Synthesis of Tricyclic Ketones with Sesquiterpene Skeletons by Acid-Catalyzed Rearrangement of β-Monocyclofarnesol

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Starting from dihydro-β-ionone (**6**) a mixture of three tricyclic ketones with sesquiterpene skeletons **14**, **15**, and **16** was prepared by *Wittig-Horner* reaction with triethyl phosphonoacetate, *Red-Al*® reduction, acid-catalyzed rearrangement of the resulting β-monocyclofarnesol (**7**), alkaline hydrolysis of the formates **8**–**10**, and subsequent molybdenium-catalyzed oxidation. The mechanistic background of the acid-catalyzed rearrangement of β-monocyclofarnesol (**7**) is discussed in detail. The resulting tricyclic ketones **14**–**16** exhibit intense woody odor notes with peppery vetiver or camphoraceous cedarwood aspects.

Introduction. – Biomimetic carbonium-ion chemistry can shed light upon the biosynthesis of terpenes[1]), can facilitate the synthetic access to complicated carbon skeletons[2]), and can lead to the discovery of new nature-like compounds with interesting properties, for instance, new fragrance materials[3])[4]).

In 1981, four years before the isolation of the unusual sequiterpene alcohol (–)-myltaylenol (**3**) from the liverwort *Mylia taylorii* (HOOK) S. GRAY by *Matsuo* and co-workers [5], and even 17 years before its first enantioselective total synthesis [6], the underlying new sesquiterpene skeleton myltaylene (**2**) was characterized by *Naegeli* and *Wetli* [7] as a product of the rearrangement of **1** with TsOH in benzene (*Scheme 1*). In 1995, junicedranol (**4**), another new sesquiterpene alcohol with a similar skeleton was isolated by *Barrero et al.* [8] from the essential oil of *Juniperus oxycedrus* ssp. *macrocarpa*. Herbanone® (**5** [9]), a perfumery synthetic with a *woody, camphoraceous odor accompanied by ionone aspects*, can be considered as a related nor-sesquiterpene with a different ring fusion not yet found in nature.

In this paper, we report on structurally related cyclization products of β-monocyclofarnesol (**7**), and on the mechanism of the underlying rearrangement. The tricyclic ketones **14**–**16**, obtained by oxidation of the hydrolyzed formates **8**–**10**, constitute valuable fragrance materials [10] [11] (*cf. Scheme 2*).

Results and Discussion. – By modification of the synthetic route of *Kitahara* and co-workers [12][13], β-monocyclofarnesol (**7**) was synthesized in 88% yield on a 200-g scale from dihydro-β-ionone (**6**) by *Wittig-Horner* reaction with triethyl phosphono-

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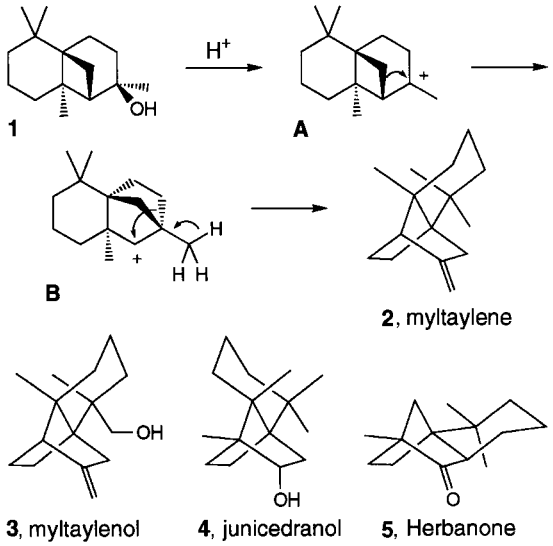
[1]) For instance, the acid-catalyzed rearrangement of dehydrobicyclo farnesol to herbertene; see [1].

[2]) For instance, the acid-catalyzed rearrangement of β-patchoulene oxide (*Patchino*®) to the taxane ring system; see [2].

[3]) For instance, the acid-catalyzed rearrangement of thujopsene to *Vertofix*®, an important commercial odorant, reminiscent of vetiver and cedarwood, with leathery aspects; see [3].

[4]) For a recent review on fragrance chemistry, see [4].

Scheme 1. *Formation of Myltaylene* (**2**) *by Acid-Catalyzed Rearrangement* (TsOH, benzene) *of* **1**, *Related Natural Products* **3** *and* **4**, *and a Commercial Fragrance, Synthetic* **5**, *with an Unnatural Ring Fusion*

