Preparation and Odor Evaluation of Both Enantiomers of 3,4,4a?,5,6,7,8,8a?-Octahydro-5,5,8a?-trimethyl-2(1H)-naphthalenone and 1,2?,3,4,4a?,5,6,7,8,8a?-Decahydro-5,5,8a?-trimethyl-...

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191. Preparation and Odor Evaluation of Both Enantiomers of 3,4,4aα,5,6,7,8,8aβ-Octahydro-5,5,8aβ-trimethyl-2(1*H*)-naphthalenone and 1,2α,3,4,4aα,5,6,7,8,8aβ-Decahydro-5,5,8aβ-trimethyl-2β-naphthalenyl Acetate, Four Woody Odorants

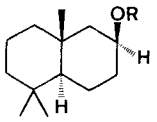
by **Antoine Gautier*, Christian Vial, Cédric Morel, Marina Lander,** and **Ferdinand Näf**

Firmenich SA, Research Laboratories, CH-1211 Geneva 8

(24.VI.87)

The enantiomeric decahydro-2-naphthalenols (+)-**5** and (−)-**5** were prepared by enantioselective hydrolysis of the racemic chloroacetate (±)-**2** catalyzed by porcine pancreatic lipase, and converted to the corresponding acetates (+)-**1** and (−)-**1** and ketones (+)-**6** and (−)-**6**. The absolute configurations of the ketones, alcohols, and acetates were established by chemical correlation with natural manool ((+)-**7**) by making use of a *retro*-ene cleavage reaction of the known manool degradation product **8** to (−)-**6**. A distinct odour difference between the two enantiomers of each pair (+)-**1**/(−)-**1** and (+)-**6**/(−)-**6** has been found.

Introduction. – The influence of the structure of an odoriferous substance on its odor strength and profile has been a rewarding topic the last 25 years[1]). As in the case of drug response [2], insect communication [3], and taste [4], olfaction may not only depend on the chemical constitution and relative configuration of an odorant but also on its absolute configuration. Examples for which different odor properties of the two enantiomers have been reported are: citronellol [5], hydroxycitronellal [6], linalool [7], carvone [8], rose oxide [9], nerol oxide [10], nootkatone [11], patchouli alcohol [12], several ambergris fragrances [13] [14], androsta-4,16-dien-3-one [15], and *cis*-2-methyl-4-propyl-1,3-oxathiane [4a]. Acetate (±)-**1** [16], known as *Polywood*®[2]), and ketone (±)-**6** [16] [17] are two



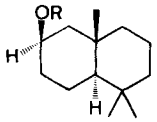
(−)-1 R = Ac

(−)-2 R = C(=O)-CH$_2$Cl

(−)-3 R = C(=O)-CHCl$_2$

(−)-4 R = C(=O)-CF$_3$

(−)-5 R = H



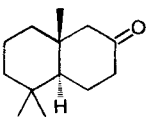
(+)-1 R = Ac

(+)-2 R = C(=O)-CH$_2$Cl

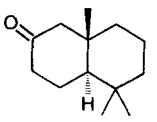
(+)-3 R = C(=O)-CHCl$_2$

(+)-4 R = C(=O)-CF$_3$

(+)-5 R = H



(−)-6



(+)-6

[1]) For a recent summary, see [1].

[2]) Registered trade mark of *Firmenich SA*.

fragrance chemicals of the woody type. So far, they have only been known as racemates. In the case of acetate (±)-**1**, a dramatic difference in odor properties between the four racemic diastereoisomers was discovered and subsequently allowed establishment of the 'triaxial rule of odor sensation' [1] [16]. This rule correlates diastereoisomerism of decalin-type compounds with ambergris odor. In this publication, we report for the first time the preparation, absolute configuration, and olfactive properties of the enantiomeric acetates (+)- and (−)-**1**, and ketones (+)- and (−)-**6**, using enzyme-catalyzed kinetic resolution of a suitable ester[3]).

Enantioselective Hydrolysis of Esters 1–4 Catalyzed by Lipases. – In an initial survey of hydrolytic enzymes[4]), only the yeast lipase from *Candida cylindracea* slowly hydrolyzed acetate (±)-**1** *(Table)*. The rate of hydrolysis was not appropriate for preparative work;

