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Synthesis and olfactory properties of (−)-(1*R*,2*S*)-Georgywood

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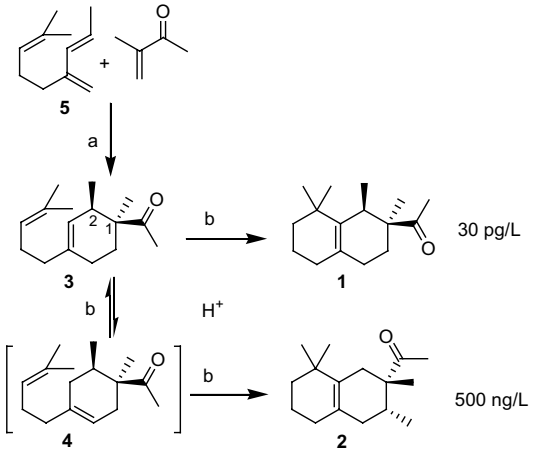
Abstract—The enantiomers of Georgywood® were synthesized from (*E*)-2-methyl-6-methylene-nona-2,7-diene and methacrylaldehyde followed by oxidation of the Diels–Alder adduct and classical racemate separation of the acid with optically-active *N*-methylephedrine. Conversion to the final ketone and olfactory evaluation showed that the (−)-(1*R*,2*S*)-enantiomer is more powerful by a factor of >100 than its antipode. The absolute configuration was determined by conformational studies and CD-analysis.

1. Introduction

The woody-ambery odorant Georgywood®,[1,2] as produced from homomyrcene **5** at Givaudan,[2a] is a racemic regioisomer mixture consisting of the olfactorily-active isomer **1** and iso-Georgywood **2** in about equal amounts (Scheme 1). The latter isomer is less powerful by a factor of >10,000. The formation of **2** can be rationalized through a preisomerization of the endocyclic double bond of pseudo-Georgywood **3** to give intermediate **4**, which readily undergoes subsequent cyclization to **2**. Steric constraints between the methyl group of C(2) and the methyl groups of the 4-methyl-pent-4-enyl side chain of **3** are thus circumvented, in analogy to our studies on the acid-promoted cyclization of similarly substituted 1,5-dienes.[3] Recent improvements on the cyclization reaction (Scheme 1b) have given excellent selectivities towards the desired isomer **1**.[4]



Scheme 1. Givaudan synthesis of Georgywood®. Reagents and conditions: (a) $AlCl_3$, CH_2Cl_2, 10 °C, 2 h, 85%; (b) H_3PO_4, toluene, 115 °C, 1 h, 74%.

The olfactory quality of fragrance compounds however, can be also improved by preparation of the enantiomers or their enriched mixtures, which can then exhibit more powerful or totally different scents.[5] Indeed a sniff-test at the outlet of a chiral GC-column showed that one of the enantiomers of **1** was ca. 200 times more powerful than the other, both having the same kind of woody-ambery tonality. For an unambiguous assignment of their absolute configuration, however, both enantiomers of **1** had to be prepared.

2. Results and discussion

The synthesis of the enantiomers was closely analogous to that described in Scheme 1, starting from (*E*)-2-methyl-6-methylene-nona-2,7-diene **5**.[2]

Diels–Alder reaction of **5** with methacrylaldehyde in the presence of substoichiometric amounts of aluminium chloride gave racemate **6** in excellent yield and selectivity. Chromic acid oxidation[6] of **6** gave acid **7**. The *cis*-configuration of compounds **6** and **7**, as expected from the *endo*-transition state of the corresponding

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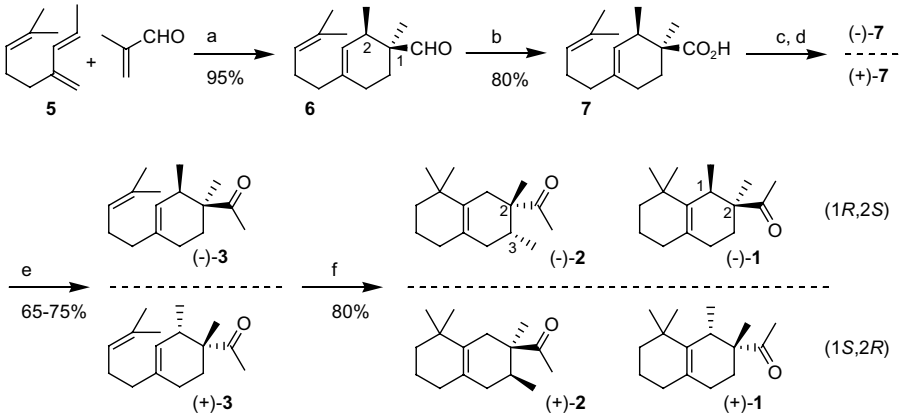

