214. New Sesquiterpenoids from Cabreuva Oil[1])

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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 *Myrocarpus 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 $C_{15}H_{24}O$ was indicated by their mass spectra ($M^{+\cdot}$ at m/z 220) and their ^{1}H-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.

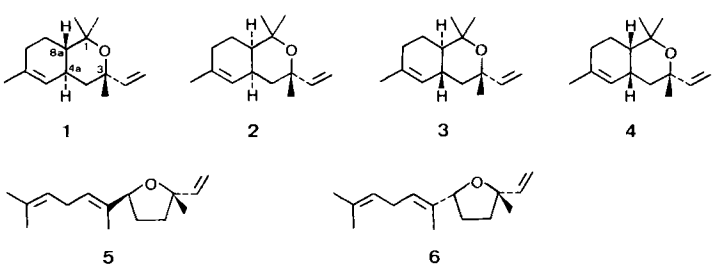


Fig. 1. *New constituents from cabreuva oil*

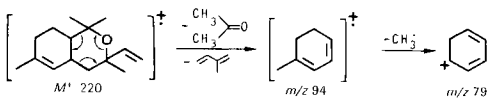
[1]) Presented, in part, at the 10th International Congress of Essential Oils, Washington, D.C., November 16–20, 1986.

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}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}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.

A **A′**

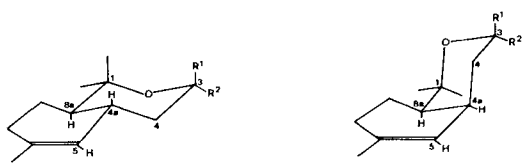
The base peak, which is at m/z 94 for all 4 isomers, was readily explained by the cyclic fragmentation of the molecular ion into acetone, isoprene, and the charge-carrying dihydrotoluene. The latter can lose a CH_3 radical, after a 1,5-H shift, giving rise to another abundant ion at m/z 79.



On the basis of the ^{1}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



ent-**1** R^1 = vinyl, R^2 = CH_3 **2** R^1 = CH_3, R^2 = vinyl

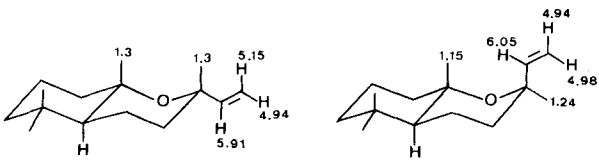
3 R^1 = CH_3, R^2 = vinyl *ent*-**4** R^1 = vinyl, R^2 = CH_3

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 CH_3/CH_3 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 CH_3 groups in the ^{1}H-NMR spectra of **1**–**4**.

The compounds **3** and **4** have their CH_3–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 CH_3 groups. Such an arrangement causes a downfield shift of *ca.* 0.08 ppm of the two axial CH_3 groups [5]. This effect was also observed for the axial CH_3–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 CH_3 groups.



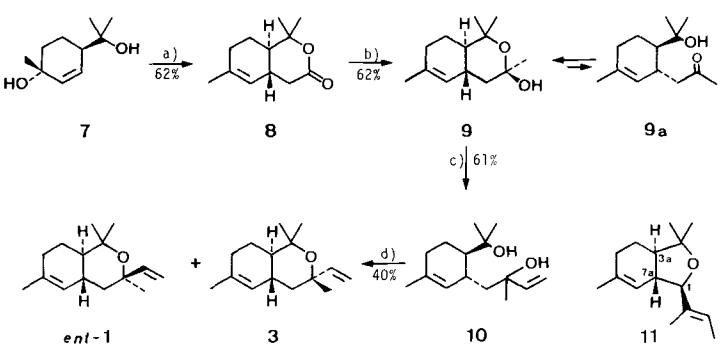
caparrapi oxide 8-*epi*-caparrapi oxide

These configurational assignments were later fully confirmed by the ^{13}C-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 CH_3 group at C(3) of **3** (25.8 ppm) and *ent*-**4** (26.7 ppm) resonates at higher field than the corresponding equatorial CH_3 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.

