Synthesis and Optical Resolution of the Floral Odorant (±)-2,3-Dihydro-2,5-dimethyl-1*H*-indene-2-methanol, and Preparation of Analogues

by **Christian Vial**[a]), **Gérald Bernardinelli**[b]), **Philippe Schneider**[a]), **Michael Aizenberg**[a]), and **Béat Winter***[a])

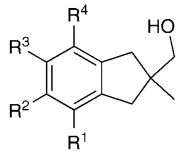
[a]) *Firmenich SA,* Corporate R&D Division, P. O. Box 239, CH-1211 Geneva 8
(phone: +41-22-7803612; fax: +41-22-780 3334; e-mail: beat.winter@firmenich.com)
[b]) Université de Genève, Laboratoire de cristallographie, 24 quai Ernest-Ansermet, CH-1211 Geneva 4
(phone: +41223796202; fax: +41223796108; e-mail: gerald.bernardinelli@cryst.unige.ch)

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

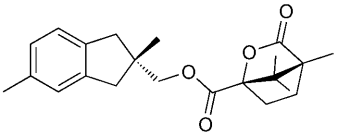
The title compound (±)-**1**, a recently discovered, valuable, floral-type odorant, has been synthesized by a straightforward procedure (*Scheme 1*). To determine the properties of the enantiomers of **1**, their separation by preparative HPLC and the determination of their absolute configuration by X-ray crystallography were carried out (*Figure*). Furthermore, the analogues **2**–**6** were synthesized, either from differently methylated 2-methylindan-1-ones (*Schemes 2* and *3*) or, in the case of the 2,4,6-trimethylated homologue **6**, by a completely different synthetic approach (*Scheme 4*). An evaluation of (+)-(*S*)-**1**, (−)-(*R*)-**1**, and (±)-**1** showed only minor differences in terms of odor (*Table*).

1. Introduction. – Racemic 2,3-dihydro-2,5-dimethyl-1*H*-indene-2-methanol ((±)-**1**[1]) [1], discovered during work on analogues of known floral-type odorants, was found to possess very valuable odoriferous properties [2], but required a cost-effective synthesis in view of commercialization. Furthermore, it became of interest to know the properties of the two enantiomers of **1**, as well as of the 2,4-isomer (±)-**2** and the homologues **3**–**6** with two Me groups on the aromatic ring.

In this work, we report a straightforward synthesis of alcohol (±)-**1**, which was applied to the preparation of the isomer (±)-**2** and the homologues **3**–**5**, **6** being prepared by an alternative route. Moreover, we report the preparative-HPLC separation of the antipodes of **1**, as well as the determination of the absolute configurations of (+)-**1** by X-ray crystallographic analysis of the camphanic acid derivative (+)-**7**.



	R^1	R^2	R^3	R^4
1	H	Me	H	H
2	Me	H	H	H
3	Me	Me	H	H
4	Me	H	Me	H
5	Me	H	H	Me
6	H	Me	Me	H

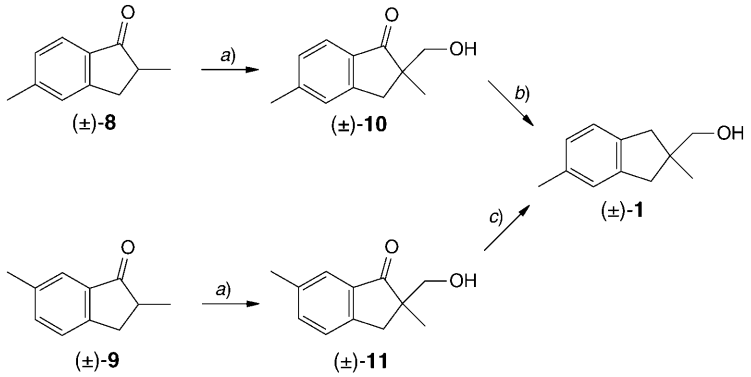


(+)-**7**

2. Results. – 2.1. *Synthesis.* As shown in *Scheme 1*, alcohol (±)-**1** was easily synthesized from the known indanones (±)-**8** [3] or (±)-**9** [4] by a sequence of aldol reactions with formaldehyde, followed by hydrogenolysis of the resulting adducts **10** and **11**,

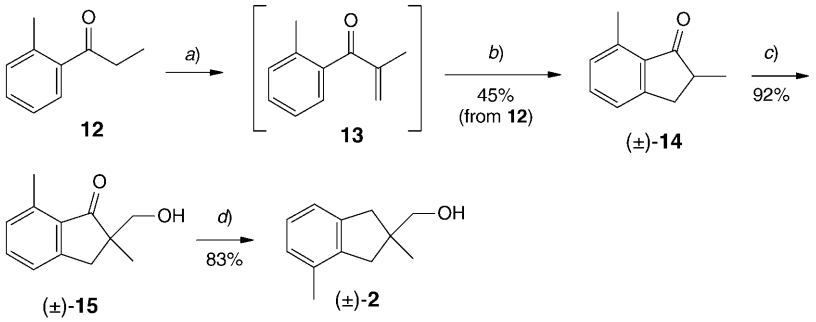
[1]) This compound has also been named '2,5-dimethyl-2-indanemethanol'.

Scheme 1



a) *Formcel* (55% CH_2O in MeOH; *Hoechst*), K_2CO_3, toluene, 50°, 2–3 h. *b*) H_2 (1 bar), 10% Pd/C, AcOH, r.t., 72 h. *c*) H_2 (3 bar), 5% Pd/C, $MeSO_3H$, i-PrOH, 80°, 7.5 h.

Scheme 2



a) Hexamethylenetetramine, Ac_2O, 80°, 6.5 h. *b*) H_2SO_4 (conc.), r.t. → 58°, 1.5 h. c) *Formcel*® (55% CH_2O in MeOH; *Hoechst*), K_2CO_3, toluene, 50°, 4.5 h. *d*) H_2 (1 bar), 10% Pd/C, AcOH, r.t., 125 h.

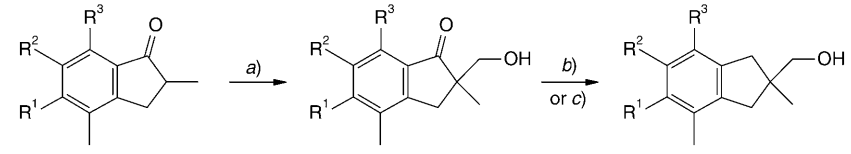
respectively. For the synthesis of the isomeric alcohol (±)-**2**, we chose the route shown in *Scheme 2*.