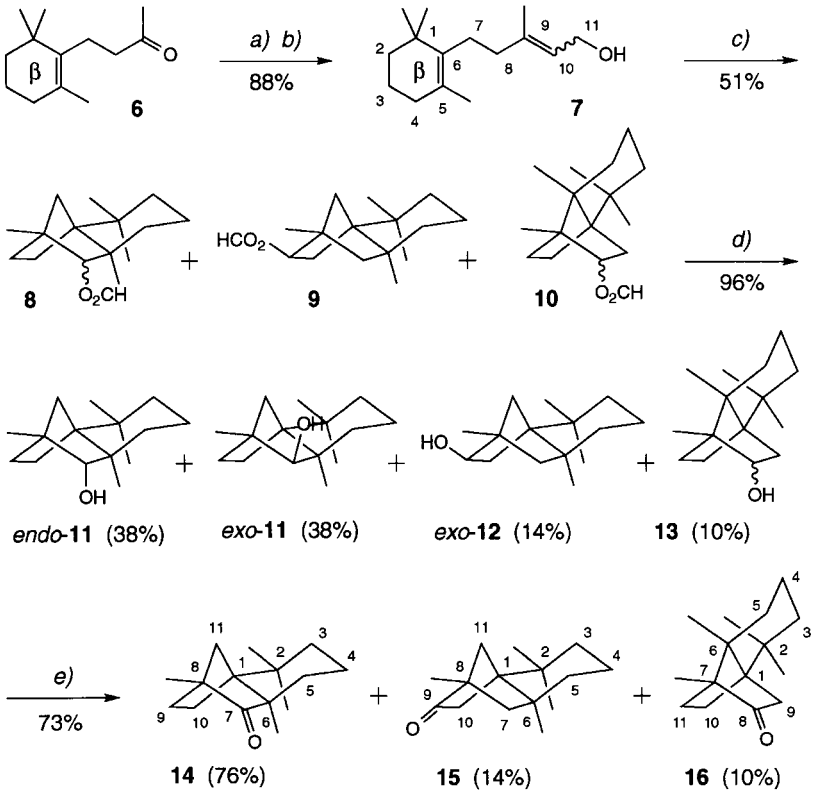


acetate, and subsequent reduction employing sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®). Treatment of **7** ($(Z)/(E) \approx 1:4$) with conc. HCOOH at 45° furnished in 51% yield a mixture of formates **8**, **9**, and **10** (*Scheme 2*). Hydrolysis of this mixture with methanolic KOH gave, in 96% yield, five alcohols in the ratio of 38 : 38 : 14 : 6 : 4. These were identified as *endo*-**11**, *exo*-**11**, *exo*-**12**, *exo*-**13**, and *endo*-**13** by co-injection with the hydride-reduction products of the corresponding ketones **14**, **15** and **16**.

The ketones **14**–**16**, which were much easier to separate than the corresponding alcohols **11**–**13**, were obtained in 73% yield by Mo-catalyzed H_2O_2 oxidation of the alcohol mixture **11**–**13** according to the general procedure of *Trost* and *Masuyama* [14]. They were separated by column chromatography, and their structure was elucidated by NOESY, NOE-DIFF, and INADEQUATE experiments.

For the structural assignment of the parent alcohols **11**–**13**, the tricyclic ketones **14**–**16** were subjected to hydride reduction ($LiAlH_4$). It is well-documented [15] [16] that the preferential *exo*-attack of the hydride on norcamphor, leading to 89% *endo*-norborneol, is inverted by the geminal dimethyl substituents of camphor to provide 91% of isoborneol (*exo*) and only 9% of borneol (*endo*). Consequently, the *endo*-alcohols *endo*-**11** and *endo*-**12** are the expected reduction products of **14** and **15**, while **16** should preferentially yield *exo*-**13** upon treatment with $LiAlH_4$. Indeed, hydride reduction of **14** and **15** gave mainly *endo*-**11** (90 : 10) and *endo*-**12** (93 : 7), while **16** predominantly furnished *exo*-**13** (94 : 6). An X-ray crystal-structure analysis of *endo*-**11** (*Fig.*) confirmed the assignmet of the structure and established the configuration. By co-injection of the synthesized *endo*-isomers of **11** and **12**, and the *exo*-isomer of **13**, the composition of the alcohol mixture **11**–**13** was established as *endo*-**11** (38%), *exo*-**11** (38%), *exo*-**12** (14%), *exo*-**13** (6%), and *endo*-**13** (4%).

Scheme 2. *Synthesis of Tricyclic Ketones* **14–16** *by Acid-Catalyzed Rearrangement of β-Monocyclofarnesol* (**7**)



a) $(EtO)_2P(O)CH_2COOEt$, NaOEt, EtOH, r.t., 2 h. *b*) $NaAlH_2(MeOCH_2CH_2O)_2$, toluene, r.t., 30 min. *c*) HCOOH, 45°, 50 min. *d*) KOH, MeOH, 65°, 30 min. *e*) $(NH_4)_2MoO_4$, H_2O_2, $MeN(C_8H_{17})_3Cl$, H_2O, 90°, 15 min.

In addition, component *exo*-**12**, the *endo*-isomer which was not found in the mixture **11**–**13**, was isolated by repeated chromatography and crystallization from hexane. Its structure was confirmed by *Jones* oxidation to the corresponding ketone **15**.

Mechanistic Considerations. – A formal mechanism of the acid-catalyzed rearrangement is presented in *Scheme 3*. Protonation of (*E*/*Z*)-**7** leads to the (*E*)- and (*Z*)-carbonium ions **C** and **D**, which are in equilibrium with one another[5]). A *6-endo-trig* cyclization of the latter gives predominantly the spirocyclic carbonium ion **E**, which, by loss of a proton, leads to α-chamigrene (**17**). Besides deprotonation, **E** can rearrange either by a *4-exo-trig* ring closure to the strained tricyclic carbonium ion **A** or by a disfavored *5-endo-trig* cyclization, to **F** with two adjacent quaternary C-atoms. The latter can also be formed by an intramolecular [3 + 2] cycloaddition reaction of **D**, but

[5]) For a related isomerization, the activation energy E_a was determined to be 21.9 kcal/mol and the pre-exponential factor A was 3.98×10^{11} [17].