Table. *Enantioselectivity of Enzymes in Function of Substrate Used*

(±)-Ester $\xrightarrow[H_2O]{\text{lipase}}$ (−)-Ester + (+)-Alcohol

Ester	*Candida cylindricea* lipase				Porcine pancreatic lipase			
	Reaction time [h]	Conversion [%]	$[\alpha]_D^{20}$ of **5**	ee of **5** [%]	Reaction time [h]	Conversion [%]	$[\alpha]_D^{20}$ of **5**	ee of **5** [%]
(±)-**1**	88[a])	14	+ 15.8°	80[b])	88[c])	< 1	–	–
(±)-**2**	16[d])	43	+ 8.2°	42[b])	64[c])	20	+ 18°	92[c])
(±)-**3**	3[d])	16	+ 4°	20[b])	25[c])	33	+ 11.7°	60[c])
(±)-**4**	24[d])	27	− 3.3°	17[b])	40[c])	17	+ 7.1°	36[c])

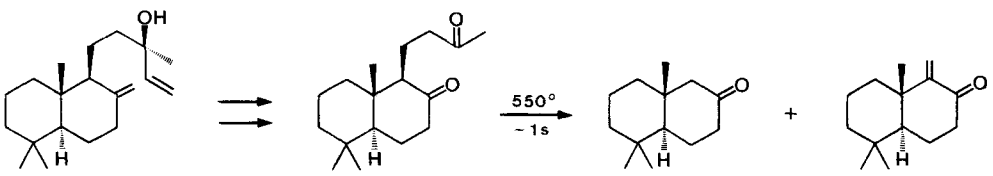
[a]) $2 \cdot 10^6$ U/g substrate.
[b]) Enantiomeric excess (ee) based on 100% ee for $[\alpha]_D^{20} = 19.6°$ ($c = 1.01$).
[c]) $5 \cdot 10^4$ U/g substrate.
[d]) 10^5 U/g substrate.
[e]) $2 \cdot 10^4$ U/g substrate.

we, therefore, tested the corresponding racemic chloro- and fluoroacetates **2**–**4** as substrates. Acceptable rates of hydrolysis of these compounds were observed using lipase from porcine pancreas or *Candida cylindracea*. The enantiomeric excess of the resulting alcohols was assessed by measuring the optical rotation of the crude alcohol after silica-gel chromatography *(Table)*. This method is not precise because contaminants can influence the measurement of the optical rotation; nevertheless, these results indicate that the nature of the acetate moiety greatly influences the overall rate and the enantioselectivity of the enzymatic reaction. This is no surprise as the enantioselectivity of lipases depends on the structure of the substrate. In practice, the choice of the substrate/enzyme pair giving the best combination of activity, selectivity, and cost is very important, and using activated esters such as these will expand the usefulness of the method.

For the preparative resolution of the alcohol (±)-**5**, chloroacetate (±)-**2** was hydrolyzed using porcine pancreatic lipase. After 30% conversion (GLC), the alcohol (+)-**5** was isolated and recrystallized in hexane to constant optical rotation ($[\alpha]_D^{20} = + 19.6°$

[3]) For some leading refcrences, see [18].
[4]) Pig-liver esterase, lipase from *Candida cylindracea*, *Rhizopus arrhizus*, porcine pancrease, and wheat germ were used in survey experiments.

Scheme



(c = 1.01)). The chloroacetate **2**, enriched in the (−)-isomer, was further hydrolyzed enzymatically. At 25% conversion, the remaining laevorotatory chloroacetate **2** was isolated. After chemical hydrolysis, the alcohol (−)-**5** was recrystallized in hexane to constant optical rotation ($[\alpha]_D^{20} = -19.6°$ (c = 1.2)). Oxidation of (+)- and (−)-**5** with CrO_3 yielded the ketones (+)- and (−)-**6**, respectively, and the acetates (+)- and (−)-**1** were obtained from (+)- and (−)-**5**, respectively. The enantiomeric excess of the acetates **1** and ketones **6** was determined by ^{1}H-NMR using the chiral shift reagent [Eu(hfc)$_3$] [19] and was better than 95%.

Absolute Configurations. – The absolute configuration of ketone (−)-**6** was established by degradation of manool (+)-**7** of known absolute configuration [20] *(Scheme)*. As described earlier [21], a sequence of $KMnO_4$ oxidation and ozonolysis transformed manool (+)-**7** into diketone **8** (48% overall yield). When diketone **8** in the vapor phase was allowed to pass through a quartz tube at 550° (residence time *ca.* 1.3 s), two competitive *retro*-ene reactions took place giving equal amounts of ketone (−)-**6** and methylidene ketone (−)-**9**. Ketone (−)-**6** *ex* manool was identical in all respects (specific rotation, melting point, ^{1}H-NMR spectrum) with ketone (−)-**6** prepared previously. Consequently, the absolute configurations of ketone (+)-**6** and of the two acetates (+)- and (−)-**1** were also assigned. Ketone (−)-**6** was found simultaneously in nature by *Maurer et al.* [22]. Racemic methylidene ketone (±)-**9** was used as a building block in the synthesis of the triterpene 8,8′-onocerandiol [23] and was proposed as versatile starting material for diterpene synthesis [24] (see also [25–27]).