Starting from the known ketone **12** [5], we selectively prepared, *via* **13**, the indanone (±)-**14** [4d] by a procedure [6] similar to the one used for the synthesis of (±)-**8** [3]. Compound **14** was then converted *via* **15** to **2** by the same methodology as above.

For the syntheses of the homologues **3**–**5**, the known indanones (±)-**16** [7], (±)-**17** [4b], and (±)-**18** [3][4b] [8] were subjected to aldol condensation to afford **19**–**21**, respectively, from which the target homologues were readily obtained (*Scheme 3*). However, in the case of the homologue **6**, we were confronted with the fact that there is no reported selective synthesis of 2,5,6-trimethylindan-1-one [4d]. Consequently, we explored another approach to **6**, starting from the known dichloride **22** [9], as shown in *Scheme 4*.

Alkylation of diethyl malonate with the dichloride **22** afforded the diester **23**, which was reduced to the diol **24** with $LiAlH_4$. Compound **24** was then converted according to

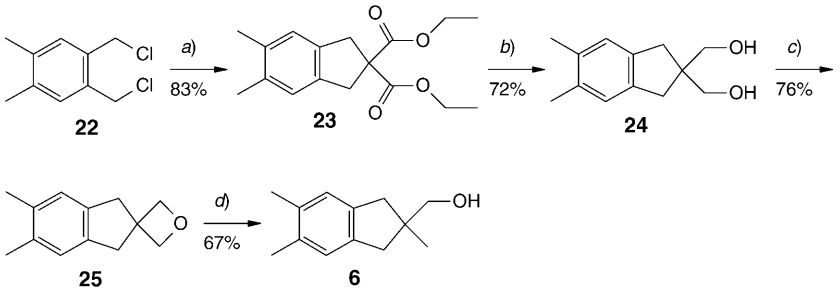
Scheme 3



(±)-**16** R^1 = Me, R^2 = R^3 = H (±)-**19** (72%) (±)-**3** (84%; *b*)
(±)-**17** R^1 = R^3 = H, R^2 = Me (±)-**20** (73%) (±)-**4** (78%; *b*)
(±)-**18** R^1 = R^2 = H, R^3 = Me (±)-**21** (92%) **5** (48%; *c*)

a) *Formcel*® (55% CH_2O in MeOH; *Hoechst*), K_2CO_3, toluene, 50°, 2–3 h. *b*) H_2 (1 bar), 10% Pd/C, AcOH, r.t., 36 h. *c*) H_2 (3 bar), 5% Pd/C, $MeSO_3H$, i-PrOH, 80°, 7.5 h.

Scheme 4



a) $CH_2(COOEt)_2$, EtONa, EtOH, reflux, 2 h. *b*) $LiAlH_4$, Et_2O, r.t., 1 h. *c*) 1. BuLi, TsCl (=4-methylbenzenesulfonyl chloride), THF, −23°, 4 h; 2. BuLi, THF, r.t., 2.5 d. *d*) $LiAlH_4$, THF, reflux, 22 h.

the method of *Picard et al.* [10] to the spiro-oxetane **25**, which was reductively ring-opened with $LiAlH_4$ to afford the desired alcohol **6**.

2.2. *Enantiomer Separation*. Initial attempts to obtain the pure enantiomers of **1** by enzymatic resolution of its acetate or chloroacetate with the aid of a variety of lipases failed [11]. Thus, we turned our attention to chiral HPLC. After screening the chiral columns found in the *Daicel* catalogue, the analytical resolution of (±)-**1** was found to be possible on a 10-μm *Chiralpack AD* column (*Daicel*), eluting with a 95 : 5 mixture of hexane/i-PrOH. The *preparative* separation[2]) was performed with a 25 × 11 cm column packed with *Chiralpack AD* (20 μm), eluting with isohexane/EtOH 95 : 5. As the crude antipodes of **1** were contaminated by solvent, they were purified by flash chromatography and bulb-to-bulb distillation, which afforded analytically pure (+)-**1** and (−)-**1** (>98% ee by chiral HPLC). Both compounds presented good olfactory properties (see *Sect. 2.4*).

2.3. *Absolute Configuration of* (+)-**1**. (−)-Camphanoyl chloride is an excellent chiral derivatizing agent often used for the determination of absolute configurations by X-ray crystallography [12]. Indeed, the condensation between (+)-**1** and (−)-camphanoyl

[2]) These experiments were performed at *Chiral Technologies Europe SAS*, Parc d'Innovation, Bd Gonthier d'Andernach, BP 80140, 67404 Illkirch, France.

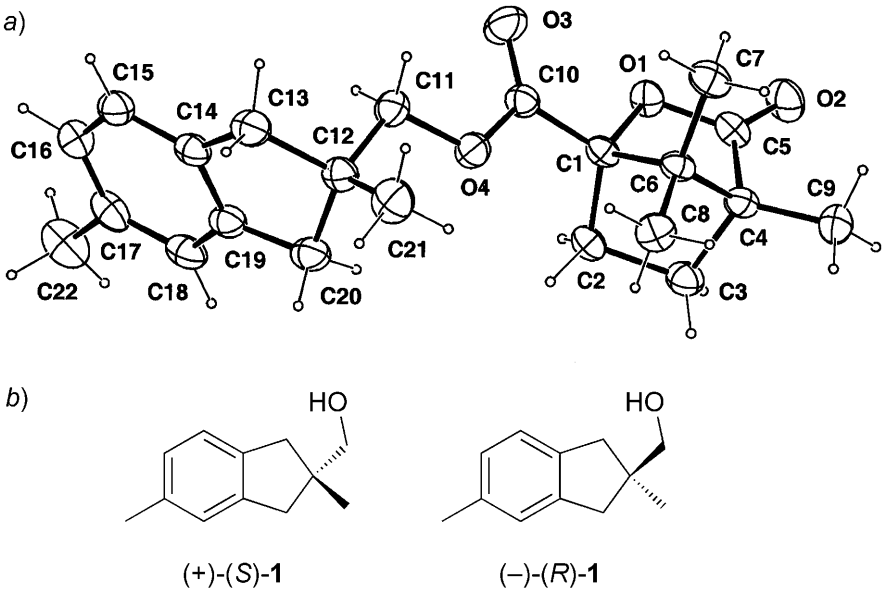


Figure. a) *Perspective view of the crystal structure of* (+)-**7**, *and* b) *absolute configurations of the antipodes of* **1**. Ellipsoids are represented at the 40% probability level.

chloride furnished the crystalline ester (+)-**7** in nearly quantitative yield. Suitable crystals for X-ray diffraction were obtained from hexane/AcOEt 2:1 at 0°. A representation of (+)-**7** is shown in the *Figure*. It turned out that the (+)-antipode of **1** corresponds to the absolute (*S*)-configuration, while (−)-**1** corresponds to the (*R*)-enantiomer.

