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Thermal Rearrangement of Bicyclogermacrane-1,8-dione. Synthesis of Humulenedione and (–)-Cubenol, Starting from Natural (+)-Aromadendrene-V[1]

Harrie J.M. Gijsen, Joannes B.P.A. Wijnberg* and Aede de Groot*

Laboratory of Organic Chemistry, Agricultural University,
Dreijenplein 8, 6703 HB Wageningen, The Netherlands

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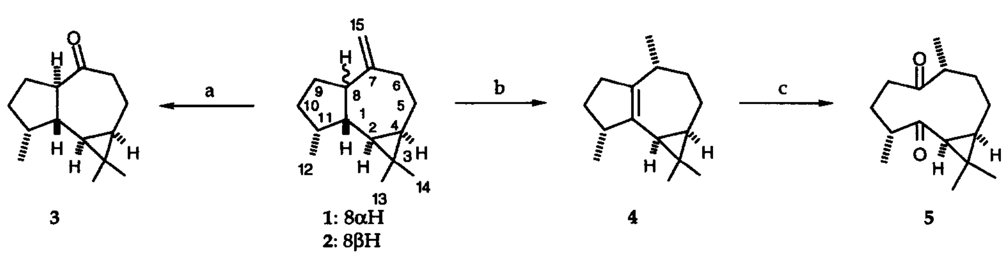
Abstract: *Treatment of a distillation tail of Eucalyptus globulus, containing mainly (+)-aromadendrene (**1**) and (–)-alloaromadendrene (**2**), with K/Al$_2$O$_3$ gives a quantitative conversion of **1** and **2** into isoledene (**4**). Oxidative cleavage of the central double bond in **4** produces (+)-bicyclogermacrane-1,8-dione (**5**). Thermal rearrangement of **5** gives via a homo [1,5] hydrogen shift at relatively low temperature the humulenedione **6**, and at higher temperature (FVP) the products **9** and **10** both with a cadinane skeleton. The naturally occurring humulenedione (**7**) and (–)-cubenol (**17**) can be synthesized starting from **6** and **9**, respectively.*

A commercially available distillation tail of the oil of *Eucalyptus globulus*[2] contains about 66% of the tricyclic sesquiterpene (+)-aromadendrene (**1**), which possesses a *trans*-fused perhydroazulene skeleton, and about 14% of its *cis*-fused epimer alloaromadendrene (**2**). Ozonolysis of this crude distillation tail, without applying any purification procedure beforehand, can be used to obtain large quantities of pure (+)-apoaromadendrone (**3**)[3]. As reported in previous papers, ketone **3** has proven to be an excellent chiral starting material in the synthesis of natural products from several classes of sesquiterpenes[4,5,6].

Scheme I[a]

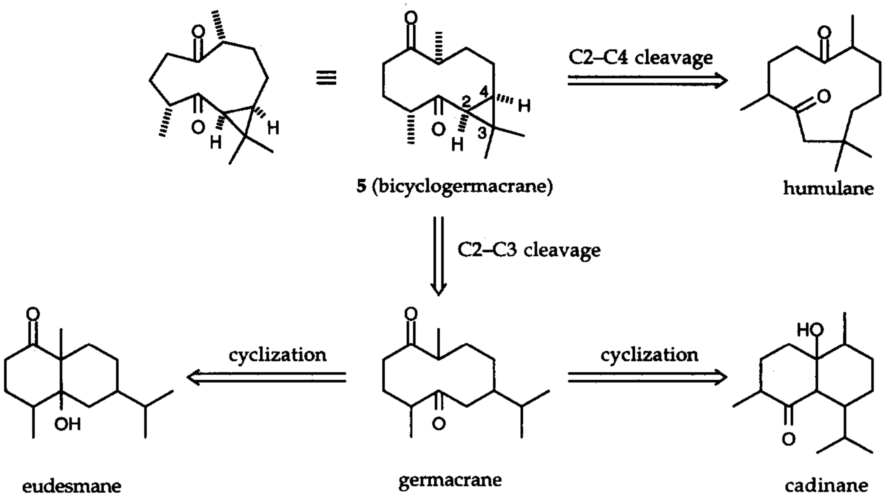


[a] (a) O$_3$; (b) K/Al$_2$O$_3$; (c) RuO$_2$, NaIO$_4$, 50°C.

Isomerization of the exocyclic double bond in **1** and/or **2** might be another possibility to obtain a suitable chiral synthon for further synthesis. In the literature the isomerization of **1** to isoledene (**4**) under the influence of potassium on aluminum oxide (K/Al_2O_3) has been described[7]. Application of this reagent on the crude distillation tail gave an oil in 94% yield which contained, according to GC-MS analysis, 85% of **4** (Scheme I). This means that both **1** and **2** are quantitatively converted into **4**. It should be noted that the same reaction conditions applied on (–)-α-gurjunene [(7α,8β)-1(11)-aromadendrene][8] did not give any **4**. Without further purification, the C1–C8 double bond in **4** (85% pure) was oxidized using ruthenium(IV)oxide (RuO_2) and sodium periodate ($NaIO_4$) in a mixture of CCl_4, MeCN, and H_2O at 45–50°C to give the bicyclogermacrane-1,8-dione (**5**) which was easily purified by means of flash chromatography. Via this procedure 7.8 g of pure **5** could be obtained from a 10 g-sample of the crude distillation tail of the oil of *E. globolus*.

