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# The Synthesis of (+)-Hedycaryol, Starting from Natural (–)-Guaiol

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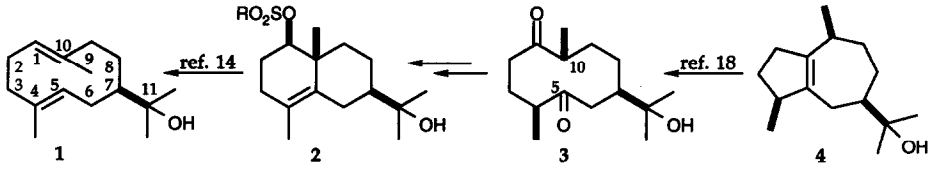
***Abstract:*** *Starting from the readily available (–)-guaiol the germacrane sesquiterpene (+)-hedycaryol can be synthesized in a 7 steps reaction sequence in an overall yield of 16%. Additionally, (+)-γ-eudesmol has been synthesized, also starting from (–)-guaiol.*

The germacrane sesquiterpene (+)-hedycaryol (**1**) has been found in several plant species, e.g. *Phebalium ozothamnoides*,[1] *Rubus rosifolius*,[2] *Thujopsis dolabrata*,[3] *Hyssopus officinalis*,[4] and two *Cryptomeria* spp.,[5] and has been used as a chemotype characterizing compound in *Thymus* spp.[6] Some years before its first isolation from *Hedycarya angustifolia*,[7] hedycaryol was proposed as an important intermediate in the biosynthesis of several classes of sesquiterpene alcohols,[8] and recently, also as a common precursor for several sesquiterpene ethers.[9] The isolation of hedycaryol is rather complicated because the compound is thermally labile and especially sensitive to acids.[10] Under the influence of elevated temperatures hedycaryol rearranges to elemol and, upon treatment with acid, it cyclizes to a mixture of α-, β-, and γ-eudesmol.[11] After a first attempt to synthesize (±)-hedycaryol,[12] two successful syntheses have been reported in the literature, both in low overall yield.[10,13] No synthesis of natural (+)-hedycaryol is known.

Because of our interest in the biogenetic-type cyclization reactions of the conformationally flexible germacrane sesquiterpenes, we are looking for an efficient and chiral synthesis of (+)-hedycaryol (**1**). The fragmentation reaction of organoboranes derived from naphthalene systems to 1,5-cyclodecadienes is very promising in this connection because both double bonds are formed regio- and stereospecifically, and deuterium can easily be incorporated at C1 and C5.[14,15] This strategy needs the synthesis of the chiral eudesmane derivative **2** (Scheme I).

**Scheme I**



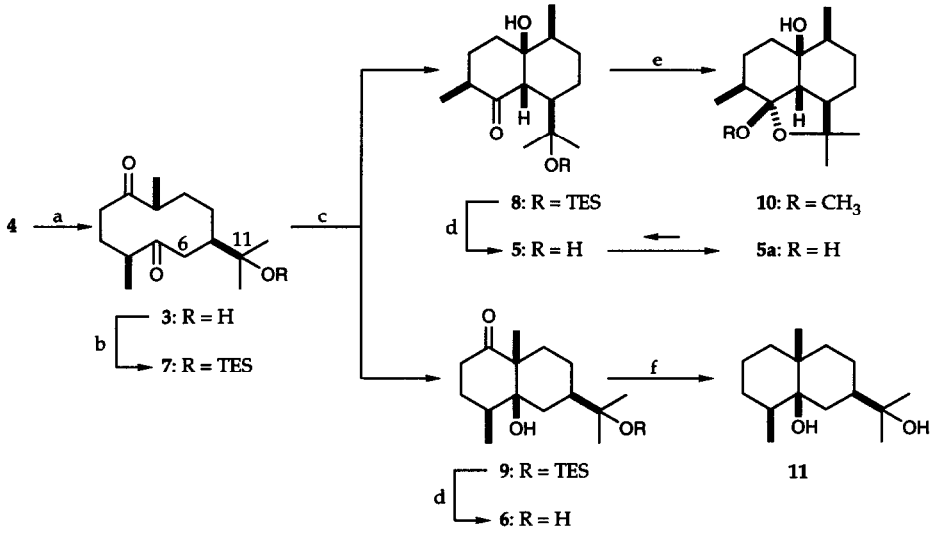

The naturally occurring sesquiterpene (–)-guaiol (**4**) seems to be a suitable starting compound for the synthesis of **2**. It is known that guaiol, which has only been used occasionally in chiral synthesis,[16,17] can be oxidized to the cyclodecane-1,5-dione **3**.[18] When a selective intramolecular aldol condensation reaction of **3**, leading to C5–C10 bond formation can be accomplished, it is possible to synthesize **2** and thus also **1**. This approach will be demonstrated in this paper.

A simple method to obtain large quantities of pure **4** from the commercially available Guaiac wood oil turned out to be crystallization of the crude oil from acetone and subsequent recrystallization of the remaining crystalline mass from water/ethanol mixtures. An extra crop of **4** was obtained when the mother liquor, which consisted mainly of bulnesol, was treated with $H_2$ and Pd/C.[16] During this reaction bulnesol isomerized to a mixture of **4** and *iso*-guaiol.

