

214. New Sesquiterpenoids from Cabreuva Oil¹⁾

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Six sesquiterpenoids **1–6**, formally derived from (+)-(*S*)-nerolidol by oxidative cyclization, have been isolated for the first time from commercial cabreuva oil. Whereas the two tetrahydrofurans **5** and **6** have already been described, the four bicyclic ethers (cabreuva oxides A–D) **1–4** are new. The structures of **1–4** are confirmed by synthesis and their absolute configurations are shown to be 3*S*. The organoleptic properties of the synthetic cabreuva oxides are discussed.

Introduction. – Cabreuva oil is obtained by steam distillation of the wood of *Myrcarpus fastigiatus* Fr. Allem. (Leguminosae) [1] [2]. This tree and various related species grow wild in Brazil, Paraguay, and Argentina, where their wood is highly appreciated as an ornamental lumber and furniture wood. The commercial oil, which is now produced by distillation of wastewood from the lumbermills, contains over 80% of (+)-(*S,E*)-nerolidol [3] and was important as a source for nerolidol and farnesol, until these sesquiterpene alcohols became more cheaply available by synthesis. Today, the oil finds limited use in perfumery. It is appreciated for its delicate sweet-woody and slightly floral odor and the tenacity it lends to perfumes [2].

In the course of analysis of a low-boiling fraction (b.p. 40–45°/0.01 Torr), in which a part of the typical odor of cabreuva oil was concentrated, we isolated six isomeric sesquiterpene ethers **1–6** (ratio *ca.* 1:5:1:5:1:1, together *ca.* 0.5% of the oil). Their empirical formula C₁₅H₂₄O was indicated by their mass spectra (M^{+} at *m/z* 220) and their ¹H-NMR spectra (24 protons). The similarity of the spectra of **1–4** suggested that these compounds belonged to one group of diastereoisomers, while **5** and **6** formed a second group.

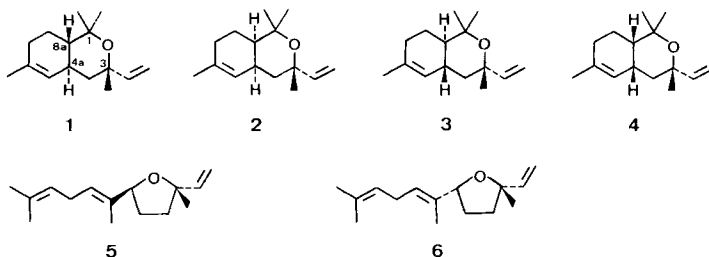
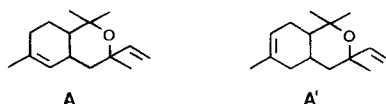


Fig. 1. New constituents from cabreuva oil

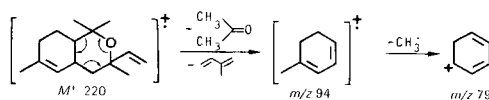
¹⁾ Presented, in part, at the 10th International Congress of Essential Oils, Washington, D.C., November 16–20, 1986.

For the novel bicyclic ethers **1–4**, we propose the names ‘cabreuva oxide A, B, C, and D’, respectively. The tetrahydrofuran derivatives **5** and **6** have previously been identified in osmanthus absolute [4]. Our spectral data (MS, $^1\text{H-NMR}$) for **5** and **6** were identical with those reported [4]; no reliable $[\alpha]_D^{20}$ values could be measured for **5** and **6**, but the absolute configuration, by analogy, is likely to be as shown.

Structure Elucidation and Configurational Assignments of 1–4. – The $^1\text{H-NMR}$ spectra (360 MHz) of **1–4** indicated the following structural elements: 3 CH_3 groups at O-bearing quaternary C-atoms, 1 trisubstituted double bond with 1 substituent being a CH_3 group, and 1 vinyl group on a quaternary C-atom. Because there was no evidence for CO or OH groups in the IR spectra and 2 of the 4 degrees of unsaturation are accounted for, the compounds **1–4** are bicyclic ethers. Based on biogenetic considerations (evident relationship to nerolidol), structures **A** or **A'** seemed likely. These structures, which contain 3 chiral centers accounting for the 4 observed diastereoisomers, were also supported by the mass spectra.



The base peak, which is at m/z 94 for all 4 isomers, was readily explained by the cyclic fragmentation of the molecular ion into acetone, isoprene, and the charge-carrying dihydrotoluene. The latter can lose a CH_3 radical, after a 1,5-H shift, giving rise to another abundant ion at m/z 79.



On the basis of the $^1\text{H-NMR}$ spectra, a decision between **A** and **A'** in favor of **A** was made, and the relative configuration of the ring fusions and the preferred conformations were deduced.

For cabreuva oxide **C** (**3**), the signal at 2.28 ppm (br. t , $J \approx 12$ Hz, 1 H) was readily assigned to an axial allylic bridgehead proton H–C(4a), which is strongly coupled to the two axial protons at C(4) and C(8a) and weakly coupled to the olefinic H–C(5) ($J(4a,5) \approx 1$ Hz). In addition, only one allylic CH_2 group was present (1.93–2.12 ppm, m , 2 H), thus ruling out **A'**. The large coupling constant of *ca.* 12 Hz between H–C(4a) and H–C(8a) indicated *trans*-fused rings for **3**. Cabreuva oxide **A** (**1**) also has *trans*-fused rings (H–C(4a) at 2.21 ppm (br. t , $J \approx 12$ Hz)).

For the *cis*-fused compound **2**, the allylic bridgehead proton was found at 2.50 ppm and for **4** at 2.55 ppm. This downfield shift of H–C(4a) by *ca.* 0.3 ppm, the presence of one large coupling constant ($J(4_{ax}, 4a) > 9$ Hz) and an increased coupling ($J \approx 4$ Hz) between H–C(4a) and H–C(5) suggested that H–C(4a) occupies the pseudo-equatorial position with respect to the cyclohexene ring. This conformation, with the sterically demanding C(1) in

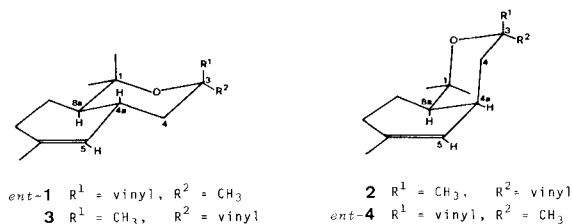
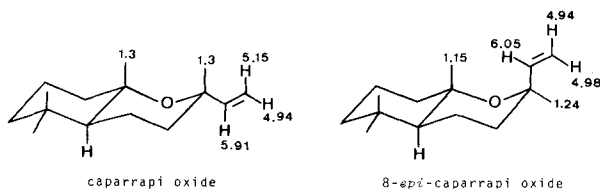


Fig. 2. The predominant conformation of the cabreuva oxides **A–D** (**1–4**)

the equatorial position, would be expected to be more stable (especially in the case of **2**, where there is no unfavorable 1,3-diaxial CH₃/CH₃ interaction) than the other possible chair-chair conformation.

Evidence for the relative configuration of the third chiral center at C(3) came mainly from the chemical shifts of the CH₃ groups in the ¹H-NMR spectra of **1–4**.

The compounds **3** and **4** have their CH₃–C(3) at lower field (1.34 and 1.33 ppm) than their C(3)-epimers **1** and **2** (1.20 and 1.26 ppm), respectively. This deshielding in **3** and **4** indicated a 1,3-diaxial arrangement of the CH₃ groups. Such an arrangement causes a downfield shift of *ca.* 0.08 ppm of the two axial CH₃ groups [5]. This effect was also observed for the axial CH₃–C(1), which is at lower field for **3** (1.23 ppm) and **4** (1.32 ppm) than for **1** (1.08 ppm) and **2** (1.15 ppm), respectively. That these arguments are still valid in the presence of a vinyl group is demonstrated by the diastereoisomeric caparrapi oxides [6]. In addition, characteristic differences in the chemical shifts of the vinyl protons were reported for the caparrapi oxides [6] depending on whether the vinyl group is axial or equatorial. Similar shift differences of the vinyl protons are exhibited by the pairs **1/3** and **2/4** (see *Exper. Part*), confirming the assignments based on the shifts of the CH₃ groups.

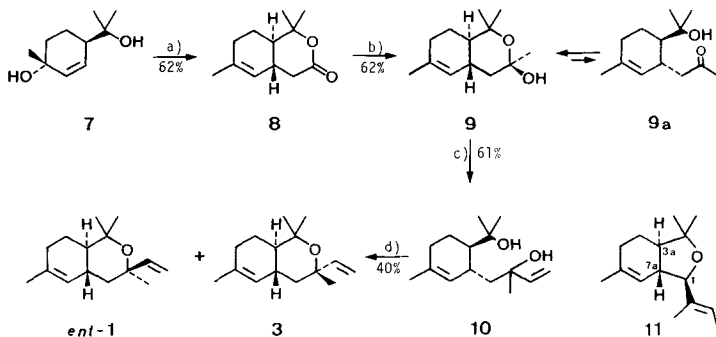


These configurational assignments were later fully confirmed by the ¹³C-NMR spectra (see the *Table*) of the synthetic compounds *ent*-**1**, **2**, **3**, and *ent*-**4**. The *cis*-fused compounds **2** and *ent*-**4** showed a marked γ -gauche effect for C(4) and C(8), just as would be expected for the conformations illustrated in *Fig. 2*. As anticipated, the axial CH₃ group at C(3) of **3** (25.8 ppm) and *ent*-**4** (26.7 ppm) resonates at higher field than the corresponding equatorial CH₃ group of *ent*-**1** (32.6 ppm) and **2** (32.8 ppm).