Scheme 2. Synthesis and resolution of racemate **6** and further conversion of the enantiomers. Reagents and conditions: (a) $AlCl_3$, CH_2Cl_2, 1.2 equiv methacrylaldehyde, −50 °C to −30 °C, 0.5 h; (b) Jones' reagent, acetone, 30 °C, 0.5 h; (c) 1 equiv (+)- or (-)-*N*-methyl ephedrine, MeOH, 65 °C, evaporation, then crystallization from hexane/methyl *tert*-butyl ether; (d) 2 M HCl/methyl *tert*-butyl ether; (e) MeLi, −50 °C to 30 °C, 1 h; (f) cryst. H_3PO_4, toluene, 120 °C, 0.5 h.

Diels–Alder reaction, was later deduced from the same known[2] relative configuration of the following compounds **1**–**3**. Acid **7** was subjected to optical resolution with (+)- and (−)-*N*-methylephedrine.[7] The (+)- or (−)-methylephedrine salts of **7** were successively crystallized until melting points and specific rotations reached their maximum values. HCl-treatment of the resolved salts and ether extraction gave the crude acids (−)-**7** or (+)-**7**.[8]

The resolved enantiomers (−)-**7** or (+)-**7** were separately converted to the methyl ketones (−)-**3** or (+)-**3**, which gave after acid-catalyzed cyclization (−)-**1** or (+)-**1** together with their rearranged by-products (−)-**2** or (+)-**2**, respectively (**1**/**2** ratios of 59:41). By-products (−)-**2** or (+)-**2** were separated from the desired enantiomers (−)-**1** or (+)-**1** by flash chromatography (Scheme 2).

The olfactory evaluation showed that (−)-**1** was the more powerful enantiomer, possessing the typical woody-ambery odour of Georgywood **1** with a fresh, minty, green and sweet bottom note (Table 1). The odour threshold value of 20 pg/L air for (−)-**1** fitted nicely with the 30 pg/L determined for the racemate. Antipode (+)-**1** was less powerful by a factor of 175.

For the determination of the absolute configuration, the conformation of ketone **1** was first determined by means of NOEs and computational geometry optimization.[9] It was found that in both isomers **1** and **2**, the methyl groups at C(1) and C(2) are pseudoaxial, with the carbonyl-group being eclipsed with the C(2)–C(3)-bond of **1** or the C(1)–C(2)-bond of **2**. An analogous conformation was found by X-ray structure analysis of oxime **8** (Fig. 1), which was prepared from **1**. In contrast to this typical conformation of the more constrained bicycles **1**, **2** and **8**, the more flexible monocyclic precursor **3** has pseudo-equatorial methyl-groups with an axial acetyl-group with the oxygen-atom located above the endocyclic double bond.

Application of the octant rule predicts a positive $n \rightarrow \pi^*$ transition for the carbonyl group of the most stable conformer of the (1*R*,2*S*)-enantiomer of **1** (Fig. 2), which was found in the CD-spectrum measured of (−)-**1** at $\lambda = 295.5$ nm with a $\Delta\varepsilon_{max}$ at +0.6 (20 °C, hexane). Measurements in $CHCl_3$ did not change the CD-spectra of

Table 1. Olfactory evaluation of the Georgywood

	Enantiomers	
	(−)-**1**	(+)-**1**
$[\alpha]_D^{22}$	−39.2	+41.2
Ee[a]	88%[b]	92%[b]
Odour description	Woody-ambery	Weakly woody
Bottom note	Fresh, minty, green, sweet	Musty
Odour threshold value[c]	20 pg/L	3.5 ng/L[b]
Absolute configuration	(1*R*,2*S*)	(1*S*,2*R*)

[a] Determined by chiral GC.
[b] We are aware of the fact that the separated enantiomers contain 4–6% of their antipodes. This means, however, that the factor of the odour threshold values is >175, because (+)-**1** is even weaker.
[c] Determined on the sniff-outlet of a chiral GC-column with a panel of three experienced fragrance chemists.

