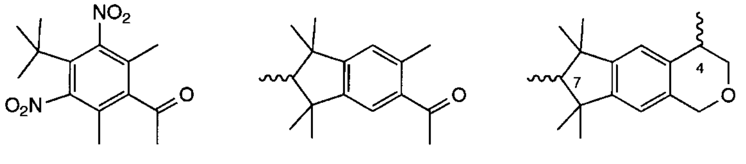
Preparation and Olfactory Characterization of the Enantiomerically Pure Isomers of the Perfumery Synthetic *Galaxolide*®

by **Georg Fráter***, **Urs Müller**, and **Philip Kraft**

Givaudan Roure Research Ltd., Überlandstrasse 138, CH-8600 Dübendorf

The commercially important isochromane musk odorant *Galaxolide*® (= 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[*g*]-2-benzopyran; HHCB; **3**) was separated into its diastereoisomers *via* the tricarbonyl(η^6-cyclopenta[*g*]-2-benzopyran)chromium complexes **10**. Since GC/olfactometry indicated that only one enantiomer of each diastereoisomer (4*RS*,7*RS*)-**3** and (4*RS*,7*SR*)-**3** determines the odor characteristics of the commercial product, all four stereoisomers (4*S*,7*R*)-, (4*S*,7*S*)-, (4*R*,7*S*)-, and (4*R*,7*R*)-**3** were synthesized by *Friedel-Crafts* alkylation of 1,1,2,3,3-pentamethylindane (**11**) with (*S*)- and (*R*)-methyloxirane ((*S*)- and (*R*)-**12**, resp.), acid-catalyzed reaction of the resulting products with paraformaldehyde, and separation of the formed diastereoisomer pairs *via* the tricarbonyl(η^6-cyclopenta[*g*]-2-benzopyran)chromium complexes **10**. The powerful musk odor of *Galaxolide*® (**3**) was thus attributed to its (−)-(4*S*)-isomers (4*S*,7*R*)- and (4*S*,7*S*)-**3**, while the (+)-(4*R*)-isomers (4*R*,7*S*)- and (4*R*,7*R*)-**3** were weak to almost odorless.

Introduction. – The surprising discovery of *Albert Bauer* in 1888 that certain nitrated derivatives of benzene like **1** possess musk odors [1–3] had a tremendous impact on the emerging fragrance industry and stimulated much research in the domain of benzoid musks. Although cheap and easy to obtain, one major problem concerning the nitro musks was their photochemical reactivity leading to discoloration and skin sensitization. Whether by serendipity or directed approach, the evolution of benzenoid musks led to the more stable compound *Phantolide*® (**2**) as the first commercial aromatic non-nitro musk [1–3]. *Galaxolide*® (= 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[*g*]-2-benzopyran; HHCB; **3**), discovered by *Heeringa* and *Beets* in 1967 [4], can be considered the final stage of this development (*Fig. 1*), and is still the most used musk in perfumery with an annual production of around 3800 t [5][6].



1 musk ketone **2** *Phantolide*® **3** *Galaxolide*®

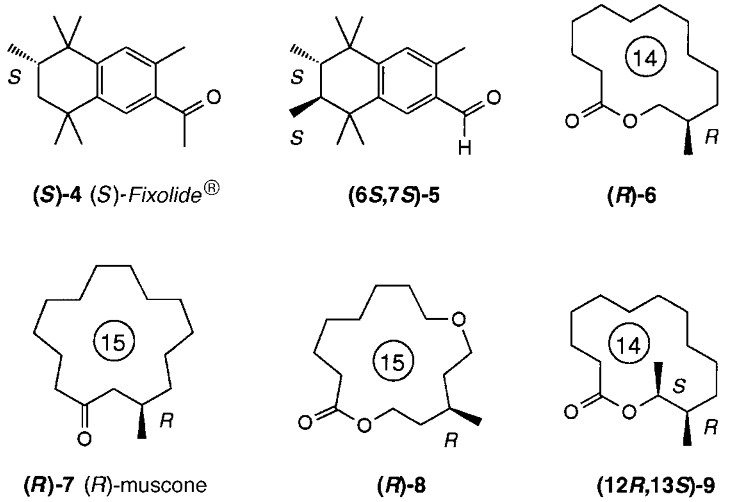
Fig. 1. *Evolution of benzenoid musk synthetics*

Our interest in *Galaxolide*® (**3**) originated, however, not only from its commercial importance but also from its rigid structure, which should allow interesting insights into the structure-odor correlation of musks, provided it is known which isomers of the commercial mixture contribute to the attractive musk scent. GC/Sniffing analyses of a commercial *Galaxolide*® (**3**) sample on chiral permethylated β-cyclodextrin phases indicated that only two out of the four stereoisomers were responsible for the attractive musk scent, but no information was available about their configuration. This might be due to the 1,6-relation of the stereogenic centers in **3**, which renders asymmetric induction impossible and causes only subtle anisometric differences between the diastereoisomers that are difficult to exploit for separation, even on standard GC columns.

In general, only very few data on the enantioselectivity of the odor sensation of musk odorants exist (*Fig. 2*). For *Fixolide*® (**4**), only the (*S*)-isomer is responsible for its strong musk odor, while the enantiomer possesses only a light and sweet aromatic odor [7]. The same spatial arrangement seems to be important for the aldehyde analog **5**, where the (6*S*,7*S*)-isomer is the most powerful musk odorant [8–10].

Concerning macrocyclic musks, (+)-(*R*)-**6** possesses a musk note with a sandalwood tonality, while the (−)-(*S*)-enantiomer has an animal musk tonality with camphoraceous aspects [11][12]. Both enantiomers are present in Angelica root oil [13]. (−)-(*R*)-Muscone ((*R*)-**7**), the principal odorous constituent of the male musk deer [14], possesses a rich and powerful musk note with an odor threshold of 61 ppb, while the musk note of (+)-(*S*)-muscone ((*S*)-**7**) is less rich and weaker with a threshold of 233 ppb [15]. The (−)-(*R*)-**8** isomer is responsible for the very characteristic musk odor of 12-methyl-9-oxa-14-tetradecanolide (= 4-methyl-1,7-dioxacyclopentadecan-8-one), while the enantiomer was odorless on GC [16]. Recently, *Bollbuck* and *Tochtermann* [17] reported that (+)-(12*R*,13*S*)-12-methyl-13-tetradecanolide (= (+)-(13*R*,14*S*)-13,14-dimethyloxacyclotetradecan-2-one; (12*R*,13*S*)-**9**) possesses a strong woody odor with a pronounced musk character, in contrast to its (−)-(12*S*,13*R*)-enantiomer (12*S*,13*R*)-**9**, which is devoid of any musk note but has an animalic cedarwood profile with camphoraceous aspects [18].