The Odor Properties of (+)- and (−)-1, and (+)- and (−)-6. – Acetate (+)-**1** exhibits a rich, voluminous woody note with a powdery ionone-like undertone. Conversely, acetate (−)-**1** is less rich, still woody, dry, and amber-like. Ketone (+)-**6** is woody patchouli-like and less strong than its enantiomer (−)-**6** which is strong, woody amber-like with a distinct note of damp earth, cellar, geosmin.

We would like to thank *A. F. Morris* and Dr. *D. Kastner, Firmenich SA*, for the organoleptic evaluations.

Experimental Part

1. *General.* Solvent was removed with a *Büchi Rotavapor-R.* Lipases (EC 3.1.1.3) were purchased from *Sigma.* The specific activity in international units/mg solid were 13 and 500 for porcine pancreatic lipase and *Candida cylindracea* lipase, respectively. Bulb-to-bulb distillation: *Büchi GKR-50* apparatus with external temperature reading. *Hewlett-Packard-5890A* instrument, glass capillary 5 m × 530 mμ coated with methyl silicone. Column chromatography: silica gel *Merck* (particle size 0.063–0.200 mm). Specific rotations: *Perkin-Elmer-141* polarimeter, $CHCl_3$ soln. The enantiomeric purities (in ee) were determined by ^{1}H-NMR using [Eu(hfc)$_3$] as shift reagent [19]. ^{1}H-NMR spectra (360 MHz): *Bruker WH 360* instrument; in $CDCl_3$ with TMS (= 0.00 ppm) as internal standard; *J* and $w_{1/2}$ in Hz. MS: *Finnigan MAT* quadrupole instrument; *m/z* (% relative abundance).

2. *(±)-1,2α,3,4,4aα,5,6,7,8,8aβ-Decahydro-5,5,8aβ-trimethyl-2β-naphthalenyl Esters* (±)-**1**, (±)-**2**, (±)-**3**, *and* (±)-**4** *from* (±)-**5**. 2.1. *(±)-Acetate* (±)-**1** [16] was prepared as described earlier.

2.2. *(±)-Chloroacetate* (±)-**2**. To 25 g (0.127 mol) of (±)-**5** (prepared according to [16]) in heptane (100 ml) and pyridine (12 ml), chloroacetyl chloride (22.5 g, 0.2 mol) was slowly added. After 3 h, the excess chloride was hydrolyzed with H_2O. The mixture was extracted with pentane, the extract washed (1N Na_2CO_3, 10% H_2SO_4 soln., H_2O), dried ($MgSO_4$), and evaporated. The crude ester was distilled in a *Vigreux* apparatus at 105°/0.03 Torr to give (±)-**2** (26 g, 75%). ^{1}H-NMR: 0.83, 0.87, 1.05 (3 *s*, 2 CH_3–C(5), CH_3–C(8a)); 4.02, 4.06 (2 *d*, *J* = 13, CH_2Cl); 5.13 (*m*, $w_{1/2}$ = 8, H_{eq}–C(2)). MS: 272/270 (0, $M^{+\cdot}$), 257/255 (1), 178 (12), 163 (37), 149 (12), 135 (11), 124 (57), 109 (37), 93 (41), 81 (100), 69 (46), 55 (39), 41 (26).

2.3. *(±)-Dichloroacetate* (±)-**3** was prepared analogously from (±)-**5** and dichloroacetyl chloride. Yield 92%. B.p. 165°/0.07 Torr (bulb-to-bulb distillation). ^{1}H-NMR: 0.84, 0.88, 1.08 (3 *s*, 2 CH_3–C(5), CH_3–C(8a)); 5.16 (*m*, $w_{1/2}$ = 8, H_{eq}–C(2)); 5.92 (*s*, $CHCl_2$). MS: 310/308/306 (0, $M^{+\cdot}$), 295/293/291 (1), 178 (13), 163 (52), 149 (7), 135 (13), 124 (46), 107 (38), 93 (47), 81 (100), 69 (57), 55 (40), 41 (23).

2.4. *(±)-Trifluoroacetate* (±)-**4** was prepared analogously from (±)-**5** and trifluoroacetic anhydride. Yield 96%. B.p. 110°/0.05 Torr (bulb-to-bulb distillation). ^{1}H-NMR: 0.84, 0.88, 1.04 (3 *s*, 2 CH_3–C(5), CH_3–C(8a)); 5.25 (*m*, $w_{1/2}$ = 8, H_{eq}–C(2)). MS: 292 (0, $M^{+\cdot}$), 277 (4), 178 (10), 163 (79), 149 (3), 135 (11), 123 (27), 107 (40), 95 (55), 81 (100), 69 (98), 55 (55), 41 (43).