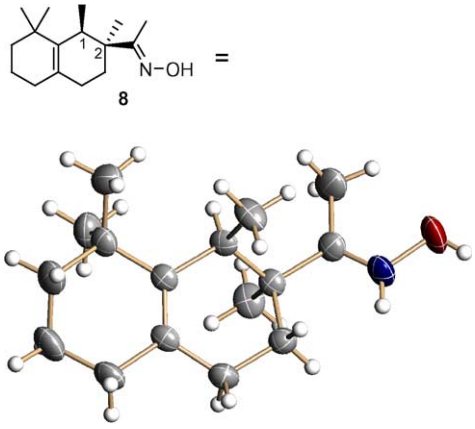

Figure 1. X-ray crystal structure of oxime **8**. The C(2)–C(3)-bond and the C=N-bond are inplane.

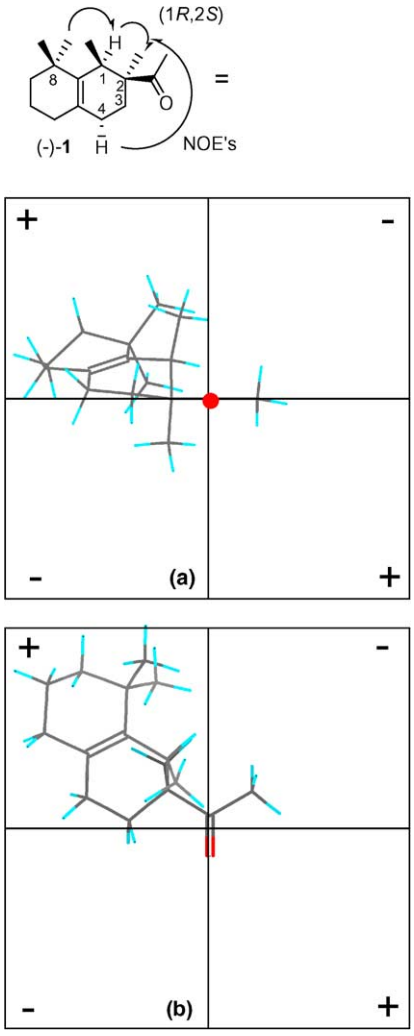

Figure 2. Chemdraw 3D plot of the energy-minimized conformer of Georgywood **1** with (a) view upon the carbonyl-axis with the oxygen-atom pointing towards the observer. Depicted are the 4 backside sectors, the 4 forefront sectors are practically empty. (b) Orthogonal view upon the carbonyl-axis. Depicted are the 4 upper sectors. NOE's: Me(α)–C(8)/H(α)–C(1), H(α)–C(1)/Me(α)–C(2), Me(α)–C(2)/H(α)–C(4).

(−)-**1** or (+)-**1**, at −90 °C, which only made the maxima slightly more pronounced;[10] another indication that the assignment is based on the most stable conformer.

The octant rule is less applicable on the most stable conformer of by-product **2** because positive and negative contributions from the different sectors are more balanced here, giving relatively low $\Delta\varepsilon$'s at $\lambda = 285$ nm. The (2*S*,3*R*)-configuration of (−)-**2**, however, follows from its ^{1}H NMR- and NOE-data and the preisomerization mechanism shown in Scheme 1.

3. Conclusion

The first synthesis of the olfactorily active (−)-(1*R*,2*S*)-enantiomer of Georgywood **1** has been accomplished via classical racemate resolution. Conformational studies and CD measurements allowed the determination of the absolute configuration. The results obtained were independently confirmed by Corey et al., who has recently synthesized both enantiomers of Georgywood (−)-**1** and (+)-**1** via an asymmetric Diels–Alder reaction of homomyrcene **5**, stating that the (−)-enantiomer with its typical woody-ambery odour has a (1*R*,2*S*)-configuration and that its antipode is practically odourless.[11] The much lower olfactory threshold in comparison to its antipode renders (−)-**1** as a promising candidate for fragrance applications, provided an industrially feasible and inexpensive asymmetric synthesis can be developed.

4. Experimental

4.1. General

Reagents and solvents were purchased from commercial suppliers and used without further purification. Solvents for moisture-sensitive reactions contained <0.1% water. Moisture-sensitive reactions were conducted in oven-dried (130 °C) glassware under nitrogen. The given temperatures refer to reaction thermometers. All reactions were carried out under stirring. The silica gel used for flash chromatography was Sorbsil, 0.04–0.063 mm (Merck). Jones' reagent was prepared as described in the literature.[6] Homomyrcene **5** was prepared and enriched as described in Ref. 2.