To confirm the structures and determine the absolute configurations of **1–4**, the compounds were synthesized from optically pure starting materials. This also allowed a reliable olfactive evaluation of these cyclic ethers.

Syntheses. – For the synthesis of the optically pure *trans*-fused cabreuva oxides **1** and **3** (*Scheme 1*), the readily available, enantiomerically pure, crystalline (1*R*,4*R*)-2-*p*-men-

Scheme 1



^a) CH₃C(OC₂H₅)₃, pivalic acid/120–150°, 16 h. ^b) CH₃MgI, Et₂O/5–10°, 2 h. ^c) CH₂=CHMgBr, THF/25°, 15 h.

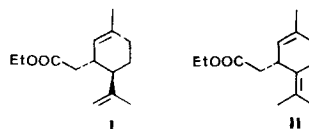
^d) TsOH, toluene/reflux, 30 min.

Table. ¹³C-NMR Chemical Shifts (90.5 MHz, CDCl₃) of **1-4**, **8**, **9**, **15**, **19**, **24**, and **25**^{a)}

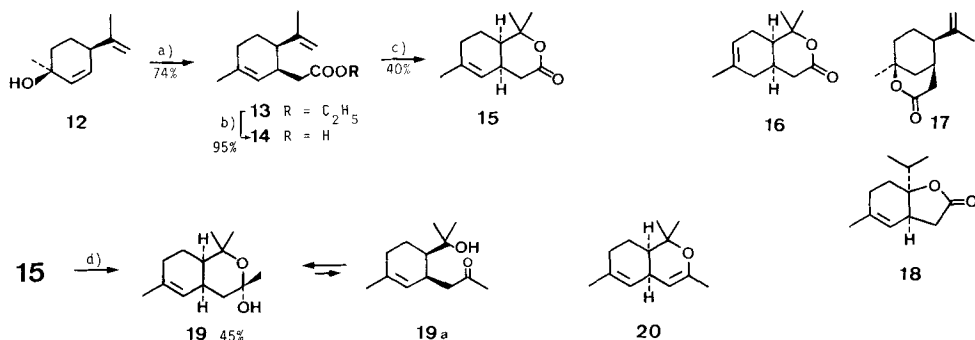
		C(1)	C(3)	C(4)	C(4a)	C(5)	C(6)	C(7)	C(8)	C(8a)	CH _{3ax} -C(1)	CH _{3eq} -C(1)	CH ₃ -C(3)	CH ₃ -C(6)	Ethinyl or vinyl	
															C(1)	C(2)
<i>trans</i>																
8 ^{b)}		86.0	170.6	37.3	31.1	122.6	135.1	30.7	24.1	45.5	23.1	28.7	—	23.1	—	—
9		76.3	96.5	42.4	29.8	125.5	133.9	31.3	24.5	48.2	(23.5)	30.0	32.2	(23.3)	—	—
<i>ent</i> - 1		76.1	74.0	40.5	30.9	125.9	134.1	31.4	24.7	48.6	22.4	30.4	32.6	23.3	147.1	110.5
3		75.4	73.6	43.1	30.4	125.6	134.3	31.3	24.6	48.5	23.7	30.7	25.8	23.3	147.9	110.1
<i>cis</i>																
15 ^{b)}		83.1	171.4	32.9	28.7	123.6	134.5	30.2	18.6	39.2	26.6	28.9	—	23.2	—	—
19		74.6	96.2	37.0	27.1	125.6	133.8	31.0	18.4	39.7	29.0	30.4	32.3	23.3	—	—
24		75.8	66.9	40.5	28.7	125.3	134.1	31.0	18.4	39.8	(28.3)	(29.3)	32.9	23.3	89.4	71.7
25		75.8	67.7	38.1	28.5	124.3	134.9	30.6	20.5	41.1	32.0	29.7	27.4	23.5	90.5	70.0
2		74.5	73.6	34.8	27.9	125.8	133.7	31.0	18.5	40.0	(29.5)	(29.3)	32.8	23.4	147.6	110.0
<i>ent</i> - 4		74.1	73.4	37.2	28.1	125.5	134.2	30.9	19.1	40.4	31.0	29.3	26.7	23.5	148.4	110.0

a) Values in parentheses within horizontal lines may be interchanged.

b) The shift assignments of the lactones **8** and **15** are based on ¹H, ¹³C correlated 2D-NMR spectra.



Scheme 2

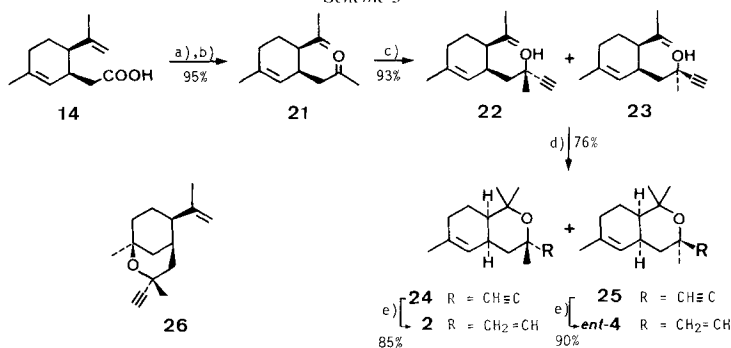


a) $\text{CH}_3\text{C}(\text{OC}_2\text{H}_5)_3$, pivalic acid/140–145°, 24 h. b) NaOH , H_2O , EtOH /reflux, 3 h. c) TsOH , toluene/reflux, 20 h. d) CH_3Li , Et_2O /–40°, 30 min $\rightarrow$ r.t., 20 h.

would be obtained by photooxygenation/reduction) is racemic. Fortunately, the closely related alcohol **12**⁵⁾ was readily prepared [8].

The *Claisen* ortho-ester rearrangement of **12** with triethyl orthoacetate in the presence of pivalic acid gave the expected *cis*-ester **13** in 74% yield. The corresponding acid **14**, obtained in 95% yield by alkaline hydrolysis of **13**, was cyclized with *p*-toluenesulfonic acid to give the desired *cis*-fused lactone **15**. Unfortunately, the cyclization was not selective under a variety of conditions, the lactones **16–18** being identified as main impurities. After flash chromatography and recrystallization from hexane, pure **15** was obtained in 40% yield. The monoaddition of CH_3MgI to **15** proceeded much more sluggishly and less selectively than for the *trans*-lactone **8**. A better result was obtained with CH_3Li in Et_2O , which gave a 45% yield of the lactol **19** after flash chromatography. However, the compound was rather unstable and showed a tendency to dehydrate to the enol ether **20**. The approach *via* the lactone **15** was, therefore, abandoned in favor of the synthesis outlined in Scheme 3.

Scheme 3



a) LiOCH_3 , CH_3OH . b) CH_3Li , Et_2O /0–5°, 2 h. c) $\text{HC}\equiv\text{CMgBr}$, THF /r.t., 3 h. d) SnCl_4 , CH_2Cl_2 /–20°, 30 min. e) H_2 , Lindlar catalyst, quinoline, cyclohexane/r.t., 3 h.

⁵⁾ $[\alpha]_{\text{D}}^{20} = +73^\circ$ ($c = 1.2$, CHCl_3); prepared by photosensitized oxygenation of limonene ($[\alpha]_{\text{D}}^{20} = +120^\circ$ (neat)) according to [8]. We are indebted to Mr. W. Giersch for carrying out the photooxygenation of 1 kg of limonene.

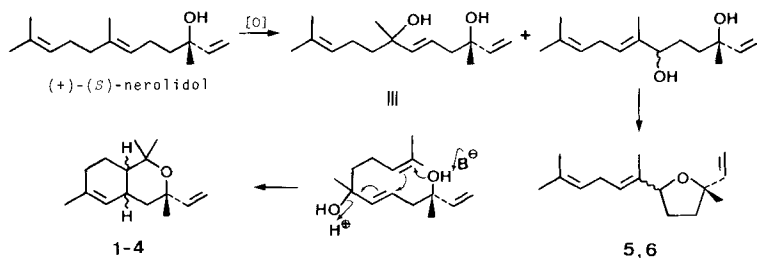
The carboxylic acid **14** was converted to the methyl ketone **21** with CH_3Li in Et_2O in high yield. Ethynylation⁶⁾ of **21** gave, in excellent yield, a mixture of the acetylenic alcohols **22** and **23**, which were partially separated by medium-pressure chromatography. The relative configuration of the newly created asymmetric centre (C(2)) of the alcohols **22** and **23** could not be determined from the spectral data at this stage, but was deduced later from the configurations of the cyclic ethers **24** and **25**. The mixture **22/23** (ratio 3:2) was cyclized with SnCl_4 ⁷⁾ in CH_2Cl_2 at -20° to give in 87% yield a mixture **24/25/26** (ratio *ca.* 6:1:1), which was separated by medium-pressure chromatography and GC.

