 ml, 776 mmol) to a NaOH soln. (124 g, 3.10 mol) in H_2O (1.1 l)). The mixture was stirred at 15° for 1 h and at r.t. for 2 h prior to quenching with 1M aq. Na_2SO_3 (250 ml). After evaporation, the residue was partitioned between Et_2O and H_2O 1 : 1 (2 l). The aq. layer was acidified with 25% aq. H_2SO_4 soln. (200 ml) and extracted with Et_2O. The combined org. extracts were washed with brine, dried ($MgSO_4$) and evaporated; diastereoisomerically pure *(±)-(3*R*)-3-[(1*R*)-2,6,6-trimethylcyclohex-2-en-1-yl)butanoic acid* (36.5 g; m.p. 41°). This crude acid was heated with $TsOH \cdot H_2O$ (2.00 g, 10.5 mmol) in PhH/MeOH 10 : 1 (330 ml) for 8 h with azeotropic removal of H_2O. Standard workup afforded crude **16** (36.2 g, 91%), sufficiently pure for further transformation. IR (film): 1739*s* (COO), 1167*s*, 1202*m* (C–O), 1384*m* (Me). ^{1}H-NMR ($CDCl_3$): 0.87, 1.00 (2*s*, 2 Me–C(6′)); 1.04 – 1.16 (*m*, 2 H–C(5′)); overlapped by 1.08 (*d*, *J* = 7.0, 3 H–C(4)); 1.41 – 1.49 (*m*, 2 H–C(4′)); 1.69 (*q*, *J* = 2.0, Me–C(2′)); 1.96 – 1.98 (*m*, H–C(1′)); 2.04 (*dd*, *J* = 15.0, 10.5, H_b–C(2)); 2.31 – 2.34 (*m*, H–C(3)); 2.43 (*dd*, *J* = 15.0, 3.5, H_a–C(2)); 3.65 (*s*, MeO); 5.37 (*s*, H–C(3′)). ^{13}C-NMR ($CDCl_3$): 23.1 (*t*, C(4′)); 23.6 (*q*, C(4)); 25.9 (*q*, Me–C(2′)); 28.1, 28.2 (2*q*, 2 Me–C(6′)); 29.9 (*d*, C(3)); 30.4 (*t*, C(5′)); 33.4 (*s*, C(6′)); 39.7 (*t*, C(2)); 51.3 (*q*, MeO); 54.9 (*d*, C(1′)); 121.9 (*d*, C(3′)); 134.4 (*s*, C(2′)); 174.6 (*s*, C(1)). MS (70 eV): 224 (10, M^+), 209 (6, $[M - Me]^+$), 168 (21, $[M - C_4H_8]^+$), 123 (100)/109 (14)/95 (23)/81 (46) ($[C_nH_{(2n-3)}]^+$ series).

*(±)-Methyl (3*R*)-3-[(1*R*)-2,2-Dimethyl-6-oxocyclohexyl]butanoate* (**18**). During 20 min, 40% aq. H_3PO_4 soln. (15 ml) was added, under cooling in an ice-water bath, to a soln. of **16** (31.1 g, 138 mmol) in hexane (75 ml) and 10% aq. NaOCl soln. (140 ml). The neutral (pH 6.5) mixture was then diluted with H_2O and the product extracted with Et_2O. The combined dried ($MgSO_4$) org. extracts were evaporated: crude **17** (31.1 g, 82% (GC) pure) as a yellow liquid. ^{1}H-NMR ($CDCl_3$): 4.54 (*t*, *J* = 5.0, H–C(3′)); 4.93 (*t*, *J* = 1.0, 1 H, CH_2=); 5.33 (*t*, *J* = 1.0, 1 H, CH_2=).