Results and Discussion. – Our attempts towards the structure-odor correlation of the isomers of *Galaxolide*® started with the separation of the two diastereoisomers



(*S*)-4 (*S*)-*Fixolide*® **(6*S*,7*S*)-5** **(*R*)-6**

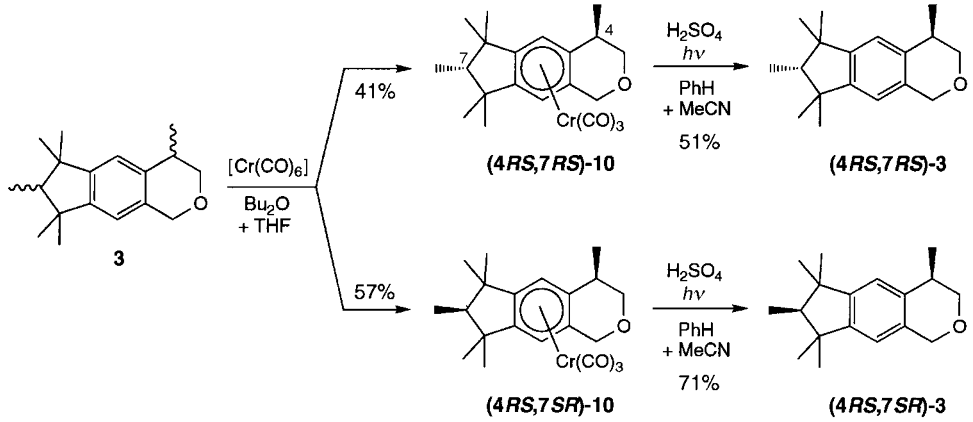
(*R*)-7 (*R*)-muscone **(*R*)-8** **(12*R*,13*S*)-9**

Fig. 2. *Enantioselectivity in the odor sensation of musks*

(4*RS*,7*SR*)- and (4*RS*,7*RS*)-**3** *via* their corresponding tricarbonyl(η^6-cyclopenta[*g*]-2-benzopyran)chromium complexes **10** [9][19] (*Scheme 1*). Arene(carbonyl)chromium complexes are easily prepared and handled, air-stable, crystalline solids, and the carbonylchromium moiety can be readily released by mild oxidation. Most important is, however, that the bulky tricarbonylchromium moiety introduces a stereogenic element that establishes a relationship between the two distant stereogenic centers in **3**, and thus accentuates the subtle differences between the two diastereoisomers (4*RS*,7*SR*)- and (4*RS*,7*RS*)-**3**. Thus, saponification of the diethyl phthalate, used as solvent of the commercial-grade *Galaxolide® 50 PHT*, with methanolic KOH solution, followed by fractional distillation and subsequent crystallization from hexane, yielded pure **3** as colorless crystals, which was transformed into the complexes (4*RS*,7*RS*)- and (4*RS*,7*SR*)-**10** by reaction with [$Cr(CO)_6$] in refluxing Bu_2O in almost quantitative yield. Crystallization from CCl_4 provided the pure complexes '*syn*'/'*anti*'-(4*RS*,7*RS*)-**10** in 41% yield, while complexes '*syn*'/'*anti*'-(4*RS*,7*SR*)-**10** were isolated in 57% yield by flash chromatography of the mother liquor ('*syn*'/'*anti*' means that the Cr-atom and Me−C(7) are on the same/opposite side of the mean ring plane). Separate UV irradiation of the complexes (4*RS*,7*RS*)- and (4*RS*,7*SR*)-**10** in benzene/MeCN and 60% aqueous H_2SO_4 solution in the presence of air gave (4*RS*,7*RS*)-**3** (51%) and (4*RS*,7*SR*)-**3** (71%), respectively, both in diastereoisomerically pure form. The relative configurations were established by X-ray crystallography[1]) of the *trans*-diastereoisomer (4*RS*,7*RS*)-**3**. A MOLOC view [20] of the unit cell of (4*RS*,7*RS*)-**3** is shown in *Fig. 3*, the anisotropic thermal ellipsoids being displayed as dotted spheres in red.

On smelling the diastereomerically pure samples (4*RS*,7*RS*)- and (4*RS*,7*SR*)-**3** on a chiral permethylated β-cyclodextrin phase, it became apparent that not the relative

Scheme 1. *Separation of Commercial* Galaxolide® *into the Diastereoisomers (4*RS,7RS*)- and (4*RS,7SR*)-***3** via *the Tricarbonyl(η^6-cyclopenta[*g*]-2-benzopyran)chromium Complexes* **10**



---

[1]) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-117905 ('*anti*'-(4*S*,7*R*)-**10**) and No. CCDC-117906 ((4*RS*,7*RS*)-**3**). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (Fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