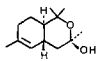
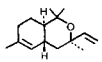
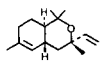
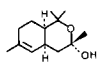
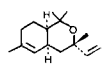
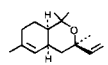
Syntheses. – For the synthesis of the optically pure *trans*-fused cabreuva oxides **1** and **3** *(Scheme 1)*, the readily available, enantiomerically pure, crystalline (1*R*,4*R*)-2-*p*-men-

Scheme 1



[a]) $CH_3C(OC_2H_5)_3$, pivalic acid/120–150°, 16 h. [b]) CH_3MgI, Et_2O/5–10°, 2 h. [c]) CH_2=CHMgBr, THF/25°, 15 h. [d]) TsOH, toluene/reflux, 30 min.

Table. *^{13}C-NMR Chemical Shifts* (90.5 MHz, $CDCl_3$) *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)	Ethynyl or vinyl	
															C(1)	C(2)
trans																
	**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)	–	–
	*ent*-**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
cis																
	**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
	*ent*-**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 ^{1}H,^{13}C correlated 2D-NMR spectra.

thene-1,8-diol (**7**)[2]) was an ideal starting material. The *Claisen* ortho ester rearrangement of **7** with triethyl orthoacetate in the presence of pivalic acid proceeded stereospecifically to give the crystalline *trans*-fused lactone **8** in 62% yield. This moderate yield was due to the tendency of **7** to dehydrate[3]) under the reaction conditions; however, **8** was easily separated from the by-products by distillation. Addition of CH_3MgI (1.1 equiv.) in Et_2O to **8** gave the desired lactol **9** in 62% yield, besides some diaddition product (a diol) and starting material **8**, indicating that the monoaddition was not entirely selective[4]). The configuration at C(3) of **9** was deduced from the ^{13}C-NMR spectrum *(Table)*, which suggested an equatorial CH_3–C(3). In addition, **9** is more stable (mainly because of the anomeric effect) than its C(3) epimer, with which it might be expected to equilibrate *via* the hydroxy ketone **9a**. The presence of *ca.* 10% of **9a** in a $CHCl_3$ solution of **9** was inferred from the ^{1}H-NMR and IR spectra. The reaction of **9**/**9a** with a large excess of vinylmagnesium bromide in THF gave a 61% yield of the diols **10** (5:2 mixture of diastereoisomers), which were not separated but directly cyclized with *p*-toluenesulfonic acid. The expected 2-benzopyran derivatives *ent*-**1** and **3** (ratio *ca.* 1:2, yield 40%) were accompanied by the unexpected 2-benzofuran derivative **11** (yield *ca.* 28%). The 3 ethers were separated by column chromatography and isolated in > 98% purity.

The first 2 compounds showed the same spectral data (^{1}H-NMR, IR, MS) and GC retention time as natural **1** and **3** (thus confirming their structures) but had different $[\alpha]_D^{20}$ values. Whereas the specific rotation in $CHCl_3$ of the natural compounds was $[\alpha]_D^{20} = +17.5°$ ($c = 0.8$) for **1** and $-27.2°$ ($c = 0.4$) for **3**, these values were $-28.4°$ ($c = 1.0$) and $-43.1°$ ($c = 1.1$), respectively, for the synthetic compounds. Because the absolute configuration of the optically pure synthetic compounds is known from **7**, natural **1** has the opposite chirality, and natural **3** the same chirality as the synthetic compounds. The optical purity of **1** and **3** from cabreuva oil is calculated to be *ca.* 60%.

The structure of **11**, including its configuration, was deduced from the ^{1}H- and ^{13}C-NMR spectrum. A trace (< 0.001%) of **11** was detected (MS, retention time) in cabreuva oil, but the specific rotation of the natural compound could not be determined. The formation of **11** can be rationalized by assuming a dehydration of the allylic alcohol **10** to give a 1,3-butadiene, followed by an intramolecular 1,4-addition of the remaining OH group to the diene.

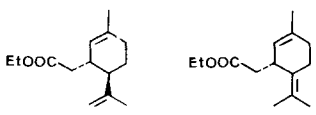
The allylic bridgehead proton H–C(7a) of **11** gives rise to a signal at 2.32 ppm (br. *t*, $J = 10.5$ Hz). The size of these coupling constants indicated *trans*-diaxial relationships with the adjacent protons at C(1) and C(3a), thus fixing the relative configuration at C(1), C(3), and C(7a). The (*E*)-configuration of the side chain was clearly indicated by the shielding of the 2 CH_3 groups (10.7 and 13.4 ppm) in the ^{13}C-NMR spectrum.