2.4. *Olfactory Evaluation*. The results of the olfactory evaluation of the alcohols prepared in this work are presented in the *Table*. In conclusion, none of the analogues of 2,3-dihydro-2,5-dimethyl-1*H*-indene-2-methanol ((±)-**1**) exhibited better olfactory properties than the parent compound. Also, neither of the two enantiomers of **1** was very different from the other, nor from the racemate, although (+)-**1** was found to be a slightly more-powerful odorant.

Table. *Olfactory Properties of Compounds* **1**–**6**

Compound	Odor description
(±)-**1**	*Lilial*®, hydroxycitronellal, aldehydic, muguet
(+)-**1**	Muguet, floral, *Lilial*®, hydroxycitronellal, stronger and more powerful, less hydroxycitronellal than enantiomer, base more *Lilial*®
(−)-**1**	Floral, muguet, hydroxycitronellal, slightly plastic, similar to enantiomer, more plastic, base more hydroxycitronellal
(±)-**2**	Floral, muguet, weaker, less character, less clear than (±)-**1**
(±)-**3**	Muguet, *Lilial*®, very weak, without character
(±)-**4**	Floral, *Lilial*®, *Lyral*®, similar to (±)-**1**, but weaker, more classical
5	Wet leather, old shoes
6	Muguet, hydroxycitronellal, *Lilial*®, base weaker and more *Lilial*® than (±)-**1**

We gratefully acknowledge the technical assistance of *Sandrine Gallo-Flückiger*, *Marina Etter*, *Amanda Villoresi*, and *Luis Nicolas*. We are also grateful to *Walter Thommen* and *Robert Brauchli* for the NMR analysis, as well as to Dr. *Pierre-Alain Blanc* for the organoleptic evaluations and to Dr. *Roger Snowden* for stimulating discussions.

Experimental Part

1. *General.* All reactions were performed under N_2. GLC: *Hewlett-Packard 5890* instrument equipped with a flame-ionization detector coupled to a *Hewlett-Packard 3395* or *3396A* integrator; with *Chrompack CP-Wax-52 CB* (10 m, 0.25 mm i.d.) and *CP-Sil-5 CB* (10 m, 0.25 mm i.d.) capillary columns. TLC: silica gel *60* F_{254} plates (0.25 mm; *Merck*). Flash column chromatography (FC): silica gel *60* (0.063–0.2 mm, 70–270 mesh, *Merck*). Anal. chiral HPLC: 10-μm *Chiralpack® AD*™ column ('amylose tris(3,5-dimethylphenyl) carbamate'; *Daicel*), with *Varian Star 9012* pump and a *Waters M-490* UV detector (270 nm). Prep. chiral HPLC: *Chiralpack® AD*™ column (25 × 11 cm; 20 μm). Bulb-to-bulb distillation: *Büchi GKR-50* or *GRK-51* oven; b.p. corresponded to the air temp. Optical rotation: *Perkin-Elmer 241* polarimeter; cell thermostated at 20°, path length 0.1 cm. IR Spectra (liquid film): *Perkin-Elmer 297* or *1600 FT-IR* spectrometers; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra ($CDCl_3$): *Bruker AMX-360*, *DPX-400*, or *AV-500* spectrometers; δ in ppm rel. to Me_4Si, *J* in Hz. MS: *HP 5972* or *5973 MSD* (70 Ev); in *m/z* (rel. intensity in %).

2. *General Procedure* (*GP 1*) *for the Aldol Reaction of 2-Methylindan-1-ones with Formaldehyde.* To a stirred mixture of the given ketone (1.0 equiv.) and K_2CO_3 (0.5 equiv.) in toluene at 50° was added dropwise a 55% soln. of formaldehyde in MeOH (*Formcel®* (*Hoechst*); 2.0 equiv.), and the mixture was stirred at 50° during 2–3 h. As the product partially decomposes by a *retro*-aldol reaction upon GC analysis, all reactions were monitored by TLC. After completion of the reaction, the mixture was diluted with Et_2O, washed with H_2O (2×) and brine, dried (Na_2SO_4), and concentrated.

3. *General Procedure* (*GP 2*) *for the Hydrogenation of Hydroxy Ketones.* To a 10% (*w*/*w*) soln. of a given hydroxy ketone (1.0 equiv.) in AcOH was added 10% Pd/C (0.03–0.05 equiv.), and the mixture was agitated under H_2 (1 bar) at r.t. during 18–125 h. The catalyst was filtered off, and the filtrate was concentrated. The crude alcohol contained variable amounts of the corresponding acetate, and the mixture was saponified with 2.5N NaOH in EtOH/H_2O 1:1 at reflux for 1 h.

4. *Synthesis of Compound* **1**. 4.1. *(±)-2-(Hydroxymethyl)-2,5-dimethylindan-1-one* (**10**). Prepared according to *GP 1* from **8** (500 g, 3.13 mol), and purified by distillation *in vacuo*. Yield: 567 g (93%; purity 98%). Colorless, viscous oil that solidified upon standing. M.p. 46–47°. B.p. 120–123°/0.1 mbar. IR (neat): 3425 (br.), 2920, 1690, 1600, 1450, 1325, 1045, 825. ^1H-NMR: 7.60 (*d*, *J* = 8, 1 H); 7.26 (br. *s*, 1 H); 7.16 (br. *d*, *J* = 8, 1 H); 3.80 (*d*, *J* = 11, 1 H); 3.60 (*d*, *J* = 11, 1 H), 3.20 (*d*, *J* = 16, 1 H); 2.82 (*d*, *J* = 16, 1 H); 2.62 (br. *s*, OH); 2.43 (*s*, 3 H); 1.21 (*s*, 3 H). ^{13}C-NMR: 210.8 (*s*); 153.9 (*s*); 146.5 (*s*); 133.5 (*s*); 128.8 (*d*); 127.0 (*d*); 124.1 (*d*); 67.7 (*t*); 51.0 (*s*); 37.8 (*t*); 22.1 (*q*); 20.7 (*q*). MS: 190 (62, M^+), 175 (100), 159 (82), 145 (70), 129 (61), 115 (60), 91 (42), 77 (31), 63 (20), 51 (19), 39 (21), 31 (22).