Although ozonolysis of **4** gave good yields (72–74%) of the dione **3**,[18] the oxidative cleavage of the central double bond was performed with $RuO_2/NaIO_4$[19] in a mixture of $CCl_4$, MeCN, and $H_2O$ at room temperature. In this way **3** could be obtained in 95% yield (Scheme II). It is known that dione **3** easily cyclizes to the cadinane **5**.[18] The stereochemistry of **5** was recently revised,[20] and the suggestion was made that the C11 hydroxyl group plays an important role in the selective deprotonation at C6 in the cyclization process. Therefore, it is reasonable to assume that protection of the C11 hydroxyl group may lead to the formation of compounds with an eudesmane skeleton, e.g. **9**, in addition to, or instead of, cadinane formation. The resulting eudesmane compound **9** would have all the structural features needed for an effective synthesis of **2**.

To confirm this assumption, it was necessary to protect the hydroxyl group at C11 in **3** as its triethylsilylether (**3** → **7**). The key step in our approach, the intramolecular aldol condensation reaction of **7**, indeed gave the eudesmane **9** as the main product. Upon treatment with KOH in EtOH, the triethylsilylether **7** afforded a ca. 1:2 mixture of **8** and **9**, respectively, from which **9** could be isolated in 55% yield after careful column chromatography. Despite an extensive search for other conditions, the yield of **9** could not be improved. Stronger bases clearly favored the formation of **8**, as did the use of other solvents. For instance KOH in THF gave exclusively **8**. The structure of **8** could be assigned after cleavage of its silylether bond with HF in MeCN, which led to the known cadinane **5**.[20] It is interesting to note that in solution **5** exists in equilibrium with its lactol form **5a**, according to the NMR spectral data. This explains the quantitative formation of the cyclic acetal **10** upon a short treatment of a methanolic solution of both **5** and **8** with *p*-TsOH.

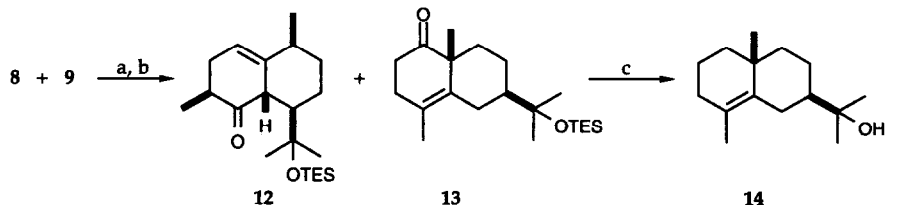
**Scheme II**[a]




[a] (a) $RuO_2$, $NaIO_4$; (b) TESCl, imidazole, DMF; (c) KOH, EtOH; (d) HF; (e) *p*-TsOH, MeOH; (f) *p*-$TsNHNH_2$, MeOH; $NaBH_3CN$, $ZnCl_2$, MeOH.

The ring junction of the eudesmane **9** as shown in scheme II was deduced from its conversion into the reported *cis*-fused compound **11**.[21] However, the stereochemistry of the methyl group at C4 in this compound was unknown. To assign this orientation, cleavage of the TES ether bond in **9** was necessary. In the $^1H$ NMR spectrum of the desilylated product **6** the doublet (δ 0.96) due to the methyl group at C4 is no longer obscured by other signals. By irradiation of this doublet, the signal of the C4 proton appears as a double doublet at δ 2.39 with couplings of 12.3 and 4.5 Hz. This means that the methyl group at C4 is equatorially oriented.

**Scheme III**[a]

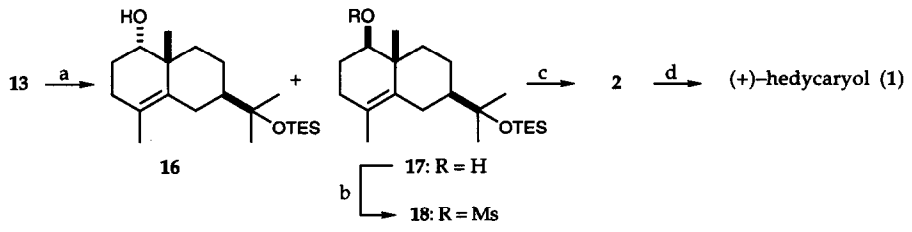



[a] (a) $SOCl_2$, pyridine; (b) separation; (c) *p*-$TsNHNH_2$, MeOH; $NaBH_3CN$, $ZnCl_2$, MeOH.

Treatment of **9** with $SOCl_2$ in pyridine gave **13** as the sole product in excellent yield (Scheme III). Furthermore, it was found that after treatment of the above-mentioned 1:2 mixture of **8** and **9** with $SOCl_2$ in pyridine, an easily separable mixture of **12** and **13**, respectively, was obtained. In this way the troublesome separation of **8** and **9** by means of column chromatography could be avoided, and a better overall yield of **13** (44% from **7**) was obtained. Additional support for the assigned structure of **13** was obtained through synthesis of the known natural sesquiterpene (+)-γ-eudesmol (**14**)[22] via a Wolff–Kishner reduction of **13**. During this reduction also cleavage of the silylether bond took place.