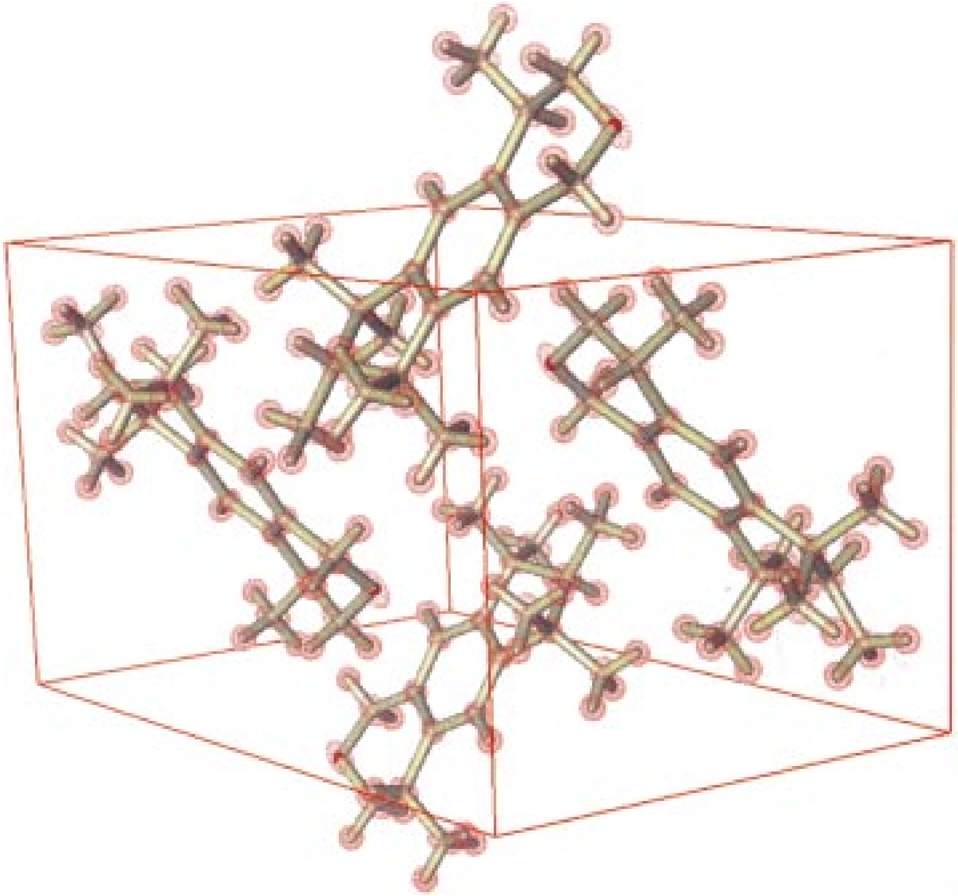


Fig. 3. *Unit-cell view of racemic (4*RS,7RS*)-***3**

configuration of the methyl groups but the configuration of one stereogenic center was important for the odor. One enantiomer of the *cis*-diastereoisomer (4*RS*,7*SR*)-**3** and one of the *trans*-diastereoisomer (4*RS*,7*RS*)-**3** were responsible for the musk odor of the commercial product **3**, that of the (4*RS*,7*SR*)-**3** being slightly more intense. Therefore, all four isomers of *Galaxolide*®, (4*S*,7*R*)-, (4*S*,7*S*)-, (4*R*,7*S*)-, and (4*R*,7*R*)-**3** had to be synthesized.

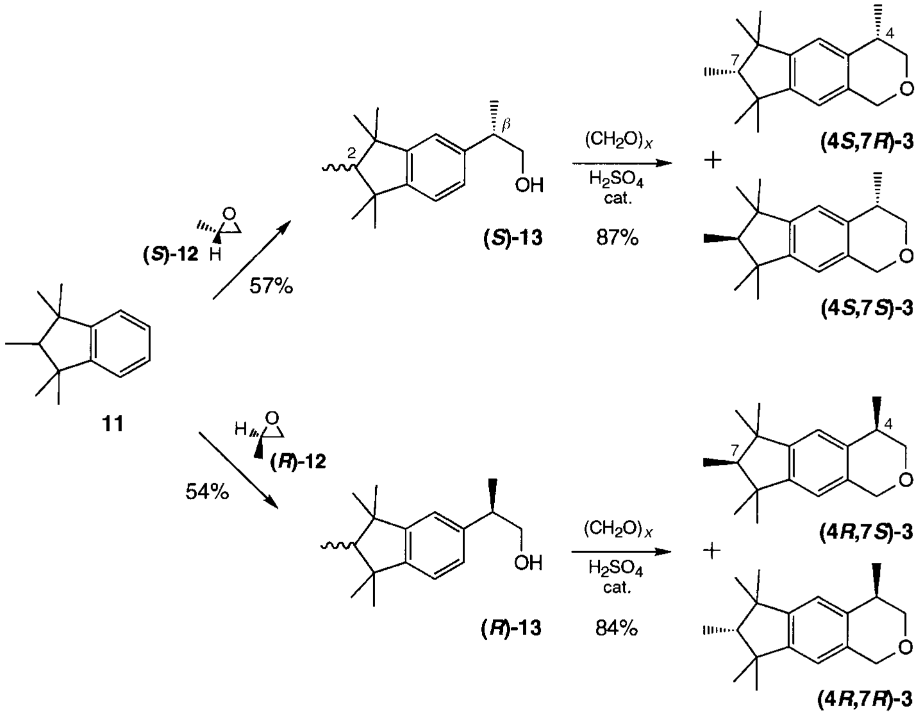
Titanium(IV) chloride (0.8 equiv.) mediated *Friedel-Crafts* alkylation of 1,1,2,3,3-pentamethylindane (**11**, 1.9 equiv.) with (*S*)- and (*R*)-methyloxirane ((*S*)- and (*R*)-**12**, resp.; 1.0 equiv.) afforded in 57 and 54% (based on **12**) (*S*)- and (*R*)-**13**, respectively, each as a 1:1 mixture of the C(2) epimers (*Scheme 2*). As established by the chirospecific GC analysis of the final products (*vide infra*), this alkylation proceeded with complete inversion of configuration, no racemization being observed²). Subsequent acid-catalyzed reaction of (*S*)- and (*R*)-**13** with paraformaldehyde [4] provided

---

²) For the reaction of (*R*)-**12** with benzene, see [21].

the corresponding C(7)-epimeric isochromane derivatives (4*S*,7*RS*)-**3** and (4*R*,7*RS*)-**3** in 87 and 84% yield, respectively. Following the procedure that had successfully been applied in the racemic series, the *cis*- and *trans*-diastereoisomers (4*S*,7*SR*)- and (4*R*,7*RS*)-**3** were separated *via* their tricarbonyl(η^6-cyclopenta[*g*]-2-benzopyran)chromium complexes by flash chromatography. Finally, the *Galaxolide*® isomers (4*S*,7*R*)-, (4*S*,7*S*)-, (4*R*,7*S*)-, and (4*R*,7*R*)-**3** were obtained in 67–92% yield from the complexes by oxidation with *Jones* reagent or by UV irradiation in the presence of air. The relative configurations were assigned by GC coinjection with the racemic mixtures (4*RS*,7*RS*)- and (4*RS*,7*SR*)-**3**. Recrystallizations furnished the enantiomerically pure isomers[3]).

Scheme 2. *Synthesis of the Two Diastereoisomer Pairs of* **3**



(–)-(4*S*,7*R*)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[*g*]-2-benzopyran ((4*S*,7*R*)-**3**) was found to be the most powerful of the *Galaxolide*® isomers. Its *cis*-configuration was independently established by an X-ray crystal-structure determination[1]) of the corresponding tricarbonylchromium complex '*anti*'-(4*S*,7*R*)-**10**. A MOLOC plot [20] with dotted thermal elipsoids is presented in *Fig. 4*. The '*syn*'- and the '*anti*'-isomer of (4*S*,7*R*)-**10** could be separated by flash chromatography (silica gel), and were isolated in the ratio of *ca.* 1:12 (*Scheme 3*).