The bridged ether **26** (structure supported by $^1\text{H-NMR}$ and MS) was formed from the minor alcohol **23** by participation of the endocyclic double bond instead of the isopropenyl group. This mode of cyclization was not observed for alcohol **22**, which gave **24** cleanly. The different behavior of **22** and **23** is readily rationalized, because only for **23** is the cyclization to **25** sterically retarded due to a 1,3-diaxial CH_3/CH_3 interaction in the chair-like transition state.

Selective catalytic hydrogenation of **24** and **25**, using *Lindlar* catalyst in the presence of quinoline, gave the corresponding vinyl compounds **2** and *ent*-**4** in good yield. The spectral data ($^1\text{H-NMR}$, IR, MS) and GC retention time of these two compounds were indistinguishable from those of natural **2** and **4**; however, their specific rotations were different (see *Exper. Part*). For **2**, the optical purity of the natural compound was *ca.* 82%, whereas it was only 42% for natural **4**⁸⁾.

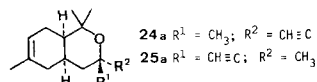
Discussion. – The structures of the cabreuva ethers A–D (**1–4**) and the tetrahydrofurans **5** and **6** are formally derived from nerolidol by an oxidative cyclization (*Scheme 4*). For all four isomers **1–4**, the absolute configuration at C(3) is *S* and corresponds to the chirality of (+)-(*S,E*)-nerolidol, which is the main component (*ca.* 80%) of cabreuva oil.

Scheme 4. Hypothetical Biogenesis of **1–6** from (+)-(*S*)-Nerolidol



⁶⁾ Ethynylation was preferred to the more direct vinylation, because previous experience [6] [9] [10] had shown that acetylenic alcohols are less prone to dehydration than allylic alcohols under the strongly acidic cyclization conditions; *cf.* also the formation of **11** during the cyclization of the allylic alcohols **10**.

⁷⁾ If the cyclization was run at r.t. using *p*-toluenesulfonic acid in CH_2Cl_2 (*cf.* [10]), the ethers **24** and **25** were accompanied by a substantial proportion (depending on the reaction time) of **24a** and **25a**, which were difficult to separate from **24** and **25**.



⁸⁾ The optical purity of natural **4** and its synthetic antipode *ent*-**4** were also determined by $^1\text{H-NMR}$ using the chiral shift reagent $\text{Eu}(\text{hfbc})_3$ in CDCl_3 solution. The natural compound has $41 \pm 5\%$ *e.e.*, whereas no splitting of signals was observed for synthetic *ent*-**4** (*e.e.* > 95%).

However, the optical purity of (+)-nerolidol *ex cabreuva* oil was $90 \pm 5\%$ (see *Exper. Part*) and is thus quite different from the optical purities of **1** (*ca.* 60%), **2** (*ca.* 82%), **3** (*ca.* 60%), and **4** (*ca.* 42%).

Odor Descriptions. – As already mentioned, only the optically pure, synthetic compounds *ent*-**1**, **2**, **3**, and *ent*-**4** were olfactively evaluated because the natural compounds were less pure. Cabreuva oxides A and C (*ent*-**1** and **3**) showed very similar odors. They are rather weak, woody-floral, without a characteristic profile. Cabreuva oxide B (**2**) was the perfumistically most interesting isomer. It displayed a woody-ambergris note accompanied by a distinct fruity (grapefruit) note. Cabreuva oxide D (*ent*-**4**) was similar to **2** but weaker. The ambergris character of *ent*-**4** was less pronounced and partly replaced by a fruity-floral note.

Experimental Part

General. All reactions were carried out under Ar. Org. extracts were dried over MgSO_4 and evaporated at $40\text{--}50^\circ$ in a rotatory evaporator at reduced pressure. Flash chromatography: see [11]. TLC: *Merck*-60-F-254 silica-gel plates. Medium-pressure chromatography: silica gel 60 (0.040–0.063 mm, *Merck*) or pre-packed *Lobar*® columns (*Merck*). Anal. GC: 15 m $\times$ 0.25 mm fused-silica-*Supelcowax-10* (film thickness 0.25 μm) or 10 m $\times$ 0.25 mm fused-silica-*SPB-5* (0.25 μm) column; t_R = retention time. Prep. GC: *FFAP* (5% on *Chromosorb W*, acid-washed, 80–100 mesh, 3.5 m $\times$ 3 mm) or *OV-101* (10% on *Chromosorb G*, acid-washed, 60–80 mesh, 4.5 m $\times$ 3 mm) column. Optical rotations: CHCl_3 solns. M.p.: uncorrected. IR: *Perkin-Elmer* 720 spectrometer, in cm^{-1} . ^1H -NMR (360 MHz) and ^{13}C -NMR (90.5 MHz): *Bruker AM 360* instrument using CDCl_3 solns. with TMS as internal standard. MS: *Finnigan 1020* automated GC/MS instrument, electron energy 70 eV, signals in m/z (rel. %).

1. Isolation from Cabreuva Oil. – Commercial Brazilian cabreuva oil (180 g) was fractionally distilled on a packed column (30 cm) to give a low-boiling fraction (10%), b.p. $40\text{--}45^\circ/0.01$ Torr. This was chromatographed on silica gel (0.063–0.2 mm, *Merck*; 600 g) using petroleum ether ($50\text{--}70^\circ$)/ Et_2O 95:5. The non-polar fraction (1.31 g, free of nerolidol and other alcohols) was rechromatographed on silica gel (600 g) using petroleum ether ($50\text{--}70^\circ$)/ Et_2O 98:2–95:5, in order to remove sesquiterpene hydrocarbons. The polar fraction of the second chromatography (1 g, *ca.* 0.6%) contained (in order of elution on *Supelcowax 10*) the following main components: **1**, caparrapi oxide and its 8-*epi* isomer [6] (identified by their MS), and **2–6**. A sample (purity $> 90\%$) of each of the compounds **1–6** was isolated from the above fraction by GC (*FFAP* first, then *OV-101*). The two most polar compounds **5** and **6** were identical (^1H -NMR, MS) with the tetrahydrofuran derivatives isolated from osmanthus oil [4]. The cabreuva oxides **1–4** were identical (IR, ^1H -NMR, MS, t_R) with the corresponding synthetic samples, except for their optical rotations. The following $[\alpha]_D^{20}$ values for the natural compounds were measured (in brackets the optical purity⁸⁾ calculated from the specific rotation of the optically pure synthetic samples): **1**, $+17.5^\circ$ ($c = 0.8$) [61.6%]; **2**, $+94.8^\circ$ ($c = 1.2$) [82.1%]; **3**, -27.2° ($c = 0.4$) [63.1%]; **4**, -75.0° ($c = 1.2$) [42.0%]. A sample of (+)-(*S,E*)-nerolidol (purity $> 98\%$) was isolated from cabreuva oil by GC. $[\alpha]_D^{20} = +13.1^\circ$ ($c = 1.1$) [3]: $[\alpha]_D^{20} = +14.12^\circ$ (*ex cabreuva* oil); [12]: $[\alpha]_D = 15.5^\circ$ (*ex Peru balsam*). The enantiomeric excess of our sample was $90 \pm 5\%$ (determined by NMR using the chiral shift reagent $\text{Eu}(\text{hfbf}_3)_3$).