For the synthesis of the *cis*-fused cabreuva oxides **2** and **4**, we hoped to apply the protocol used for the *trans*-fused series; *i.e.* our first target was the optically pure *cis*-fused lactone **15** *(Scheme 2)*. The optically active diastereoisomer of the diol **7**, which would be needed in large quantity if the route of *Scheme 1* were to be followed for the *cis*-fused series, was not readily available because commercial α-terpineol (from which it

[2]) $[\alpha]_D^{20} = +40.6°$ ($c = 0.98$, $CHCl_3$), m.p. 114°; prepared from (+)-2-carene according to [7]. We thank Dr. *A. Boschung* for a generous gift of **7**.

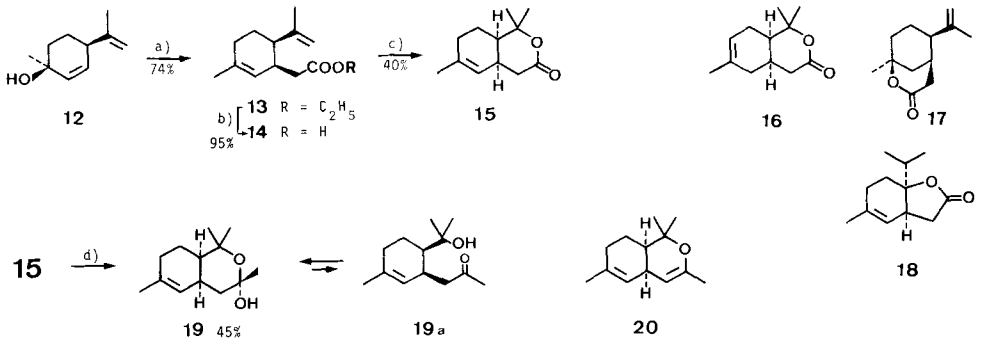
[3]) Varying amounts of **I** and **II** (and other unidentified compounds) were present in the reaction mixture.

[4]) Similar results were obtained using CH_3Li in Et_2O at 0–5°.



I II

Scheme 2

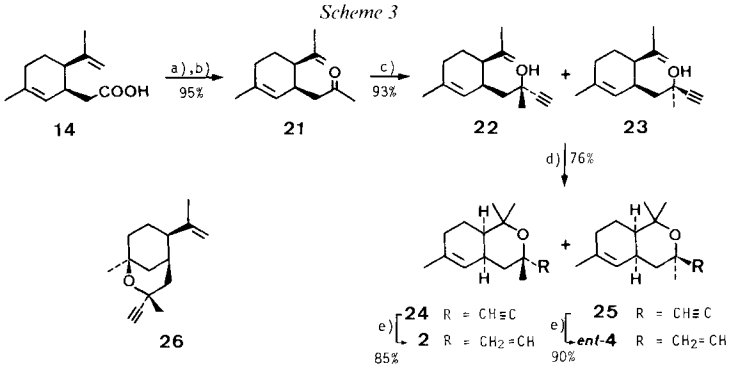


[a]) $CH_3C(OC_2H_5)_3$, pivalic acid/140–145°, 24 h. [b]) NaOH, H_2O, EtOH/reflux, 3 h. [c]) TsOH, toluene/reflux, 20 h. [d]) CH_3Li, Et_2O/−40°, 30 min→r.t., 20 h.

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]) HC≡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.

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

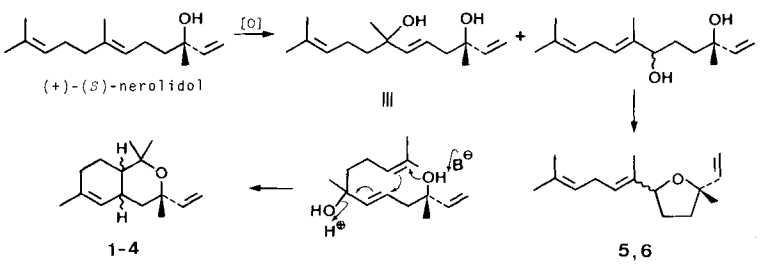
The carboxylic acid **14** was converted to the methyl ketone **21** with CH_3Li in Et_2O in high yield. Ethynylation[6]) of **21** gave, in excellent yield, a mixture of the acetylenic alcohols **22** and **23**, which were partially separated by medium-pressure chromatography. The relative configuration 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}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}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*