Olfactory Evaluation. – With an odor threshold of 0.63 ng/l, (–)-(4*S*,7*R*)-1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[*g*]-2-benzopyran ((4*S*,7*R*)-**3**) is not only

---

[3]) For melting points and optical rotations, see *Exper. Part.*

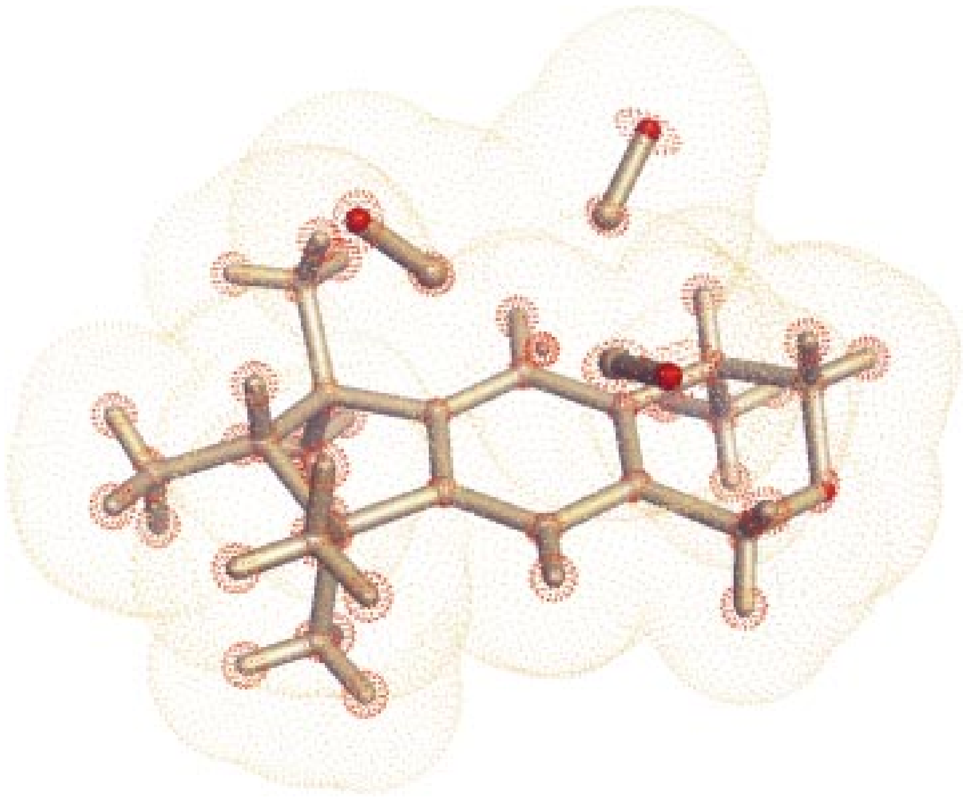
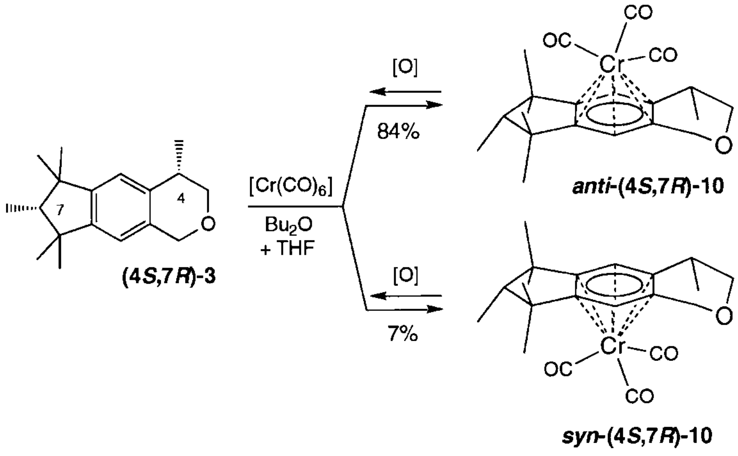


Fig. 4. *X-Ray crystal structure of the tricarbonyl(η^6-cyclopenta[*g*]-2-benzopyran)chromium complex* 'anti'-*(4*S*,7*R*)*-**10**

Scheme 3. *Tricarbonyl(η^6-cyclopenta[*g*]-2-benzopyran)chromium complexes of (4*S*,7*R*)*-**3**



the most intense of the *Galaxolide*® isomers, it is also the most typical, possessing a very pleasant clean musk note. Only slightly less powerful is the *trans*-diastereoisomer (4*S*,7*S*)-**3** with an odor threshold of *ca*. 1.0 ng/l, and a similar musk odor that, however, differs from that of (4*S*,7*R*)-**3** by its dry character.

The (+)-(4*R*)-isomers are much weaker and do not contribute to the odor profile of the commercial product. Isomer (4*R*,7*S*)-**3**, with an odor threshold of 130 ng/l, is still a bit musky, but uncharacteristic overall, while the odor of (4*R*,7*R*)-**3** is very weak, with an odor threshold as high as 440 ng/l. The odor characteristics of (4*R*,7*R*)-**3** are mainly fruity, and some perfumers even consider (4*R*,7*R*)-**3** odorless.

These striking differences in the odor sensation of the (−)-(4*S*)- and the (+)-(4*R*)-isomers were in agreement with the superposition analysis of the *Galaxolide*® stereoisomers on 5α-androst-16-en-3-one [22], the two products being related by a specific anosmia association [23]4).

Experimental Part

General. Reagents and solvents: *Fluka* (*puriss.* or *purum*), used without further purification, except *Pluriol-E-1500* (*techn.*) purchased from *BASF*. Optical rotations: *Perkin-Elmer-241* spectrometer. X-Ray: *Siemens-R3m/V* four-circle diffractometer; SHELXTL PLUS (VMS) system. IR: *Perkin-Elmer-681* and *Nicolet-510-FT-IR* spectrometer, $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR: *Bruker-AM-400* or *Bruker-AC-F-200* spectrometer, resp., δ in ppm rel. to SiMe$_4$, *J* in Hz. MS: *Finnigan-MAT-212* instrument; *m*/*z* rel. int. in %.

*Diastereoisomer Separation and X-Ray Analysis of Racemic (4*RS*,7*RS*)*-**3**. Commercial-grade *Galaxolide*® *50 PHT* (300 g of soln. in diethyl phthalate) was added to a soln. of KOH (100 g, 1.78 mol) in 90% aq. MeOH (1 l), and the resulting mixture was refluxed for 90 min. The solvent was evaporated, the residue taken up in hexane, the hexane phase washed thoroughly with H_2O, dried (Na_2SO_4), and evaporated, and the crude material submitted to fractional distillation (70-cm vacuum-jacketed silvered column): 85% quality of **3** (113 g). This material was crystallized first from hexane (600 ml, −80°) and then from MeOH (200 ml): **3** (41 g). Colorless crystals. M.p. 57–58°.