The diketone **5** possesses the *bicyclogermacrane* skeleton and has the capability of being transformed into a variety of chiral derivatives and naturally occurring sesquiterpenes (Scheme II). Cleavage of the C2–C3 or C2–C4 bond of the fused cyclopropane ring may lead to diones with a *germacrane* or *humulane* skeleton, respectively. Intramolecular aldol condensations with the dione having a germacrane skeleton can give *eudesmanes* and/or *cadinanes*[9]. The usefulness of this approach is demonstrated in the first syntheses of humulenedione (**7**) and (–)-cubenol (**17**). The humulane sesquiterpene **7** has been isolated from *Lippia integrifolia* recently[10]. The cadinane sesquiterpene (–)-cubenol has been found in many plant species[11]. Recently the cell-destroying activity of (–)-cubenol against red tide planktons has been reported[12].

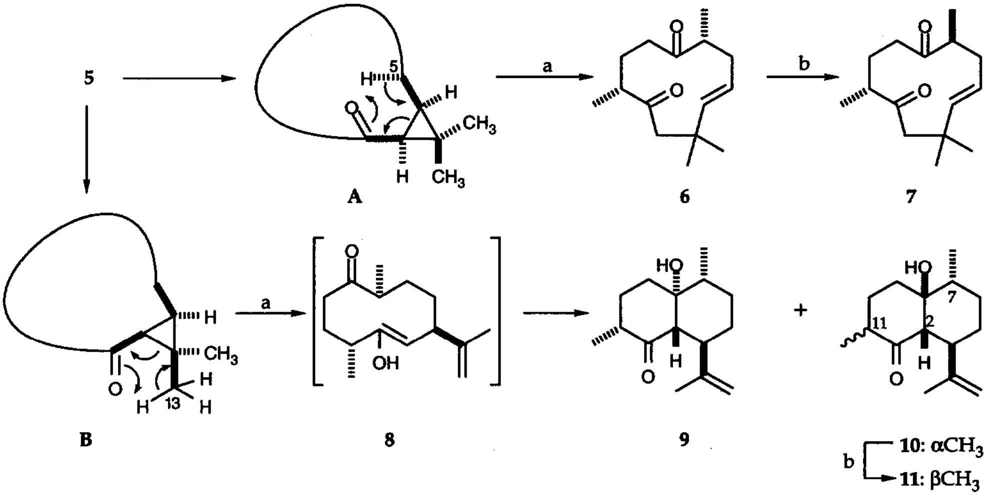
Scheme II



Initial experiments showed that **5** is unstable at elevated temperatures. Heating of **5** in refluxing xylene afforded a 1:1:1 mixture of **6**, **9**, and **10**. When dioxane (bp 101°C) was used instead of xylene (bp 140°C) for the thermolysis of **5**, predominantly **6** was formed. After a reflux period of 8 days, the yield of isolated **6** was 81%. The influence of higher temperatures on the thermal rearrangement of **5** was investigated with flash vacuum pyrolysis (FVP)[13]. With this technique at a temperature of 500°C **9** and **10** were obtained in 55 and 40%, respectively.

These results can be explained with two competing homo [1,5] hydrogen shifts[14,15,16], represented as in the partial structures **A** and **B** (Scheme III). In both **A** and **B** the requirement of a *cis* relationship between the carbonyl and alkyl group (C5 and C13, respectively) is present. The reaction path via **A** gives directly the humulane **6** via cleavage of the C2-C4 bond of the cyclopropane ring. The ^{1}H NMR spectrum of **6** measured in $CDCl_3$ did not give a clear answer about the *cis* or *trans* relationship of the double bond in **6**. By using C_6D_6 as a solvent, the coupling constants of the vinylic proton signals from **6** could be determined, indicating a *trans*-double bond. This was confirmed by treatment of **6** with $NaOCH_3$ in CH_3OH, giving the epimerized **7**, whose spectral data were in full agreement with those reported for the natural *trans*-humulenedione, isolated from *L. integrifolia*[10]. Unfortunately, during the reaction with $NaOCH_3$ extensive racemization took place.