2. Synthesis of the *trans*-Fused Cabreuva Oxides *ent*-1** and **3**.** – 2.1. (*4aR,8aR*)-*4a,7,8,8a*-Tetrahydro-1,1,6-trimethyl-1H-2-benzopyran-3(4H)-one (**8**). To a hot soln. (120°) of (1*R,4R*)-2-*p*-menthene-1,8-diol²⁾ (**7**; 34.0 g, 0.20 mol) in triethyl orthoacetate (200 ml) was added in portions (*ca.* 1 ml) a soln. of pivalic acid (1.0 g, 9.8 mmol) in triethyl orthoacetate (10 ml) over 16 h⁹⁾. During this period, the temp. was slowly increased to 150° , and the *EtOH* and some orthoacetate were allowed to distill. At the end of the reaction (monitored by GC), the excess of triethyl orthoacetate was distilled until $60^\circ/10$ Torr, and the residue was fractionally distilled through a *Vigreux* column (10 cm). The fraction with b.p. $92\text{--}95^\circ/0.2$ Torr (24.4 g, 62.8%) solidified on standing and was *ca.* 95% pure. The material was recrystallized from AcOEt /pentane to give 21.9 g (56.4%) of pure **8**, m.p. $52.5\text{--}53.5^\circ$, $[\alpha]_D^{20} = +72.9^\circ$ ($c = 1.3$). IR (neat): 1730s, 1290s, 1125s, 990m. ^1H -NMR¹⁰⁾: 1.29 (s, $\text{CH}_{3\text{ax}}\text{--C(1)}$); 1.38 (m, $\text{H}_{\text{ax}}\text{--C(8)}$); 1.46 (s, $\text{CH}_{3\text{eq}}\text{--C(1)}$); 1.48 (m, H--C(8a)); 1.68 (br. s, $\text{CH}_3\text{--C(6)}$); 1.79 (m, $\text{H}_{\text{eq}}\text{--C(8)}$); 2.06 (dd, $J = 17.5, 12.5$, overlapped, 1 H, $\text{H}_{\text{ax}}\text{--C(4)}$); 2.08 (m, overlapped, 2 H, $\text{CH}_2(7)$); 2.46 (m, $w_{1/2} \approx 28$, H--C(4a)); 2.67 (dd, $J = 17.5, 5$, $\text{H}_{\text{eq}}\text{--C(4)}$); 5.15 (br. s, H--C(5)). ^{13}C -NMR: *Table*. MS: 194 (14, M^+), 179 (4), 136 (64), 108 (56), 94 (100), 93 (77), 91 (28), 79 (90), 77 (24), 69 (31), 53 (12), 43 (30), 41 (31).

⁹⁾ If the entire quantity of pivalic acid was added at the beginning, the yield dropped to 32%.

¹⁰⁾ The assignments were obtained from a ^1H , ^{13}C correlated 2D-NMR spectrum.

2.2. (3*R*,4*aR*,8*aR*)-3,4,4*a*,7,8,8*a*-Hexahydro-1,1,3,6-tetramethyl-1*H*-2-benzopyran-3-ol (**9**). A soln. of CH_3MgI (60 mmol) in Et_2O (prepared from 1.44 g (60 mmol) of Mg and 8.7 g (60 mmol) of CH_3I in 100 ml of dry Et_2O) was added within 30 min at -5 – 10° to a stirred soln. of **8** (9.7 g, 50 mmol) in dry Et_2O (100 ml). A white precipitate formed during the addition. The mixture was stirred for 2 h at 10° , poured into a large excess of ice/ NH_4Cl soln., and extracted ($3 \times$) with Et_2O . The crude extract (11 g) was subjected to flash chromatography ($\varnothing = 10$ cm) using cyclohexane/ AcOEt 7:3. The 1st eluates (0.5 g) contained some **9** and a non-polar compound, presumably the enol ether resulting from the dehydration of **9** (not fully characterized). The 2nd fraction (6.5 g, 62%) was **9** (purity by TLC and $^1\text{H-NMR} > 95\%$). The 3rd fraction (2.4 g) was a mixture **8/9** (ca. 1:1), and the last fraction (0.6 g) was the diol resulting from the addition of a 2nd mol of CH_3MgI to **9**. The white solid **9** contained ca. 10% (by NMR) of the ring-opened hydroxy ketone **9a**. IR (CHCl_3): 3570*m*, 3420 (br.), 1710*w* (**9a**), 1390*s*, 1180*s*, 1155*s*, 990*s*, 930*s*. $^1\text{H-NMR}$: 1.20, 1.26 (2*s*, 3 H each, 2 $\text{CH}_3\text{-C}(1)$); 1.39 (*s*, $\text{CH}_3\text{-C}(3)$); 1.65 (br. *s*, $\text{CH}_3\text{-C}(6)$); 1.84 (*dd*, $J = 13, 3.5, 1$ H); 1.92 (br. *s*, 1 H, exchanges with D_2O , OH); ca. 2.0 (*m*, 2 H); 2.49 (*m*, $\text{H-C}(4a)$); 5.14 (br. *s*, $\text{H-C}(5)$); signals at 2.13 (*s*, 0.3 H, CH_3CO) and 5.24 (br. *s*, 0.1 H) indicate ca. 10% of **9a**. $^{13}\text{C-NMR}$: Table. MS: not recorded, because **9** was dehydrated in the inlet system.

2.3. (3'*R*,4'*R*)-1-(8'-Hydroxy-1'-*p*-menthen-3'-yl)-2-methyl-3-buten-2-ol (**10**, mixture of C(2)-epimers). A soln. of **9** (6.3 g, 30 mmol) in dry THF (50 ml) was added within 15 min to a stirred soln. (temp. 5°) of an excess (150 mmol) of vinylmagnesium bromide (prepared from Mg (3.6 g) and vinyl bromide (17.1 g) in 200 ml dry THF). The mixture was stirred at r.t. overnight. TLC still indicated the presence of **9**; thus, the soln. was stirred for 8 h at 60° , but no further change was observed. The mixture was hydrolyzed with an excess of ice/ NH_4Cl soln. and extracted with Et_2O ($3 \times$). The crude product (7.6 g) was flash chromatographed ($\varnothing = 10$ cm) with cyclohexane/ AcOEt 7:3 to give in the 1st eluates 2.4 g (38%) of **9**, and in the late fractions 4.5 g (61.7%) of **10**. A separation of the diastereoisomers by column chromatography was not possible, but GC on a Supelcowax capillary column and $^1\text{H-NMR}$ showed a 5:2 ratio of two diastereoisomers (the main peak has the shorter t_R). IR (neat): 3320*s* (br.), 3100*w*, 1650*w*, 930*s*. $^1\text{H-NMR}$: major (2*S*)-isomer: 1.13 (*s*, 3 H); 1.26 (*s*, 3 H); 1.27 (*s*, 3 H); 1.48 (*dd*, $J = 14, 4$, $\text{H-C}(1)$); 1.62 (br. *s*, $\text{CH}_3(7')$); 1.92 (*dd*, $J = 14, 6$, $\text{H-C}(1)$); 2.34 *m*, $w_{1/2} = 13$, $\text{H-C}(3')$); 5.11 (*dd*, $J = 11, 1$, $\text{H-C}(4)$ *trans* to C(2)); 5.21 (*m*, overlapped, 1 H, $\text{H-C}(2')$); 5.28 (*dd*, $J = 17, 1$, $\text{H-C}(4)$ *cis* to C(2)); 5.92 (*dd*, $J = 17, 11$, $\text{H-C}(3)$); minor (2*R*)-isomer: 1.17 (*s*, 3 H); 1.27 (*s*, 3 H); 1.32 (*s*, 3 H); 1.52 (*dd*, $J \approx 14, 5, 1$ H, overlapped, $\text{H-C}(1)$); 1.65 (br. *s*, $\text{CH}_3(7')$); 1.90 (*dd*, $J \approx 14, 5, 1$ H, overlapped, $\text{H-C}(1)$); 2.52 (*m*, $w_{1/2} = 16$, $\text{H-C}(3')$); 5.00 (*dd*, $J = 11, 1$, $\text{H-C}(4)$ *trans* to C(2)); 5.22 (*dd*, $J = 17, 1$, $\text{H-C}(4)$ *cis* to C(2)); 5.31 (*m*, overlapped, 1 H, $\text{H-C}(2')$); 5.95 (*dd*, $J = 17, 11$, $\text{H-C}(3)$). MS (both isomers): 220 (< 1 , M^+), 202 (6), 187 (9), 159 (22), 147 (23), 135 (33), 119 (28), 107 (41), 94 (83), 79 (51), 71 (69), 59 (100), 43 (80).

2.4. Acid-Catalyzed Cyclization of **10**. A soln. of **10** (5:2 mixture of C(2)-epimers; 4.3 g, 18.1 mmol) and $\text{TsOH} \cdot \text{H}_2\text{O}$ (50 mg) in toluene (100 ml) was heated to reflux for 30 min using a H_2O separator. The mixture was cooled to r.t., 0.2 ml of Et_3N were added, and the solvent was evaporated in *vacuo*. Bulb-to-bulb distillation (80–100°/0.2 Torr) of the crude product gave 3.7 g (93%) of a mixture containing *ent*-**1**, **3**, and **11** (in order of increasing t_R on Carbowax) as main components (ratio ca. 2:5:4). Chromatography on silica gel (300 g) with pentane/ Et_2O 95:5→90:10 gave a mixture of unidentified nonpolar impurities (300 mg), *ent*-**1/3** (ratio ca. 1:2; 1.6 g (40%)), and **11** (purity ca. 90%; 1.1 g, 28%). Mixture *ent*-**1/3** was further chromatographed on silica gel (600 g, < 0.063 mm) with pentane/ Et_2O 98:2→95:5 to give enriched samples of **3** (eluted first) and *ent*-**1**. A pure sample of each compound was isolated by GC (Carbowax, 170°). (3*R*,4*aR*,8*aR*)-3,4,4*a*,7,8,8*a*-Hexahydro-1,1,3,6-tetramethyl-3-vinyl-1*H*-2-benzopyran (= Cabreuva Oxide A; *ent*-**1**). Colorless oil, $[\alpha]_D^{20} = -28.4^\circ$ ($c = 1.0$). IR (neat): 3090*w*, 1640*w*, 1460*m*, 1390*m*, 1375*m*, 1205*m*, 1150*s*, 1110*m*, 1070*s*, 995*s*, 920*s*, 825*m*. $^1\text{H-NMR}$: 1.08 (*s*, $\text{CH}_{3ax}\text{-C}(1)$); 1.16 (*s*, $\text{CH}_{3eq}\text{-C}(1)$); 1.20 (*s*, $\text{CH}_3\text{-C}(3)$); 1.66 (br. *s*, $\text{CH}_3\text{-C}(6)$); 1.92–2.10 (*m*, $\text{CH}_2(7)$); 2.01 (*dd*, $J = 12, 3$, $\text{H}_{eq}\text{-C}(4)$); 2.21 (br. *t*, $J \approx 12$, $\text{H-C}(4a)$); 4.94 (*d*, $J = 11$, $\text{H-C}(2')$ *trans* to C(3)); 4.95 (*d*, $J = 18$, $\text{H-C}(2')$ *cis* to C(3)); 5.16 (br. *s*, $\text{H-C}(5)$); 5.99 (*dd*, $J = 18, 11$, $\text{H-C}(1')$). $^{13}\text{C-NMR}$: Table. MS: 220 (5, M^+), 205 (15), 162 (7), 148 (8), 147 (9), 135 (36), 119 (7), 107 (20), 94 (100), 93 (35), 79 (40), 69 (26), 43 (35). The compound was identical ($^1\text{H-NMR}$, MS, t_R) with natural **1**, except for $[\alpha]_D$.