At r.t. under Ar, [Cr(CO)$_6$] (10.0 g, 45.4 mmol) and THF (5 ml) were added to a soln. of **3** (8.0 g, 31.0 mmol) in Bu$_2$O (150 ml). The mixture was heated to 130° for 48 h and evaporated. The resulting residue was washed with hexane (100 ml), dissolved in CH_2Cl_2 (50 ml), and filtered through a pad of silica gel (20 g) to remove [Cr(CO)$_6$]. The filtrate was evaporated and the residue crystallized from CCl_4 (15 ml) to provide (4*RS*,7*RS*)-**10** (5.0 g, 41%; m.p. 152–154°). The mother liquor was chromatographed (silica gel, hexane/*t*-BuOMe 8:2; R_f 0.44) to furnish (4*RS*,7*SR*)-**10** (7.0 g, 57%; m.p. 120–123°).

Under ambient conditions 60% aq. H_2SO_4 soln. (8.0 ml, 74 mmol) was added to a stirred soln. of (4*RS*,7*RS*)-**10** (150 mg, 380 mmol) in PhH (10 ml) and MeCN (2 ml). Until the yellow color disappeared (*ca*. 7 h), the soln, was irradiated every 60 min with a UV medium-pressure lamp for 15 s. Then hexane (100 ml) and H_2O (50 ml) were added. The org. layer was washed with H_2O (3×50 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the resulting residue purified by FC (SiO_2 (5 g), hexane/*t*-BuOMe 8:2; R_f 0.67): (4*RS*,7*RS*)-**3** (50 mg, 51%; m.p. 67–68° (MeOH)). For spectroscopic data, see the enantiomerically pure compounds (4*S*,7*S*)- and (4*R*,7*R*)-**3** below.

Crystallographic data of (4*RS*,7*RS*)-**3**: $C_{18}H_{26}O$ (258.40), $0.3 \times 0.4 \times 0.4$ mm (163 K), monoclinic, $P2_1/c$, $a = 10.781(2)$ Å, $b = 10.074(2)$ Å, $c = 15.028(3)$ Å, $\beta = 104.66(3)°$, $Z = 4$, $D_x = 1.087$ g/cm^3; $\mu(\mathrm{Mo}K_\alpha)$ 0.065 mm^{-1}, $F(000)$ 568, 2θ range 0.0–56.0°; total reflections collected 4239; symmetry-independent reflections 3723; $R_{int} = 0$, refinement full-matrix least-squares on F^2, parameters 172, final *R* indices ($I > 2 \cdot \sigma(I)$) $R = 0.0618$, $wR = 0.0578$. For a MOLOC view of the unit cell, see *Fig. 3*1)).

Analogous treatment of a soln. of (4*RS*,7*SR*)-**10** (300 mg, 761 mmol) in PhH (20 ml) and MeCN (5 ml) with 60% aq. H_2SO_4 soln. (15 ml) and THF (2 ml) at r.t. with UV irradiation (15 s/h) furnished, after 12 h, usual

---

4) For a recent review on fragrance chemistry and a survey of existing olfactophore models of musk odorants, see [24].

workup, and bulb-to-bulb distillation (4*RS*,7*SR*)-**3** (140 mg, 71%; m.p. 67°). For spectroscopic data, see the enantiomerically pure compounds (4*R*,7*R*)- and (4*R*,7*S*)-**3** below.

(−)-(βS,2R)/(βS,2S)-β,1,1,2,3,3-Hexamethylindan-5-ethanol ((*S*)-**13**). At −40° under N_2, $TiCl_4$ (50 ml, 456 mmol) was added to a stirred soln. of 1,1,2,3,3-pentamethylindane (**11**; 100 g, 531 mmol) in CH_2Cl_2 (750 ml). Within 2 h, a mixture of (−)-(*S*)-methyloxirane ((*S*)-**12**; 33.0 g, 568 mmol) and 1,1,2,3,3-pentamethylindane (100 g, 531 mmol) in CH_2Cl_2 (100 ml) was added dropwise with stirring below −40°. Stirring was continued at −20° for 30 min. Then the mixture was cooled to −40° and poured into ice/2N HCl/*t*-BuOMe 1:1:1 (2 l). The aq. phase was extracted with hexane (2 l), the combined org. phase washed with H_2O (2 ×) and sat. aq. $NaHCO_3$ soln., dried (Na_2SO_4), and evaporated, and the crude product (259 g) purified by FC (silica gel, hexane/*t*-BuOMe 7:3; R_f 0.38): (*S*)-**13** (123 g, 88%). Colorless solid. Two recrystallizations from hexane (400 ml, 150 ml) gave (*S*)-**13** (61 g, 57%). Colorless crystals. M.p. 78.5–79.5°. $[\alpha]_D^{21} = -5.83$, $[\alpha]_{546}^{21} = -7.20$ ($c = 5.0$, EtOH). IR (KBr): 1036*s* (C−O), 3237*m* (O−H), 1460*m* (CH_2), 824*m* (arom. C−C), 1363*m* (Me). ^1H-NMR ($CDCl_3$): 0.99 (*d*, $J = 7.0$, Me−C(2)); 1.06 (*s*, Me_{ax}−C(1), Me_{ax}−C(3)); 1.26 (*s*, Me_{eq}−C(1), Me_{eq}−C(3)); 1.29 (*d*, $J = 6.0$, Me−C(β)); 1.37 (br. *t*, $J = 6.0$, OH); 1.86 (*q*, $J = 7.0$, H−C(2)); 2.95 (*sext.*, $J = 6.0$, H−C(β)); 3.69 (*t*, $J = 6.0$, 2 H−C(α)); 7.00–7.25 (*m*, H−C(4), H−C(6), H−C(7)). ^{13}C-NMR ($CDCl_3$): 8.39 (*q*, *Me*−C(2)); 17.6, 17.7 (2*q*, *Me*−C(β)); 25.7, 25.8, 28.9, 29.0 (4*q*, Me−C(1), Me−C(3)); 42.3 (*d*, C(β)); 44.2, 44.5 (*s*, C(1), C(3)); 54.4 (*d*, C(2)); 68.7 (*t*, C(α)); 121.5 (*d*, C(4)); 122.4 (*d*, C(6)); 125.6 (*d*, C(7)); 142.0 (*s*, C(7a)); 149.5 (*s*, C(3a)); 151.5 (*s*, C(5)). MS (70 eV): 246 (22, M^+), 231 (100, $[M - Me]^+$), 215 (85, $[M - CH_2OH]^+$), 185 (39), 171 (29), 157 (28), 143 (31), 129 (32), 115 (28, $C_nH_{2n-11}^+$ series), 57 (58, $C_3H_5O^+$).