Scheme III[a]

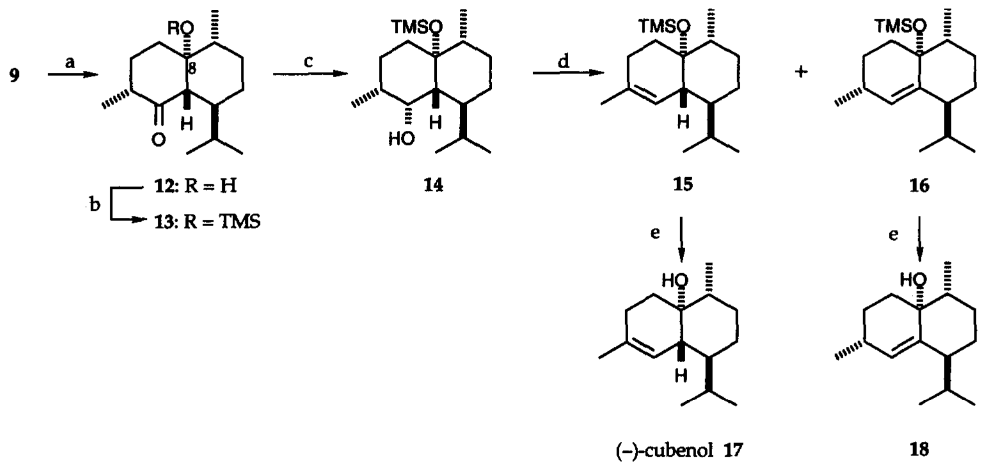


[a] (a) xylene, Δ; (b) $NaOCH_3$, CH_3OH.

If reaction path **B** is followed (cleavage of the C2-C3 bond of the cyclopropane ring), compound **8** with a *germacrane* skeleton must be an intermediate. A subsequent non-selective aldol cyclization of **8** leads to the cadinanes **9** and **10**. Since NMR analysis (NOE in combination with coupling constants) could not give a definite answer about the stereochemistry of the tertiary hydroxyl group in **9** as well as in **10**, the assignment was based on indications obtained from chemical experiments. Upon treatment with 1 M $NaOCH_3$ in CH_3OH **9** did not react, whereas **10** largely epimerized to **11**. From these results we concluded that in **9** all the alkyl substituents have an equatorial orientation, and that the ring junction is *trans*. The most likely structure for **10** is thought to be the *cis*-fused isomer of **9**. The relatively bulky isopropenyl and the methyl group at C7 both possess the equatorial orientation in this structure, the methyl group at C11, on the other hand, is axially oriented. Thus, epimerization at C11 leading to **11** will be an easy process. Epimerization at C2 is not likely because in that case the isopropenyl group and the methyl group at C7 both should adopt the unfavorable axial orientation.

Since the stereochemistry of **9**, as proposed by us, is identical to that of (–)-cubenol (**17**), compound **9** can be considered as an ideal starting material for the synthesis of natural (–)-cubenol. Therefore, to develop an effective synthesis of **17** the yield of **9** in the thermal rearrangement reaction had to be improved. This could be done by further elevating the temperature in the FVP reaction. An optimum yield (71%) of **9** was found at a FVP temperature of 700°C. At this temperature the yield of **10** was diminished to 19%. Higher temperatures decreased the yield of **9** (and **10**) because of charring and desintegration.

Scheme IV[a]



[a] (a) H_2, Pt/C, 60 psi; (b) TMSCl, Et_3N, DMF, 120°C; (c) $LiAlH_4$; (d) $SOCl_2$; (e) TBAF.

The next step towards **17** was the reduction of the double bond in **9**. Upon hydrogenation with H_2 and Pt/C at 60 psi, **9** was quantitatively converted into **12** (Scheme IV). The planned transformation of the carbonyl group into a double bond (**12** → **17**) via the Bamford-Stevens reaction[17] was not possible because the tosylhydrazone of **12** could not be prepared. The alternative conversion of **12** into **17** via reduction and dehydration requires the protection of the angular hydroxyl group at C8. However, this axial hydroxyl group proved to be very unreactive. Standard methods to prepare trimethylsilylethers were unsuccessful. Finally, we found that this conversion could be realized after prolonged heating (5 days, 120°C) of a solution of **12** in DMF in the presence of TMSCl and Et_3N. In this way the trimethylsilylether **13** was formed in 91% yield. It should be noted that these reaction conditions have been used previously to prepare enol trimethylsilylethers from ketones[5]. In this specific case however, no enol silylether formation was observed at all, which confirmed the unreactivity of this carbonyl group. Reduction with $LiAlH_4$, however, proceeded without any difficulty and afforded the alcohol **14** in good yield. Subsequent dehydration of **14** with $SOCl_2$ in pyridine gave an inseparable 3:2 mixture of two double bond isomers **15** and **16**, respectively. Removal of the protecting trimethylsilyl group with TBAF, followed by separation by means of column chromatography finally gave (–)-cubenol (**17**) together with its double bond isomer **18** in 44 and 31% overall yield from **13**, respectively. The physical and spectroscopic data of our synthetic **17** were in full agreement with those reported in the literature[11], thereby supporting our original assignment of the stereochemistry of **9**.