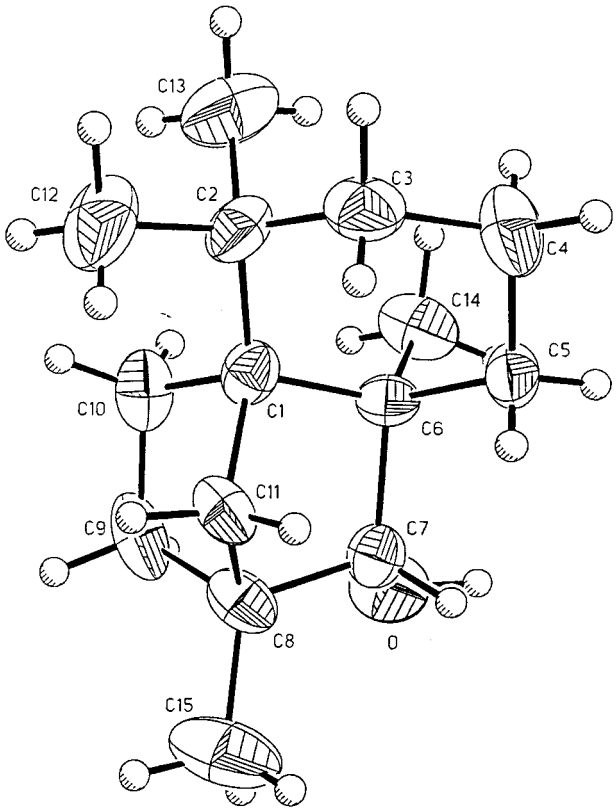


Figure. *X-Ray Crystal Structure of* endo-**11**

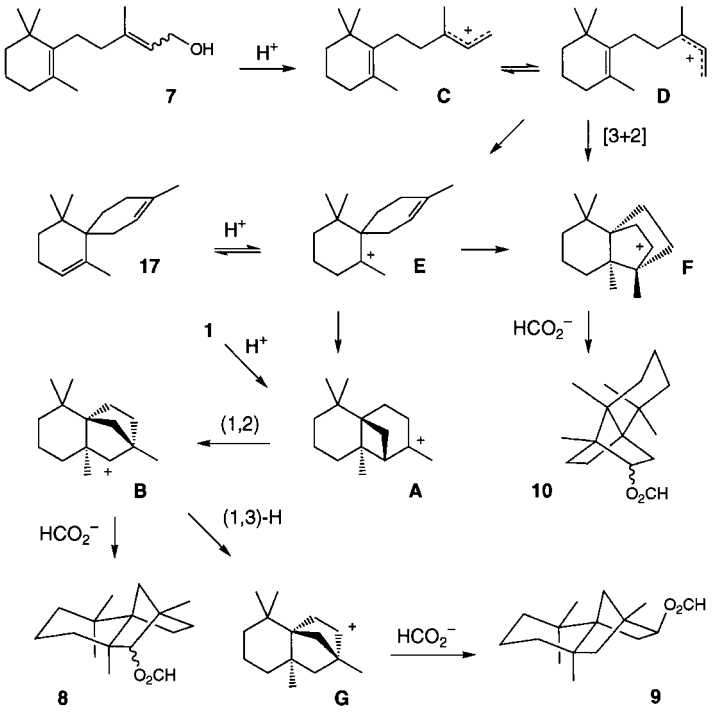
this is sterically demanding, thus explaining why the corresponding formiate **10** is only a minor reaction product.

The strain of the favored *4-exo-trig* cyclization product **A** can be released by a 1,2-*Wagner-Meerwein* rearrangement to carbonium ion **B**, which is either captured by the nucleophile to give the main reaction product **8**, or, after a fast 1,3-*endo*-H shift, leads to the carbonium ion **G**, from which the *exo*-formiate **9** is stereoselectively formed.

According to this mechanistic proposal, also compound **1** from the work of *Naegeli* and *Wetli* [7] as well as α-chamigrene (**17**) [12] [13] should rearrange to the formates **8**–**10** under acidic conditions. Indeed, subjecting **1** to the rearrangement conditions, formates **8**–**10** were obtained, which, after hydrolysis and oxidation, gave the tricyclic ketones **14**/**15**/**16** in the ratio of 69 : 12 : 19. Treatment of **17**, prepared according to [12] [13], with $HClO_4$ in conc. HCOOH, also provided, after hydrolysis and oxidation with the *Jones* reagent, the ketones **14**/**15**/**16**; however, in a different ratio of 22 : 77 : 1. If $HClO_4$ is added to the reaction of β-monocyclofarnesol (**7**) in conc. HCOOH, the *exo*-**12** isomer as well becomes the main hydrolysis product (**11**/*exo*-**12** *ca.* 1 : 3) [10].

This effect has recently been reported also by *Oritani* and co-workers [18], who found *exo*-**12** to be the only rearrangement product of **7** employing $ClSO_3H$ or

Scheme 3. *Proposed Mechanism for the Acid-Catalyzed Cyclization*



$BF_3 \cdot Et_2O$. For an X-ray crystal structure of *exo*-**12**, see [18]. Unfortunately, the oxidation product **15** of *exo*-**12** is olfactorily less interesting than **14**, and about hundred times weaker.

Olfactory Evaluation. – Interestingly, **14** with the sterically most hindered C=O group is the most intense constitutional isomer of the ketone mixture **14**–**16**, with an odor threshold of 0.2 ng/l. Furthermore, it is also olfactorily the most interesting one, possessing a dry, peppery, woody odor note of vetiver tonality with a slightly fruity aspect. In comparison to **14**, the odor of **15**, which is about hundred times weaker, is much more shifted to a pine and cedarwood direction with a camphoraceous background and some aspects of tobacco. Compound **16** is similar to **15** in having mainly a woody-camphoraceous odor profile, but differs by earthy, borneol-like, and peppery facets. The overall olfactory impression of the mixture **14**–**16** is principally determined by compound **14**. All alcohols **11**–**13** exhibit only a very faint, uncharacteristic odor.

Experimental Part

General. Reagents and solvents were purchased from *Fluka* and used without further purification. IR: *Perkin-Elmer 681* spectrometer, $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR: *Bruker-AM-400* spectrometer, δ in ppm rel. to Me_4Si, J in Hz. Assignment of the signals of **14**–**16** by NOESY, NOE-DIFF, and INADEQUATE experiments. MS: *Varian-MAT-CH-5* instrument, rel. int. in % of the base peak. X-Ray: *Nicolet-R3m* four-circle diffractometer, SHELXTL 3.0 software.