(−)-(4S,7R)/(4S,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran ((4*S*,7*RS*)-**3**). At r.t., 80% aq. H_2SO_4 soln. (1.0 ml, 8.2 mmol) was added to a stirred slurry of (*S*)-**13** (56.0 g, 227 mmol), paraformaldehyde (20.0 g, 666 mmol), glycerol (30.0 g, 326 mmol), and *Pluriol-E-1500* (*BASF*, 1 g) in PhMe (50 ml), and the resulting mixture was heated under N_2 to 90° for 30 min, when it became homogeneous. At 140°, the H_2O/PhMe mixture was distilled off through a short fractionating column, and then the temp. was raised to *ca.* 165° until an exothermic reaction was initiated and the temperature rose to *ca.* 175°. After *ca.* 10 min, this exothermic reaction ceased, and the mixture was allowed to cool to r.t. and poured into hexane (1 l). The org. soln. was washed with H_2O (30 ml), and yellow impurities and off-odorants were removed by careful extraction (5 min) with 15% KOH in 60% aq. MeOH (50 ml). The hexane layer was washed again with H_2O (30 ml), dried ($NaSO_4$), and evaporated. The crude product (64.8 g) was purified by FC (silica gel, hexane/*t*-BuOMe 92:8; R_f 0.63): (4*S*,7*RS*)-**3** (51.3 g, 87%) as colorless solid. Recrystallization from MeOH (250 ml) furnished (4*S*,7*RS*)-**3** (31.0 g, 53%). Colorless crystals. M.p. 46–58°. $[\alpha]_D^{21} = -18.0$, $[\alpha]_{546}^{21} = -20.8$ ($c = 5.2$, EtOH).

*Separation of the Diastereoisomeric [Cr(CO)$_3$[η^6-(4S,7RS)-3]] Complexes (4S,7S)-***10** *and (4S,7R)-***10**. Under Ar, $[Cr(CO)_6]$ (20.0 g, 90.9 mmol) was added to a stirred soln. of (4*S*,7*RS*)-**3** (15.0 g, 58.0 mmol) in Bu_2O (180 ml). THF (10 ml) was added, and the mixture was refluxed for 40 h, prior to complete evaporation of the solvent at 60°/1.3 mbar. The resulting residue was purified by FC (silica gel (1 kg), hexane/*t*-BuOMe 3:1) to afford (4*S*,7*R*)-**10** (10.4 g, 46%; R_f 0.34) and (4*S*,7*S*)-**10** (7.30 g, 32%; R_f 0.24). (4*S*,7*R*)-**10**: m.p. 160–161° (i-Pr_2O). (4*S*,7*S*)-**10**: m.p. 145–146° (i-Pr_2O).

(−)-(4S,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran ((4*S*,7*R*)-**3**). *Jones* reagent [25] (7 ml, 18 mmol) was added dropwise with stirring at 0° to a soln. of (4*S*,7*R*)-**10** (6.0 g, 15.2 mmol) in Me_2CO (150 ml), upon which vigorous gas evolution occurred. The mixture was poured into H_2O (750 ml), the product extracted twice with hexane, the combined org. extract washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), filtered through a pad of silica gel, and the filtrate evaporated. Crystallization of the crude product (4.0 g) from MeOH (10 ml) furnished (4*S*,7*R*)-**3** (3.0 g, 76%). Colorless crystals. M.p. 78–78.5°. $[\alpha]_D^{24} = -23.5$, $[\alpha]_{546}^{24} = -27.3$ ($c = 5.0$, EtOH). ^1H-NMR ($CDCl_3$): 0.99 (*d*, $J = 7.0$, Me−C(7)); 1.06 (*s*, Me_b−C(8)); 1.07 (*s*, Me_b−C(6)); 1.24 (*s*, Me_a−C(8)); 1.27 (*s*, Me_a−C(6)); 1.32 (*d*, $J = 7.0$, Me_{ax}−C(4)); 1.84 (*q*, $J = 7.0$, H−C(7)); 2.91 (*m*, H−C(4)); 3.66 (*dd*, $J = 10.0$, 6.5, H_{eq}−C(3)); 3.94 (*dd*, $J = 10.0$, 5.0, H_{ax}−C(3)); 4.76 (*d*, $J = 12.0$, H_{ax}−C(1)); 4.82 (*d*, $J = 12.0$, H_{eq}−C(1)); 6.76 (*s*, H−C(9)); 7.00 (*s*, H−C(5)). ^{13}C-NMR ($CDCl_3$): 8.46 (*q*, *Me*−C(7)); 19.4 (*q*, *Me*−C(4)); 25.8, 26.0 (2*q*, Me_b−C(6), Me_b−C(8)); 29.0, 29.1 (2*q*, Me_a−C(6), Me_a−C(8)); 32.2 (*d*, C(4)); 44.4 (*s*, C(8)); 44.5 (*s*, C(6)); 54.4 (*d*, C(7)); 68.8 (*t*, C(1)); 71.5 (*t*, C(3)); 118.1 (*d*, C(9)); 121.6 (*d*, C(5)); 132.6 (*s*, C(9a)); 137.0 (*s*, C(4a)); 149.3 (*s*, C(8a)); 150.0 (*s*, C(5a)). Odor: Typical musk, very pleasant, most powerful. Threshold: 0.63 ng/l.

X-Ray Analysis of 'anti'-*Tricarbonyl[(4a,5,5a,8a,9,9a-η)-(4S,7R)-1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran]chromium* ('*anti*'-(4*S*,7*R*)-**10**). To a soln. of (4*S*,7*R*)-**3** (4.0 g, 15.5 mmol) in Bu_2O (100 ml), $[Cr(CO)_6]$ (5.0 g, 22.7 mmol) was added under Ar. After addition of THF (3 ml), the mixture was refluxed for 60 h and then completely evaporated. The solid residue (6.3 g) was crystallized from i-Pr_2O (100 ml): '*anti*'-(4*S*,7*R*)-**10** (3.9 g, 64%). M.p. 161–162°.