Besides the synthesis of *humulanes* or *cadinanes* like humulenedione or (–)-cubenol, respectively, it also might be possible to prepare sesquiterpenes with a *bicyclogermacrane,* a *germacrane,* or an *eudesmane* skeleton from **5**. These possibilities may considerably enlarge the synthetic applicability of synthon **5** and thus also of (+)-aromadendrene (**1**).

EXPERIMENTAL SECTION

Melting points were determined on a Mettler FP80 HT. Optical rotations were obtained from $CHCl_3$ solutions on a Perkin-Elmer 241 polarimeter. ^1H NMR spectra were recorded at 200 MHz on a Bruker AC-E 200 spectrometer, or, where indicated, at 500 MHz on a Bruker AMX 500. ^{13}C NMR spectra were recorded at 50 MHz 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 in $CDCl_3$ as the solvent. Mass spectral data were determined on either an AEI MS 902 spectrometer or a Hewlett Packard 5970 B series MSD coupled with a Hewlett Packard 5890 A gas chromatograph with a DB-17 fused silica capillary column. Elemental analyses were determined on a Carlo Erba elemental analyzer 1106. GC analyses were carried out on a Hewlett Packard 5890 II 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 Spectra-Physics integrator SP 4290. Flash chromatography was performed using Merck silica gel 60 (230-400 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, unless otherwise noted. Product solutions were dried over anhydrous $MgSO_4$ prior to evaporation of the solvent under reduced pressure by using a rotary evaporator.

Isoledene (4). To 100 g of mechanically stirred Al_2O_3 (ICN, basic, activity grade Super, dried at 250°C at reduced pressure) was added 10 g (0.25 mol) of potassium in small portions at 200°C, under an argon atmosphere. The resulting blue powder was allowed to come to room temperature, cooled to 0°C, and then 80 mL of dry hexane was added. To this stirred suspension 32.5 g of crude distillation tail of the oil of *Eucalyptus globulus*[2] in 50 mL of dry hexane was added. The ice-bath was removed and stirring was continued for 4 h. The green suspension was filtered through a glass-filter and the catalyst was washed carefully with an ether-hexane mixture. After removal of the solvent via distillation, 30.44 g of a colourless oil was obtained, containing, according to GC-analysis, 85% of isoledene (**4**). ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 1.13 (s, 3H), 1.00-2.58 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 15.76 (q), 19.01 (q), 20.49 (s), 21.50 (q), 22.54 (t), 23.94 (d), 28.12 (q), 30.16 (d), 31.19 (t), 34.34 (t), 34.74 (t), 38.26 (d), 44.73 (d), 136.64 (s), 138.35 (s); mass spectrum, *m/e* (relative intensity) 204 (M^+, 25), 199 (12), 161 (83), 147 (16), 133 (31), 119 (62), 105 (100), 91 (63).

(+)-Bicyclogermacrane-1,8-dione (5). To a solution of 16.00 g of the crude oil containing 85 % (66 mmol) of **4** in 120 mL of CCl_4 were added 120 mL of CH_3CN, 180 mL of H_2O, 25 g (117 mmol) of $NaIO_4$ and 250 mg of $RuO_2{\cdot}xH_2O$. The mixture was stirred at 45-50°C for 3 h and an additional 10 g (46 mmol) of $NaIO_4$ was added. After stirring for another 1.5 h, the mixture was allowed to come to room temperature, and 25 mL of isopropanol was added. The mixture was stirred for 15 min, filtered through celite, and the filter cake was washed with 200 mL of H_2O and 150 mL of CH_2Cl_2. The combined filtrates were separated, and the aqueous layer was extracted with three 150-mL portions of CH_2Cl_2. The combined organic layers were washed with 250 mL of aqueous 10% $Na_2S_2O_3$ and 250 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was flash chromatographed [15:1 to 10:1 petroleum ether (bp 40-60°C)/EtOAc] to give 13.36 g (86%) of **5**: mp 54-55°C (from CH_3CN); $[\alpha]_D$ +227° (c 1.86); ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 7.2 Hz, 3H), 1.06 (s, 3H), 1.07 (s, 3H), 1.09 (d, J = 6.6 Hz, 3H), 1.09-1.33 (m, 2H), 1.52 (d, J = 8.5 Hz, 1H), 1.62-2.06 (m, 4H), 2.17-2.57 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.59 (q), 17.40 (q), 18.91 (q), 20.74 (t), 28.80 (q), 30.61 (t), 30.91 (s), 31.89 (t), 32.50 (d), 40.14 (t), 41.60 (d), 48.29 (d), 52.71 (d), 214.56 (s), 216.21 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 44), 221 (21), 218 (25), 208 (18), 151 (21), 137 (100), 124 (36), 111 (43), 96 (49), 84 (32); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1776. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.01; H, 10.21.