The crude **17** was then taken up in anh. MeOH (700 ml) and ozonized at −70° O_3 until the soln. became blue. Excess O_3 was removed by passing N_2 through the soln. until the blue color disappeared. The mixture was poured into a stirred suspension of Zn powder (100 g, 1.53 mol) in H_2O (300 ml), and after adjustment to pH 3 with H_3PO_4, stirring was continued at r.t. for 24 h prior to filtration and evaporation. The resulting residue was partitioned between Et_2O and H_2O to afford, after standard workup, **18** (24.8 g, 64% (GC) pure; 51%). An anal. sample was obtained by FC (silica-gel, hexane/*t*BuOMe, 10 : 1). IR (film): 1736*s* (COO), 1707*s* (C=O), 1170*s* (C–O), 1371 and 1337*m* (Me). ^{1}H-NMR ($CDCl_3$): 0.97 (*s*, Me_{ax}–C(2)); 1.04 (*d*, *J* = 8.5, 3 H–C(4)); 1.12 (*s*, Me_{eq}–C(2′)); 1.59 – 1.65 (*m*, 2 H–C(3′)); 1.82 – 1.88 (*m*, 2 H–C(4′)); 2.18 (*d*, *J* = 2.0, H–C(1′)); 2.29 (*dd*, *J* = 7.5, 6.0, 2 H–C(5′)); 2.44 (*m*, H–C(3)); 2.46 (*dd*, *J* = 16.0, 2.5, H_b–C(2)); 2.61 (*dd*, *J* = 16.0, 10.0, H_a–C(2)); 3.67 (*s*, MeO). ^{13}C-NMR ($CDCl_3$): 21.7 (*q*, C(4)); 22.2 (*t*, C(4′)); 24.2 (*q*, Me_{ax}–C(2)); 27.6 (*d*, C(3)); 30.1 (*q*, Me_{eq}–C(2′)); 38.6 (*t*, C(2)); 39.7 (*s*, C(2′)); 40.7 (*t*, C(5′)); 42.1 (*t*, C(3′)); 51.3 (*q*, MeO); 65.0 (*d*, C(1′)); 174.2 (*s*, C(1)); 212.7 (*s*, C(2′)). MS (70 eV): 226 (3, M^+), 211 (5, $[M - Me]^+$), 195 (8, $[M - MeO]^+$), 179 (62, $[M - H_2O - CO]^+$), 151 (32, $[M - C_3H_7O_2]^+$), 137 (24, $[M - C_4H_9O_2]^+$), 126 (21, $C_9H_{18}^+$), 111 (100, $C_8H_{15}^+$), 69 (59, $C_5H_9^+$).

*(±)-(4*R*,4a*R*,8a*S*)-Octahydro-8a-ethenyl-4,5,5-trimethyl-2*H*-1-benzopyran-2-one* (**20**). At 0°, a soln. of crude **18** (8.00 g, 22.7 mmol) in THF (20 ml) was added during 15 min to a soln. of ethynylmagnesium bromide (12.9 g, 0.1 mol) in THF (100 ml). The mixture was allowed to warm to r.t. within 4 h, poured into ice-water/sat. aq. NH_4Cl soln. 1 : 1, and extracted with Et_2O to provide, after drying ($MgSO_4$) and evaporation, crude **19** (8.83 g) as a red, viscous liquid. This was dissolved in EtOH (150 ml) and hydrogenated at r.t. in the presence of *Lindlar*'s catalyst (0.5 g). Filtration and evaporation, followed by FC (silica gel, hexane/*t*BuOMe 9 : 1) afforded crystalline **20** (3.80 g, 75%): M.p. (hexane) 84 – 88°. IR ($CHCl_3$): 1730*s* (COO). ^{1}H-NMR ($CDCl_3$): 0.85 (*s*, Me_{ax}–C(5)); 0.94 (*s*, Me_{eq}–C(5)); 1.15 (*d*, *J* = 7.0, Me–C(4)); 1.23 (*m*, H_{ax}–C(6)); 1.38 (*m*, H_{ax}–C(4a)); 1.43 (*m*, H_{eq}–C(7)); 1.44 (*m*, H_{ax}–C(8)); 1.47 (*m*, H_{eq}–C(6)); 1.81 (*m*, H_{ax}–C(7)); 1.83 (*m*, H_{eq}–C(8)); 2.10