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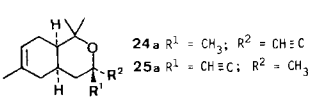
[6]) Ethynylation was preferred to the more direct vinylation, because previous experience [6] [9] [10] had shown that acetylenic alcohols are less prone to dehydration than allylic alcohols under the strongly acidic cyclization conditions; *cf.* also the formation of **11** during the cyclization of 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}H-NMR using the chiral shift reagent Eu(hfbc)$_3$ in $CDCl_3$ solution. The natural compound has 41 ± 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 ± 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 40–50° 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 × 0.25 mm fused-silica-*Supelcowax-10* (film thickness 0.25 μm) or 10 m × 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 × 3 mm) or *OV-101* (10% on *Chromosorb G*, acid-washed, 60–80 mesh, 4.5 m × 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. 40–45°/0.01 Torr. This was chromatographed on silica gel (0.063–0.2 mm, *Merck;* 600 g) using petroleum ether (50–70°)/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 (50–70°)/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 purity[8]) calculated from the specific rotation of the optically pure synthetic samples): **1**, +17.5° (*c* = 0.8) [61.6%]; **2**, +94.8° (*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° (*c* = 1.1) ([3]: $[\alpha]_D^{20}$ = +14.12° (*ex* cabreuva oil); [12]: $[\alpha]_D$ = 15.5° (*ex* Peru balsam)). The enantiomeric excess of our sample was 90 ± 5% (determined by NMR using the chiral shift reagent Eu(hfbc)$_3$).

2. Synthesis of the *trans*-Fused Cabreuva Oxides *ent*-1 and 3. – 2.1. *(4a*R,*8a*R*)-4a,7,8,8a-Tetrahydro-1,1,6-trimethyl-1*H*-2-benzopyran-3(4*H*)-one* (**8**). To a hot soln. (120°) of (1*R*,4*R*)-2-*p*-menthene-1,8-diol[2] (**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 h[9]). 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°/10 Torr, and the residue was fractionally distilled through a *Vigreux* column (10 cm). The fraction with b.p. 92–95°/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.52.5–53.5°, $[\alpha]_D^{20}$ = +72.9° (*c* = 1.3). IR (neat): 1730*s*, 1290*s*, 1125*s*, 990*m*. ^1H-NMR[10]): 1.29 (*s*, CH_{3ax}–C(1)); 1.38 (*m*, H_{ax}–C(8)); 1.46 (*s*, CH_{3eq}–C(1)); 1.48 (*m*, H–C(8a)); 1.68 (br. *s*, CH_3–C(6)); 1.79 (*m*, H_{eq}–C(8)); 2.06 (*dd*, *J* = 17.5, 12.5, overlapped, 1 H, H_{ax}–C(4)); 2.08 (*m*, overlapped, 2 H, CH_2(7)); 2.46 (*m*, $w_{½} \approx 28$, H–C(4a)); 2.67 (*dd*, *J* = 17.5, 5, H_{eq}–C(4)); 5.15 (br. *s*, H–C(5)). ^{13}C-NMR: *Table*. MS: 194 (14, $M^{+\cdot}$), 179 (4), 136 (64), 108 (56), 94 (100), 93 (77), 91 (28), 79 (90), 77 (24), 69 (31), 53 (12), 43 (30), 41 (31).