To complete the synthesis of (+)-hedycaryol, the carbonyl group of **13** had to be reduced to a β-hydroxyl function. The use of $NaBH_4$ in EtOH gave, after separation, 17% of the α-alcohol **16** and 73% of the desired β-alcohol **17**[23] (Scheme IV). Treatment of **17** with MsCl in pyridine afforded the mesylate **2**. Fragmentation was accomplished using Marshall's procedure[24] to give, after extraction with aqueous $AgNO_3$,[1] pure **1** in 55% yield. It must be noted that during the NMR measurements slow decomposition of **1** was observed in commercial $CDCl_3$, even when this solvent was pretreated with basic alumina. In $C_6D_6$ solutions **1** appeared to be stable.

**Scheme IV**[a]




[a] (a) $NaBH_4$, EtOH; (b) MsCl, pyridine; (c) HF; (d) $BH_3$·THF; NaOMe, MeOH.

Thus, starting from the readily available (–)-guaiol (**4**), (+)-hedycaryol (**1**) has been synthesized in a 7 steps reaction sequence in an overall yield of 16%.

## EXPERIMENTAL SECTION

Melting points were determined on a Mettler FP80 HT melting point apparatus and are uncorrected. Optical rotations were obtained from $CHCl_3$ solutions on a Perkin-Elmer 241 polarimeter. $^1H$ and $^{13}C$ NMR spectra were determined in $CDCl_3$ (unless indicated otherwise) at 200 MHz and 50 MHz, respectively, on a Bruker AC-E 200 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectral data were determined on an AEI MS 902 spectrometer. FT-IR spectra were determined on a BIO-RAD FTS-7 infra-red spectrometer. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. GC analyses were carried out on a Varian Vista 6000 gas chromatograph with a flame ionization detector and a DB-17 fused silica capillary column, 30 m x 0.25 mm i.d., film thickness 0.25 μm. Peak areas were integrated electronically with a

Fisons integrator DP700. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh), unless otherwise noted. The silica gel used for column chromatography was Merck silica gel 60 (70-230 mesh). Solvents were dried and distilled fresh by common practice. For all dry reactions, flasks were dried at 150°C and flushed with dry nitrogen just before use, and reactions were carried out under an atmosphere of dry nitrogen. Product solutions were dried over anhydrous $MgSO_4$ (unless otherwise noted) prior to evaporation of the solvent under reduced pressure by using a rotary evaporator.

**Isolation of (–)-guaiol (4).** A solution of 323 g of Guaiac wood oil[25] (guaiol content ca. 37% according to GC) in 430 mL of acetone was stored for two days at –20 °C. The formed crystals were isolated by suction filtration and dried under reduced pressure to give 125 g of crude guaiol, (GC purity 70%). Recrystallization from a 3:1 mixture of EtOH/$H_2O$ (380 mL) afforded 83 g of pure guaiol as white crystals, (GC purity >97%). A second crop (7 g) of guaiol was obtained from the mother liquor after treatment with Pd/C in a $H_2$ atmosphere as described in the literature,[16] followed by the above-mentioned crystallization procedure using EtOH/$H_2O$.

**[2S-(2R*,6R*,9S*)]-9-(1-hydroxy-1-methylethyl)-2,6-dimethyl-1,5-cyclodecanedione (3).** To a vigorously stirred solution of 60.0 g (0.262 mol) of **4** in a mixture of 350 mL of MeCN, 350 mL of $CCl_4$, and 600 mL of $H_2O$ was added 87.0 g (0.407 mol) of $NaIO_4$ and 0.36 g of $RuO_2.xH_2O$. The flask was closed air-tight, and the reaction mixture was stirred at room temperature until completion (45 min, according to GC). After dropwise addition of 20 mL of 2-propanol, the mixture was stirred for an additional 30 min. Then 200 mL of saturated aqueous $Na_2S_2O_3$ and 300 mL of $CH_2Cl_2$ were added. The mixture was stirred for 10 min and filtered. The two-phase filtrate was separated, and the aqueous layer was extracted with three portions of $CH_2Cl_2$. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed on silica gel (70-230 mesh) [30% EtOAc in petroleum ether (bp 40-60°C)] to give 63.2 g (95%) of **3** as white crystals. Physical and spectroscopic data were consistent with those reported in the literature.[18]