The mother liquor was evaporated and the residue separated by FC (silica gel, hexane/*t*-BuOMe 8 : 2): '*anti*'-(4*S*,7*R*)-**10** (1.2 g, 20%) and '*syn*'-(4*S*,7*R*)-**10** (410 mg, 7%). M.p. 173 – 174° (i-Pr_2O)].

Crystallographic data of '*anti*'-(4*S*,7*R*)-**10**: $C_{18}H_{26}O \cdot Cr(CO)_3$ (394.42), 0.15 × 0.25 × 0.55 mm (173 K), orthorhombic, $P2_12_12_1$, $a = 8.629(2)$ Å, $b = 11.141(3)$ Å, $c = 20.200(6)$ Å, $Z = 4$, $D_X = 1.3349$ g/cm^3; $\mu(\mathrm{Mo}K_\alpha) = 0.611$ mm^{-1}, $F(000)$ 832, θ range 2.02 – 28.00°; total reflections collected 2668, symmetry-independent reflections 2668; $R_{int} = 0$, refinement full-matrix least-squares on F^2, parameters 235, final R indices $(I > 2 \cdot \sigma(I))$ $R = 0.0325$, $wR = 0.1001$. For a MOLOC view of the crystal structure, see *Fig. 4*[1]).

*(−)-(4*S*,7*S*)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[*g*]-2-benzopyran* ((4*S*,7*S*)-**3**). Under ambient conditions, 60% aq. H_2SO_4 soln. (200 ml, 1.84 mol) was added to a stirred soln. of (4*S*,7*S*)-**10** (6.80 g, 17.2 mmol) in THF/MeCN/PhMe/PhH 1 : 1 : 1 : 1 (200 ml). Stirring was continued at 50° for 30 h, with UV radiation every 30 min using a medium-pressure lamp for 1 min. The mixture was then poured into H_2O, the aq. phase extracted with hexane, the combined org. soln. dried (Na_2SO_4) and evaporated, and the crude oil (4.10 g, 92%) crystallized twice from hexane (12 ml and 4 ml) at −20°: (4*S*,7*S*)-**3** (0.95 g, 21%). Colorless crystals. M.p. 57 – 58°. $[\alpha]_D^{23} = -25.1$, $[\alpha]_{546}^{23} = -29.2$ ($c = 5.0$, EtOH). ^{1}H-NMR ($CDCl_3$): 0.99 (*d*, $J = 7.0$, Me−C(7)); 1.05 (*s*, Me_b−C(8)); 1.07 (*s*, Me_b−C(6)); 1.25 (*s*, Me_a−C(8)); 1.28 (*s*, Me_a−C(6)); 1.31 (*d*, $J = 7.0$, Me_{ax}−C(4)); 1.86 (*q*, $J = 7.0$, H−C(7)); 2.93 (*qdd*, $J = 7.0$, 5.0, 5.0, H_{eq}−C(4)); 3.64 (*dd*, $J = 10.0$, 6.5, H_{eq}−C(3)); 3.96 (*dd*, $J = 10.0$, 5.0, H_{ax}−C(3)); 4.79 (*s*, 2 H−C(1)); 6.76 (*s*, H−C(9)); 7.01 (*s*, H−C(5)). ^{13}C-NMR ($CDCl_3$): 8.46 (*q*, *Me*−C(7)); 19.3 (*q*, *Me*−C(4)); 25.9, 26.0 (2*q*, Me_b−(6), Me_b−C(8)); 28.9, 29.1 (2*q*, Me_a−C(6), Me_a−C(8)); 32.1 (*d*, C(4)); 44.4 (*s*, C(8)); 44.5 (*s*, C(6)); 54.3 (*d*, C(7)); 68.8 (*t*, C(1)); 71.5 (*t*, C(3)); 118.0 (*d*, C(9)); 121.6 (*d*, C(5)); 132.6 (*s*, C(9a)); 137.0 (*s*, C(4a)); 149.3 (*s*, C(8a)); 149.9 (*s*, C(5a)). Odor: Musky, but dry aspects, on blotter only slightly less powerful than (4*S*,7*R*)-**3**. Threshold: 1.0 ng/l.

(+)-(βR,2R)/(βR,2S)-β,1,1,2,3,3-Hexamethylindan-5-ethanol ((*R*)-**13**). As described for (*S*)-**13**, with 1,1,2,3,3-pentamethylindane (**11**; 80.0 g, 425 mmol), (+)-(*R*)-methyloxirane ((*R*)-**12**; 12.5 g, 215 mmol), CH_2Cl_2 (550 ml), and $TiCl_4$ (15 ml, 137 mmol). The crude product (97.0 g) was purified by FC (silica gel, hexane/*t*-BuOMe 7 : 3; R_f 0.38) and recrystallized from hexane: (*R*)-**13** (28.8 g, 54%). Colorless crystals. M.p. 78.5 – 79.5°. $[\alpha]_D^{21} = +5.99$, $[\alpha]_{546}^{21} = +7.43$ ($c = 5.1$, EtOH). Spectral data: identical to those of (*S*)-**13**.

(+)-(4R,7R)/(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran ((4*R*,7*RS*)-**3**). As described for (4*S*,7*RS*)-**3**, with (*R*)-**13** (26.0 g, 106 mmol), paraformaldehyde (10.0 g, 333 mmol), glycerol (15.0 g, 163 mmol), *Pluriol-E-1500* (*BASF*, 0.5 g), PhMe (25 ml), and 80% aq. H_2SO_4 soln. (0.5 ml, 4.1 mmol). The crude product (28.0 g) was purified by FC (silica gel, hexane/*t*-BuOMe 92 : 8; $R_f = 0.62$): (4*R*,7*RS*)-**3** (23.0 g, 84%) as colorless solid. Recrystallization from MeOH furnished (4*R*,7*RS*)-**3** (4.50 g, 16%). Colorless crystals. M.p. 44 – 46°. $[\alpha]_D^{23} = +21.1$, $[\alpha]_{546}^{23} = +24.4$ ($c = 5.0$, EtOH). Spectral data: identical to those of (4*S*,7*RS*)-**3**.

*Separation of the Diastereoisomeric [Cr(CO)$_3$\{η^6-(4R,7RS)-**3**\}] Complexes (4R,7S)-**10** and (4R,7R)-**10**.* [$Cr(CO)_6$] (25.0 g, 114 mmol) was added to a stirred soln. of (4*R*,7*RS*)-**3** (20.2 g, 78.2 mmol) in Bu_2O (350 ml) and THF (12.5 ml), and the resulting mixture was refluxed for 48 h. The solvent was evaporated and the resulting residue purified by FC (silica gel (1.5 kg), hexane/*t*-BuOMe 8 : 2) to afford (4*R*,7*S*)-**10** (16.0 g 52%; R_f 0.31) and (4*R*,7*R*)-**10** (9.0 g, 29%; R_f 0.19). (4*R*,7*S*)-**10**: M.p. 156 – 158° (i-Pr_2O). (4*R*,7*R*)-**10**: M.p. 112 – 114°.