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[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. *(3R,4aR,8aR)-3,4,4a,7,8,8a-Hexahydro-1,1,3,6-tetramethyl-1H-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 ×) with Et_2O. The crude extract (11 g) was subjected to flash chromatography (∅ = 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}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}H-NMR: 1.20, 1.26 (2*s*, 3 H each, 2 CH_3–C(1)); 1.39 (*s*, CH_3–C(3)); 1.65 (br. *s*, CH_3–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*, H–C(4a)); 5.14 (br. *s*, 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}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×). The crude product (7.6 g) was flash chromatographed (∅ 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}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}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, H–C(1)); 1.62 (br. *s*, CH_3(7′)); 1.92 (*dd*, *J* = 14, 6, H–C(1)); 2.34 *m*, $w_{1/2}$ = 13, H–C(3′)); 5.11 (*dd*, *J* = 11, 1, H–C(4) *trans* to C(2)); 5.21 (*m*, overlapped, 1 H, H–C(2′)); 5.28 (*dd*, *J* = 17, 1, H–C(4) *cis* to C(2)); 5.92 (*dd*, *J* = 17, 11, 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* ≈ 14, 5, 1 H, overlapped, H–C(1)); 1.65 (br. *s*, CH_3(7′)); 1.90 (*dd*, *J* ≈ 14, 5, 1 H, overlapped, H–C(1)); 2.52 (*m*, $w_{1/2}$ = 16, H–C(3′)); 5.00 (*dd*, *J* = 11, 1, H–C(4) *trans* to C(2)); 5.22 (*dd*, *J* = 17, 1, H–C(4) *cis* to C(2)); 5.31 (*m*, overlapped, 1 H, H–C(2′)); 5.95 (*dd*, *J* = 17, 11, H–C(3)). MS (both isomers): 220 (< 1, $M^{+\cdot}$), 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 $TsOH \cdot H_2O$ (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°). *(3R,4aR,8aR)-3,4,4a,7,8,8a-Hexahydro-1,1,3,6-tetramethyl-3-vinyl-1H-2-benzopyran* (= Cabreuva Oxide A; *ent*-**1**). Colorless oil, $[\alpha]_D^{20} = -28.4°$ (*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}H-NMR: 1.08 (*s*, CH_{3ax}–C(1)); 1.16 (*s*, CH_{3eq}–C(1)); 1.20 (*s*, CH_3–C(3)); 1.66 (br. *s*, CH_3–C(6)); 1.92–2.10 (*m*, CH_2(7)); 2.01 (*dd*, *J* = 12, 3, H_{eq}–C(4)); 2.21 (br. *t*, *J* ≈ 12, H–C(4a)); 4.94 (*d*, *J* = 11, H–C(2′) *trans* to C(3)); 4.95 (*d*, *J* = 18, H–C(2′) *cis* to C(3)); 5.16 (br. *s*, H–C(5)); 5.99 (*dd*, *J* = 18, 11, H–C(1′)). ^{13}C-NMR: *Table*. MS: 220 (5, $M^{+\cdot}$), 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}H-NMR, MS, t_R) with natural **1**, except for $[\alpha]_D$.

(3S,4aR,8aR)-3,4,4a,7,8,8a-Hexahydro-1,1,3,6-tetramethyl-3-vinyl-1H-2-benzopyran (= Cabreuva Oxide C, **3**). Colorless oil, $[\alpha]_D^{20} = -43.1°$ (*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}H-NMR: 1.18 (*s*, CH_{3eq}–C(1)); 1.23 (*s*, CH_{3ax}–C(1)); 1.34 (*s*, CH_3–C(3)); 1.58 (*dd*, *J* = 12, 4, H_{eq}–C(4)); 1.66 (br. *s*, CH_3–C(6)); 1.93–2.12 (*m*, CH_2(7)); 2.28 (br. *t*, *J* ≈ 12, H–C(4a)); 4.92 (*dd*, *J* = 11, 1, H–C(2′) *trans* to C(3)); 5.13 (br. *s*, H–C(5)); 5.14 (*dd*, *J* = 18, 1, H–C(2′) *cis* to C(3)); 5.87 (*dd*, *J* = 18, 11, H–C(1′)). ^{13}C-NMR: *Table*. MS: 220 (1, $M^{+\cdot}$), 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}H-NMR, MS, t_R) with natural **3**, except for $[\alpha]_D$.