4.2. *(±)-2-(Hydroxymethyl)-2,6-dimethylindan-1-one* (**11**). Prepared according to *GP 1* from **9** (350 g, 2.18 mol), and purified by distillation *in vacuo.* Yield: 405 g (97%; purity 99%). Colorless, viscous oil that solidified upon standing. M.p. 49–50°. B.p. 119–122°/0.1 mbar. IR ($CHCl_3$): 3430, 2910, 1685, 1600, 1485, 1380, 1035, 810. ^1H-NMR: 7.48 (br. *s*, 1 H); 7.40 (br. *d*, *J* = 8, 1 H); 7.33 (*d*, *J* = 8, 1 H); 3.60 (*d*, *J* = 11, 1 H); 3.22 (*d*, *J* = 16, 1 H); 2.82 (*d*, *J* = 16, 1 H); 2.78 (br., OH); 2.36 (*s*, 3 H); 1.20 (*s*, 3 H). ^{13}C-NMR: 211.4 (*s*); 150.8 (*s*); 137.4 (*s*); 136.5 (*d*); 136.0 (*s*); 126.3 (*d*); 124.1 (*d*); 67.6 (*t*); 51.3 (*s*); 37.6 (*t*); 21.0 (*q*); 20.7 (*q*). MS: 190 (56, M^+), 175 (65), 172 (78), 159 (100), 145 (72), 129 (73), 115 (62), 104 (27), 91 (44), 77 (33), 63 (18), 51 (20), 39 (19), 31 (21).

4.3. *(±)-2,3-Dihydro-2,5-dimethyl-1*H*-indene-2-methanol* (**1**). 4.3.1. *Synthesis from* **10**. Prepared according to *GP 2* from **10** (62.7 g, 0.33 mol), and purified by distillation *in vacuo.* Yield: 32.1 g (55%). Colorless, viscous oil. B.p. 83–91°/0.1 mbar. IR (neat): 3330 (br.), 2910, 1485, 1035, 810. ^1H-NMR: 7.04 (*d*, *J* = 8, 1 H); 6.98 (*s*, 1 H); 6.93 (*d*, *J* = 8, 1 H); 3.49 (*s*, 2 H); 2.87 (*d*, *J* = 16, 1 H); 2.85 (*d*, *J* = 16, 1 H); 2.60 (*d*, *J* = 16, 2 H); 2.30 (*s*, 3 H); 1.80 (*s*, OH); 1.16 (*s*, 3 H). ^{13}C-NMR: 142.6 (*s*); 139.4 (*s*); 135.8 (*s*); 127.0 (*d*); 125.5 (*d*); 124.5 (*d*); 70.5 (*t*); 45.0 (*s*); 42.7 (*t*); 42.4 (*t*); 24.0 (*q*); 21.2 (*q*). MS: 176 (33, M^+), 158 (11), 143 (100), 128 (35), 115 (21), 105 (11), 91 (11), 77 (8), 51 (6), 39 (7), 31 (15).

4.3.2. *Synthesis from* **11**. To a soln. of **11** (200 g, 1.04 mol) in i-PrOH (3 kg) was added 5% Pd/C (20 g) and methanesulfonic acid (2.0 g, 21.0 mmol), and the mixture was stirred under H_2 (3 bar) at 80° during 7.5 h. The

mixture was diluted with toluene (200 g), washed with 5% aq. H_2SO_4, H_2O, sat. aq. $NaHCO_3$ soln., and H_2O, and concentrated. Distillation *in vacuo* (0.08 mbar) afforded **1** (161.2 g, 83%; purity 95%). Colorless viscous liquid that solidified on standing. M.p. 42–44°.

5. *Synthesis of Compound* **2**. 5.1. *(±)-2,7-Dimethylindan-1-one* (**14**). A stirred mixture of ketone **7** (5.9 g, 39.0 mmol; purity 98%), hexamethylenetetramine (7.89 g, 55.0 mmol), and Ac_2O (7.2 g, 71.0 mmol) was heated to 80° (bath temp.) for 7 h. The mixture was cooled, and then poured onto a mixture of 2.5N aq. NaOH soln. and CH_2Cl_2. The org. phase was washed with brine, 1.5N aq. HCl, dried (Na_2SO_4), and concentrated on a rotary evaporator to an orange oil. GC Analysis indicated the presence of 12% of **7** (starting material) and 87% of the intermediate **13**. The oil was added dropwise to conc. H_2SO_4 (23 ml), and the mixture was kept at *ca.* 15° with a water bath. The mixture was then heated to 58° (bath temp.) during 1.5 h. The cooled mixture was poured into a mixture of iced H_2O and Et_2O. The org. phase was washed with H_2O, sat. aq. $NaHCO_3$ soln., dried (Na_2SO_4), and concentrated to a yellow liquid (4.06 g), which was purified by FC (200 g SiO_2; CH_2Cl_2) followed by bulb-to-bulb distillation (oven temp. 50 → 85° at 0.3 mbar). Yield of **14**: 2.85 g (45%; purity 98%). Colorless oil. IR (neat): 2980, 2950, 1715, 1605, 1485, 1340, 1240, 1210, 875, 790. ^{1}H-NMR: 7.41 (*t*, *J* = 8, 1 H); 7.24 (*d*, *J* = 8, 1 H); 7.08 (*d*, *J* = 8, 1 H); 3.33 (br. *q*, *J* = 8, 1 H); 2.70–2.64 (*m*, 2 H); 2.63 (*s*, 3 H); 1.28 (*s*, 3 H). ^{13}C-NMR: 210.3 (*s*); 154.1 (*s*); 139.0 (*s*); 133.9 (*d*); 133.8 (*s*); 129.1 (*d*); 123.8 (*d*); 43.3 (*d*); 34.6 (*t*); 18.3 (*q*); 16.4 (*q*). MS: 160 (60, M^+), 145 (100), 115 (28), 91 (14), 77 (9), 63 (9), 51 (11), 39 (8), 27 (4).