(*m*, H–C(4)); 2.31 (*dd*, *J* = 16.0, 9.5, H_b–C(3)); 2.53 (*dd*, *J* = 16.0, 8.5, H_a–C(3)); 5.13 (*d*, *J* = 11.0, H–C(2′) *cis* to H–C(1′)); 5.20 (*d*, *J* = 17.5, H–C(2′) *trans* to H–C(1′)); 5.94 (*dd*, *J* = 17.5, 11.0, H–C(1′)). ^{13}C-NMR ($CDCl_3$): 17.3 (*t*, C(7)); 21.6 (*q*, Me_{ax}–C(5)); 24.9 (*q*, *Me*–C(4)); 26.5 (*d*, C(4)); 31.1 (*q*, Me_{eq}–C(5)); 33.9 (*s*, C(5)); 36.3 (*t*, C(3)); 39.2 (*t*, C(8)); 40.1 (*t*, C(6)); 52.4 (*d*, C(4a)); 83.8 (*s*, C(8a)); 113.3 (*t*, C(2′)); 144.1 (*d*, C(1′)); 174.0 (*s*, C(2)). MS (70 eV): 222 (9, M^+), 207 (3, $[M-Me]^+$), 195 (3, $[M-C_2H_3]^+$), 179 (10, $[M-C_2H_3O]^+$), 110 (36, $C_8H_{14}^+$), 97 (39, $C_7H_{13}^+$), 83 (100, $C_6H_{11}^+$), 69 (57, $C_5H_9^+$), 55 (81, $C_4H_7^+$), 41 (68, $C_3H_5^+$).

*(±)-1-[(1*R*,2*R*,8a*S*)-*1,2,3,5,6,7,8,8a-Octahydro-1,2,8,8-*tetramethylnaphthalen-2-yl]ethan-1-one* (**5**). At –70° under N_2, a soln. of **20** (2.22 g, 10.0 mmol) in anh. THF (10 ml) was added with stirring to 0.37M lithium diisopropylamide in THF (30 ml, 11.1 mmol; freshly prep. by addition of 1.4M BuLi in hexanes (8.0 ml, 11.2 mmol) to a soln. of $^iPr_2NH$ (2.0 ml, 15.2 mmol) in anh. THF (20 ml)). Then, a soln. of MeI (0.75 ml, 12 mmol) in THF/DMPU 5 : 1 (6 ml) was injected, and the mixture was allowed to warm to 0°. After recooling to –70°, 1.4M BuLi in hexanes (10.0 ml, 14.0 mmol) was introduced, and stirring was continued at –70° for 1 h, prior to the addition of an excess of chlorotrimethylsilane. The mixture was allowed to warm to r.t. and evaporated. The resulting residue was taken up in hexane and filtered through a sintered-glass funnel. After evaporation, the crude product was refluxed in PhMe (50 ml) for 24 h. The solvent was evaporated and the resulting residue dissolved in Et_2O (50 ml) and treated at 0° with 1.3M MeLi in Et_2O (20.0 ml, 26.0 mmol). The mixture was refluxed for 90 min, cooled in an ice-water bath, and poured on vigorously stirred cold 0.5N HCl (100 ml). Usual workup, followed by FC (silica-gel, hexane/AcOEt, 20 : 1) afforded **5** (749 mg, 32%). Colorless fragrant oil. IR ($CHCl_3$): 1700*s* (C=O). ^{1}H-NMR ($CDCl_3$): 0.84 (*s*, ax. Me_β–C(8′)); 0.88 (*d*, *J* = 6.5, eq. Me–C(1′)); 1.01 (*s*, ax. Me_α–C(2′)); 1.05 (*s*, eq. Me_α–C(8′)); 1.38, 1.42 (2 *m*, 2 H–C(7′)); 1.53 (*m*, H–C(8a′)); 1.50, 1.57 (2 *m*, 2 H–C(6′)); 1.71 (*dd*, *J* = 15.0, 7.0, ax. H_α–C(3′)); 1.86, 2.20 (2 *m*, 2 H–C(5′)); 2.08 (*m*, eq. H_β–C(3′)); 2.15 (*s*, 3 H–C(2)); 2.22 (*m*, H–C(1′)); 5.44 (*dq*, *J* = 7.0, 1.0, H–C(4′)). ^{13}C-NMR ($CDCl_3$): 15.8 (*q*, ax. Me_α–C(2′)); 20.0 (*q*, eq. *Me*–C(1′)); 20.3 (*q*, ax. Me_β–C(8′)); 24.0 (*t*, C(6′)); 25.5 (*q*, C(2)); 31.7 (*q*, eq. Me_α–C(8′)); 33.4 (*d*, C(1′)); 35.3 (*t*, C(3′)); 36.1 (*t*, C(5′)); 37.6 (*s*, C(8′)); 43.2 (*t*, C(7′)); 52.4 (*s*, C(2′)); 53.5 (*d*, C(8a′)); 116.5 (*d*, C(4′)); 140.7 (*s*, C(4a′)); 214.7 (*s*, C(1)). MS (70 eV): 234 (23, M^+), 219 (7, $[M-Me]^+$), 191 (100, $[M-C_2H_3O]^+$).