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

Colorless oil, $[\alpha]_D^{20} = -8.1°$ ($c = 1.75$). IR (neat): 3030*w* (sh), 1660*w*, 1000*s*. ^{1}H-NMR[10]): 1.09, 1.29 (2*s*, 3 H each, 2 CH_3–C(3)); 1.44 (*m*, H_{ax}–C(4)); 1.61 (*d*, $J \approx 1$, CH_3–C(1')); 1.63 (*d*, $J = 6.5$, CH_3–C(3')); 1.65 (br. *s*, CH_3–C(6)); 1.67 (*m*, H–C(3a), overlapped); 1.77 (*m*, H_{eq}–C(4)); 2.13 (*m*, 2 H–C(5)); 2.32 (br. *t*, $J = 10.5$, H–C(7a)); 3.79 (*d*, $J = 10$, H–C(1)); 5.33 (br. *s*, H–C(7)); 5.53 (*q*, $J = 6.5$, H–C(2')). ^{13}C-NMR[10]): 10.7 (*q*, CH_3–C(1')); 13.4 (*q*, C(3')); 22.8 (*t*, C(4)); 23.1 (*q*, CH_3–C(6)); 24.4 (*q*, CH_{3ax}–C(3)); 28.5 (*q*, CH_{3eq}–C(3)); 31.8 (*t*, C(5)); 44.8 (*d*, C(7a)); 52.7 (*d*, C(3a)); 80.2 (*s*, C(3)); 87.4 (*d*, C(1)); 120.2 (*d*, C(7)); 123.2 (*d*, C(2')); 134.3 (*s*, C(6)); 135.9 (*s*, C(1')). MS: 220 (< 1, $M^{+\cdot}$), 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 (1*S*,4*R*)-2,8-*p*-menthadien-1-ol[5]) (**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°/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. 58–60°/0.09 Torr) were obtained as a colorless oil. $[\alpha]_D^{20} = +288°$ ($c = 1.1$). IR (neat): 3100*w*, 1740*s*, 1650*m*, 1455*m*, 1380*m*, 1360*m*, 1190*s*, 1160*s*, 1050*m*, 900*m*. ^{1}H-NMR: 1.25 (*t*, $J = 7$, CH_3CH_2O); 1.48–1.70 (*m*, CH_2(5)); 1.65 (*s*, CH_3(7)); 1.75 (*s*, CH_3(10)); 1.97 (*dd*, $J = 15$, 10, 1 H, CH_2CO); 2.00 (*m*, CH_2(6)); 2.22 (*m*, H–C(4)); 2.26 (*dd*, $J = 15$, 4, 1 H, CH_2CO); 2.78 (*m*, H–C(3)); 4.12 (*m*, CH_3CH_2O); 4.66, 4.85 (2 br. *s*, 1 H each, CH_2(9)); 5.50 (*m*, H–C(2)). ^{13}C-NMR: 14.3 (*q*, CH_3CH_2); 22.5 (*t*, C(5)); 22.8 (*q*, C(10)); 23.5 (*q*, C(7)); 30.8 (*t*, C(6)); 32.9 (*d*, C(3)); 36.1 (*t*, CH_2CO); 43.3 (*d*, C(4)); 60.1 (*t*, CH_3CH_2O); 110.5 (*t*, C(9)); 124.2 (*d*, C(2)); 134.8 (*s*, C(1)); 147.5 (*s*, C(8)); 173.6 (*s*, C=O). MS: 222 (14, $M^{+\cdot}$), 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×). Distillation of the extract (120–130°/0.05 Torr) gave 43.5 g (95%) of pure **14**. Oil, $[\alpha]_D^{20} = +330°$ ($c = 1.07$). IR (neat): 3500–2400*s* (br.), 1700*s*, 1650*m*, 1440*s*, 1300*s*, 900*s*. ^{1}H-NMR: 1.53, 1.67 (2*m*, 1 H each, CH_2(5)); 1.66 (*s*, CH_3(7)); 1.75 (*s*, CH_3(10)); *ca.* 2.0 (*m*, CH_2(6)); 2.01 (*dd*, $J = 15$, 10, 1 H, CH_2CO); 2.22 (br. *d*, $J \approx 12$, H–C(4)); 2.32 (*dd*, $J = 15$, 4, 1 H, CH_2CO); 2.76 (*m*, H–C(3)); 4.68, 4.87 (2 br. *s*, 1 H each, CH_2(9)); 5.55 (*m*, H–C(2)). ^{13}C-NMR: 22.4 (*t*, C(5)); 22.8 (*q*, C(10)); 23.5 (*q*, C(7)); 30.8 (*t*, C(6)); 32.6 (*d*, C(3)); 35.9 (*t*, CH_2CO); 43.1 (*d*, C(4)); 110.7 (*t*, C(9)); 123.8 (*d*, C(2)); 135.1 (*s*, C(1)); 147.3 (*s*, C(8)); 180.5 (*s*, C=O). MS: 194 (22, $M^{+\cdot}$), 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 $TsOH \cdot H_2O$ (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 (110–120°/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 (∅ 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)*.