**[2S-(2R*,6R*,9S*)]-9-[1-(triethylsilyl)oxy-1-methylethyl]-2,6-dimethyl-1,5-cyclodecanedione (7).** To a stirred solution of 38.3 g (0.151 mol) of **3** and 35.0 g (0.515 mol) of imidazole in 300 mL of DMF was added 27.8 mL (0.166 mol) of TESCl. After stirring at room temperature for 4.5 h, the reaction mixture was poured into an ice-cooled mixture of saturated aqueous $NaHCO_3$ and petroleum ether (bp 40-60°C). The two-phase mixture was separated, and the aqueous layer was extracted with four portions of petroleum ether (bp 40-60°C). The combined organic layers were washed with brine and dried. Evaporation gave 53.3 g of crude **7** which, according to NMR, contained some residual triethylsilanol. A sample (5.96 g) of crude **7** was purified by flash chromatography [5% EtOAc in petroleum ether (bp 40-60°C)] to give 5.72 g (92%) of **7** as a colorless oil: $[\alpha]_D$ –13.2° (c 1.67); $^1H$ NMR δ 0.61 (q, *J* = 8.0 Hz, 6H), 0.98 (t, *J* = 8.0 Hz, 9H), 1.06 (d, *J* = 5.9 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.07(s, 3H), 1.28 (s, 3H), 1.48-2.02 (m, 8H), 2.09 (m, 1H), 2.38 (m, 1H), 2.67 (m, 1H), 2.93-3.12 (m, 2H); $^{13}C$ NMR δ 6.48 (3·t), 6.87 (3·q), 17.66 (q), 19.23 (q), 24.90 (q), 26.84 (t), 28.39 (q), 29.79 (t), 30.50 (t), 33.91 (t), 40.78 (d), 45.11 (t), 45.11 (d), 50.05 (d), 75.35 (s), 216.60 (s), 218.48 (s); mass spectrum, *m/z* (relative intensity) 339 ($M^+$–29, 14), 321 (3), 263 (4), 219 (7), 218 (6), 173 (100), 116 (26), 104 (13), 88 (11), 76 (13); calcd for $C_{19}H_{35}O_3Si$ ($M^+$–29) *m/z* 339.2355, found *m/z* 339.2355.

**[2S-(2α,4aα,5α,8α,8aα)]-Octahydro-2,5-dimethyl-8-[1-(triethylsilyl)oxy-1-methylethyl]-1(2*H*)-naphthalenone (8) and [4S-(4α,4aα,6α,8aα)]-Octahydro-4,8a-dimethyl-6-[1-(triethylsilyl)oxy-1-methylethyl]-1(2*H*)-naphthalenone (9).** To a stirred solution of 49.3 g (ca. 0.13 mol) of crude **7** in 200 mL of EtOH was added a solution of 3.0 g (53 mmol) of KOH in 50 mL of EtOH. The reaction

mixture was stirred at room temperature for 1.5 h, and then 35 ml of saturated aqueous $NH_4Cl$ was added. After dilution with $H_2O$, the reaction mixture was extracted with five portions of EtOAc. The combined organic layers were washed with brine, dried, and evaporated. Crystallization of the resulting residue from diisopropylether and careful chromatography of the mother liquor [25% ether in petroleum ether (bp 40-60°C)] gave 14.0 g (30%) of pure **8**, 3.5 g of a mixture of **8** and **9**, and 26.0 g (55%) of pure **9**.

**8**: mp 106-107°C (from diisopropylether); $[\alpha]_D$ +54.4° (c 1.21); $^1H$ NMR (main peaks)[26] δ 0.57 (q, *J* = 7.7 Hz, 6H), 0.89 (t, *J* = 7.7 Hz, 9H), 0.93 (d, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 1.18 (s, 6H); $^{13}C$ NMR (main peaks)[26] δ 6.25 (3·t), 6.83 (3·q), 13.24 (q), 21.82 (t), 28.36 (t), 28.81 (q), 31.65 (t), 214.96 (s); mass spectrum, *m/z* (relative intensity) 339 ($M^+$–29, 12), 321 (12), 310 (9), 263 (6), 229 (29), 173 (100), 116 (27), 104 (15), 88 (15), 76 (15); calcd for $C_{19}H_{35}O_3Si$ ($M^+$–29) *m/z* 339.2355, found *m/z* 339.2354. Anal. Calcd for $C_{21}H_{40}O_3Si$: C, 68.44; H, 10.94. Found: C, 68.66; H, 11.11.

**9**: mp 71°C (from diisopropylether); $[\alpha]_D$ –62.1° (c 1.77); $^1H$ NMR δ 0.59 (q, *J* = 7.8 Hz, 6H), 0.95 (d, *J* = 5.4 Hz, 3H), 0.96 (t, *J* = 7.8 Hz, 9H), 1.17 (s, 3H), 1.19 (s, 3H), 1.21 (s, 3H), 1.28-2.08 (m, 10H), 2.26-2.54 (m, 2H), 2.67 (m, 1H); $^{13}C$ NMR δ 6.57 (3·t), 6.91 (3·q), 14.13 (q), 14.51 (q), 21.17 (t), 27.01 (q), 27.62 (q), 28.78 (t), 31.94 (d), 32.80 (t), 34.04 (t), 37.37 (t), 46.00 (d), 53.72 (s), 74.27 (s), 78.03 (s), 215.85 (s); mass spectrum, *m/z* (relative intensity) 310 ($M^+$–58, 4), 292 (7), 174 (17), 173 (100), 169 (6), 116 (17), 104 (7), 88 (7), 76 (9); calcd for $C_{19}H_{35}O_3Si$ ($M^+$–29) *m/z* 339.2355, found *m/z* 339.2354. Anal. Calcd for $C_{21}H_{40}O_3Si$: C, 68.44; H, 10.94. Found: C, 68.59; H, 11.16.