β-Monocyclofarnesol (**7**). Under N_2, a mixture of triethyl phosphonoacetate (322 g, 1.44 mol) and *dihydro-β-ionone* (**6**, 243 g, 1.25 mol) was added dropwise with stirring at 25–35° to a soln. of Na (34.5 g, 1.50 mol) in anh. EtOH (625 ml). After stirring for 2 h at r.t., the mixture was poured into H_2O (2.5 l), and the product extracted with toluene (2 × 500 ml). The combined org. extracts were washed with H_2O, 0.1N aq. HCl, and H_2O, and concentrated on a rotary evaporator. Distillation at 136–148°/0.05 mbar provided ethyl β-monocyclofarnesoate (281 g, 85%). At 25–35° under nitrogen, a 3.5M soln. of sodium bis(2-methoxyethoxy)aluminum hydride in toluene (314 ml, 1.10 mol) was added dropwise with stirring during 30 min to a soln. of ethyl β-monocyclofarnesoate (264 g, 1.00 mol) in toluene (500 ml). Stirring at r.t. was continued for 30 min, prior to cautious quenching by dropwise addition of H_2O (240 ml). The hydrolysis residue was filtered off and extracted with toluene (2 × 300 ml), and the combined org. extracts were washed with H_2O, 0.1N aq. HCl, and H_2O. After evaporation of the solvent, distillation at 131–138°/0.09 mbar furnished **7** (196 g, 88%, (*Z*)/(*E*) ≈ 1:4). IR (neat): 1003*m* (C–O), 3306*m* (O–H). ^{1}H-NMR ($CDCl_3$): 0.99 (*s*, 2 Me–C(1)); 1.42 (*dd*, *J* = 6.0, 3.0, 2 H–C(2)); 1.43 (*s*, OH); 1.55–1.59 (*m*, 2 H–C(3)); 1.60 (*s*, Me–C(5)); 1.72 (*s*, Me–C(9)); 1.91 (*t*, *J* = 6.0, 2 H–C(4)); 2.03–2.11 (*m*, 2 H–C(7), 2 H–C(8)); 4.17 (*d*, *J* = 7.0, 2 H–C(11)); 5.42–5.47 (*m*, H–C(10)). EI-MS: 222 (1, M^+), 204 (1, $[M-H_2O]^+$), 191 (5, $[M-CH_3O]^+$), 137 (88, $[M-C_5H_9O]^+$), 95 (100, $C_7H_{11}^+$), 81 (89, $C_6H_9^+$).

Acid-Catalyzed Cyclization of **7**. At r.t., **7** (444 g, 2.00 mol) was added dropwise with stirring to conc. HCOOH (2 l). After the addition was complete, the mixture was heated to 45° for 50 min, and then poured into ice-water. The products were extracted with hexane, and the combined org. extracts were washed to neutrality, dried, and concentrated under reduced pressure. Fractional distillation provided, besides a hydrocarbon fraction at 60–90°/0.08 mbar (182 g) consisting mainly of α-chamigrene (**17**), at 90–120°/0.07 mbar a mixture of formates **8**–**10** (252 g, 51%). This mixture (250 g, 1.00 mol) was added to a soln. of KOH (100 g, 1.78 mol) in MeOH (400 ml) and H_2O (100 ml), upon which the temp. rose to 65°. At this temp., stirring was continued for 30 min, before the mixture was poured into ice-water (2 l) and extracted with hexane/Et_2O 5:1. The org. extracts were combined, dried, and concentrated on a rotary evaporator, and the crude material (260 g) was purified by distillation to furnish at 93–115°/0.08 mbar an alcohol mixture *endo*-**11**/*exo*-**11**/*exo*-**12**/*exo*-**13**/*endo*-**13** (214 g, 96%, GC ratio 38:38:14:6:4) as a waxy solid.

Mo-Catalyzed Oxidation of the Alcohol Mixture **11**–**13**. The alcohol mixture **11**–**13** (150 g, 675 mmol) was added, at 50°, to a stirred soln. of $(NH_4)_2MoO_4$ (2.50 g, 12.8 mmol, 1.9 mol-%) in H_2O (100 ml), followed by (tricapryl)(methyl)ammonium chloride (6.00 g, 14.8 mmol, 2.2 mmol-%). Keeping the temp. below 90°, 30% aq. H_2O_2 (90 ml, 1.42 mol) was added dropwise, and the mixture was stirred for 15 min at 90°. The mixture was worked up with H_2O/hexane, and the combined org. extracts were washed with 10% aq. NaOH, dried, and concentrated on a rotary evaporator. Distillation of the resulting crude material (159 g) provided, at 85–87°/0.12 mbar, a mixture of the tricyclic ketones **14**/**15**/**16** (109 g, 73%, GC ratio 76:14:10). These ketones **14**–**16** were separated by silica-gel CC (hexane/Et_2O, 9:1), with compound **14** (66.1 g, 45%) eluting first, followed by compound **15** (13.3 g, 10%) and then **16** (9.94 g, 7%).

*(±)-(1*RS*,6*SR*,8*SR*)-2,2,6,8-Tetramethyltricyclo[6.2.1.0^{1,6}]undecan-7-one* (**14**). IR (neat): 1736*s* (C=O), 1372*m* (Me). ^{1}H-NMR ($CDCl_3$): 0.94, 0.97 (2*s*, 2 Me–C(2)); 1.12 (*s*, Me–C(8)); 1.18 (*s*, Me–C(6)); 1.31–1.65 (*m*, 2 H–C(3), 2 H–C(4), 2 H–C(5), 2 H–C(11), H_{endo}–C(9), H_{endo}–C(10)); 1.71–1.80 (*m*, H_{exo}–C(9), H_{exo}–C(10)). ^{13}C-NMR ($CDCl_3$): 14.8 (*q*, Me–C(8)); 18.0 (*t*, C(4)); 19.5 (*q*, Me–C(6)); 24.6, 27.6 (2*q*, 2 Me–C(2)); 25.5 (*t*, C(10)); 30.9 (*t*, C(5)); 32.5 (*t*, C(9)); 32.8 (*s*, C(2)); 39.0 (*t*, C(3)); 42.4 (*t*, C(11)); 49.7 (*s*, C(6)); 53.3 (*s*, C(8)); 53.9 (*s*, C(1)); 222.9 (*s*, C(7)). EI-MS: 220 (59, M^+), 205 (2, $[M-Me]^+$), 192 (27, $[M-CO]^+$), 137 (77, $[M-C_5H_7O]^+$), 121 (63, $C_9H_{13}^+$), 95 (65, $C_7H_{11}^+$), 81 (100, $C_6H_9^+$). Odor: Woody, vetiver, peppery, dry.