*(4aS,8aR)-4a,7,8,8a-Tetrahydro-1,1,6-trimethyl-1*H*-2-benzopyran-3(4*H*)-one* (**15**). M.p. 47.5–48.5°, $[\alpha]_D^{20} = +118°$ ($c = 1.2$). IR (neat): 1730*s*, 1290*s*, 1180*s*, 1135*s*, 1000*s*. ^{1}H-NMR[10]): 1.42 (*m*, overlapped, 1 H, H_{ax}–C(8)); 1.43 (*s*, CH_{3ax}–C(1)); 1.46 (*s*, CH_{3eq}–C(1)); 1.69 (*s*, CH_3–C(6)); 1.70 (*m*, overlapped, 1 H, H–C(8a)); 1.89 (*m*, H_{eq}–C(8)); 2.06 (*m*, CH_2(7)); 2.26 (*dd*, $J = 19$, 10, H_{ax}–C(4)); 2.70 (*dd*, $J = 19$, 8, H_{eq}–C(4)); 2.80 (*m*, H–C(4a)); 5.43 (*m*, H–C(5)). ^{13}C-NMR: *Table*. MS: 194 (7, $M^{+\cdot}$), 179 (5), 136 (30), 108 (29), 94 (100), 93 (48), 91 (25), 79 (74), 43 (23), 41 (21), 39 (17).

*(4aR,8aR)-4a,5,8,8a-Tetrahydro-1,1,6-trimethyl-1*H*-2-benzopyran-3(4*H*)-one* (**16**). ^{1}H-NMR: 1.36, 1.46 (2*s*, 3 H each, 2 CH_3–C(1)); 1.67 (br. *s*, CH_3–C(6)); 2.36 (*AB* of *ABX*, $\delta_A = 2.32$, $\delta_B = 2.40$, $J_{AB} = 18$, $J_{AX} = 12.5$, $J_{BX} = 5.5$, CH_2(4)); 2.61 (*m*, H–C(4a)); 5.37 (*m*, H–C(7)). MS: 194 (2, $M^{+\cdot}$), 179 (6), 161 (3), 151 (4), 134 (94), 119 (64), 105 (22), 94 (86), 93 (46), 91 (27), 79 (100), 43 (30).

(1S,5R,6R)-6-Isopropenyl-1-methyl-2-oxobicyclo[3.3.1]nonan-3-one (**17**). ^{1}H-NMR: 1.39 (*s*, CH_3–C(1)); 1.73 (br. *s*, CH_3–C=C); 4.71, 4.92 (2 br. *s*, 1 H each, CH_2=C). MS: 194 (6, $M^{+\cdot}$), 179 (10), 149 (37), 111 (88), 93 (35), 79 (70), 67 (42), 53 (35), 43 (100).

*(3aS,7aS)-3a,6,7,7a-Tetrahydro-7a-isopropyl-5-methyl-1-benzofuran-2(3*H*)-one* (**18**). IR (neat): 1770*s*. ^{1}H-NMR: 1.00, 1.04 (2*d*, $J = 7$, 3 H each, $(CH_3)_2CH$)); 1.70 (*ddd*, $J = 14$, 10, 5, H_{ax}–C(7)); 1.71 (br. *s*, CH_3–C(5)); 1.89 (*dt*, $J = 17$, 4.5, H_{eq}–C(6)); 1.96 (*m*, overlapped, 1 H, $(CH_3)_2CH$); 1.98 (*dt*, $J = 14$, 4.5, H_{eq}–C(7)); 2.14 (*m*, H_{ax}–C(6)); 2.24 (*dd*, $J = 17$, 2.5, H–C(3)); 2.85 (*dd*, $J = 17$, 9, H–C(3)); 2.91 (*m*, H–C(3a)); 5.22 (*m*, H–C(4)). MS: 194 (2, $M^{+\cdot}$), 151 (100), 133 (35), 123 (8), 119 (6), 109 (34), 107 (26), 81 (29), 71 (21), 43 (22).