3. *Enzyme-Catalyzed, Kinetic Resolutions of Esters (±)-***1** *to (±)-***4**. 3.1. *(2*R*,4a*R*,8a*S*)-1,2α,3,4,4aα,5,6,7,8,8aβ-Decahydro-5,5,8aβ-trimethyl-2β-naphthalenol* ((±)-**5**). A suspension of (±)-**3** (7 g, 25.6 mmol) in 0.1 M potassium phosphate buffer at pH 7.5 (500 ml) was hydrolyzed using porcine pancreatic lipase (3.5 g) at 37° for 112 h. The mixture was extracted with Et_2O, the extract washed and dried, and the solvent distilled. The crude product was chromatographed on silica gel to yield 3.57 g (13 mmol) of chloroacetate, $[\alpha]_D^{20}$ = – 7.6° (*c* = 1.125), and 1.6 g (8.1 mmol) of (+)-**5**, $[\alpha]_D^{20}$ = + 18.08° (*c* = 1.25). The alcohol was recrystallized (hexane) to give 825 mg of pure (+)-**5**. M.p. 89–90°. $[\alpha]_D^{20}$ = + 19.6° (*c* = 1.01). For spectral data, see racemic compound [12].

3.2. *(2*S*,4a*S*,8a*R*)-Alcohol* (–)-**5**. A suspension of the chloroacetate formed during the previous experiment (3.4 g, 12.4 mmol; $[\alpha]_D^{20}$ = – 7.6° (*c* = 1.125)) in 0.1 M potassium phosphate buffer at pH 7.5 (500 ml) was hydrolyzed using porcine pancreatic lipase (3.5 g) at 37° for 144 h. The mixture was extracted with Et_2O, the extract washed and dried, and the solvent distilled. The crude product was chromatographed on silica gel to yield 1.83 g (6.7 mmol) of chloroacetate, $[\alpha]_D^{20}$ = – 14.05° (*c* = 2.32), and 0.52 g (2.5 mmol) of (+)-**5**, $[\alpha]_D^{20}$ = + 12.3° (*c* = 2.05). The chloroacetate with $[\alpha]_D^{20}$ = – 14.05° (*c* = 2.32) (1.8 g, 6 mmol) was heated at reflux in 0.5 M KOH/MeOH (20 ml) for 30 min, the product extracted with Et_2O, the extract was washed and dried, and the solvent distilled to yield 1.2 g of (–)-**5**, $[\alpha]_D^{20}$ = – 14.1° (*c* = 0.85). Recrystallization (hexane) yielded 870 mg of pure (–)-**5**. M.p. 89–90°. $[\alpha]_D^{20}$ = – 19.6° (*c* = 1.2). For spectral data, see racemic compound [12].

3.3. *Enzymatic Hydrolysis of (±)-***1**, *(±)-***3**, *and (±)-***4**. Using either porcine pancreatic lipase or *Candida cylindracea*, the resolutions were performed as described in *3.1.* The results obtained are summarized in the *Table.*

4. *(2*R*,4a*R*,8a*S*)-1,2α,3,4,4aα,5,6,7,8,8aβ-Decahydro-5,5,8aβ-trimethyl-2β-naphthalenyl Acetate ((±)-***1***) from (+)-***5**. To (+)-**5** (1 g, 5.1 mmol) in heptane (15 ml) containing pyridine (0.5 ml), acetyl chloride (480 mg, 6.1 mmol) was slowly added. After 24 h at r.t., H_2O (20 ml) was added, the mixture extracted with pentane, the extract washed (1N Na_2CO_3, 10% H_2SO_4 soln., H_2O), dried ($MgSO_4$), and evaporated, and the crude acetate (1.15 g) bulb-to-bulb distilled, b.p. 100°/0.04 Torr, to yield 1.08 g (88%) of pure (+)-**1**. $[\alpha]_D^{20}$ = – 16.69° (*c* = 1.4). For spectral data, see racemic compound [16].

5. *(2*S*,4a*S*,8a*R*)-Acetate* (–)-**1** was prepared analogously from (–)-**5**: 940 mg (96%) of pure, bulb-to-bulb distilled material. $[\alpha]_D^{20}$ = – 16.47° (*c* = 1.42). For spectral data, see racemic compound [16].