5.2. *(±)-2-(Hydroxymethyl)-2,7-dimethylindan-1-one* (**15**). Prepared according to *GP 1* from **14** (1.17 g, 7.3 mmol), and purified by crystallization from Et_2O/pentane at −30°. Yield: 1.29 g (92%). Colorless crystals. M.p. 93.5–94°. IR (neat): 3482, 2963, 2915, 2867, 1687, 1592, 1473, 1376, 1199, 1055, 928, 800, 784. ^{1}H-NMR: 7.44 (*t*, *J* = 7, 1 H); 7.27 (*d*, *J* = 7, 1 H); 7.10 (*d*, *J* = 7, 1 H); 3.79 (*dd*, *J* = 10, 6, 1 H); 3.60 (*dd*, *J* = 10, 4, 1 H), 3.18 (*d*, *J* = 16, 1 H); 2.83 (*d*, *J* = 16, 1 H); 2.61 (*s*, 3 H), 2.61–2.53 (br. *m*, OH); 1.22 (*s*, 3 H). ^{13}C-NMR: 212.1 (*s*); 153.9 (*s*); 139.4 (*s*); 134.4 (*d*); 133.2 (*s*); 129.3 (*d*); 124.0 (*d*); 67.9 (*t*); 50.7 (*s*); 37.5 (*t*); 20.9 (*q*); 18.3 (*q*). MS: 190 (86, M^+), 175 (32), 172 (43), 159 (100), 145 (54), 129 (40), 115 (37), 91 (23), 77 (13), 63 (6), 51 (5), 39 (5).

5.3. *(±)-2,3-Dihydro-2,4-dimethyl-1*H*-indene-2-methanol* (**2**). Prepared according to *GP 2* from **15** (0.67 g, 3.5 mmol), and purified by bulb-to-bulb distillation (oven temp. 75 → 135° at 0.2 mbar). Yield: 0.51 g (83%). Colorless oil. IR (neat): 3320 (br.), 2900, 1585, 1455, 1370, 1030, 760. ^{1}H-NMR: 7.04 (*t*, *J* = 7, 1 H); 6.99 (*d*, *J* = 7, 1 H); 6.94 (*d*, *J* = 7, 1 H); 3.50 (*s*, 2 H); 2.91 (*d*, *J* = 16, 1 H); 2.83 (*d*, *J* = 16, 1 H); 2.67 (*d*, *J* = 16, 1 H); 2.58 (*d*, *J* = 16, 1 H); 2.21 (*s*, 3 H); 1.84 (br. *s*, OH); 1.18 (*s*, 3 H). ^{13}C-NMR: 142.2 (*s*); 141.3 (*s*); 134.1 (*s*); 127.0 (*d*); 126.4 (*d*); 122.1 (*d*); 70.8 (*t*); 44.2 (*s*); 43.0 (*t*); 41.5 (*t*); 24.3 (*q*); 19.0 (*q*). MS: 176 (32, M^+), 158 (15), 143 (100), 128 (32), 115 (19), 105 (11), 91 (10), 77 (8), 63 (4), 51 (6), 39 (7), 31 (6).

6. *Synthesis of Compound* **3**. 6.1. *(±)-2-(Hydroxymethyl)-2,4,5-trimethylindan-1-one* (**19**). Prepared according to *GP 1*. from **16** (1.27 g, 7.3 mmol), and purified by crystallization from CH_2Cl_2/Et_2O at −30°. Yield: 1.08 g (72%). Colorless crystals. M.p. 110–111°. IR (neat): 3402, 2963, 2927, 2861, 1675, 1592, 1454, 1300, 1277, 1243, 1055, 830. ^{1}H-NMR: 7.47 (*d*, *J* = 8, 1 H); 7.16 (*d*, *J* = 8, 1 H); 3.82 (*d*, *J* = 10, 1 H); 3.61 (*d*, *J* = 10, 1 H); 3.14 (*d*, *J* = 16, 1 H); 2.78 (*d*, *J* = 16, 1 H); 2.66 (br. *s*, OH); 2.36 (*s*, 3 H); 2.24 (*s*, 3 H); 1.22 (*s*, 3 H). ^{13}C-NMR: 211.3 (*s*); 152.5 (*s*); 144.5 (*s*); 134.0 (*s*); 133.7 (*s*); 129.7 (*d*); 121.4 (*d*); 67.9 (*t*); 51.1 (*s*); 37.3 (*t*); 20.8 (*q*); 20.3 (*q*); 14.6 (*q*). MS: 204 (68, M^+), 189 (22), 186 (40), 173 (100), 159 (72), 143 (21), 128 (26), 115 (24), 105 (9), 91 (14), 77 (9), 51 (4), 39 (4).

6.2. *(±)-2,3-Dihydro-2,4,5-trimethyl-1*H*-indene-2-methanol* (**3**). Prepared according to *GP 2* from **19** (1.03 g, 5.0 mmol), and purified by bulb-to-bulb distillation (oven temp. 90 → 200° at 0.2 mbar). Yield: 0.82 g (84%; purity 98%). Colorless oil. IR (neat): 3330, 2900, 2860, 1450, 1370, 1030, 880. ^{1}H-NMR: 6.94 (*d*, *J* = 8, 1 H); 3.50 (*s*, 2 H); 2.88 (*d*, *J* = 16, 1 H); 2.84 (*d*, *J* = 16, 1 H); 2.63 (*d*, *J* = 16, 1 H); 2.59 (*d*, *J* = 16, 1 H); 2.23 (*s*, 3 H); 2.13 (*s*, 3 H); 1.78 (br. *s*, OH); 1.18 (*s*, 3 H). ^{13}C-NMR: 141.5 (*s*); 139.7 (*s*); 134.1 (*s*); 132.6 (*s*); 128.0 (*d*); 121.8 (*d*); 70.9 (*t*); 44.4 (*s*); 42.9 (*t*); 42.0 (*t*); 24.4 (*q*); 19.6 (*q*); 15.8 (*q*). MS: 190 (47, M^+), 172 (16), 157 (100), 142 (19), 128 (19), 115 (11), 105 (4), 91 (5), 77 (4), 51 (2), 39 (2), 31 (2).

7. *Synthesis of Compound* **4**. 7.1. *(±)-2-(Hydroxymethyl)-2,4,6-trimethylindan-1-one* (**20**). Prepared according to *GP 1* from **17** (0.53 g, 3.0 mmol), and purified by crystallization from Et_2O at −30°. Yield: 0.45 g (73%). Colorless crystals. M.p. 110°. IR (neat): 3396, 2914, 2869, 1674, 1482, 1309, 1047, 993, 871. ^{1}H-NMR: 7.35 (br. *s*, 1 H); 7.25 (br. *s*, 1 H); 3.82 (*dd*, *J* = 10, 7, 1 H); 3.62 (*dd*, *J* = 10, 4, 1 H); 3.08 (*d*, *J* = 16, 1 H); 2.73 (*d*, *J* = 16, 1 H); 2.56 (br. *dd*, *J* = 7, 4, OH); 2.35 (*s*, 3 H); 2.31 (*s*, 3 H); 1.23 (*s*, 3 H). ^{13}C-NMR: 211.6 (*s*); 149.8 (*s*); 137.6 (*s*); 137.0 (*d*); 135.7 (*s*); 135.5 (*s*); 121.5 (*d*); 68.0 (*t*); 51.1 (*s*); 36.6 (*t*); 21.0 (*q*); 20.8 (*q*); 17.7 (*q*). MS: 174 (50), 159 (100), 131 (21), 128 (8), 115 (12), 91 (8), 77 (4), 51 (3), 39 (2).