*(±)-(1*RS*,6*SR*,8*SR*)-2,2,6,8-Tetramethyltricyclo[6.2.1.0^{1,6}]undecan-9-one* (**15**). IR ($CHCl_3$): 1731*s* (C=O), 1379*m* (Me). ^{1}H-NMR ($CDCl_3$): 0.90, 0.97 (2*s*, 2 Me–C(2)); 1.07 (*s*, Me–C(8)); 1.11 (*s*, Me–C(6)); 1.25 (*dd*, *J* = 13.0, 2.5, H_{endo}–C(7)); 1.32–1.38 (*m*, H_b–C(3)); 1.42 (*dd*, *J* = 10.0, 2.5, H_{syn}–C(11)); 1.44–1.62 (*m*, H_a–C(3), 2 H–C(4), 2 H–C(5)); 1.53 (*d*, *J* = 13.0, H_{exo}–C(7)); 2.10 (*d*, *J* = 18.0, H_{exo}–C(10)); 2.13 (*dd*, *J* = 10.0, 4.0, H_{anti}–C(11)); 2.30 (*dd*, *J* = 18.0, 5.0, H_{endo}–C(10)). ^{13}C-NMR (C_6D_6): 14.6 (*q*, Me–C(8)); 19.6 (*t*, C(4)); 24.6 (*q*, Me–C(6)); 25.2 (*q*, Me_{ax}–C(2)); 29.2 (*q*, Me_{eq}–C(2)); 33.1 (*s*, C(2)); 38.2 (*t*, C(3)); 39.8 (*s*, C(6)); 40.9 (*t*, C(5)); 42.2 (*t*, C(10)); 44.1 (*t*, C(11)); 52.2 (*t*, C(7)); 53.3 (*s*, C(1)); 53.7 (*s*, C(8)); 215.1 (*s*, C(9)). NOE-DIFF ($CDCl_3$): 0.90 (Me–C(2)) → 1.42 (H_b–C(11), 7%), 2.10 (H_{exo}–C(10), 10%); 0.97 (Me–C(2)) → 2.30 (H_{endo}–C(10), 7%); 1.07 (Me–C(8)) → 1.53 (H_{exo}–C(7), 4%); 1.11 (Me–C(6)) → 1.25 (H_{endo}–C(7), 8%), 2.30 (H_{endo}–C(10), 9%). EI-MS: 220 (43, M^+), 205 (3, $[M-Me]^+$), 191 (47, $[M-CO]^+$), 176 (70, $[M-C_2H_4O]^+$), 161 (100, $[M-C_2H_4O]^+$), 107 (72, $C_8H_{11}^+$), 95 (48, $C_7H_{11}^+$), 41 (75, $C_3H_5^+$). Odor: Woody, camphoraceous, cedarwood, tobacco.

(±)-(1RS,6RS,7RS)-2,2,6,7-Tetramethyltricyclo[5.2.2.0^{1,6}]undecan-8-one (**16**). IR (neat): 1742*s* (C=O), 1382*m* (Me). ^{1}H-NMR ($CDCl_3$): 0.86 (*s*, Me_{eq}–C(2)); 0.88 (*s*, Me–C(7)); 0.98 (*ddd*, *J* = 15.0, 15.0, 4.5, H_{ax}–C(5)); 1.01 (*s*, Me–C(6)); 1.08 (*s*, Me_{ax}–C(2)); 1.19 (*ddd*, *J* = 15.0, 3.5, 3.5, H_{eq}–C(5)); 1.26–1.31 (*m*, H_{eq}–C(3)); 1.35–1.40 (*m*, H_{endo}–C(11)); 1.37–1.42 (*m*, H_{endo}–C(10)); 1.42–1.55 (*m*, H_{ax}–C(3), H_{eq}–C(4)); 1.62–1.73 (*m*, H_{ax}–C(4), H_{exo}–C(11)); 1.78 (*d*, *J* = 18.0, H_{endo}–C(9)); 1.88–1.97 (*m*, H_{exo}–C(10)); 2.41 (*dd*, *J* = 18.0, 3.5, H_{exo}–C(9)). ^{13}C-NMR ($CDCl_3$): 9.26 (*q*, Me–C(7)); 16.3 (*q*, Me–C(6)); 18.7 (*t*, C(4)); 23.4 (*q*, Me_{ax}–C(2)); 27.3 (*t*, C(10)); 28.6 (*t*, C(5)); 28.7 (*q*, Me_{eq}–C(2)); 29.9 (*t*, C(11)); 33.6 (*s*, C(2)); 36.0 (*t*, C(3)); 45.2 (*t*, C(9)); 47.9 (*s*, C(6)); 52.3 (*s*, C(1)); 60.5 (*s*, C(7)); 216.5 (*s*, C(8)). NOE ($(CD_3)_2CO$): 1.03 (Me–C(6)) → 1.08 (Me_{ax}–C(2)), 1.65–1.75 (H_{ax}–C(4)), H_{exo}–C(10), 1.97 (H_{exo}–C(11)). EI-MS: 220 (81, M^+), 205 (9, $[M-Me]^+$), 177 (23, $[M-C_2H_3O]^+$), 150 (29, $[M-C_5H_{10}]^+$), 135 (100, $[M-C_6H_{13}]^+$), 69 (69, $C_5H_9^+$), 41 (78, $C_3H_5^+$). Odor: Woody, camphoraceous, earthy, borneol, peppery.