**[2S-(2α,4aα,5α,8α,8aα)]-Octahydro-2,5-dimethyl-8-[1-hydroxy-1-methylethyl]-1(2*H*)-naphthalenone (5).** To a solution of 0.40 g (1.08 mmol) of **8** in 5 mL of MeCN was added 0.13 mL of 40% aqueous HF. The reaction mixture was stirred at room temperature for 15 min and then poured into saturated aqueous $NaHCO_3$. After extraction of the aqueous layer with four portions of EtOAc, the combined organic layers were dried and evaporated. Crystallization of the resulting residue from acetone gave 0.248 g (90 %) of **5**: mp 224-225°C (lit.[20]: 223-225°C); $[\alpha]_D$ +48.9° (c 1.59, MeOH) (lit.[20]: +50°, MeOH); mass spectrum, calcd for $C_{15}H_{24}O_2$ ($M^+$–18) *m/z* 236.1776, found *m/z* 236.1777. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.71; H, 10.37. The $^1H$- and $^{13}C$ NMR spectra of **5** revealed the presence of **5a** in about 80%.

**5**: $^1H$ NMR (main peaks) δ 2.96 (m, 1H); $^{13}C$ NMR (main peaks) δ 13.03, 21.57, 23.55, 30.24, 32.41, 38.20, 40.63, 49.93, 56.84, 78.78.

**5a**: $^1H$ NMR (main peaks) δ 0.97 (d, *J* = 6.4 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.17 (s, 3H), 1.21 (s, 3H); $^{13}C$ NMR δ 12.50 (q), 14.22 (q), 20.09 (t), 24.44 (q), 27.23 (t), 28.94 (q), 31.11 (t), 32.86 (t), 37.80 (d), 38.67 (d), 49.62 (d), 50.77 (d), 73.41 (s), 81.15 (s), 103.82 (s).

**[4S-(4α,4aα,6α,8aα)]-Octahydro-4,8a-dimethyl-6-[1-hydroxy-1-methylethyl]-1(2*H*)-naphthalenone (6).** A sample (0.307 g, 0.83 mmol) of **9** was desilylated with HF as described above. Workup and flash chromatography [35% EtOAc in petroleum ether (bp 40-60°C)] afforded 0.193 g (91%) of **6**: mp 111°C (from diisopropylether); $[\alpha]_D$ –80.6° (c 2.10); $^1H$ NMR δ 0.96 (d, *J* = 6.7 Hz, 3H), 1.18 (s, 3H), 1.22 (s, 6H), 1.25-2.10 (m, 11H), 2.30 (ddd, *J* = 2.2, 4.4, 15.1 Hz, 1H), 2.45 (m, 1H), 2.68 (ddd, *J* = 7.1, 13.9, 15.1 Hz, 1H); $^{13}C$ NMR δ 14.21 (q), 14.64 (q), 21.27 (t), 26.62 (q), 26.97 (q), 28.73 (t), 31.94 (d), 32.85 (t), 33.90 (t), 37.39 (t), 44.71 (d), 53.67 (s), 71.94 (s), 77.97 (s), 215.90 (s); mass spectrum, *m/z* (relative intensity) 254 ($M^+$, 9), 236 (50), 178 (44), 153 (69), 141 (63), 137 (55), 70 (62), 60 (62), 43 (50), 28 (100); calcd for $C_{15}H_{26}O_3$ ($M^+$) *m/z* 254.1882, found *m/z* 254.1882. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.99: H, 10.56.

**Cyclic acetal (10).** To a stirred solution of 0.50 g (1.36 mmol) of **8** in 5 mL of MeOH was added a catalytic amount of *p*-TsOH. After stirring at room temperature for 10 min, water was added to the reaction mixture followed by extraction with three portions of EtOAc. The

combined organic layers were washed with brine and dried. Evaporation gave 0.357 g (98%) of **10**: mp 96-98°C (from diisopropylether); $[\alpha]_D$ +43.0° (c 1.37); $^1$H NMR δ 0.87 (d, *J* = 6.3 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 1.12 (s, 3H), 1.15-1.97 (m, 11H), 1.20 (s, 3H), 2.23 (s, OH), 2.28 (d, *J* = 13.8 Hz, 1H), 3.25 (s, 3H); $^{13}$C NMR δ 12.89 (q), 14.16 (q), 20.25 (t), 23.71 (t), 27.21 (q), 29.03 (q), 31.14 (t), 33.04 (t), 37.65 (d), 38.90 (d), 41.63 (d), 48.24 (q), 48.98 (d), 73.59 (s), 80.08 (s), 106.79 (s); mass spectrum, *m/z* (relative intensity) 268 ($M^+$, 35), 250 (18), 236 (88), 218 (100), 203 (29), 186 (41), 149 (60), 142 (43); calcd for $C_{16}H_{28}O_3$ ($M^+$) *m/z* 268.2038, found *m/z* 268.2038. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.79; H, 10.75.