Thermolysis of 5. A solution of 472 mg (2.0 mmol) of **5** in 30 mL of *p*-xylene was heated at reflux for 18 h. Evaporation of the solvent under reduced pressure followed by flash chromatography [12:1 to 3:1 petroleum ether (bp 40-60°C)/EtOAc] of the resulting residue afforded, in order of elution, 131 mg (28%) of **6**, 142 mg (30%) of **9**, and 145 mg (31%) of **10**.

(+)-7α,11α-*trans*-Humulene-1,8-dione (6): mp 76.5-77.5°C (from n-heptane); $[\alpha]_D$ +248° (c 2.18); ^{1}H NMR ($CDCl_3$, 500MHz) δ 0.99 (d, J = 7.3 Hz, 3H), 1.01 (s, 3H), 1.15 (s, 3H), 1.19 (d, J = 7.1 Hz, 3H), 1.68-1.73 (m, 2H), 1.93 (dd, J = 1.2, 11.1 Hz, 1H), 2.03-2.16 (m, 2H), 2.39-2.53 (m, 3H), 2.56 (d, J = 11.1 Hz, 1H), 2.60-2.68 (m, 1H), 5.36-5.42 (m, 2H); ^{1}H NMR (C_6D_6, 500MHz) δ 0.79 (d, J = 7.2 Hz, 3H), 0.82 (s, 3H), 0.90 (d, J = 7.3 Hz, 3H), 1.20 (s, 3H), 1.72-1.91 (m, 5H), 2.21 (d, J = 11.1 Hz, 1H), 2.32-2.47 (m, 3H), 2.63-2.71 (m, 1H), 5.18 (dd, J = 1.5, 15.5 Hz, 1H), 5.27 (ddd, 4.4, 10.4, 15.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.95 (q), 17.89 (q), 23.57 (q), 24.68 (t), 31.04 (q), 36.85 (s), 37.51 (t), 38.10 (t), 45.57 (d), 45.85 (d), 52.05 (t), 121.07 (d), 140.22 (d), 213.76 (s), 215.29 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 46), 165 (100), 154 (22), 111 (34), 110 (29), 96 (47), 70 (26); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1776. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.11; H, 10.20.

(–)-[2R-(2α,4aα,5α,8β,8aβ)]-Octahydro-4a-hydroxy-2,5-dimethyl-8-(1-methylethenyl)-1(2H)-naphthalenone (9): mp 64.5-65.5°C (from *n*-heptane); $[\alpha]_D$ -7.3° (c 2.11); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (d, J = 6.7 Hz,3H), 0.98 (d, J = 6.3 Hz, 3H), 1.12 (dq, J = 3.8, 13.1 Hz, 1H), 1.17 (s, 1H), 1.34 (dq, J = 3.4, 13.1 Hz, 1H), 1.47 (ddd, J = 3.5, 7.0, 13.1 Hz, 1H), 1.56-1.70 (m, 3H), 1.78 (s, 3H), 1.82 (ddd, J = 3.4, 7.0, 13.1 Hz, 1H), 1.96-2.07 (m, 2H), 2.36 (dt, J = 3.8, 12.0 Hz, 1H), 2.42-2.49 (m, 1H), 2.61 (d, J = 12.0 Hz, 1H), 4.50 (s, 1H), 4.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.00 (q), 14.72 (q), 22.35

(q), 29.61 (t), 31.98 (t), 32.27 (t), 35.34 (t), 38.64 (d), 40.86 (d), 45.15 (d), 60.96 (d), 79.19 (s), 107.21 (t), 150.16 (s), 211.64 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 65), 218 (44), 203 (35), 175 (44), 162 (31), 149 (42), 148 (55), 135 (100), 94 (47); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1775. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.99; H, 10.56.

(+)-[2R-(2α,4aβ,5α,8β,8aβ)]-Octahydro-4a-hydroxy-2,5-dimethyl-8-(1-methylethenyl)-1(2H)-naphthalenone (10): mp 158°C [from petroleum ether (bp 80-100°C)]; $[\alpha]_D$ +62.8° (c 1.63); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.11 (d, J = 7.2 Hz, 3H), 1.20 (d, J = 7.3 Hz, 3H), 1.29 (dq, J = 3.6, 13.6 Hz, 1H), 1.31 (s, 1H), 1.34-1.39 (m, 2H), 1.58-1.66 (m, 2H), 1.69-1.76 (m, 1H), 1.80 (s, 3H), 1.94 (tt, J = 4.3, 13.6 Hz, 1H), 2.16-2.27 (m, 2H), 2.38 (dt, J = 4.3, 12.0 Hz, 1H), 2.51-2.57 (m, 1H), 3.01 (d, J = 12.0 Hz, 1H), 4.50 (s, 1H), 4.65 (s,1H); ^{13}C NMR ($CDCl_3$) δ 15.41 (q), 15.73 (q), 22.31 (q), 26.42 (t), 27.72 (t), 28.18 (t), 30.96 (t), 38.17 (d), 39.46 (d), 44.49 (d), 49.91 (d), 79.73 (s), 106.83 (t), 150.42 (s), 214.20 (s); mass spectrum, *m/e* (relative intensity) 236 (M^+, 72), 218 (59), 203 (34), 175 (45), 162 (40), 149 (68), 148 (49), 135 (100), 94 (52); calcd for $C_{15}H_{24}O_2$ (M^+) *m/e* 236.1776, found *m/e* 236.1776. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.42; H, 10.41.