(±)-(1RS,6SR,7RS,8SR)-2,2,6,8-Tetramethyltricyclo[6.2.1.0^{1,6}]undecan-7-ol (*endo*-**11**). Under N_2 at r.t., a soln. of **14** (2.00 g, 9.25 mmol) in Et_2O (20 ml) was added dropwise with stirring to a suspension of $LiAlH_4$ (0.50 g, 13.1 mmol) in Et_2O (30 ml). After stirring at r.t. for 30 min., H_2O (2 ml) was added dropwise, followed by 15% aq. NaOH (2 ml) and again H_2O (5 ml). The org. layer was dried, filtered and evaporated to furnish a 90:10 mixture *endo*-**11**/*exo*-**11** (1.80 g, 88%) as colorless solid; m.p. 70–71°. Crystallization from hexane provided the *endo*-**11** isomer as colorless crystals. M.p. 83–84°. IR ($CHCl_3$): 1023*s* (*sec.* C–O), 1377*m* (Me), 3605*w* (*sec.* OH), 3460*w* (br. O–H). ^{1}H-NMR ($CDCl_3$): 0.84, 0.92 (2*s*, 2 Me–C(2)); 1.02, 1.06 (*s*, Me–C(6), Me–C(8)); 1.12 (*d*, *J* = 10.0, H_{syn}–C(11)); 1.23–1.70 (*m*, 2 H–C(3), 2 H–C(4), 2 H–C(5), 2 H–C(9), 2 H–C(10), H_{anti}–C(11), HO); 3.20 (*d*, *J* = 2.0, H–C(7)). ^{13}C-NMR ($CHCl_3$): 18.1 (*q*, Me–C(8)); 19.2 (*t*, C(4)); 19.9 (*q*, Me–C(6)); 25.2, 28.7 (2*q*, 2 Me–C(2)); 26.7 (*t*, C(10)); 27.0 (*t*, C(5)); 33.4 (*s*, C(2)); 39.9 (*t*, C(3)); 41.2 (*t*, C(11)); 42.0 (*s*, C(8)); 42.5 (*t*, C(9)); 47.4 (*s*, C(6)); 55.1 (*s*, C(1)); 87.2 (*d*, C(7)). EI-MS: 222 (51, M^+), 204 (18, $[M-H_2O]^+$), 191 (45, $[M-CH_2OH]^+$), 179 (13, $[M-C_3H_7]^+$), 166 (15, $[M-C_4H_8]^+$), 151 (20, $[M-C_4H_7O]^+$), 138 (51, $C_{10}H_{18}^+$), 123 (58, $C_9H_{15}^+$), 109 (77, $C_8H_{13}^+$), 95 (90, $C_7H_{11}^+$), 81 (100, $C_6H_9^+$), 69 (55, $C_5H_9^+$), 55 (56, $C_4H_7^+$). X-Ray Analysis (MoK_α): $C_{15}H_{26}O$ (222.37), 0.36 × 0.336 × 0.44 mm (170 K), tetragonal, $P4_1/n$, $a = b = 16.985(5)$ Å, $c = 9.444(2)$ Å, $Z = 8$, $D_x = 1.082$ g/cm^3, $\mu = 0.061$ mm^{-1}, $\theta_{min/max} = 0/25°$, 2741 measured, 1043 observed reflections $[I > 2.5 \cdot \sigma(I)]$ for 148 parameters, $R = 0.0947$. For an ORTEP view, see the *Fig.*[6]). Co-injection proved *endo*-**11** to be present in 38% in the mixture of the alcohols **11**–**13**. The *exo*-isomer, which was formed as a 10% by-product of the $LiAlH_4$ reduction, was also found to be present in 38% in the alcohol mixture **11**–**13**.

(±)-(1RS,6SR,8SR,9RS)-2,2,6,8-Tetramethyltricyclo[6.2.1.0^{1,6}]undecan-9-ol (*endo*-**12**). Under N_2 at r.t., a soln. of **15** (1.80 g, 8.18 mmol) in Et_2O (20 ml) was added dropwise with stirring to a suspension of $LiAlH_4$ (0.40 g, 10.5 mmol) in Et_2O (30 ml). After stirring at r.t. for 30 min, usual workup and distillation at 110°/0.13 mbar provided **12** (1.60 g, 88%) as an oil, which solidified. M.p. 78–79°. IR ($CHCl_3$): 1100*m* (*sec.* C–O), 1373*m* (Me), 3610*w* (*sec.* O–H), 3450*w* (br., O–H). ^{1}H-NMR ($CDCl_3$): 0.82, 0.86 (2*s*, 2 Me–C(2)); 0.99 (*s*, Me–C(8)); 1.06 (*dd*, *J* = 13.0, 1.5, H_{exo}–C(7)); 1.13 (*dd*, *J* = 10.0, 3.0, H_{syn}–C(11)); 1.18 (*s*, Me–C(6)); 1.22–1.46 (*m*, 2 H–C(4), 2 H–C(5)); 1.41 (*ddd*, *J* = 14.0, 4.0, 4.0, H_{endo}–C(10)); 1.47–1.59 (*m*, 2 H–C(3), OH); 1.72 (*dd*, *J* = 13.0, 3.0, H_{endo}–C(7)); 1.79 (*dd*, *J* = 10.0, 4.0, H_{anti}–C(11)); 1.95 (*dd*, *J* = 14.0, 10.0, H_{exo}–C(10)); 3.79 (*m*, H–C(9)). ^{13}C-NMR ($CHCl_3$): 19.5 (*q*, Me–C(8)); 19.5 (*t*, C(4)); 24.0, 24.7 (2*q*, Me–C(6), Me_{ax}–C(2)); 29.2 (*q*, Me_{eq}–C(2)); 33.0 (*s*, C(2)); 35.8 (*t*, C(10)); 39.2 (*t*, C(3)); 40.1 (*s*, C(6)); 41.2 (*t*, C(5)); 44.8 (*t*, C(11)); 46.5 (*s*, C(1)); 47.2 (*t*, C(7)); 55.4 (*s*, C(8)); 77.3 (*d*, C(9)). EI-MS: 222 (33, M^+), 207 (12, $[M-Me]^+$), 191 (13, $[M-CH_2OH]^+$), 177 (37, $[M-C_2H_4OH]^+$), 138 (30, $[M-C_6H_{12}]^+$), 107 (66, $C_8H_{11}^+$), 95 (51, $C_7H_{11}^+$), 69 (61, $C_5H_9^+$), 55 (69, $C_4H_7^+$), 41 (100, $C_3H_5^+$). NMR and GC analysis showed 7% of the *exo*-isomer to be present, which, in contrast to *endo*-**12**, was identified by co-injection to be present in 14% in the mixture of the alcohols **11**–**13**.