7.2. *(±)-2,3-Dihydro-2,4,6-trimethyl-1*H*-indene-2-methanol* (**4**). Prepared according to *GP 2* from **20** (0.40 g, 1.96 mmol), and purified by bulb-to-bulb distillation (oven temp. 100 → 155° at 0.2 mbar). Yield: 0.30 g (78%; purity 98%). Colorless oil. IR (neat): 3330 (br.), 2900, 1470, 1370, 1030, 840. ^{1}H-NMR: 6.82 (br. *s*, 1 H); 6.78 (br.

s, 1 H); 3.50 (*s*, 2 H); 2.87 (*d*, *J* = 16, 1 H); 2.78 (*d*, *J* = 16, 1 H); 2.62 (*d*, *J* = 16, 1 H); 2.53 (*d*, *J* = 16, 1 H); 2.28 (*s*, 3 H); 2.18 (*s*, 3 H); 1.80 (*s*, OH); 1.18 (*s*, 3 H). ^{13}C-NMR: 142.4 (*s*); 138.2 (*s*); 136.1 (*s*); 133.8 (*s*); 128.0 (*d*); 122.8 (*d*); 70.9 (*t*); 44.4 (*s*); 42.9 (*t*); 41.1 (*t*); 24.4 (*q*); 21.1 (*q*); 19.0 (*q*). MS: 190 (46, M^+), 172 (14), 157 (100), 142 (18), 128 (19), 115 (10), 105 (4), 91 (5), 77 (3), 65 (2), 51 (2), 39 (2).

8. *Synthesis of Compound* **5**. 8.1. *(±)-2-(Hydroxymethyl)-2,4,7-trimethylindan-1-one* (**21**). Prepared according to *GP 1* from **18** (30 g, 165.0 mmol; purity 95%), and purified by crystallization. Yield: 33.1 g (92%; purity 94%). Colorless crystals. M.p. 113–114°. IR (neat): 3437 (br.), 2965, 2922, 2865, 1682, 1585, 1499, 1250, 1055, 968, 848. ^{1}H-NMR: 7.26 (*d*, *J* = 7.2, 1 H); 7.03 (*d*, *J* = 7.2, 1 H); 3.80 (*d*, *J* = 10.7, 1 H); 3.62 (*d*, *J* = 10.7, 1 H); 3.03 (*d*, *J* = 17.4, 1 H); 2.73 (*d*, *J* = 17.4, 1 H); 2.58 (*s*, 3 H); 2.34 (br. *s*, OH); 2.29 (*s*, 3 H); 1.24 (*s*, 3 H). ^{13}C-NMR: 212.5 (*s*); 152.7 (*s*); 136.5 (*s*); 135.0 (*s*); 132.9 (*s*); 132.8 (*s*); 129.5 (*d*); 67.9 (*t*); 50.3 (*s*); 36.6 (*t*); 21.0 (*q*); 18.0 (*q*); 17.5 (*q*). MS: 204 (55, M^+), 189 (9), 186 (29), 174 (47), 173 (100), 171 (37), 159 (56), 145 (12), 143 (17), 130 (12), 129 (18), 128 (23), 117 (8), 116 (6), 115 (20), 105 (7), 91 (10), 77 (6), 65 (3), 51 (3), 39 (2).

8.2. *2,3-Dihydro-2,4,7-trimethyl-1*H-*indene-2-methanol* (**5**). To a soln. of **21** (17.0 g, 78.0 mmol; purity 94%) in i-PrOH (30 ml) was added 5% Pd·C (2 g) and methanesulfonic acid (0.2 g, 2.1 mmol), and the mixture was stirred under H_2 (3 bar) at 80° for 7.5 h. The mixture was diluted with toluene (20 ml), washed with 5% aq. H_2SO_4, H_2O, sat. aq. $NaHCO_3$ soln., and H_2O, and then concentrated. Bulb-to-bulb distillation (oven temp. 170 → 195° at 1.5 mbar) gave **5** (7.4 g, 48%; purity 96%). Colorless oil that solidified on standing. M.p. 40–41°. IR (neat): 3291 (br.), 2952, 2916, 2865, 1498, 1460, 1433, 1376, 1030, 803. ^{1}H-NMR: 6.87 (*s*, 2 H); 3.50 (*s*, 2 H); 2.83 (*d*, *J* = 15.8, 2 H); 2.58 (*d*, *J* = 15.8, 2 H); 2.18 (*s*, 6 H); 1.94 (*s*, OH); 1.18 (*s*, 3 H). ^{13}C-NMR: 140.9 (2*s*); 131.2 (2*s*); 127.3 (2*d*); 71.0 (*t*); 43.7 (*s*); 41.8 (2*t*); 24.7 (*q*); 18.7 (2*q*). MS: 190 (46, M^+), 173 (9), 172 (17), 160 (10), 159 (72), 158 (20), 157 (100), 145 (7), 144 (20), 143 (24), 142 (22), 141 (15), 129 (20), 128 (23), 127 (6), 119 (5), 115 (12), 91 (5), 77 (4), 65 (2), 51 (2), 39 (1).

9. *Synthesis of Compound* **6**. 9.1. *Diethyl 1,3-Dihydro-5,6-dimethyl-2*H-*indene-2,2-dicarboxylate* (**23**). Elemental Na (0.31 g, 13.5 mmol) was dissolved in EtOH (10 ml), and a soln. of diethyl malonate (0.94 g, 5.9 mmol) in EtOH (3 ml) was added dropwise with stirring. After 5 min, a soln. of the dichloride **22** (1.1 g, 5.4 mmol) [9] in EtOH (12 ml) was added, and the mixture was heated at reflux for 3 h. The cooled mixture was diluted with Et_2O, washed with brine (2×), dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation (oven temp. 100 → 150° at 0.3 mbar) afforded **23** (0.81 g, 46%; purity 88%). Colorless oil. IR (neat): 2970, 2920, 1730, 1440, 1360, 1275, 1230, 1180, 1155, 1075, 860. ^{1}H-NMR: 6.97 (*s*, 2 H); 4.18 (*q*, *J* = 7, 4 H); 3.52 (*s*, 4 H); 2.21 (*s*, 6 H); 1.24 (*t*, *J* = 7, 6 H). ^{13}C-NMR: 171.8 (2*s*); 137.5 (2*s*); 135.1 (2*s*); 125.3 (2*d*); 61.6 (2*t*); 60.6 (*s*); 40.2 (2*t*); 19.7 (2*q*); 14.0 (2*q*). MS: 290 (36, M^+), 245 (5), 216 (100), 189 (18), 171 (12), 157 (13), 143 (42), 128 (21), 115 (6), 91 (2), 77 (1), 29 (4).