^{1}H and ^{13}C NMR: Bruker-DPX-400 MHz spectrometer; all spectra were recorded at 400 MHz and in $CDCl_3$; δ in ppm rel. to $SiMe_4$; coupling constants *J* in Hz. GC/MS: Agilent 5973 MSD with 6890 GC; relative intensities in % of the base peak. High resolution GC/MS: Finnigan MAT95 with HP 5890 series II GC. IR: Bruker FT-IR Vector 22 spectrometer, $\nu\sim$ in cm^{-1}. Peak intensities are assigned as strong (s), middle (m) and weak (w). Optical rotations: Perkin–Elmer 241 Polarimeter. Chiral GC: Column OV-1701/Octakis (6-methyl-2,3-pentyl)-γ-CD 1:1; 25 m × 0.25 mm; produced by König (University of Hamburg);[12] 0.7 bar H_2; split 1:50; flow 2.75 mL/min; GC F 2150 from Carlo Erba Instruments; 80 °C isotherm; retention times 156.6 min for (+)-**1** and 160.8 min for (−)-**1**. Chiral Sniff-GC: Column OV 61/β-CDM produced by Givaudan, 20 m × 0.32 mm; split 1:25 at 250 °C; 120 °C isotherm; 0.5 μL injection with 80 ng/μL starting concentration; 0.3 kPa H_2; flow 2 mL/min; GC 8185 from Carlo Erba Instruments; retention times 34.9 min for (+)-**1** and 36.2 min for (−)-**1**. CD-spectra: recorded in the range 200–400 nm on a Jobin-Yvon instrument; 0.1 cm cell; solvent hexane at 20 °C.

4.2. (±)-(1*S**,2*R**)-1,2-Dimethyl-4-(4-methyl-pent-3-enyl)-cyclohex-3-enecarbaldehyde 6

A suspension of $AlCl_3$ (26.6 g, 0.2 mol) in CH_2Cl_2 (450 mL) was cooled to −50 °C. Methacrylaldehyde (58 g, 0.8 mol) in CH_2Cl_2 (100 mL) was added dropwise within 15 min, followed by 70% (*E*)-2-methyl-6-methyl-ene-nona-2,7-diene **5** (100 g, 0.47 mol). The mixture was quenched after another 15 min at −25 °C with water

and extracted with hexane. Washing with $NaHCO_3$, drying over $MgSO_4$, filtration and evaporation of the solvent gave an oily residue, which was distilled under high vacuum to give **6** (102 g, 98%) as a colourless oil at 105 °C/0.2 mbar. ^{1}H NMR: δ 0.98 (d, 3H, J = 7.5), 1.06 (s, 3H), 1.53 (ddd, 1H, J = 7/7/13.5), 1.6 (s, 3H), 1.67 (s, 3H), 1.84 (ddd, 1H, J = 7/7/13.5), 1.9–2.2 (6H), 2.2 (m, 1H) 5.07 (dd, 1H, J = 7/7), 5.32 (m, 1H), 9.67 (s, 1H). ^{13}C NMR: δ 17.0 (q), 17.6 (q), 19.8 (q), 25.3 (t), 25.6 (q), 26.3 (t), 27.9 (t), 36.9 (d), 37.2 (t), 47.1 (s), 124.0 (d), 125.1 (d), 131.4 (s), 136.5 (s), 207.3 (d). MS (EI): *m/z* (%) 220 (M^+, 8), 205 (10), 191 (12), 177 (23), 123 (32), 107 (87), 69 (100). IR (film): ν = 2965 (s), 2922 (s), 2724 (w), 1725 (s), 1453 (m), 1375 (m), 1103 (w) cm^{-1}. HRMS calcd for $C_{15}H_{24}O$: 220.1824; found 220.1827. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.82; H, 10.95.