In another experiment, a solution of 1.18 g (5.0 mmol) of **5** in 100 mL of 1,4-dioxane was heated at reflux for 7 d. Evaporation of the solvent under reduced pressure followed by flash chromatography [15:1 petroleum ether (bp 40-60°C)/EtOAc] of the resulting residue afforded 961 mg (81%) of **6**.

(±)-7β,11α-*trans*-Humulene-1,8-dione (7). A solution of 354 mg (1.0 mmol) of **6** in 10 mL of 1 M MeONa in MeOH was stirred at room temperature for 90 h. After dilution with 40 mL of H_2O, the reaction mixture was extracted with four 25-mL portions of ether. The combined organic layers were washed with 30 mL of brine, dried, and evaporated under reduced pressure. The remaining residue (354 mg), according to GC-analysis a 1:15 mixture of **6** and **7**, respectively, was flash chromatographed [15:1 to 10:1 petroleum ether (bp 40-60°C)/EtOAc] to give 322 mg (91%) of **7**: mp 64.5-65°C (from methanol); $[\alpha]_D$ +12.8° (c 1.2) (lit.[10]: +201°). According to GC-analysis with a chiral column (WCOT fused silica 50 m x 0.25 mm i.d. coated with CP-cyclodextrin-β-2,3,6-M-19, film thickness 0.25 µm), **7** was a mixture of two enantiomers in a 53 : 47 ratio; ^1H NMR, ^{13}C NMR, and MS spectroscopic data were consistent with those reported in the literature[10]. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.30; H, 10.38.

Flash Vacuum Pyrolysis of 5. The FVP experiments were performed using standard FVP equipment[18] with a vertically placed quartz tube of 20 cm long and 13 mm in diameter. The diketone **5** was preheated at 70°C with a Büchi TO 50 oven and pyrolyzed at a pressure of $1 \cdot 10^2$ mbar using different temperatures. The products were trapped at the end of the quartz tube with a cold finger, cooled at -78°C. In this way 1.00 g (4.23 mmol) of **5** was pyrolyzed at 500°C in a 1 h period. Flash chromatography [6:1 to 3:1 petroleum ether (bp 40-60°C)/EtOAc] of the resulting product mixture afforded 550 mg (55%) of **9** and 398 mg (40%) of **10**.

In a similar experiment 118 mg (0.5 mmol) of **5** was pyrolyzed at 700°C to give 84 mg (71%) of **9** and 23 mg (19%) of **10**.

(+)-[2S-(2β,4aβ,5α,8β,8aβ)]-Octahydro-4a-hydroxy-2,5-dimethyl-8-(1-methylethenyl)-1(2H)-naphthalenone (11). A solution of 236 mg (1.0 mmol) of **10** in 5 mL of 1 M MeONa in MeOH was stirred at room temperature for 60 h. After dilution with 20 mL of H_2O, the reaction mixture was extracted with four 15-mL portions of ether. The combined organic layers were washed with 20 mL of brine, dried, and evaporated under reduced pressure. The remaining residue (236 mg), according to GC-analysis a 1:8 mixture of **10** and **11**, respectively, was flash chromatographed [5:1 petroleum ether (bp 40-60°C)/EtOAc] to give 27 mg (11%) of **10** and 205 mg (86%) of **11**: mp 120°C (from n-heptane); $[\alpha]_D$ +0.6° (c 2.79); ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6.1

Hz, 3H), 1.06 (d, J = 7.1 Hz, 3H), 1.39 (s, 1H), 1.78 (s, 3H), 1.20-2.14 (m, 9H), 2.36 (dt, J = 2, 12 Hz, 1H), 2.38 (t, J = 12 Hz, 1H), 2.73 (d, J = 12 Hz), 4.49 (s, 1H), 4.63 (d, J = 1.6 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 14.07 (q), 15.38 (q), 22.44 (q), 26.31 (t), 27.74 (t), 31.63 (t), 35.88 (t), 38.64 (d), 39.32 (d), 45.31 (d), 54.90 (d), 79.90 (s), 107.20 (d), 150.39 (s), 212.00 (s); mass spectrum, *m/e* (relative intensity) 236 (M$^+$, 71), 218 (64), 203 (27), 175 (38), 162 (34), 149 (94), 148 (56), 135 (100), 94 (50); calcd for C$_{15}$H$_{24}$O$_2$ (M$^+$) *m/e* 236.1776, found *m/e* 236.1776. Anal. Calcd for C$_{15}$H$_{24}$O$_2$: C, 76.22; H, 10.24. Found: C, 76.33; H, 10.49.