(±)-(1RS,6SR,8SR,9SR)-2,2,6,8-Tetramethyltricyclo[6.2.1.0^{1,6}]undecan-9-ol (*exo*-**12**). Colorless crystals of *exo*-**12** were also isolated as an anal. sample from the alcohol mixture **11**–**13** by repeated chromatography and crystallization from hexane. M.p. 124–125°. IR ($CHCl_3$): 1018*s* (*sec.* C–O), 1378*m* (Me), 3615*w* (*sec.* O–H), 3465*w* (br., O–H). ^{1}H-NMR ($CDCl_3$): 0.91 (*s*, 2 Me–C(2)); 1.01, 1.03 (2*s*, Me–C(6), Me–C(8)); 1.25–1.53 (*m*, 2 H–C(3), 2 H–C(4), 2 H–C(5), 2 H–C(7), H_{syn}–C(11), OH); 1.30 (*dd*, *J* = 14.5, 3.0, H_{exo}–C(10));

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[6]) Crystallographic data (excluding structure factors) for the *endo*-**11** have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-110976. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, Fax: +44 (1223) 336033, E-mail: deposit@ccdc.cam.ac.uk.

1.56 (*ddd*, *J* = 10.0, 3.0, 3.0, H_{anti}–C(11)); 2.15 (*ddd*, *J* = 14.0, 7.0, 3.0, H_{endo}–C(10)); 3.49 (*m*, H_{endo}–C(9)). ^{13}C-NMR ($CHCl_3$): 16.8 (*q*, Me–C(8)); 19.8 (*t*, C(4)); 24.5, 25.0 (2*q*, 2 Me–C(6), Me_{ax}–C(2)); 29.3 (*q*, Me_{eq}–C(2)); 33.2 (*s*, C(2)); 39.2, 39.7 (2*t*, C(3), C(5)); 39.6 (*s*, C(6)); 40.9, 41.1 (2*t*, C(7), C(11)); 46.9 (*s*, C(1)); 54.6 (*t*, C(10)); 55.0 (*s*, C(8)); 77.8 (*d*, C(9)). EI-MS: 222 (54, M^+), 207 (16, $[M - Me]^+$), 191 (17, $[M - CH_2OH]^+$), 177 (32, $[M - C_2H_4OH]^+$), 138 (44, $[M - C_6H_{12}]^+$), 107 (56, $C_8H_{11}^+$), 95 (48, $C_7H_{11}^+$), 69 (51, $C_5H_9^+$), 55 (55, $C_4H_7^+$), 41 (100, $C_3H_5^+$).

(±)-(1RS,6RS,7RS,8RS)-2,2,6,7-Tetramethyltricyclo[5.2.2.0^{1,6}]undecan-8-ol (*exo*-**13**). Under N_2 at r.t., a soln. of **16** (0.50 g, 2.27 mmol) in Et_2O (1 ml) was added to a stirred suspension of $LiAlH_4$ (0.20 g, 5.27 mmol) in Et_2O (2 ml). After stirring at r.t. for 30 min, usual workup and silica-gel CC (hexane/*t*-BuOMe, 1 : 1) provided **13** (0.35 g, 70%) as an oil, which solidified. M.p. 58–60°. GC showed *ca.* 6% of the *endo*-isomer to be present. Recrystallization (hexane) furnished pure *exo*-**13**. M.p. 64–66°. IR ($CHCl_3$): 1022*s* (*sec.* C–O), 1382*m* (Me), 3610*w* (*sec.* O–H), 3450*w* (br., O–H). ^{1}H-NMR ($CDCl_3$): 0.81 (*s*, Me_{eq}–C(2)); 0.87 (*s*, Me–C(7)); 0.91 (*s*, Me–C(6)); 0.93–0.99 (*m*, H_{ax}–C(5)); 1.00 (*s*, Me_{ax}–C(2)); 1.02–1.13 (*m*, 2 H–C(5)); 1.16–1.21 (*m*, H_{eq}–C(3)); 1.41–1.54 (*m*, H_{endo}–C(10), H_{endo}–C(11)); 1.55–1.66 (*m*, H_{ax}–C(3), 2 H–C(4), H_{exo}–C(11)); 1.69 (*dd*, *J* = 14.0, 9.0, H_{endo}–C(9)); 1.94 (*ddd*, *J* = 14.0, 3.5, 3.5, H_{exo}–C(9)); 2.16 (*ddd*, *J* = 14.0, 14.0, 4.0, H_{exo}–C(10)); 3.57 (*dd*, *J* = 9.0, 3.5, H–C(8)). (*endo*-**13**: ^{1}H-NMR ($CDCl_3$): 3.94 (*ddd*, *J* = 10.5, 4.0, 2.0, H–C(8))). ^{13}C-NMR ($CHCl_3$): 11.9 (*q*, Me–C(7)); 17.7 (*q*, Me–C(6)); 19.4 (*t*, C(4)); 23.9 (*q*, Me_{ax}–C(2)); 27.5 (*t*, C(10)); 28.4 (*t*, C(5)); 28.8 (*q*, Me_{eq}–C(2)); 33.6 (*t*, C(11)); 33.7 (*s*, C(2)); 36.9 (*t*, C(3)); 43.1 (*t*, C(9)); 47.6 (*s*, C(6)); 52.4 (*s*, C(1)); 53.3 (*s*, C(7)); 78.4 (*d*, C(8)). EI-MS: 222 (1, M^+), 204 (16, $[M - H_2O]^+$), 189 (6, $[M - H_2O - Me]^+$), 119 (41, $C_9H_{11}^+$), 109 (16, $C_8H_{13}^+$), 93 (21, $C_7H_9^+$), 81 (22, $C_6H_9^+$), 67 (37, $C_5H_7^+$), 55 (46, $C_4H_7^+$), 41 (100, $C_3H_5^+$). In the alcohol mixture **11**–**13**, both isomers were found by co-injection to be present in a total amount of 10% with an *exo/endo*-ratio of 60 : 40.