4.3. (±)-(1*S**,2*R**)-1,2-Dimethyl-4-(4-methyl-pent-3-enyl)-cyclohex-3-enecarboxylic acid 7

Jones' reagent[6] (230 mL, 0.6 mol CrO_3) was added at 30 °C under vigorous stirring to aldehyde **6** (90 g, 0.4 mol) in acetone (40 mL). At 85% conversion, water was added. After extraction with methyl *tert*-butyl ether, the organic phase was washed with water and extracted with 15% K_2CO_3. The aqueous layer was acidified to pH 3 and extracted with methyl *tert*-butyl ether. The resulting organic phase was dried over $MgSO_4$, filtered and evaporated to give 79.8 g of a crystalline mass, which was recrystallized from methanol at −70 °C to give **7** (61 g, 65%) as white crystals; mp 64–67 °C. ^{1}H NMR: δ 0.96 (d, 3H, J = 8), 1.23 (s, 3H), 1.57 (m, 1H), 1.6 (s, 3H), 1.67 (s, 3H), 1.88 (m, 1H), 1.9–2.0 (4H), 2.07 (m, 2H), 2.2 (m, 2H), 5.07 (dd, 1H, J = 7/7), 5.32 (d, 1H, J = 5). ^{13}C NMR: δ 17.7 (q), 18.2 (q), 19.8 (q), 22.1 (q), 25.1 (t), 25.3 (t), 25.7 (q), 26.4 (t), 37.2 (t), 37.6 (d), 43.9 (s), 124.2 (d), 124.6 (d), 131.4 (s), 134.2 (s), 184.6 (s). MS (EI): *m/z* (%) 236 (M^+, 10), 221 (7), 193 (23), 147 (22), 121 (88), 107 (40), 69 (70), 41 (100). IR (KBr): ν = 2962 (m), 2912 (m), 2873 (m), 1696 (s), 1449 (w), 1374 (w), 1295 (m), 1146 (w), 936 (w) cm^{-1}. HRMS calcd for $C_{15}H_{24}O_2$: 236.1776; found 236.1774. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.74; H, 10.08.

4.3.1. Resolution of the racemate 7

4.3.1.1. (−)-(1*S*,2*R*)-1,2-Dimethyl-4-(4-methyl-pent-3-enyl)-cyclohex-3-enecarboxylic acid (−)-7. (−)-(1*R*,2*S*)-Methylephedrine (25 g, 0.14 mol) and racemate **7** (33 g, 0.14 mol) were dissolved in methanol at 65 °C. The methanol was evaporated in vacuo and the residue dissolved in methyl *tert*-butyl ether (50 mL) and hexane (150 mL). The solution was cooled to −30 °C, where crystallization occurred, giving after filtration mother liquor ML-1 and the crystalline (−)-methylephedrine salt. Two recrystallizations from *tert*-butyl ether/hexane at 4 and 45 °C, filtration and drying raised the mp to 86–87 °C with $[\alpha]_D^{22} = -102.4$ (c 2.1, EtOH). The thus obtained (−)-methylephedrine salt was treated with 2 M HCl and extracted with methyl *tert*-butyl ether. Drying of the organic phase over $MgSO_4$, filtration and evaporation of the solvent gave (−)-**7** as crystalline residue (5.9 g, 36%); mp 39–43 °C. $[\alpha]_D^{22} = -145.9$ (c 2.2, EtOH). The spectral data of (−)-**7** was superimposable on the ones of racemate **7**.

4.3.1.2. (+)-(1*R*,2*S*)-1,2-Dimethyl-4-(4-methyl-pent-3-enyl)-cyclohex-3-enecarboxylic acid (+)-7. The mother liquor ML-1 of procedure 4.3.1.1. was treated with 2 M HCl and extracted with methyl *tert*-butyl ether. Drying of the organic phase over $MgSO_4$ and evaporation of the solvent in vacuo gave slightly enriched acid (20.8 g, 0.11 mol) with $[\alpha]_D^{22} = +57.5$ (c 2.1, EtOH). The crude acid (25 g, 0.11 mol) and (+)-(1*S*,2*R*)-methylephedrine (20 g, 0.11 mol) were dissolved in methanol at 65 °C. The methanol was evaporated in vacuo. The residue was dissolved in methyl *tert*-butyl ether (60 mL) and hexane (180 mL) and crystallized at −80 °C. The mixture was warmed up to 30 °C and kept for 36 h at 0 °C. Filtration and recrystallization from methyl *tert*-butyl ether/hexane at 30–50 °C followed by filtration and evaporation of the solvents gave 19 g (+)-methylephedrine salt; mp 88 °C with $[\alpha]_D^{22} = +112.7$ (c 2.1, EtOH). The thus-obtained (+)-methylephedrine salt was treated with 2 M HCl and extracted with methyl *tert*-butyl ether. Drying of the organic phase over $MgSO_4$, filtration and evaporation of the solvent gave (+)-**7** as crystalline residue (6.2 g, 50%); mp 40–43 °C. $[\alpha]_D^{22} = +157.3$ (c 2.0, EtOH). NMR, IR and MS-spectra of (+)-**7** were superimposable on the ones of the racemate **7**.