(3*S*,4*aR*,8*aR*)-3,4,4*a*,7,8,8*a*-Hexahydro-1,1,3,6-tetramethyl-3-vinyl-1*H*-2-benzopyran (= Cabreuva Oxide C, **3**). Colorless oil, $[\alpha]_D^{20} = -43.1^\circ$ ($c = 1.1$). IR (neat): 3090*w*, 1645*w*, 1450*m*, 1385*m*, 1370*m*, 1240*m*, 1180*m*, 1155*m*, 1105*m*, 1025*m*, 925*m*, 830*w*. $^1\text{H-NMR}$: 1.18 (*s*, $\text{CH}_{3eq}\text{-C}(1)$); 1.23 (*s*, $\text{CH}_{3ax}\text{-C}(1)$); 1.34 (*s*, $\text{CH}_3\text{-C}(3)$); 1.58 (*dd*, $J = 12, 4$, $\text{H}_{eq}\text{-C}(4)$); 1.66 (br. *s*, $\text{CH}_3\text{-C}(6)$); 1.93–2.12 (*m*, $\text{CH}_2(7)$); 2.28 (br. *t*, $J \approx 12$, $\text{H-C}(4a)$); 4.92 (*dd*, $J = 11, 1$, $\text{H-C}(2')$ *trans* to C(3)); 5.13 (br. *s*, $\text{H-C}(5)$); 5.14 (*dd*, $J = 18, 1$, $\text{H-C}(2')$ *cis* to C(3)); 5.87 (*dd*, $J = 18, 11$, $\text{H-C}(1')$). $^{13}\text{C-NMR}$: Table. MS: 220 (1, M^+), 205 (30), 187 (3), 162 (2), 159 (2), 147 (7), 135 (64), 107 (24), 94 (100), 93 (45), 79 (42), 69 (38), 55 (19), 43 (42). The compound was identical ($^1\text{H-NMR}$, MS, t_R) with natural **3**, except for $[\alpha]_D$.

(1*R*,3*aR*,7*aR*)-1,3,3*a*,4,5,7*a*-Hexahydro-3,3,6-trimethyl-1-((*E*)-1'-methyl-1'-propenyl)-2-benzofuran (**11**).

Colorless oil, $[\alpha]_D^{20} = -8.1^\circ$ ($c = 1.75$). IR (neat): 3030w (sh), 1660w, 1000s. $^1\text{H-NMR}^{10}$: 1.09, 1.29 (2s, 3 H each, $\text{CH}_3\text{-C}(3)$); 1.44 (m, $\text{H}_{\text{ax}}\text{-C}(4)$); 1.61 (d, $J \approx 1$, $\text{CH}_3\text{-C}(1')$); 1.63 (d, $J = 6.5$, $\text{CH}_3\text{-C}(3')$); 1.65 (br. s, $\text{CH}_3\text{-C}(6)$); 1.67 (m, $\text{H-C}(3a)$, overlapped); 1.77 (m, $\text{H}_{\text{eq}}\text{-C}(4)$); 2.13 (m, 2 H-C(5)); 2.32 (br. t, $J = 10.5$, $\text{H-C}(7a)$); 3.79 (d, $J = 10$, $\text{H-C}(1)$); 5.33 (br. s, $\text{H-C}(7)$); 5.53 (q, $J = 6.5$, $\text{H-C}(2')$). $^{13}\text{C-NMR}^{10}$: 10.7 (q, $\text{CH}_3\text{-C}(1')$); 13.4 (q, $\text{C}(3')$); 22.8 (t, $\text{C}(4)$); 23.1 (q, $\text{CH}_3\text{-C}(6)$); 24.4 (q, $\text{CH}_{3\text{ax}}\text{-C}(3)$); 28.5 (q, $\text{CH}_{3\text{eq}}\text{-C}(3)$); 31.8 (t, $\text{C}(5)$); 44.8 (d, $\text{C}(7a)$); 52.7 (d, $\text{C}(3a)$); 80.2 (s, $\text{C}(3)$); 87.4 (d, $\text{C}(1)$); 120.2 (d, $\text{C}(7)$); 123.2 (d, $\text{C}(2')$); 134.3 (s, $\text{C}(6)$); 135.9 (s, $\text{C}(1')$). MS: 220 (< 1 , M^+), 147 (2), 137 (9), 136 (80), 122 (9), 121 (100), 107 (13), 105 (10), 93 (54), 91 (14), 79 (13), 55 (10), 43 (14), 41 (14).

3. Synthesis of the *cis*-Fused Cabreuva Oxides 2 and *ent*-4. – 3.1. *Ethyl (3S,4R)-(1,8-p-Menthadien-3-yl)-acetate (13)*. To a hot soln. (140°) of (1S,4R)-2,8-*p*-menthadien-1-ol⁵ (**12**; 76.0 g, 0.50 mol) in triethyl orthoacetate (350 ml) was slowly added (ca. 2 ml/h) a soln. of pivalic acid (3.0 g, 29.4 mmol) in triethyl orthoacetate (50 ml). The EtOH (and some orthoacetate) was allowed to distill off as formed through a short Vigreux column. After 24 h, the excess of orthoacetate was distilled at $60^\circ/10$ Torr, and the residue was fractionally distilled on a packed column (20 cm). After a fore-run (11 g), 82.1 g (74%) of **13** (b.p. $58\text{--}60^\circ/0.09$ Torr) were obtained as a colorless oil. $[\alpha]_D^{20} = +288^\circ$ ($c = 1.1$). IR (neat): 3100w, 1740s, 1650m, 1455m, 1380m, 1360m, 1190s, 1160s, 1050m, 900m. $^1\text{H-NMR}$: 1.25 (t, $J = 7$, $\text{CH}_3\text{CH}_2\text{O}$); 1.48–1.70 (m, $\text{CH}_2(5)$); 1.65 (s, $\text{CH}_3(7)$); 1.75 (s, $\text{CH}_3(10)$); 1.97 (dd, $J = 15$, 10, 1 H, CH_2CO); 2.00 (m, $\text{CH}_2(6)$); 2.22 (m, $\text{H-C}(4)$); 2.26 (dd, $J = 15$, 4, 1 H, CH_2CO); 2.78 (m, $\text{H-C}(3)$); 4.12 (m, $\text{CH}_3\text{CH}_2\text{O}$); 4.66, 4.85 (2 br. s, 1 H each, $\text{CH}_2(9)$); 5.50 (m, $\text{H-C}(2)$). $^{13}\text{C-NMR}$: 14.3 (q, CH_3CH_2); 22.5 (t, $\text{C}(5)$); 22.8 (q, $\text{C}(10)$); 23.5 (q, $\text{C}(7)$); 30.8 (t, $\text{C}(6)$); 32.9 (d, $\text{C}(3)$); 36.1 (t, CH_2CO); 43.3 (d, $\text{C}(4)$); 60.1 (t, $\text{CH}_3\text{CH}_2\text{O}$); 110.5 (t, $\text{C}(9)$); 124.2 (d, $\text{C}(2)$); 134.8 (s, $\text{C}(1)$); 147.5 (s, $\text{C}(8)$); 173.6 (s, C=O). MS: 222 (14, M^+), 207 (5), 194 (5), 177 (11), 135 (47), 119 (42), 105 (49), 93 (35), 91 (28), 88 (48), 81 (100), 67 (20), 41 (28).