**[2R-(2α,4aα,8α,8aα)]-Decahydro-8a-hydroxy-α,α,4a,8-tetramethyl-2-naphthalenemethanol (11).** To a stirred solution of 0.307 g (0.83 mmol) of **9** in 3 mL of dry MeOH was added 0.174 g (0.94 mmol) of *p*-toluenesulfonhydrazide. The reaction mixture was refluxed for 45 min and then cooled to room temperature. After the addition of 5 mL of dry MeOH, 0.065 g (1.03 mmol) of $NaBH_3CN$, and a solution of 0.085 g (0.63 mmol) of anhydrous $ZnCl_2$ in 15 mL of dry MeOH, the mixture was refluxed for another 2 h. The reaction mixture was allowed to come to room temperature, poured into 0.5% aqueous NaOH, and extracted with four portions of EtOAc. The combined organic layers were washed with brine, dried, and evaporated. The remaining residue was flash chromatographed [35% EtOAc in petroleum ether (bp 40-60°C)] to give 0.097 g (49%) of **11**: $[\alpha]_D$ +37.0° (c 1.15) (lit.[21]: 37.4°, $CHCl_3$); $^1$H NMR δ 0.88 (d, *J* = 6.8 Hz, 3H), 1.00 (s, 3H), 1.10-1.83 (m, 14H), 1.22 (s, 6H), 1.93-2.14 (m, 2H); $^{13}$C NMR δ 14.69 (q), 21.09 (t), 22.01 (t), 22.51 (q), 26.65 (q), 26.86 (q), 30.30 (t), 31.93 (t), 32.23 (d), 32.76 (t), 36.05 (t), 37.40 (s), 45.03 (d), 72.28 (s), 74.94 (s); mass spectrum, *m/z* (relative intensity) 240 ($M^+$, 22), 222 (19), 207 (22), 202 (52), 181 (30), 173 (50), 149 (37), 126 (100), 113 (59); calcd for $C_{15}H_{28}O_2$ ($M^+$) *m/z* 240.2089, found *m/z* 240.2088.

**[6R-(6α,8aα)]-2,3,5,6,7,8,8a-Hexahydro-4,8a-dimethyl-6-[1-(triethylsilyl)oxy-1-methylethyl]-1(2*H*)-naphthalenone (13).** To a stirred solution of 10.5 g (28.5 mmol) of **9** in 100 mL of pyridine was added 2.3 mL (31.4 mmol) of $SOCl_2$ at –10°C. After stirring for 15 min, the reaction mixture was poured into ice-water and extracted with four portions of petroleum ether (bp 40-60°C). The combined organic layers were washed with brine, dried, and evaporated. After removal of the residual pyridine by azeotropic distillation with toluene, 9.7 g of crude **13** was obtained as a yellow oil. This crude **13** could be used in the next reactions without further purification. A sample (0.527 g) of crude **13** was flash chromatographed [3% ether in petroleum ether (bp 40-60°C)] to give 0.515 g (95%) of pure **13**: $[\alpha]_D$ –7.5° (c 1.26); $^1$H NMR δ 0.61 (q, *J* = 7.6 Hz, 6H), 1.00 (t, *J* = 7.6 Hz, 9H), 1.10-1.57 (m, 3H), 1.22 (s, 3H), 1.25 (s, 6H), 1.64-1.96 (m, 3H), 1.73 (br s, 3H), 2.27-2.77 (m, 5H); $^{13}$C NMR δ 6.65 (3·t), 6.94 (3·q), 18.61 (q), 21.82 (q), 22.31 (t), 26.29 (t), 26.66 (q), 27.94 (q), 31.97 (t), 34.85 (t), 35.96 (t), 47.08 (s), 50.49 (d), 74.65 (s), 123.59 (s), 134.78 (s), 216.25 (s); mass spectrum, *m/z* (relative intensity) 321 ($M^+$–29, 3), 219 (13), 218 (69), 201 (8), 174 (17), 173 (100), 159 (31), 145 (19), 116 (34); calcd for $C_{20}H_{35}O_2Si$ ($M^+$–15) *m/z* 335.2406, found *m/z* 335.2405.

In a similar way, a crude mixture of **8** and **9**, obtained from treatment of 0.939 g (2.55 mmol) of **7** with KOH in EtOH, gave an easily separable mixture of **12** and **13**. Flash chromatography [3% ether in petroleum ether (bp 40-60°C)] afforded 0.254 g of **12**[27] and 0.470 g (44% overall from **7**) of **13**.

**12**: $^1$H NMR δ 0.58 (q, *J* = 7.5 Hz, 6H), 0.91 (t, *J* = 7.5 Hz, 9H), 0.99 (d, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 6.0 Hz, 3H), 1.17 (s, 6H), 1.20-2.10 (m, 5H), 2.30-2.60 (m, 3H), 2.88 (br d, *J* = 13.8 Hz, 1H), 2.97 (m, 1H), 5.38 (br d, J = 5.2 Hz, 1H); $^{13}$C NMR δ 6.46 (3·t), 6.92 (3·q), 13.78 (q), 17.66 (q), 22.78 (t), 26.26 (q), 27.16 (q), 33.28 (t), 37.10 (d), 37.28 (t), 39.10 (d), 51.37 (d), 57.61 (d), 75.65 (s), 116.94 (d), 145.61 (s), 215.40 (s); mass spectrum, *m/z* (relative intensity) 321 ($M^+$–29, 32), 292 (35), 263 (42), 218 (53), 174 (47), 173 (100), 159 (37), 116 (74), 104 (81); calcd for $C_{19}H_{33}O_2Si$ ($M^+$–29) *m/z* 321.2249, found *m/z* 321.2248.