4.4. Conversion of the acids (−)-7 or (+)-7 to the ketones (−)-3 or (+)-3

4.4.1. (−)-(1*S*,2*R*)-1-[1,2-Dimethyl-4-(4-methyl-pent-3-enyl)-cyclohex-3-enyl]-ethanone (−)-3. Methyllithium 0.9 M in diethyl ether (110 mL, 0.1 mol) was added dropwise at −50 °C to a solution of (−)-**7** (6.5 g, 28 mmol) in methyl *tert*-butyl ether (70 mL). After 1 h at 35 °C, acetone (5 mL) was added under cooling, followed by water. Hexane extraction, drying of the organic phase over $MgSO_4$, filtration and evaporation of the solvent gave an oily residue, which was purified by bulb-to-bulb distillation giving (−)-**3** (4.9 g, 70%) as a colourless oil at 120 °C/0.1 mbar. $[\alpha]_D^{22} = -170.4$ (c 2.1, EtOH). ^{1}H NMR: δ 0.81 (d, 3H, J = 7.4), 1.12 (s, 3H), 1.5 (m, 1H), 1.6 (s, 3H), 1.67 (s, 3H), 1.92 (m, 1H), 1.96 (4H), 2.07 (m, 2H), 2.13 (s, 3H), 2.21 (m, 1H), 5.07 (dd, 1H, J = 6.4/6.4), 5.32 (d, 1H, J = 5.2). ^{13}C NMR: δ 17.5 (q), 18.0 (q), 20.9 (q), 23.6 (t), 25.2 (t), 25.4 (q), 25.5 (q), 26.2 (t), 37.1 (t), 37.2 (d), 48.9 (s), 124.0 (d), 124.4 (d), 131.1 (s), 135.0 (s), 213.5 (s). MS (EI): *m/z* (%) 234 (M^+, 6), 219 (2), 191 (40), 165 (8), 121 (45), 121 (88), 107 (100). IR (film): ν = 2966 (m), 2931 (m), 2875 (m), 1705 (s), 1454 (m), 1354 (m), 1239 (w), 1108 (w), 1086 (w) cm^{-1}. HRMS calcd for $C_{16}H_{26}O$: 234.1984; found 234.1979. Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 82.04; H, 11.19.

4.4.2. (+)-(1*R*,2*S*)-1-[1,2-Dimethyl-4-(4-methyl-pent-3-enyl)-cyclohex-3-enyl]-ethanone (+)-3. Acid (+)-**7** (6 g, 25 mmol) was treated in analogy to procedure 4.4.1. with methyllithium (100 mL, 90 mmol) to give after work-up and distillation (+)-**3** (3.8 g, 65%) as a colourless oil.

$[\alpha]_D^{22} = +189.8$ (*c* 2.1, EtOH). Physical and spectral data are identical to the ones of antipode (−)-**3**.

4.5. Acid-catalyzed cyclization of the ketones (−)-3 or (+)-3

4.5.1. (−)-(1*R*,2*S*)-1-(1,2,8,8-Tetramethyl-1,2,3,4,5,6,7,8-octahydro-naphthalen-2-yl)-ethanone (−)-1. Crystalline phosphoric acid (2.9 g, 30 mmol) and ketone (−)-**3** (4.6 g, 20 mmol) in toluene (8 mL) were rapidly heated to 120 °C and kept at this temperature for 30 min. The mixture was cooled below 0 °C and hydrolyzed with ice. After extraction with methyl *tert*-butyl ether, the organic layers were washed until pH 7, dried over $MgSO_4$, filtered and evaporated in vacuo. Bulb-to-bulb distillation of the residue at 150 °C/0.1 mbar gave 4 g of a colourless oil (**1**/**2** ratio 59:41), which was purified by flash chromatography over silica gel with hexane/methyl *tert*-butyl ether 95:5 as eluent. All fractions containing >80% **1** were pooled, the solvents evaporated in vacuo and the residue crystallized 4 times from methanol at −80 °C to give after evaporation of the solvent below 0 °C, white crystals, which were liquefied above 0 °C to give (−)-**1** as a colourless oil (1 g, 22%). Olfactory evaluation 0.2% in diethylphthalate: typical Georgywood, fresh, minty, sweet. $[\alpha]_D^{22} = -39.2$ (*c* 2.0, EtOH). 88% ee (chiral GC). ^{1}H NMR: δ 0.85 (d, 3H, $J = 6.9$), 0.99 (s, 3H), 1.02 (s, 3H), 1.06 (s, 3H), 1.4–2.2 (10H), 2.15 (s, 3H,), 2.36 (q, 1H, $J = 6.9$ Hz). ^{13}C NMR: δ 19.15 (t), 19.7 (q), 21.1 (q), 22.5 (t), 24.9 (q), 27.7 (t), 28.4 (q), 29.4 (q), 30.8 (t), 34.0 (s), 35.4 (d), 40.1 (t), 50.7 (s), 125.9 (s), 136.95 (s), 214.5 (s). MS (EI): *m*/*z* (%) 234 (M^+, 25), 219 (15), 191 (100), 161 (20), 135 (65), 121 (40), 105 (40), 91 (30). IR (film): $\nu = 2930$ (m), 1700 (s), 1460 (m), 1377 (m), 1357 (m), 1240 (w), 1220 (w), 1090 (m) cm^{-1}. CD: λ_{max} ($\Delta\varepsilon$) 295.5 (0.6), 240 (0), 212 (−1.7). HRMS calcd for $C_{16}H_{26}O$: 234.1984; found 236.1981.