3.2. *(3S,4R)-(1,8-p-Menthadien-3-yl)acetic Acid (14)*. A mixture of **13** (52.2 g, 0.235 mol), NaOH (10 g, 0.25 mol), EtOH (900 ml), and H_2O (100 ml) was heated to reflux for 3 h. The bulk of the EtOH was distilled off, H_2O (200 ml) was added, and the mixture was acidified with 30% aq. H_2SO_4 soln. The aq. phase was saturated with NaCl and extracted with Et_2O ($3 \times$). Distillation of the extract ($120\text{--}130^\circ/0.05$ Torr) gave 43.5 g (95%) of pure **14**. Oil, $[\alpha]_D^{20} = +330^\circ$ ($c = 1.07$). IR (neat): 3500–2400s (br.), 1700s, 1650m, 1440s, 1300s, 900s. $^1\text{H-NMR}$: 1.53, 1.67 (2m, 1 H each, $\text{CH}_2(5)$); 1.66 (s, $\text{CH}_3(7)$); 1.75 (s, $\text{CH}_3(10)$); ca. 2.0 (m, $\text{CH}_2(6)$); 2.01 (dd, $J = 15$, 10, 1 H, CH_2CO); 2.22 (br. d, $J \approx 12$, $\text{H-C}(4)$); 2.32 (dd, $J = 15$, 4, 1 H, CH_2CO); 2.76 (m, $\text{H-C}(3)$); 4.68, 4.87 (2 br. s, 1 H each, $\text{CH}_2(9)$); 5.55 (m, $\text{H-C}(2)$). $^{13}\text{C-NMR}$: 22.4 (t, $\text{C}(5)$); 22.8 (q, $\text{C}(10)$); 23.5 (q, $\text{C}(7)$); 30.8 (t, $\text{C}(6)$); 32.6 (d, $\text{C}(3)$); 35.9 (t, CH_2CO); 43.1 (d, $\text{C}(4)$); 110.7 (t, $\text{C}(9)$); 123.8 (d, $\text{C}(2)$); 135.1 (s, $\text{C}(1)$); 147.3 (s, $\text{C}(8)$); 180.5 (s, C=O). MS: 194 (22, M^+), 179 (17), 166 (18), 135 (52), 119 (51), 111 (79), 105 (72), 91 (78), 81 (100), 79 (64), 77 (51), 67 (47), 41 (60).

3.3. *Acid-Catalyzed Cyclization of 14*. A soln. of **14** (13.6 g, 70 mmol) in toluene (700 ml) was heated at reflux in the presence of $\text{TsOH} \cdot \text{H}_2\text{O}$ (300 mg) for 20 h. The soln. was allowed to cool, Et_3N (2 ml) was added and the solvent evaporated. Distillation of the residue in a bulb-tube ($110\text{--}120^\circ/0.05$ Torr) gave 12.9 g of a mixture containing **14** (10%), **18** (5%), **17** (15%), **15** (60%), and **16** (10%) (in order of their t_R on Supelcowax). Flash chromatography ($\varnothing$ 10 cm) with cyclohexane/ Et_2O 7:3 gave 7.3 g of **15** (purity ca. 95%), which was recrystallized from hexane to give pure **15** (5.5 g, 40%). Anal. samples of **16–18** were isolated by GC (Carbowax).

(4a*S*,8a*R*)-4a,7,8,8a-Tetrahydro-1,1,6-trimethyl-1H-2-benzopyran-3(4H)-one (**15**). M.p. $47.5\text{--}48.5^\circ$, $[\alpha]_D^{20} = +118^\circ$ ($c = 1.2$). IR (neat): 1730s, 1290s, 1180s, 1135s, 1000s. $^1\text{H-NMR}^{10}$: 1.42 (m, overlapped, 1 H, $\text{H}_{\text{ax}}\text{-C}(8)$); 1.43 (s, $\text{CH}_{3\text{ax}}\text{-C}(1)$); 1.46 (s, $\text{CH}_{3\text{eq}}\text{-C}(1)$); 1.69 (s, $\text{CH}_3\text{-C}(6)$); 1.70 (m, overlapped, 1 H, $\text{H-C}(8a)$); 1.89 (m, $\text{H}_{\text{eq}}\text{-C}(8)$); 2.06 (m, $\text{CH}_2(7)$); 2.26 (dd, $J = 19$, 10, $\text{H}_{\text{ax}}\text{-C}(4)$); 2.70 (dd, $J = 19$, 8, $\text{H}_{\text{eq}}\text{-C}(4)$); 2.80 (m, $\text{H-C}(4a)$); 5.43 (m, $\text{H-C}(5)$). $^{13}\text{C-NMR}$: Table. MS: 194 (7, M^+), 179 (5), 136 (30), 108 (29), 94 (100), 93 (48), 91 (25), 79 (74), 43 (23), 41 (21), 39 (17).

(4a*R*,8a*R*)-4a,5,8,8a-Tetrahydro-1,1,6-trimethyl-1H-2-benzopyran-3(4H)-one (**16**). $^1\text{H-NMR}$: 1.36, 1.46 (2s, 3 H each, 2 $\text{CH}_3\text{-C}(1)$); 1.67 (br. s, $\text{CH}_3\text{-C}(6)$); 2.36 (AB of ABX, $\delta_A = 2.32$, $\delta_B = 2.40$, $J_{AB} = 18$, $J_{AX} = 12.5$, $J_{BX} = 5.5$, $\text{CH}_2(4)$); 2.61 (m, $\text{H-C}(4a)$); 5.37 (m, $\text{H-C}(7)$). MS: 194 (2, M^+), 179 (6), 161 (3), 151 (4), 134 (94), 119 (64), 105 (22), 94 (86), 93 (46), 91 (27), 79 (100), 43 (30).

(1*S*,5*R*,6*R*)-1-Isopropenyl-1-methyl-2-oxobicyclo[3.3.1]nonan-3-one (**17**). $^1\text{H-NMR}$: 1.39 (s, $\text{CH}_3\text{-C}(1)$); 1.73 (br. s, $\text{CH}_3\text{-C=C}$); 4.71, 4.92 (2 br. s, 1 H each, $\text{CH}_2=\text{C}$). MS: 194 (6, M^+), 179 (10), 149 (37), 111 (88), 93 (35), 79 (70), 67 (42), 53 (35), 43 (100).

(3a*S*,7a*S*)-3a,6,7,7a-Tetrahydro-7a-isopropyl-5-methyl-1-benzofuran-2(3H)-one (**18**). IR (neat): 1770s. $^1\text{H-NMR}$: 1.00, 1.04 (2d, $J = 7$, 3 H each, $(\text{CH}_3)_2\text{CH}$); 1.70 (ddd, $J = 14$, 10, 5, $\text{H}_{\text{ax}}\text{-C}(7)$); 1.71 (br. s, $\text{CH}_3\text{-C}(5)$); 1.89 (dt, $J = 17$, 4.5, $\text{H}_{\text{eq}}\text{-C}(6)$); 1.96 (m, overlapped, 1 H, $(\text{CH}_3)_2\text{CH}$); 1.98 (dt, $J = 14$, 4.5, $\text{H}_{\text{eq}}\text{-C}(7)$); 2.14 (m, $\text{H}_{\text{ax}}\text{-C}(6)$); 2.24 (dd, $J = 17$, 2.5, $\text{H-C}(3)$); 2.85 (dd, $J = 17$, 9, $\text{H-C}(3)$); 2.91 (m, $\text{H-C}(3a)$); 5.22 (m, $\text{H-C}(4)$). MS: 194 (2, M^+), 151 (100), 133 (35), 123 (8), 119 (6), 109 (34), 107 (26), 81 (29), 71 (21), 43 (22).

3.4. (3*S*,4*aS*,8*aR*)-3,4,4*a*,7,8,8*a*-Hexahydro-1,1,3,6-tetramethyl-1*H*-2-benzopyran-3-ol (**19**). To a stirred soln. of **15** (1.94 g, 10 mmol) in dry Et₂O (20 ml) was added at –40° during 30 min 1*M* CH₃Li in Et₂O (12 ml, 12 mmol). The initially formed white precipitate dissolved at the end of the addition. The mixture was stirred at r.t. for 20 h, poured into ice/H₂O, and extracted (3×) with Et₂O. The crude extract (2 g) was flash chromatographed (Ø 5 cm) with cyclohexane/AcOEt 7:3 to give, in the 1st eluates, 60 mg (3%) of **20**. The 2nd fraction contained 950 mg (45.2%) of **19** (m.p. 62–64°), and the last 2 fractions gave 800 mg (41.2%) of **15** and 100 mg (4.4%) of the diol resulting from the addition of 2 mol of CH₃Li to **15**. As in the case of the *trans*-fused isomer **9**, **19** contained ca. 25% of the corresponding ring-opened hydroxy ketone **19a**. **19/19a**: IR (CHCl₃): 3580*m*, 3400 (br.), 1710*m* (**19a**), 1390*s*, 1180*s*, 1105*m*. ¹H-NMR (**19**): 1.16 (*s*, CH_{3eq}–C(1)); 1.36 (*s*, CH_{3ax}–C(1)); 1.44 (*s*, CH₃–C(3)); 1.64 (br. *s*, CH₃–C(6)); 2.77 (*m*, H–C(4*a*)); 5.41 (*m*, H–C(5)). ¹H-NMR (**19a**, *p*-menthane numbering): 1.22, 1.25 (2*s*, 3 H each, 2 CH₃–C(8)); 2.14 (*s*, CH₃CO); 2.42 (*dd*, *J* = 17, 10, 1 H, CH₂CO); 2.88 (br. *m*, H–C(3)); 3.02 (*dd*, *J* = 17, 4, 1 H, CH₂CO); 5.44 (*m*, H–C(2)). MS: not recorded, because **19** was dehydrated easily to give **20**.