(+)-(4R,7S)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran ((4*R*,7*S*)-**3**). *Jones* reagent [25] (20 ml, 52 mmol) was added dropwise with stirring at −10° to a soln. of (4*R*,7*S*)-**10** (16.0 g, 40.6 mmol) in Me_2CO (300 ml). When the vigorous gas evolution had stopped, H_2O (200 ml) and hexane (100 ml) were added. The mixture was then poured into H_2O (1 l), the product extracted with hexane, the combined org. extract washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and filtered through a pad of silica gel, and the filtrate evaporated. The crude material (7.50 g, 72%) was crystallized twice from MeOH: (4*R*,7*S*)-**3** (3.5 g, 33%). Colorless crystals. M.p. 77 – 78°. $[\alpha]_D^{24} = +24.1$, $[\alpha]_{546}^{24} = +28.0$ ($c = 5.2$, EtOH). Spectral data: identical to those of (4*S*,7*R*)-**3**. Odor: Weak, musky, uncharacteristic. Threshold: 130 ng/l.

(+)-(4R,7R)-1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyran ((4*R*,7*R*)-**3**). As described for (4*R*,7*S*)-**3**, with (4*R*,7*R*)-**10** (9.0 g, 23 mmol), *Jones* reagent [25] (12 ml, 31 mmol), and Me_2CO (250 ml). The crude product (4.0 g, 67%) was chromatographed (silica gel, hexane/*t*-BuOMe 8 : 2; R_f 0.48). Several crystallizations from hexane finally provided (4*R*,7*R*)-**3** (300 mg, 5%). Colorless crystals. M.p. 52 – 53°. $[\alpha]_D^{23} = +25.2$, $[\alpha]_{546}^{23} = +29.3$ ($c = 5.0$, EtOH). Spectral data: identical to those of (4*S*,7*S*)-**3**. Odor: Very weak, mainly fruity. Threshold: 440 ng/l.

We are indebted to *J. Daly* and *P. Schönholzer* of *F. Hoffmann-La Roche AG*, Basel, for the X-ray crystal-structure determinations. We would also like to thank *E. Billeter* and *J. Märki* for NMR experiments, as well as *F. Etzweiler* for chirospecific GC analyses and the determination of odor thresholds.

REFERENCES

[1] P. J. Teisseire, 'Chemistry of Fragrant Substances', VCH Publishers, Inc., New York, 1994, pp. 333–358.

[2] T. F. Wood, 'Synthetic Benzenoid Musks', in 'Fragrance Chemistry – The Science of the Sense of Smell', Ed. E. T. Theimer, Academic Press, Orlando, 1982, pp. 509–534.

[3] G. Fráter, D. Lamparsky, 'Synthetic Products', in 'Perfumes: Art, Science, and Technology', Ed. P. M. Müller, D. Lamparsky, Elsevier Science Publishers, Barking, 1991, pp. 533–628.

[4] L. G. Heeringa, M. G. J. Beets, to *IFF*, U.S. Pat. 3360530, 1967.

[5] R. A. Ford, *Soap, Perfumery, Cosmetics* **1999** (Feb.), 33.

[6] H.-E. Muermann, *Parf. Kosmet.* **1999**, *80*, 12.

[7] G. Suzukamo, to *Sumitomo*, US 4767882, 1981.

[8] C. Fehr, J. Galindo, R. Haubrichs, R. Perret, to *Firmenich*, EP 405427, 1989.

[9] C. Fehr, J. Galindo, R. Haubrichs, R. Perret, *Helv. Chim. Acta* **1989**, *72*, 1537.

[10] C. Fehr, F. Delay, P.-A. Blanc, N. Chaptal-Gradoz, to *Firmenich*, EP 664286, 1995.

[11] P. Kraft, W. Tochtermann, *Liebigs Ann. Chem*. **1994**, 1161.

[12] P. Kraft, W. Tochtermann, *Liebigs Ann. Chem.* **1995**, 1409.

[13] K. Schultz, P. Kraft, *J. Essent. Oil Res.* **1997**, *9*, 509.

[14] S. Ställberg-Stenhagen, *Ark. Kemi* **1951**, *3*, 517.

[15] W. Pickenhagen, 'Enantioselectivity in Odor Perception', in 'Flavor Chemistry: Trends and Developments', Ed. R. Teranishi, R. G. Buttery, and F. Shahidi, ACS Symposium Series No. 388, American Chemical Society, Washington DC, 1989, p. 151.

[16] P. Kraft, R. Cadalbert, *Synthesis* **1998**, 1662.

[17] B. Bollbuck, W. Tochtermann, *Tetrahedron* **1999**, *55*, 7191.

[18] P. Kraft, W. Tochtermann, *Tetrahedron* **1995**, *51*, 10875.

[19] B. Ohlson, C. Ullenius, S. Jaguer, C. Grivet, E. Wenger, E. P. Kündig, *J. Organomet. Chem.* **1989**, *365*, 243, and ref. cit. therein.

[20] 'MOLOC. Software Package for Interactive Manipulation, Visualization, and Evaluation of Molecular Structures', F. Hoffmann-La Roche Ltd., Basel, March 3, 1999, installed on a 'SGI Octane' workstation.

[21] T. Nakajima, S. Sugo, T. Sugita, K. Ichiawa, *Tetrahedron* **1969**, *25*, 1807.

[22] G. Fráter, U. Müller, J. A. Bajgrowicz, M. Petrzilka, 'Musky and Odorless Diastereomers of Galaxolide', in 'Proceedings of the 13th International Congress of Flavours, Fragrances and Essential Oils', Istanbul, October 15–19, 1995, AREP Publications, Istanbul, 1995, Vol. 3, p. 151.

[23] A. Baydar, M. Petrzilka, M.-P. Schott, *Chem. Senses* **1993**, *18*, 661.

[24] G. Fráter, J. A. Bajgrowicz, P. Kraft, *Tetrahedron* **1998**, *54*, 7633.

[25] J. Meinwald, J. Crandall, W. E. Hymans, *Org. Synth.* **1965**, *45*, 77.

Received June 21, 1999