4.5.2. (+)-(1*S*,2*R*)-1-(1,2,8,8-Tetramethyl-1,2,3,4,5,6,7,8-octahydro-naphthalen-2-yl)-ethanone (+)-1. Cryst. phosphoric acid (1.7 g, 18 mmol) and ketone (+)-**3** (4.6 g, 20 mmol) in toluene (5 mL) were treated as described in procedure 4.5.1. to give, after bulb-to-bulb distillation, flash chromatography and crystallization, (+)-**1** as colourless oil (0.7 g, 23%). $[\alpha]_D^{22} = +41.2$ (*c* 2.0, EtOH). 92% ee (chiral GC). CD: λ_{max} ($\Delta\varepsilon$) 295.5 (−0.6), 240 (0), 212 (1.7). NMR, IR and MS spectra were identical to the ones of antipode (−)-**1**.

4.5.3. (−)-(2*S*,3*R*)-1-(2,3,8,8-Tetramethyl-1,2,3,4,5,6,7,8-octahydro-naphthalen-2-yl)-ethanone (−)-2. Evaporation of the prefractions of the flash chromatography described in procedure 4.5.1. in vacuo gave (−)-**2** (0.25 g, 5%) as a colourless oil. $[\alpha]_D^{22} = -9.1$ (*c* 2.0, EtOH). ^{1}H NMR: δ 0.75 (d, 3H, $J = 6.8$), 0.99 (s, 3H), 0.97 (s, 3H), 1.01 (s, 3H), 1.06 (s), 1.5 (m, 2H), 1.6 (m, 2H), 1.65–1.85 (4H), 1.94 (ddd, $J = 3.5/6.8/6.8$, 1H), 2.22 (d, $J = 17.2$, 1H), 2.35 (d, $J = 17.2$, 1H). ^{13}C NMR: δ 16.6 (q), 19.2 (t), 22.2 (q), 24.7 (q), 27.0 (q), 27.9 (t), 28.0 (q), 30.9 (t), 33.2 (d), 33.5 (s), 35.4 (t), 39.5 (t), 49.5 (s), 123.6 (s), 131.6 (s), 213.9 (s). NOE's: H(α)–C(1)/Me(α)–C(3), Me(β)–C(2)/H(β)–C(4). MS (EI): *m*/*z* (%) 234 (M^+, 8), 219 (14), 191 (100), 177 (10), 161 (8), 135 (20), 121 (32), 105 (25), 91 (19). IR (film): $\nu = 2964$ (m), 2943 (m), 2905 (m), 2893 (m), 2873 (m), 2835 (w), 1697 (s), 1456 (w), 1430 (w), 1379 (w), 1361 (m), 1216 (w), 1201 (w), 1121 (w), 1091 (w), 1081 (w), 970 (w) cm^{-1}. CD: λ_{max} ($\Delta\varepsilon$) 285 (−0.1), 245 (0), 230 (0.3), 219 (−0.1). HRMS calcd for $C_{16}H_{26}O$: 234.1984; found 234.1978. Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.98; H, 11.20.