**(+)-γ-Eudesmol (14).** This compound was prepared from **13** (0.15 g, 0.43 mmol) as described for the synthesis of **11**. The workup and flash chromatography [10% EtOAc in petroleum ether (bp 40-60°C)] afforded 0.038 g (40%) of **14**: $[\alpha]_D$ +91.5° (c 1.55, $CHCl_3$) (lit.[22] +66.7°, neat). The spectroscopic data of **14** were consistent with those reported in the literature.[28]

**[1S-(1α,6α,8aα)]- and [1R-(1α,6β,8aβ)]-1,2,3,5,6,7,8,8a-Octahydro-4,8a-dimethyl-6-[1-(triethylsilyl)oxy-1-methylethyl]-1-naphthalenols (16 and 17).** To a stirred solution of 3.01 g (8.60 mmol) of **13** in 20 mL of EtOH was added 0.36 g (9.40 mmol) of $NaBH_4$ at 0°C. After stirring at room temperature for 1 h, ice-water was added to the reaction mixture followed by extraction with four portions of EtOAc. The combined organic layers were washed successively with 0.01 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine. After drying and evaporation, the remaining residue was flash chromatographed [8% EtOAc in petroleum ether (bp 40-60°C)] to give 0.515 g (17%) of **16** and 2.21 g (73%) of **17**, both as colorless oils.

**16**: $[\alpha]_D$ +57.0° (c 1.95); $^1H$ NMR δ 0.61 (q, $J$ = 8.0 Hz, 6H), 0.99 (t, $J$ = 8.0 Hz, 9H), 1.08 (s, 3H), 1.10-2.30 (m, 11H), 1.21 (s, 3H), 1.23 (s, 3H), 1.66 (br s, 3H), 2.72 (dt, $J$ = 1.4, 13.9 Hz, 1H), 3.52 (m, $W_{1/2}$ = 12.5 Hz, 1H); $^{13}C$ NMR δ 6.67 (3·t), 6.94 (3·q), 18.84 (q), 22.51 (t), 24.24 (q), 25.48 (t), 26.13 (t), 26.77 (q), 27.81 (t), 27.82 (q), 33.16 (t), 39.01 (s), 50.70 (d), 74.73 (d), 74.73 (s), 122.84 (s), 133.07 (s); mass spectrum, *m/z* (relative intensity) 305 (9), 220 (41), 202 (53), 187 (24), 173 (100), 159 (47), 145 (20), 116 (35), 77 (24); calcd.for $C_{20}H_{37}O_2Si$ ($M^+$–15) *m/z* 337.2563, found *m/z* 337.2563.

**17**: $[\alpha]_D$ +51.6° (c 1.36); $^1H$ NMR δ 0.62 (q, $J$ = 8.1 Hz, 6H), 1.00 (t, $J$ = 8.1 Hz, 9H), 1.04 (s, 3H), 1.05-2.30 (m, 11H), 1,22 (s, 3H), 1.24 (s, 3H), 1.63 (br s, 3H), 2.69 (dt, $J$ = 2.0, 13.6 Hz, 1H), 3.49 (t, $J$ = 7.5 Hz, 1H); $^{13}C$ NMR δ 6.67 (3·t), 6.94 (3·q), 17.02 (q), 18.67 (q), 22.65 (t), 26.15 (t), 26.69 (q), 26.90 (t), 27.85 (q), 31.71 (t), 38.77 (t), 39.26 (s), 50.48 (d), 74.83 (s), 78.20 (d), 123.12 (s), 134.09 (s); mass spectrum, *m/z* (relative intensity) 231 (4), 220 (75), 219 (28), 202 (19), 173 (100), 116 (30), 69 (53); calcd for $C_{21}H_{38}OSi$ ($M^+$–18) *m/z* 334.2691, found *m/z* 334.2692.

**[1R-(1α,6β,8aβ)]-1,2,3,5,6,7,8,8a-Octahydro-4,8a-dimethyl-6-[1-(triethylsilyl)oxy-1-methylethyl]-1-naphthalenol 1-(Methanesulfonate) (18).** To a stirred solution of 1.70 g (4.83 mmol) of **17** in 15 ml of pyridine was added 0.5 mL (6.41 mmol) of MsCl at 0°C. After stirring at room temperature for 1.5 h, 20 mL of saturated aqueous $NaHCO_3$ was added. The reaction mixture was stirred for an additional 5 min, and then extracted with four portions of EtOAc. The combined organic layers were washed with brine, dried, and evaporated. After removal of the residual pyridine by azeotropic distillation with toluene, 2.06 g of crude **18** was obtained which could be used in the next step without further purification. A sample (0.539 g) of crude **18** was flash chromatographed [10% EtOAc in petroleum ether (bp 40-60°C)] to give 0.496 g (91%) of pure **17**: $[\alpha]_D$ +57.2° (c 1.73); $^1H$ NMR δ 0.60 (q, $J$ = 8.0 Hz, 6H), 0.98 (t, $J$ = 8.0 Hz, 9H), 1.05-2.35 (m, 10H), 1.10 (s, 3H), 1.22 (s, 3H), 1,26 (s, 3H), 1.62 (br s, 3H), 2.68 (dt, $J$ = 2.4, 14.0 Hz, 1H), 3.04 (s, 3H), 4.56 (t, $J$ = 7.8 Hz, 1H); $^{13}C$ NMR δ 6.65 (3·t), 6.92 (3·q), 17.94 (q), 18.49 (q), 22.39 (t), 25.10 (t), 26.05 (t), 26.69 (q), 27.77 (q), 31.28 (t), 38.41 (q), 38.71 (t), 38.71 (s), 50.23 (d), 74.65 (s), 89.73 (d), 123.28 (s), 133.44 (s); mass spectrum, *m/z* (relative intensity) 334 ($M^+$–96, 4), 305 (6), 202 (80), 187 (26), 174 (100), 159 (58), 116 (39), 104 (34); calcd for $C_{21}H_{38}OSi$ ($M^+$–96) *m/z* 334.2691, found *m/z* 334.2692.