(4*aR*,8*aR*)-4*a*,7,8,8*a*-Tetrahydro-1,1,3,6-tetramethyl-1*H*-2-benzopyran (**20**). IR (neat): 1675*s*, 1305*s*, 1140*s*, 995*m*, 885*m*. ¹H-NMR: 1.23, 1.30 (2*s*, 3 H each, 2 CH₃–C(1)); 1.67 (br. *s*, CH₃–C(6)); 1.68 (*d*, *J* ≈ 1, CH₃–C(3)); 1.95 (*m*, CH₂(7)); 2.84 (br. *m*, H–C(4*a*)); 4.25 (br. *s*, H–C(4)); 5.23 (*m*, H–C(5)). MS: 192 (61, *M*⁺), 177 (61), 159 (43), 149 (52), 135 (70), 119 (80), 107 (65), 93 (60), 81 (63), 69 (62), 43 (100).

3.5. (3'*S*,4'*R*)-1-(1',8'-*p*-Menthadien-3'-yl)-2-propanone (**21**). To a soln. of LiOCH₃ in dry CH₃OH (prepared by dissolving 700 mg (100 mmol) of Li in 200 ml of dry CH₃OH) was added at r.t. **14** (19.4 g, 100 mmol). The soln. was evaporated to dryness and the Li salt pulverized and dried overnight (40°/0.1 Torr). Yield 20.1 g (100%). To a stirred suspension of the Li salt (19.0 g, 95 mmol) in dry Et₂O (200 ml) was added slowly (2 h) at 0–5° 1*M* CH₃Li in Et₂O (150 ml, 150 mmol). The homogeneous soln. was stirred for 1 h at r.t. and then slowly added with efficient stirring to an excess of ice/H₂O. The aq. layer was extracted with Et₂O (3×), the combined extract evaporated, and the residue bulb-to-bulb distilled (70–80°/0.2 Torr) to give 17.3 g (95%) of pure **21**. Oil, [α]_D²⁰ = +313° (*c* = 0.6). IR (neat): 3090*w*, 1710*s*, 1645*m*, 1360*s*, 1160*m*, 900*s*. ¹H-NMR: 1.52 (*m*, H_{ax}–C(5')); 1.64 (br. *s*, CH₃(7')); 1.67 (*m*, overlapped, 1 H, H_{eq}–C(5')); 1.71 (*s*, CH₃(10')); 1.98 (*m*, CH₂(6')); 2.10 (*s*, CH₃CO); 2.16 (*dd*, *J* = 17, 9.5, H–C(1)); 2.20 (*m*, overlapped, 1 H, H–C(4')); 2.36 (*dd*, *J* = 17, 4, H–C(1)); 2.84 (*m*, H–C(3')); 4.66, 4.84 (2 br. *s*, 1 H each, CH₂(9')); 5.47 (*m*, H–C(2')). ¹³C-NMR: 22.7 (*t*, C(5')); 22.9 (*q*, C(10')); 23.4 (*q*, C(7')); 30.7 (*q*, C(3)); 30.8 (*t*, C(6')); 31.7 (*d*, C(3')); 43.2 (*d*, C(4')); 45.1 (*t*, C(1)); 110.3 (*t*, C(9')); 124.7 (*d*, C(2')); 134.3 (*s*, C(1')); 148.1 (*s*, C(8')); 208.7 (*s*, C(2)). MS: 192 (6, *M*⁺), 177 (13), 159 (22), 149 (9), 135 (21), 134 (21), 119 (35), 107 (23), 93 (26), 91 (24), 82 (23), 81 (22), 43 (100).

3.6. (2*S*,3'*S*,4'*R*)- and (2*R*,3'*S*,4'*R*)-1-(1',8'-*p*-Menthadien-3'-yl)-2-methyl-3-butyn-2-ol (**22** and **23**). To a stirred soln. of ethynylmagnesium bromide (0.15 mol) in THF (180 ml) [**13**] was added during 15 min at 5–10° a soln. of **21** (14.4 g, 75 mmol) in dry THF (50 ml). The mixture was stirred for 3 h at r.t. and then added carefully to ice-cold sat. NH₄Cl soln. The aq. phase was extracted with Et₂O (3 × 200 ml), the Et₂O extracts were combined with the THF phase, dried (MgSO₄), and evaporated. The residue (16.5 g) was bulb-to-bulb distilled (110–120°/0.5 Torr) to give 15.2 g (93%) of **22/23** (ratio ca. 6:4). Medium-pressure chromatography on silica gel (1200 g) with hexane/Et₂O 8:2 gave a partial separation of the epimeric alcohols, **23** being eluted before **22**. Rechromatography of the enriched fractions under the same conditions gave the isomers in ca. 80% purity. **22**: IR (neat): 3420 (br.), 3300*s*, 2120*w*, 1650*m*, 900*s*. ¹H-NMR: 1.51 (*s*, CH₃–C(2)); 1.66 (br. *s*, CH₃(7')); 1.73 (*dd*, *J* = 14, 3, H–C(1)); 1.76 (br. *s*, CH₃(10')); 1.89 (*s*, OH); 2.00 (*m*, CH₂(6')); 2.20 (br. *d*, *J* ≈ 12, H–C(4')); 2.47 (*s*, H–C(4)); 2.55 (*m*, H–C(3')); 4.67, 4.89 (2 br. *s*, 1 H each, CH₂(9')); 5.82 (*m*, H–C(2')). ¹³C-NMR: 22.9 (*t*, C(5')); 22.9 (*q*, C(10')); 23.5 (*q*, C(7')); 30.5 (*t*, C(6')); 30.8 (*q*, CH₃–C(2)); 32.3 (*d*, C(3')); 44.5 (*d*, C(4')); 44.6 (*t*, C(1)); 67.8 (*s*, C(2)); 71.5 (*d*, C(4)); 88.4 (*s*, C(3)); 110.6 (*t*, C(9')); 126.8 (*d*, C(2')); 132.9 (*s*, C(1')); 148.0 (*s*, C(8')). MS: 200 (< 1, *M*⁺ – H₂O), 185 (3), 143 (4), 135 (9), 119 (9), 107 (22), 93 (30), 91 (37), 82 (88), 79 (31), 69 (100), 67 (38), 53 (20), 43 (58).

23: IR (neat): same bands as for **22**. ¹H-NMR: 1.45 (*m*, H_{ax}–C(5')); 1.48 (*s*, CH₃–C(2)); 1.62 (*m*, 1 H); 1.68 (br. *s*, CH₃(7')); 1.75 (br. *s*, CH₃(10')); 2.02 (*m*, CH₂(6')); 2.18 (br. *d*, *J* ≈ 12, H–C(4')); 2.31 (*s*, OH); 2.47 (*s*, H–C(4)); 2.67 (*m*, H–C(3')); 4.65, 4.86 (2 br. *s*, 1 H each, CH₂(9')); 5.86 (*m*, H–C(2')). ¹³C-NMR: 22.4 (*t*, C(5')); 22.8 (*q*, C(10')); 23.6 (*q*, C(7')); 30.8 (*t*, C(6')); 31.2 (*q*, CH₃–C(2)); 32.8 (*d*, C(3')); 43.9 (*t*, C(1)); 44.2 (*d*, C(4')); 68.3 (*s*, C(2)); 71.6 (*d*, C(4)); 87.7 (*s*, C(3)); 110.3 (*t*, C(9')); 125.5 (*d*, C(2')); 135.2 (*s*, C(1')); 147.6 (*s*, C(8')). MS: very similar to that of **22**.