4.5.4. (+)-(2*R*,3*S*)-1-(2,3,8,8-Tetramethyl-1,2,3,4,5,6,7,8-octahydro-naphthalen-2-yl)-ethanone (+)-2. Evaporation of the prefractions of the flash chromatography of procedure 4.5.2. in vacuo gave (+)-**2** (0.2 g, 7%) as a colourless oil. $[\alpha]_D^{22} = +10.2$ (*c* 2.0, EtOH). CD: λ_{max} ($\Delta\varepsilon$) 285 (0.1), 245 (0), 232 (−0.3), 221 (0.1). NMR, IR and MS spectra were identical to the ones of antipode (−)-**2**.

4.6. (±)-*E*-(1*R**,2*S**)-1-(1,2,8,8-Tetramethyl-1,2,3,4,5,6,7,8-octahydro-naphthalen-2-yl)-ethanone oxime 8

Georgywood **1** (1 g, 4.3 mmol) was added dropwise to a slurry of hydroxylamine hydrochloride (3 g, 40 mmol), sodium acetate (4 g, 50 mmol) and water (3 mL). After addition of ethanol (20 mL), the mixture was heated for 1.5 h to reflux until complete conversion was detected by GC. After addition of water (100 mL) and extraction with methyl *tert*-butyl ether, filtration and evaporation of the filtrate under reduced pressure a crystalline residue was obtained, which was dissolved in hot ethanol (10 mL). Upon cooling, the oxime crystallized. Filtration, washing with cold ethanol and drying of the crystals under high vacuum gave oxime **8** (0.85 g, 79%); mp 145 °C. ^{1}H NMR: δ 0.86 (d, 3H, $J = 7$), 0.97 (s, 3H), 0.99 (s, 3H), 1.06 (s, 3H), 1.4–1.55 (3H), 1.57–1.67 (m, 2H), 1.7–1.8 (m, 1H), 1.82–1.87 (1H), 1.89 (s, 3H), 1.9–2.07 (2H), 2.15–2.22 (dd, 1H, $J = 6.4$, 12.8), 9.57 (s, 1H). ^{13}C NMR: δ 10.2 (q), 19.3 (t), 19.4 (q), 21.7 (q), 23.9 (t), 28.1 (t), 28.5 (q), 29.7 (q), 30.9 (t), 34.2 (s), 35.3 (d), 40.3 (t), 43.5 (s), 126.0 (s), 137.2 (s), 164.2 (s). MS (EI): *m*/*z* (%) 249 (M^+, 40), 234 (52), 232 (78), 2.6 (65), 191 (18), 150 (18), 135 (100), 121 (37), 112 (55). IR (film): IR (film): $\nu = 3237$ (m), 2931 (s), 2900 (s), 2869 (s), 2829 (m), 1662 (w), 1450 (m), 1379 (m), 1261 (w), 984 (w), 740 (s) cm^{-1}. HRMS calcd for $C_{16}H_{27}NO$: 249.2093; found 249.2095. Anal. Calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.62. Found: C, 77.00; H, 10.86; N, 5.67.

Crystal data: $C_{16}H_{27}NO$, formula weight 249.39, crystal size $0.3 \times 0.4 \times 0.3$ mm, monoclinic, space group *P*2(1)/n, $Z = 4$, $a = 9.398$ (19) Å, $b = 14.160$ (3) Å, $c = 11.386$ (2) Å, $\alpha = \gamma = 90°$, $\beta = 94.97$ (3)°, $V = 1509.5(5)$ Å^3, $d = 1.097$ g/cm^3, absorption coefficient = 0.512 mm^{-1}, $F(000) = 552$, $\lambda = 1.54178$ Å (CuKα, rotating anode), 3466 reflections collected ($0 \leqslant h \leqslant 12$, $0 \leqslant k \leqslant 18$, $-14 \leqslant l \leqslant 14$) on a Siemens P4 diffraction measurement device. $T = 293$ (2) K. Theta range for data collection: 5.00°–80.36°. Independent reflections: 1891 [*R*(int) = 0.2358]. Refinement method: Full-matrix least-squares on F^2. Completeness to theta = 80.36: 99.0%. Data/restraints/parameters: 3270/0/168. Goodness-of-fit on F^2: 1.073. Final *R* indices [$I > 2$sigma(I)]:

$R1 = 0.1111$, $wR2 = 0.2685$. R indices (all data): $R1 = 0.1592$, $wR2 = 0.3193$. Largest diff. peak and hole: 0.421 and $-0.445\,e\,Å^{-3}$. Full crystallographic results have been deposited as CIF-file at the Cambridge Crystallographic Data Centre, UK.[13]

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