Rearrangement of **1**. Compound **1** was prepared according to the procedure of *Naegeli* and *Wetli* [7]. A soln. of **1** (350 mg, 1.59 mmol) in conc. HCOOH (20.0 ml) was stirred at r.t. for 45 min, prior to standard workup with H_2O/hexane. The crude material was treated with 20% methanolic KOH (10 ml) for 30 min at 50°. Workup with H_2O/*t*-BuOMe was followed by oxidation of the crude material with the *Jones* reagent (4 ml, 8 mmol) in Me_2CO (20 ml) to provide a mixture **14**/**15**/**16** in the ratio of 69 : 12 : 19.

Rearrangement of α-Chamigrene (**17**). Compound **17** was synthesized according to the procedure of *Kitahara* and co-workers [12] [13] by treatment of *β*-monocyclofarnesol (**7**, 20.0 g, 90.0 mmol) with I_2 (3.00 g, 11.8 mmol) in benzene (200 ml). After stirring for 2 d at r.t., workup with H_2O/hexane and hydrolysis of the resulting crude material with KOH (2.00 g, 35.7 mmol) in MeOH (50 ml), bulb-to-bulb distillation at 90°/0.13 mbar furnished **17** (9.30 g, 51%) as a colorless oil. 70% aq. $HClO_4$ (0.3 ml, 3.5 mmol) was added at r.t. to a soln. of **17** (6.00 g, 29.4 mmol) in conc. HCOOH (30 ml). After stirring for 10 min at this temp., the mixture was heated to 40° for 30 min prior to usual workup. Silica-gel CC (hexane/Et_2O 8 : 2) provided the mixture of formiates **8**–**10** (1.80 g, 25%) as a colorless oil, which solidified upon standing. 50% aq. KOH (2 ml, 18 mmol) was added to a soln. of the formiates **8**–**10** (1.20 g, 4.79 mmol) in MeOH (10 ml). After stirring for 1 h at 50° and subsequent workup with H_2O/Et_2O, the crude product was taken up Me_2CO (50 ml) and oxidized with *Jones* reagent (2.0 ml, 4 mmol) to provide a mixture of the ketones **14**/**15**/**16** (1.0 g, 95%) in the ratio of 22 : 77 : 1.

Thanks are due to *J. Daly* and *P. Schönholzer* of *F. Hoffmann-La Roche* AG, Basel, for the X-ray structure determination, and to *E. Billeter* and *J. Märki* for NMR experiments.

REFERENCES

[1] G. Fráter, U. Müller, *J. Chem. Soc., Chem. Commun.* **1988**, 1198.
[2] R. A. Holton, *J. Am. Chem. Soc.* **1984**, *106*, 5731.
[3] H. U. Daeniker, A. R. Hochstetler, K. Kaiser, G. C. Kitchens, J. F. Blount *J. Org. Chem.* **1972**, *37*, 6.
[4] G. Fráter, J. A. Bajgrowicz, P. Kraft, *Tetrahedron* **1998**, *54*, 7633.
[5] D. Takaoka, A. Matsuo, J. Kuramoto, M. Nakayama, S. Hayashi *J. Chem. Soc., Chem. Commun.* **1985**, 482.
[6] S. Doye, T. Hotopp, R. Wartchow, E. Winterfeld, *Chem. Eur. J.* **1998**, *4*, 1480.
[7] P. Naegeli, M. Wetli, *Tetrahedron* **1981**, *37*, Suppl. 1, 247.
[8] A. F. Barrero, E. Alvarez-Manzaneda, A. Lara, *Tetrahedron Lett.* **1995**, *36*, 6347.
[9] W. Lenselink, G. Sipma, to *PFW*, EP 29 259, 1979.
[10] G. Fráter, U. Müller, to *Givaudan*, EP 315 895, US 4947002, 1988.

[11] G. Fráter, in 'Proceedings of the 12th International Congress of Flavours, Fragrances and Essential Oils', Ed. H. Woidich, G. Buchbauer, Austrian Association of Flavour and Fragrance Industry, Wien, 1992, pp. 117–126.
[12] S. Kanno, T. Kato, Y. Kitahara, *Chem. Commun.* **1967**, 1257.
[13] T. Kato, S. Kanno, Y. Kitahara, *Tetrahedron* **1970**, *26*, 4287.
[14] B. M. Trost, Y. Masuyama, *Tetrahedron Lett.* **1984**, *25*, 173.
[15] E. C. Ashby, J. R. Boone, *J. Org. Chem.* **1976**, *41*, 2890.
[16] H. C. Brown, H. R. Deck, *J. Am. Chem. Soc.* **1965**, *87*, 5620.
[17] J. M. Bollinger, J. M. Brinich, G. A. Olah, *J. Am. Chem. Soc.* **1970**, *92*, 4025.
[18] H. Tanimoto, H. Kiyota, T. Oritani, K. Matsumoto, *Synlett* **1997**, 121.

Received January 12, 1999