6. *(4aR,8aS)-3,4,4aα,5,6,7,8,8aβ-Octahydro-5,5,8aβ-trimethyl-2(1H)-naphthalenone ((+)-**6**) from (+)-**5**.* To (+)-**5** (337 mg, 1.7 mmol) in AcOH (5 ml) was added dropwise 2M aq. CrO_3 (1 ml). The mixture was heated at 60° for 1 h. After normal workup and recrystallization (hexane), pure (+)-**6** (222 mg, 67%) was obtained. M.p. 88–89°, $[\alpha]_D^{20} = +84.9°$ ($c = 1.07$).

7. *(4aS,8aR)-Ketone (−)-**6** from (−)-**5*** was prepared analogously by CrO_3 oxidation: 428 mg (70%). M.p. 87–89°. $[\alpha]_D^{20} = -84°$ ($c = 1.3$). For spectral data, see *Exper. 8* and [16].

8. *Ketone (−)-**6** and (4aS,8aS)-3,4,4aα,5,6,7,8,8aβ-Octahydro-5,5,8aβ-trimethyl-1-methylidene-2(1H)-naphthalenone ((−)-**9**) by Thermolysis of Diketone (−)-**8**.* Apparatus according to [28]. Diketone **8** (5 g, 18.9 mmol; $[\alpha]_D^{20} = -28.5°$ ($c = 1.53$); prepared from manool ((+)-**7**) of m.p. 43–46° and $[\alpha]_D^{20} = +30.7°$ ($c = 10$) according to [21]) was vaporized at 443 K (vapor pressure at 443 K: $p_s = 1.5$ Torr) in a stream of N_2 (V_{N_2}/t at 294 K and 760 Torr = 0.011 l/s). The gas mixture was then allowed to pass through the heated quartz tube ($T = 823$ K, volume $V = 0.0417$ l). Flow rate and contact time were estimated as $m/t = 0.000277$ g/s (0.997 g/h) and $ct = 1.3$ s, resp. The products were collected using two traps (dry ice) followed by a wash bottle (toluene filled). The contents of the traps and wash bottle were evaporated (*Rotavapor;* 3.35 g) and purified by bulb-to-bulb distillation. *Fraction 1* (b.p. 75–85°/0.3 Torr; 1.2 g) contained mainly (−)-**6** and (−)-**9** (*ca.* 1:1). *Fraction 2* (b.p. 120–130°/0.3 Torr; 1.7 g) consisted mainly of starting material. *Fraction 1* was further separated by repeated chromatography (silica gel, cyclohexane/Et_2O 9:1), **9** being eluted first and **6** second. Both ketones were recrystallized (pentane) to constant m.p. and [α] yielding (−)-**9** (32 mg, 97% chemically pure by GC; > 95% optically pure by ^{1}H-NMR) and (−)-**6** (79 mg, 99% chemically pure; > 95% optically pure).

(−)-**9**. M.p. 56–58°. $[\alpha]_D^{20} = -71.96°$ ($c = 1.088$). ^{1}H-NMR: 0.92, 0.96, 1.02 (3 *s*, 2 CH_3–C(5), CH_3–C(8a)); 2.33, 2.67 (*ddd*, $J = 7$, 11,17, and *ddd*, $J = 2$,5,17, CH_2–C(3)); 5.01, 5.24 (2 *s*, CH_2=C(1)). MS: 206 (5, $M^{+\cdot}$), 191 (7), 178 (10), 163 (16), 150 (18), 136 (19), 122 (51), 109 (71), 93 (57), 79 (72), 69 (83), 55 (82), 41 (100).

(−)-**6**. M.p. 88–90°. $[\alpha]_D^{20} = -86.1°$ ($c = 1.231$). ^{1}H-NMR: 0.86, 0.89, 0.97 (3 *s*, 2 CH_3–C(5), CH_3–C(8a)); 1.27 (*m*, H_{ax}–C(8), H_{ax}–C(6)); 1.47 (*m*, H_{eq}–C(8), H_{eq}–C(7), H_{eq}–C(6), H_{eq}–C(4a)); 1.64 (*m*, H_{ax}–C(7), H_{ax}–C(4)); 2.01 (*m*, H_{eq}–C(4), H_{eq}–C(1)); 2.15 (*d*, $J = 13$, H_{ax}–C(1)); 2.28 (*m*, H_{ax}–C(3)); 2.42 (*m*, H_{eq}–C(3)). MS: 194 (23, $M^{+\cdot}$), 179 (21), 161 (27), 151 (9), 137 (26), 123 (47), 109 (66), 95 (97), 81 (73), 69 (100), 55 (84), 41 (77).

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