We thank *F. Etzweiler* for GC-sniffing analyses, *D. Helmlinger* and *M. Pesaro* for valuable discussions, *J. Märki* and *G. Brunner* for NMR experiments, and *M. Ambühl* as well as *H. Jenal* for their skillful experimental work.

REFERENCES

[1] G. Fráter, J. A. Bajgrowicz, P. Kraft, *Tetrahedron* **1998**, *54*, 7633.
[2] J.-C. Ellena, in 'Perfumes: Art, Science and Technology', Ed. P. M. Müller and D. Lamparsky, Elsevier, London, 1991, p. 333.
[3] B. D. Mookherjee, R. W. Trenkle, R. A. Wilson, M. J. Zampino, E. S. Everett, S. M. Patel, in 'Flavours, Fragrances and Essential Oils. Proceedings of the 13th International Congress of Flavours, Fragrances and Essential Oils, Istanbul, Turkey, 15–19 October, 1995', Ed. K. H. C. Baser, AREP Publ., Istanbul, 1995, Vol. 2, pp. 27–54.
[4] J. B. Hall, J. M. Sanders, to *IFF*, U.S. Pat. 3929677, 1973.
[5] M. Gras, *Perfum. Flavor.* **1992**, *17* (1), 7.
[6] N. Neuner-Jehle, F. Etzweiler, in: 'Perfumes: Art, Science and Technology', Ed. P. M. Müller and D. Lamparsky, Elsevier, London, 1991, p. 197.
[7] F. Etzweiler, D. Helmlinger, C. Nussbaumer, M. Pesaro, to *Givaudan*, U.S. Pat. 5214160, 1990.
[8] G. Fráter, U. Müller, C. Nussbaumer, 'Abstracts of Papers. Part 2, 213th ACS National Meeting, San Francisco, April 13–17', American Chemical Society, Washington, D.C., 1997.
[9] M. P. Zink, H. R. Wolf, E. P. Müller, W. B. Schweizer, O. Jeger, *Helv. Chim. Acta* **1976**, *59*, 32.
[10] S. G. Hegde, M. K. Vogel, J. Saddler, T. Hrinyo, N. Rockwell, R. Haynes, M. Oliver, J. Wolinsky, *Tetrahedron Lett.* **1980**, *21*, 441.
[11] V. Prelog, L. Ruzicka, P. Barman, L. Frenkiel, *Helv. Chim. Acta* **1948**, *31*, 92.
[12] V. Prelog, *J. Chem. Soc.* **1950**, 420.
[13] J. Otera, M. Kishi, K. Kanehira, S. Suzuki, M. Shiono, Y. Fujita, *Synth. Commun.* **1984**, *14*, 347.
[14] 'MOLOC, Molecular Modeling Software on Silicon Graphics Workstations, Version 06/17/96', F. Hoffman–La Roche Ltd., Basel, 1996.

[15] E. L. Eliel, S. H. Wilen, 'Stereochemistry of Organic Compounds', Wiley Interscience, New York, 1994, p. 732.
[16] G. Ohloff, E. Otto, V. Rautenstrauch, G. Snatzke, *Helv. Chim. Acta.* **1973**, *56*, 1874.
[17] S. Danishefsky, R. L. Funk, J. F. Kerwin, Jr., *J. Am. Chem. Soc.* **1980**, *102*, 6889.

Received March 10, 1999