**[2R-(2α,4aα,5α)]-1,2,3,4,4a,5,6,7-Octahydro-5-[(methylsulfonyl)oxy]-α,α,4a,8-tetramethyl-2-naphthalenemethanol (2).** To a stirred solution of 1.72 g (ca. 3.7 mmol) of the crude **18** in 10 mL of $CH_3CN$ was added 0.67 mL of 40% aqueous HF over 0.5 h. After stirring for 1 h at room temperature, water was added and the mixture was extracted four times with EtOAc. The combined organic layers were washed with brine, dried, and evaporated. The crude oil was purified by flash chromatography [40% EtOAc in petroleum ether (bp 40-60°C)] to give 1.142 g

(98%) of **2** as pale yellow crystals: mp 82°C (from diisopropylether); $[\alpha]_D$ +80.5° (c 1.25); $^1$H NMR δ 1.11 (s, 3H), 1.23 (s, 6H), 1.63 (br s, 3H), 1.10-1.87 (m, 6H), 1.95-2.35 (m, 6H), 2.68 (br d, $J$ = 13.6 Hz, 1H), 3.05 (s, 3H), 4.56 (t, $J$ = 7.7 Hz, 1H); $^{13}$C NMR δ 18.01 (q), 18.59 (q), 22.42 (t), 25.03 (t), 26.14 (t), 26.36 (q), 27.09 (q), 31.25 (t), 38.52 (q), 38.52 (t), 38.52 (s), 49.24 (d), 72.32 (s), 89.55 (d), 123.81 (s), 132.76 (s); mass spectrum, *m/z* (relative intensity) 298 (8), 220 (27), 202 (47), 187 (41), 159 (100), 145 (25), 131 (34), 106 (25), 60 (25); calcd for $C_{16}H_{28}O_4S$ ($M^+$) *m/z* 316.1707, found *m/z* 316.1707. Anal. Calcd for $C_{16}H_{28}SO_4$: C, 60.73; H, 8.92. Found: C, 60.49; H, 9.12.

**(+)-Hedycaryol (1).** To a stirred solution of 0.946 g (2.99 mmol) of **2** in 10 mL of dry THF was added dropwise 18 mL of $BH_3$·THF (1 M in THF) at 0°C. The reaction mixture was stirred at 0°C for 2 h and additionally at room temperature for 2 h. The reaction mixture was then cooled to 0°C, after which 3 mL of MeOH was added dropwise, immediately followed by dropwise addition of 40 mL of NaOMe (2 M in MeOH). The reaction mixture was allowed to come to room temperature and stirred overnight. After addition of a mixture of 40 mL of saturated aqueous $NH_4Cl$ and 10 mL of 25% ammonia to the cooled reaction mixture, 100 mL of petroleum ether (bp 40-60°C) was added. Stirring was continued for an additional 30 min after which the mixture was extracted with four portions of petroleum ether (bp 40-60°C). The combined organic layers were washed with brine and dried ($Na_2SO_4$). Evaporation afforded a pale yellow oil which was dissolved in a mixture of 30 ml of hexane and 10 mL of *t*-butylmethylether. This solution was extracted with four portions of 20% aqueous $AgNO_3$. The combined aqueous layers were washed with one portion of *t*-butyl-methylether and then cooled on an ice-bath. After addition of 70 mL of 25% ammonia, the aqueous layer was extracted with four portions of *t*-butylmethylether. The combined organic layers were washed with brine and dried ($Na_2SO_4$). Evaporation gave 0.365 g (55%) of pure **1**: $[\alpha]_D$ +24.2° (c 2.57) (lit.[1]: +24.5°); FT IR (film) 3404, 2969, 2928, 2853, 1656, 1449, 1383, 1366, 1127, 845 cm$^{-1}$; The $^1$H NMR and the mass spectral data corresponded with those reported in the literature[6a].

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    **20**: $[\alpha]_D$ +81.2° (c 2.47) (lit. +77.3°); $^{13}$C NMR δ 18.86 (q), 22.50 (t), 24.22 (q), 25.40 (t), 26.26 (t), 26.37 (q), 26.75 (q), 27.80 (t), 32.99 (t), 38.94 (s), 49.72 (d), 72.73 (s), 74.57 (d), 123.33 (s), 132.40 (s).
    **21**: mp 135°C (lit. 136-137°C); $[\alpha]_D$ +106.2° (c 1.49) (lit. +102.4°); $^{13}$C NMR δ 17.08 (q), 18.75 (q), 22.65 (t), 26.29 (t), 26.50 (q), 26.91 (t), 26.91 (q), 31.68 (t), 38.62 (t), 39.22 (s), 49.53 (d), 72.48 (s), 78.10 (d), 123.66 (s), 133.20 (s).
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