9.2. *1,3-Dihydro-5,6-dimethyl-2*H-*indene-2,2-dimethanol* (**24**). To a stirred suspension of $LiAlH_4$ (0.17 g, 4.4 mmol) in Et_2O (5 ml) was added dropwise a soln. of **23** (0.64 g, 2.1 mmol; purity 96%) in Et_2O (10 ml), and the mixture was stirred at r.t. for 15 h. The mixture was cooled to 4–5°, 10% aq. NaOH soln. (0.9 ml) was added cautiously, and the mixture was stirred at r.t. for 1 h, dried (Na_2SO_4), and filtered. The solids were rinsed with Et_2O, and the filtrate was concentrated to a solid (0.38 g), which was crystallized from AcOEt at 0° to afford **24** (0.31 g, 72%). Colorless needles. M.p. 168–168.5°. IR (neat): 3287 (br.), 2923, 2873, 1429, 1377, 1219, 1081, 1044, 1023, 990, 884. ^{1}H-NMR ((D$_6$)acetone): 6.90 (*s*, 2 H); 3.59 (*s*, 4 H); 2.86 (br. *s*, 2 OH); 2.72 (*s*, 4 H); 2.18 (*s*, 6 H). ^{13}C-NMR ((D$_6$)acetone): 140.7 (2*s*); 134.7 (2*s*); 126.7 (2*d*); 67.2 (2*t*); 50.5 (*s*); 38.5 (2*t*); 19.7 (2*q*). MS: 206 (12, M^+), 188 (2), 173 (6), 157 (100), 142 (20), 128 (12), 115 (8), 91 (4), 77 (3), 31 (2).

9.3. *1,3-Dihydro-5,6-dimethyl-spiro[indene-2,3′-oxetane]* (**25**). To a stirred soln. of **24** (1.37 g, 6.6 mmol) in THF (20 ml) at −23° was added dropwise BuLi (1.6M soln. in hexane, 4.6 ml, 7.3 mmol). After 30 min at −23°, a soln. of TsCl (1.28 g, 6.6 mmol) in THF (13 ml) was added dropwise, and the mixture was stirred at −23° for 4 h (TLC control: toluene/AcOEt 1:1). A second portion of BuLi (4.6 ml, 7.3 mmol) was added dropwise at −23°, and the mixture was stirred at r.t. for 60 h. Then, the mixture was diluted with Et_2O, washed with sat. aq. $NaHCO_3$ soln. and brine, dried (K_2CO_3), and concentrated to a solid, which was purified by FC (150 g SiO_2; toluene/AcOEt 4:1) to afford **25** (0.95 g, 76%). An anal. sample was crystallized from pentane at −30° to afford colorless crystals. M.p. 82–83°. IR (neat): 2920, 2855, 1492, 1451, 1431, 1023, 992, 967, 859, 829. ^{1}H-NMR: 6.98 (*s*, 2 H); 4.65 (*s*, 4 H); 3.17 (*s*, 4 H); 2.22 (*s*, 6 H). ^{13}C-NMR: 139.0 (2*s*); 134.9 (2*s*); 125.7 (2*d*); 83.6 (2*t*); 47.0 (*s*); 43.8 (2*t*); 19.7 (2*q*). MS: 188 (55, M^+), 158 (52), 143 (100), 128 (32), 115 (15), 91 (3), 77 (4), 51 (2), 32 (2).

9.4. *2,3-Dihydro-2,5,6-trimethyl-1*H-*indene-2-methanol* (**6**). To a stirred suspension of $LiAlH_4$ (0.16 g, 4.1 mmol) in THF (10 ml) was added dropwise a soln. of **25** (0.77 g, 4.1 mmol) in THF (5 ml), and the mixture was heated to reflux for 22 h. To the cooled mixture was added 10% aq. NaOH soln. (1 ml), and the mixture was stirred at r.t. for 1 h. Then, Na_2SO_4 was added, the solids were filtered off, and the filtrate was concentrated to a solid, which was crystallized from Et_2O/pentane at 0° to afford **6** (0.52 g, 67%). Colorless crystals. M.p.

68.5–69°. IR (neat): 3264 (br.), 2919, 2865, 2840, 1490, 1450, 1433, 1358, 1095, 1042, 888, 859. ^{1}H-NMR: 6.94 (*s*, 2 H); 3.50 (br. *s*, 2 H); 2.84 (*d*, *J* = 16, 2 H); 2.58 (*d*, *J* = 16, 2 H); 2.21 (*s*, 6 H); 1.16 (*s*, 3 H). ^{13}C-NMR: 140.0 (2*s*); 134.4 (2*s*); 126.0 (2*d*); 70.8 (*t*); 45.0 (*s*); 42.5 (2*t*); 24.1 (*q*); 19.7 (2*q*). MS: 190 (45, M^+), 172 (16), 157 (100), 142 (20), 128 (22), 115 (12), 105 (5), 91 (7), 77 (5), 51 (3), 39 (4), 31 (4).

10. *Enantiomer Separation of* (±)-**1**. Racemic **1** (14.4 g) was resolved in portions of 1 g on a prep. HPLC column (*Chiralpack AD*; 25 × 11 cm, 20 μm), eluting with isohexane/EtOH 95 : 5. After concentration to dryness, (+)-(*S*)-**1** (6.39 g) and (−)-(*R*)-**1** (6.15 g) were obtained and further purified by FC and bulb-to-bulb distillation (boiling at 110° oven temp./0.01 mbar). The (*S*)- and (*R*)-isomers of **1** were > 99% and > 98% pure according to anal. HPLC. $[\alpha]_D^{20} = +3.2$ (*c* = 1.5, $CHCl_3$) for (+)-(*S*)-**1**; $[\alpha]_D^{20} = -3.1$ (*c* = 1.5, $CHCl_3$) for (−)-(*R*)-**1**. The IR, NMR, and MS data were identical with those of the racemic compound (see above).