3.7. (3*S*,4*aS*,8*aR*)- and (3*R*,4*aS*,8*aR*)-3-Ethynyl-3,4,4*a*,7,8,8*a*-hexahydro-1,1,3,6-tetramethyl-1*H*-2-benzopyran (**24** and **25**). To a stirred soln. of **22/23** (ratio 6:4; 4.8 g, 22 mmol) in CH₂Cl₂ (100 ml) was added at –20° with a syringe SnCl₄ (960 mg, 0.43 ml, 3.7 mmol). Stirring at –20° was continued (30 min) until conversion was complete. Pyridine (2 ml) was added, and the mixture was allowed to warm to r.t. The solvent was evaporated, the residue taken up in hexane, and filtered from the insoluble SnCl₄-pyridine complex. The soln. was washed with ice-cold 2*N* H₂SO₄ and sat. NaCl soln., dried (MgSO₄), and concentrated. Bulb-to-bulb distillation (90–100°/0.1

Torr) of the residue gave 4.2 g (87.6%) of **26/24/25** (ratio *ca.* 1:6:1, in order of increasing t_R on *Carbowax*). A sample of this mixture (1.75 g), when submitted to chromatography (*Lobar*[®] prepacked column, size *C*, *Merck*) using hexane/Et₂O 98:2, gave the following fractions: 0.20 g of pure **24**, 1.1 g of **24/26** (95:5), 0.25 g of **24/26** (1:1) and 0.15 g of pure **25**. Anal. samples of **24–26** were isolated by GC (*Carbowax*). **24**: $[\alpha]_D^{20} = +135^\circ$ ($c = 1.9$). IR (neat): 3300s, 1095s, 1005m. ¹H-NMR: 1.16 (s, CH_{3eq}–C(1)); 1.39 (t, $J = 14$, H_{ax}–C(4)); 1.46 (s, CH_{3ax}–C(1)); 1.56 (s, CH₃–C(3)); 1.64 (br. s, CH₃–C(6)); 1.73 (dd, $J = 14, 4$, H_{eq}–C(4)); 1.97 (m, CH₂(7)); 2.36 (s, HC≡C); 2.78 (m, H–C(4a)); 5.40 (m, H–C(5)). ¹³C-NMR: *Table*. MS: 218 (< 1 , M^{+}), 203 (6), 145 (21), 117 (10), 105 (11), 94 (100), 93 (22), 91 (19), 79 (48), 43 (28).

25: $[\alpha]_D^{20} = +199.8^\circ$ ($c = 1.2$). IR (neat): 3300s, 1375s, 1185s, 1165s, 1095s, 990s. ¹H-NMR: 1.28, 1.33 (2s, 3 H each, 2 CH₃–C(1)); 1.54 (s, CH₃–C(3)); 1.62 (dd, $J = 14, 4$, H_{eq}–C(4)); 1.66 (br. s, CH₃–C(6)); 1.87 (t, $J = 14$, H_{ax}–C(4)); 1.95 (m, CH₂(7)); 2.38 (m, H–C(4a)); 2.40 (s, CH≡C); 5.27 (m, H–C(5)). ¹³C-NMR: *Table*. MS: 218 (1.5, M^{+}), 203 (12), 145 (13), 117 (9), 105 (10), 94 (100), 93 (19), 91 (17), 79 (50), 43 (23).

(1*S*,3*R*,5*R*,6*R*)-3-Ethynyl-6-isopropenyl-1,3-dimethyl-2-oxabicyclo[3.3.1]nonane (**26**). IR (neat): 3300s, 3095w, 1645m, 1455s, 1370s, 1240s, 1090s, 1060m, 1010m, 895s. ¹H-NMR: 1.28 (s, CH₃–C(1)); 1.48 (s, CH₃–C(3)); 1.73 (br. s, CH₃–C=); 1.90 (m, 2 H); 2.40 (m, 1 H); 2.42 (s, CH≡C); 2.97 (m, H_{syn}–C(9)); 4.69, 4.85 (2 br. s, 1 H each, CH₂=C). MS: 218 (< 1 , M^{+}), 203 (1), 175 (3), 145 (2), 135 (100), 109 (15), 107 (14), 93 (15), 91 (13), 79 (16), 67 (12), 55 (11), 43 (65).

3.8. (3*S*,4*aS*,8*aR*)-3,4,4*a*,7,8,8*a*-Hexahydro-1,1,3,6-tetramethyl-3-vinyl-1*H*-2-benzopyran (= Cabreuva Oxide B; **2**). A soln. of **24** (87 mg, 0.4 mmol) in cyclohexane (5 ml) was hydrogenated at r.t. in the presence of *Lindlar* catalyst (10 mg, *Fluka AG*) and quinoline (0.02 ml) until the calculated amount of H₂ (0.4 mmol) was absorbed (*ca.* 3 h). The soln. was filtered, washed with aq. 2*N* HCl and sat. NaCl soln., dried (MgSO₄), and evaporated. Distillation of the residue in a bulb-tube (70–80°/0.1 Torr) gave 75 mg (85%) of a pure compound, which was identical (¹H-NMR, MS, t_R) with natural **2**, except for $[\alpha]_D$. Colorless oil, $[\alpha]_D^{20} = +115.4^\circ$ ($c = 1.4$). IR (neat): 3100w, 3075w, 1645w, 1455m, 1390m, 1375m, 1205m, 1095s, 1000s, 920s, 860m. ¹H-NMR: 1.14, 1.16 (2s, 3 H each, 2 CH₃–C(1)); 1.26 (s, CH₃–C(3)); 1.32 (t, $J \approx 14$, overlapped, 1 H, H_{ax}–C(4)); 1.65 (br. s, CH₃–C(6)); 1.86 (dd, $J = 14, 4$, H_{eq}–C(4)); 1.98 (m, CH₂(7)); 2.50 (m, H–C(4a)); 4.94 (d, $J = 11$, H–C(2') *trans* to C(3)); 4.98 (d, $J = 18$, H–C(2') *cis* to C(3)); 5.40 (m, H–C(5)); 5.98 (dd, $J = 18, 11$, H–C(1')). ¹³C-NMR: *Table*. MS: 220 (2, M^{+}), 205 (15), 177 (5), 162 (4), 147 (8), 135 (14), 119 (8), 107 (11), 105 (11), 94 (100), 93 (33), 91 (23), 79 (51), 77 (20), 55 (15), 43 (48).

3.9. (3*R*,4*aS*,8*aR*)-3,4,4*a*,7,8,8*a*-Hexahydro-1,1,3,6-tetramethyl-3-vinyl-1*H*-2-benzopyran (= Cabreuva Oxide D; *ent*-**4**). Prepared in 90% yield by catalytic hydrogenation of **25**, as described above for **2**. Oil, $[\alpha]_D^{20} = +178.5^\circ$ ($c = 0.9$). The compound was identical with natural **4**, except for the $[\alpha]_D$. IR (neat): 3100w, 3070w, 1650w, 1390m, 1380m, 1190m, 1110m, 1050m, 1000s, 930s, 860m. ¹H-NMR: 1.17 (s, CH_{3eq}–C(1)); 1.32, 1.33 (2s, 3 H each, CH_{3ax}–C(1), CH₃–C(3)); 1.42 ('d', $J \approx 9$, CH₂(4)); 1.65 (br. s, CH₃–C(6)); 1.96 (m, CH₂(7)); 2.55 (m, H–C(4a)); 4.90 (dd, $J = 11, 1$, H–C(2') *trans* to C(3)); 5.10 (dd, $J = 17, 1$, HC(2') *cis* to C(3)); 5.37 (m, H–C(5)); 5.89 (dd, $J = 17, 11$, H–C(1')). ¹³C-NMR: *Table*. MS: 220 (4, M^{+}), 205 (15), 187 (2), 177 (1), 162 (3), 147 (6), 135 (18), 119 (6), 107 (12), 105 (10), 94 (100), 93 (31), 91 (22), 79 (47), 55 (18), 43 (41).

REFERENCES

- [1] E. Gildemeister, F. Hoffmann, 'Die ätherischen Öle', Akademie-Verlag, Berlin, 1959, Vol. 5, p. 321.
- [2] S. Arctander, 'Perfume and Flavor Materials of Natural Origin', Ed. S. Arctander, Elizabeth, N.J., USA, 1960, p. 108.
- [3] Y. R. Naves, *Helv. Chim. Acta* **1947**, *30*, 275, 278.
- [4] R. Kaiser, D. Lamparsky, *Helv. Chim. Acta* **1979**, *62*, 1887.
- [5] H. Werner, H. J. Köhler, M. Mühlstädt, A. Zschunke, G. Mann, *Org. Magn. Reson.* **1973**, *5*, 119.
- [6] P. Lombardi, R. C. Cookson, H. P. Weber, W. Renold, A. Hauser, K. H. Schulte-Elte, B. Willhalm, W. Thommen, G. Ohloff, *Helv. Chim. Acta* **1976**, *59*, 1158.
- [7] G. Ohloff, W. Giersch, *Helv. Chim. Acta* **1968**, *51*, 1328.
- [8] G. O. Schenck, K. Gollnick, G. Buchwald, S. Schroeter, G. Ohloff, *Liebigs Ann. Chem.* **1964**, *674*, 93.
- [9] K. H. Schulte-Elte, T. Umiker, G. Ohloff, *Helv. Chim. Acta* **1980**, *63*, 284.
- [10] B. Maurer, A. Hauser, W. Thommen, K. H. Schulte-Elte, G. Ohloff, *Helv. Chim. Acta* **1980**, *63*, 293.
- [11] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.
- [12] L. Ruzicka, *Helv. Chim. Acta* **1923**, *6*, 483.
- [13] L. Skattebøl, E. R. H. Jones, M. C. Whiting, *Org. Synth.* **1963**, *4*, 792.