(–)-[2R-(2α,4aα,5α,8β,8aβ)]-Octahydro-4a-hydroxy-2,5-dimethyl-8-(1-methylethyl)-1(2H)-naphthalenone (12). To a solution of 4.72 g (20 mmol) of **9** in 35 mL of ethanol was added 250 mg of 10% Pt on carbon. The mixture was hydrogenated in a hydrogen atmosphere at a pressure of 60 psi for 4 h. The reaction mixture was filtered through celite and a short SiO$_2$-column [1:1 petroleum ether (bp 40-60°C)/EtOAc] to give 4.71 g (99%) of **12**: mp 48-49°C (from EtOH); [α]$_D$ -36.1° (c 0.95); ^{1}H NMR (CDCl$_3$) δ 0.60 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.0 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 6.5 Hz, 3H), 1.25 (s,1H), 0.88-2.03 (m, 11H), 2.41 (d, J = 11.9 Hz, 1H), 2.37-2.56 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 14.02 (q), 14.98 (q), 15.51 (q), 21.18 (q), 22.37 (t), 26.93 (d), 29.13 (t), 32.71 (t), 35.40 (t), 36.04 (d), 41.16 (d), 45.75 (d), 59.90 (d), 79.74 (s), 212.88 (s); mass spectrum, *m/e* (relative intensity) 238 (M$^+$, 15), 220 (100), 195 (39), 192 (36), 175 (47), 162 (39), 151 (44), 138 (51), 128 (94), 127 (67); calcd for C$_{15}$H$_{24}$O$_2$ (M$^+$) *m/e* 238.1933, found *m/e* 238.1933. Anal. Calcd for C$_{15}$H$_{26}$O$_2$: C, 75.58; H, 11.00. Found: C, 75.47; H, 11.20.

(–)-[2R-(2α,4aα,5α,8β,8aβ)]-Octahydro-4a-trimethylsilyloxy-2,5-dimethyl-8-(1-methylethyl)-1(2H)-naphthalenone 13). To a solution of 3.00 g (12.6 mmol) of **12** in 20 mL of DMF and 5.0 mL (57 mmol) of Et$_3$N, was added 3.8 mL (30 mmol) of TMSCl. The reaction mixture was heated at 120°C for 6 d, allowed to come to room temperature, and then 75 mL of petroleum ether (bp 40-60°C) was added. The resulting mixture was washed twice with 50 mL of saturated aqueous NaHCO$_3$, and the combined aqueous layers were back-extracted with two 50-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were dried and evaporated under reduced pressure. The resulting residue was flash chromatographed [15:1 petroleum ether (bp 40-60°C)/EtOAc] to give 3.56 g (91%) of **13**: mp 91°C (from n-heptane); [α]$_D$ -2.8° (c 1.13); ^{1}H NMR (CDCl$_3$) δ 0.02 (s, 9H), 0.53 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.6 Hz, 6H), 0.93 (d, J = 6.2 Hz, 3H), 1.21-1.64 (m, 7H), 1.81-2.09 (m, 4H), 2.22 (d, J = 11.3 Hz, 1H), 2.28-2.48 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 2.55 (3xq), 14.26 (q), 15.51 (q), 15.90 (q), 21.16 (q), 22.57 (t), 26.52 (d), 29.14 (t), 32.43 (t), 34.92 (t), 35.55 (d), 42.29 (d), 45.02 (d), 61.12 (d), 85.22 (s), 210.68 (s); mass spectrum, *m/e* (relative intensity) 310 (M$^+$, 16), 295 (18), 268 (22), 267 (100), 220 (94), 199 (31), 183(28), 162 (31), 73 (59); calcd for C$_{18}$H$_{34}$O$_2$Si (M$^+$) *m/e* 310.2328, found *m/e* 310.2327. Anal. Calcd for C$_{18}$H$_{34}$O$_2$Si: C, 69.63; H, 11.04. Found: C, 69.23; H, 11.05.