11. *[(2*S*)-2,3-Dihydro-2,5-dimethyl-1*H*-inden-2-yl]methyl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane-1-carboxylate* (**7**).

To a soln. of (+)-**1** (2.0 g, 11.3 mmol; > 99% pure) in anh. pyridine (20 g) at 0° was added (−)-camphanoyl chloride (2.5 g, 11.5 mmol; *Fluka*), and the mixture was stirred overnight at r.t. After usual workup (extraction with Et_2O), the crude crystalline product (4.13 g, 100%) was recrystallized at 0° from hexane/AcOEt 2 : 1 to afford 2.45 g (61%) of pure (+)-**7**. The crystals were suitable for X-ray analysis. M.p. 85.5–86.6°. $[\alpha]_D^{20} = +3.2°$ (*c* = 1.34, $CHCl_3$). ^{1}H-NMR: 0.97 (*s*, 3 H); 1.04 (*s*, 3 H); 1.12 (*s*, 3 H); 1.21 (*s*, 3 H); 1.64–1.72 (*m*, 1 H); 1.86–1.94 (*m*, 1 H); 1.98–2.06 (*m*, 1 H); 2.31 (*s*, 3 H); 2.33–2.41 (*m*, 1 H); 2.70 (*d*, *J* = 15.8, 2 H); 2.89 (*d*, *J* = 15.8, 2 H); 3.71 (*d*, *J* = 10.7, 1 H); 3.76 (*d*, *J* = 10.7, 1 H); 6.95 (*d*, *J* = 7.5, 1 H); 6.98 (*s*, 1 H); 7.05 (*d*, *J* = 7.5, 1 H). ^{13}C-NMR: 9.7 (*q*); 16.8 (2*q*); 21.2 (*q*); 24.4 (*q*); 28.9 (*t*); 30.6 (*t*); 42.8 (*t*); 43.1 (*s*); 43.3 (*t*); 54.1 (*s*); 54.8 (*s*); 72.7 (*t*); 91.3 (*s*); 124.5 (*d*); 125.5 (*d*); 127.3 (*d*); 136.1 (*s*); 138.8 (*s*); 141.9 (*s*); 167.5 (*s*); 178.2 (*s*). MS: 365 (12, M^+), 158 (100), 143 (92), 129 (13). X-Ray analysis: see the *Figure* and *Sect. 12*.

12. *X-Ray Crystal-Structure Determination of* **7**[3]). Crystal data: colorless prism, 0.10 × 0.17 × 0.40 mm; formula, $C_{22}H_{28}O_4$; M_r 356.5; $\mu = 0.082$ mm^{-1}, $D_x = 1.211$ g/cm^3; crystal system, orthorhombic; space group, $P2_12_12_1$; lattice parameters: $a = 6.5599(3)$, $b = 12.1982(7)$, $c = 24.4410(12)$ Å, $V = 1955.7(2)$ Å^{-3}, $Z = 4$. Cell dimensions and intensities were measured at 200 K on a *Stoe IPDS* diffractometer with graphite-monochromated MoK_α radiation (0.71073 Å), 24426 measured reflections, 3799 unique reflections of which 2145 were observables ($|F_o| > 4\sigma(F_o)$); R_{int} for 20627 equivalent reflections, 0.052. Data were corrected for *Lorentz* and polarization effects, and for absorption (T_{min} 0.9792, T_{max} 0.9922). The structure was solved by direct methods (SIR-97) [13], and all other calculations were performed with the XTAL system [14] and ORTEP [15] programs. Full-matrix least-squares refinement based on *F* using a weight of $1/(\sigma^2(F_o) + 0.00015(F_o^2))$ gave $R_{final} = \omega R = 0.030$, and $S = 1.46(2)$ for 235 variables and 2376 contributing reflections. The maximum shift/error on the last cycle was 0.21×10^{-3}. With the absolute configuration of the camphor moiety being known, the *Flack* parameter was fixed at zero.

REFERENCES

[1] B. Winter, S. Gallo-Flückiger, *Helv. Chim. Acta* **2005**, *88*, 3118.
[2] B. Winter, P. Schneider, to *Firmenich SA*, Eur. Pat. Appl. E.P. 1022265, priority 22 Jan, 1999 (*Chem. Abstr.* **2000**, *133*, 135119f).
[3] J. Colonge, G. Weinstein, *Bull. Soc. Chim. Fr.* **1952**, 462.
[4] a) W. E. Bachmann, J. W. Cook, C. L. Hewett, J. Iball, *J. Chem. Soc.* **1936**, 54; b) J. Colonge, G. Weinstein, *Bull. Soc. Chim. Fr.* **1951**, 691; c) H. W. Pinnick, S. P. Brown, E. A. McLean, L. W. Zoller III, *J. Org. Chem.* **1981**, *46*, 3758; d) M. Fukuoka, K. Yoshihira, S. Natori, K. Mihashi, M. Nishi, *Chem. Pharm. Bull.* **1983**, *31*, 3113.
[5] D. M. Kalendra, B. R. Sickles, *J. Org. Chem.* **2003**, *68*, 1594.
[6] A. Bhattacharya, B. Segmuller, A. Ybarra, *Synth. Commun.* **1996**, *26*, 1775.
[7] W. Herz, J. L. Rogers, *J. Am. Chem. Soc.* **1953**, *75*, 4498; B. B. Elsner, K. J. Parker, *J. Chem. Soc.* **1957**, 592.
[8] R. T. Hart, R. F. Tebbe, *J. Am. Chem. Soc.* **1950**, *72*, 3286; W. Herz, *J. Am. Chem. Soc.* **1951**, *73*, 4923.
[9] I. Shahak, E. D. Bergmann, *J. Chem. Soc. C* **1966**, 1005.
[10] P. Picard, D. Leclerc, J.-P. Bats, J. Moulines, *Synthesis* **1981**, 550.
[11] M. Lander, *Firmenich SA*, unpublished results.

---

[3]) The crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication number CCDC-282417. Copies of the data can be obtained, free of charge, *via* the internet at http://www.ccdc.cam.ac.uk/data_request/cif.

[12] P. Kraft, S. Gallo, *Synthesis* **2004**, 381; G. Helmchen, G. Staiger, *Angew. Chem., Int. Ed.* **1977**, *16*, 116.
[13] A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115.
[14] XTAL3.2 (User's Manual), Eds. S. R. Hall, H. D. Flack, J. M. Stewart, Universities of Western Australia and Maryland, 1992.
[15] C. K. Johnson, ORTEP II, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.

Received September 30, 2005