Trimethylsilylethers of cubenol (15) and isocubenol (16). To a solution of 655 mg (2.1 mmol) of **13** in 10 mL of dry THF was added 80 mg (2.1 mmol) of LiAlH$_4$ at -78°C. The mixture was allowed to warm to -30°C over a 2-h period and then cooled again to -50°C. The mixture was diluted with 20 mL of ether, and then carefully quenched with a few drops of 4N NaOH. The resulting mixture was dried and concentrated under reduced pressure to give 659 mg of a solid, containing, according to GC-analysis, 91% of **14** [^{1}H NMR (CDCl$_3$) δ 0.25 (s, 9H), 0.73 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 7.6 Hz, 3H), 1.05 (d, J = 5.9 Hz, 3H), 1.08-2.24 (m, 13H), 3.27 (d, J = 9.4 Hz, 1H), 3.69 (br d, J = 9.4 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 2.86 (3xq), 15.11 (q), 15.54 (q), 18.52 (q), 21.51 (q), 24.03 (t), 24.14 (t), 25.39 (d), 30.06 (t), 35.70 (t), 37.50 (d), 37.61 (d), 42.73 (d), 50.17 (d), 70.24 (d), 80.88 (s); mass spectrum, *m/e* (relative intensity) 312 (M$^+$, 4), 269 (100), 251 (99), 205 (10), 179 (9), 149 (10), 105 (15), 73 (68)] which was used immediately for the next reaction.

To a solution of the crude **14** in 5 mL of dry pyridine was added 1.25 mL (17 mmol) of $SOCl_2$ at -20°C. The reaction mixture was stirred at -20°C for 1.5 h, poured into 40 mL of ice-water, and extracted with four 25-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were washed with 40 mL of 4N HCl, 40 mL of saturated $NaHCO_3$ and 40 mL of brine, and then dried. Evaporation of the solvent under reduced pressure gave 600 mg of a crude mixture of mainly **15** and **16**, in a 3:2 ratio, respectively. The unseparable mixture was used immediately for the next reaction.

15: ^1H NMR (major peaks, $CDCl_3$) δ 0.11 (s, 9H), 0.77 (d, J = 6,9 Hz, 3H), 0.90 (d, J = 6.3 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 1.71 (s, 3H), 5.42 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 2.40 (3xq), 14.71 (q), 15.43 (q), 21.23 (q), 23.39 (q), 23.93 (t), 25.69 (d), 27.28 (t), 30.12 (t), 31.65 (t), 39.19 (d), 41.13 (d), 46.56 (d), 75.74 (s), 120.45 (d), 132.22 (s); mass spectrum, *m/e* (relative intensity) 294 (M^+, 1), 279 (2), 251 (100), 161 (8), 119 (10), 105 (21), 73 (40).

16: ^1H NMR (major peaks, $CDCl_3$) δ 0.11 (s, 9H), 0.89 (d, J = 7 Hz, 3H), 0.90 (d, J = 7 Hz, 3H), 1.00 (d, J = 7 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 5.24 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 1.95 (3xq), 14.71 (q), 18.40 (q), 21.23 (q), 22.34 (q), 26.86 (d), 27.28 (t), 28.60 (t), 30.45 (t), 30.62 (d), 34.95 (t), 43.39 (d), 44.50 (d), 74.60 (s), 125.23 (d), 143.50 (s); mass spectrum, *m/e* (relative intensity) 294 (M^+, 8), 279 (16), 251 (100), 204 (33), 161 (30), 119 (32), 105 (32), 73 (73).

(–)-Cubenol (17). The crude mixture of **15** and **16** (600 mg) was dissolved in 6 mL of THF and 5 mL of 1.1 M TBAF in THF was added. The reaction mixture was heated at 60°C for 3 h, cooled to room temperature, and then 25 mL of water and 20 mL of petroleum ether (bp 40-60°C) were added. The two-phase mixture was separated, and the aqueous layer was extracted with two 20-mL portions of petroleum ether (bp 40-60°C). The combined organic layers were washed with 25 mL of brine, dried, and then evaporated under reduced pressure. The resulting residue was carefully flash chromatographed [22:1 petroleum ether (bp 40-60°C)/EtOAc] to give, in order of elution, 208 mg of cubenol (**17**) (44% from **13**) and 145 mg of isocubenol (**18**) (31% from **13**), both as colourless oils.

17: $[\alpha]_D$ -30.4° (c 0.90) (lit.[11a,12]: -30°); ^1H NMR, ^{13}C NMR, and MS spectroscopic data were consistent with those reported in the literature[11b].

18: $[\alpha]_D$ -87.5° (c 0.91); ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 6.1 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 1.04 (d, J = 7.1 Hz, 3H), 1.35 (s, 1H), 1.08-1.84 (m, 8H), 1.97-2.20 (m, 4H), 5.31 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.53 (q), 17.40 (q), 21.68 (q), 22.05 (q), 26.48 (t), 26.48 (d), 27.14 (t), 30.37 (t), 31.27 (d), 36.63 (t), 43.05 (d), 43.20 (d), 70.81 (s), 127.66 (d), 141.53 (s); mass spectrum, *m/e* (relative intensity) 222 (M^+, 2), 204 (7), 179 (100), 161 (37), 119 (8), 105 (13), 82 (8); calcd for $C_{15}H_{26}O$ (M^+) *m/e* 222.1983, found *m/e* 222.1983.

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