3.4. *(3S,4aS,8aR)-3,4,4a,7,8,8a-Hexahydro-1,1,3,6-tetramethyl-1H-2-benzopyran-3-ol* (**19**). To a stirred soln. of **15** (1.94 g, 10 mmol) in dry Et_2O (20 ml) was added at −40° during 30 min 1M CH_3Li in Et_2O (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/H_2O, and extracted (3×) with Et_2O. The crude extract (2 g) was flash chromatographed (∅ 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 CH_3Li 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 ($CHCl_3$): 3580*m*, 3400 (br.), 1710*m* (**19a**), 1390*s*, 1180*s*, 1105*m*. ^{1}H-NMR (**19**): 1.16 (*s*, CH_{3eq}–C(1)); 1.36 (*s*, CH_{3ax}–C(1)); 1.44 (*s*, CH_3–C(3)); 1.64 (br. *s*, CH_3–C(6)); 2.77 (*m*, H–C(4a)); 5.41 (*m*, H–C(5)). ^{1}H-NMR (**19a**, *p*-menthane numbering): 1.22, 1.25 (2*s*, 3 H each, 2 CH_3–C(8)); 2,14 (*s*, CH_3CO); 2.42 (*dd*, *J* = 17, 10, 1 H, CH_2CO); 2.88 (br. *m*, H–C(3)); 3.02 (*dd*, *J* = 17, 4, 1 H, CH_2CO); 5.44 (*m*, H–C(2)). MS: not recorded, because **19** was dehydrated easily to give **20**.

(4aR,8aR)-4a,7,8,8a-Tetrahydro-1,1,3,6-tetramethyl-1H-2-benzopyran (**20**). IR (neat): 1675*s*, 1305*s*, 1140*s*, 995*m*, 885*m*. ^{1}H-NMR: 1.23, 1.30 (2*s*, 3 H each, 2 CH_3–C(1)); 1.67 (br. *s*, CH_3–C(6)); 1.68 (*d*, *J* ≈ 1, CH_3–C(3)); 1.95 (*m*, CH_2(7)); 2.84 (br. *m*, H–C(4a)); 4.25 (br. *s*, H–C(4)); 5.23 (*m*, H–C(5)). MS: 192 (61, $M^{+\cdot}$), 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 $LiOCH_3$ in dry CH_3OH (prepared by dissolving 700 mg (100 mmol) of Li in 200 ml of dry CH_3OH) 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 Et_2O (200 ml) was added slowly (2 h) at 0–5° 1M CH_3Li in Et_2O (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/H_2O. The aq. layer was extracted with Et_2O (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, $[\alpha]_D^{20} = +313°$ (*c* = 0.6). IR (neat): 3090*w*, 1710*s*, 1645*m*, 1360*s*, 1160*m*, 900*s*. ^{1}H-NMR: 1.52 (*m*, H_{ax}–C(5′)); 1.64 (br. *s*, CH_3(7′)); 1.67 (*m*, overlapped, 1 H, H_{eq}–C(5′)); 1.71 (*s*, CH_3(10′)); 1.98 (*m*, CH_2(6′)); 2.10 (*s*, CH_3CO); 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, CH_2(9′)); 5.47 (*m*, H–C(2′)). ^{13}C-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, $M^{+\cdot}$), 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. *(2S,3′S,4′R)- and (2R,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. NH_4Cl soln. The aq. phase was extracted with Et_2O (3 × 200 ml), the Et_2O extracts were combined with the THF phase, dried ($MgSO_4$), 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/Et_2O 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*. ^{1}H-NMR: 1.51 (*s*, CH_3–C(2)); 1.66 (br. *s*, CH_3(7′)); 1.73 (*dd*, *J* = 14, 3, H–C(1)); 1.76 (br. *s*, CH_3(10′)); 1.89 (*s*, OH); 2.00 (*m*, CH_2(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, CH_2(9′)); 5.82 (*m*, H–C(2′)). ^{13}C-NMR: 22.9 (*t*, C(5′)); 22.9 (*q*, C(10′)); 23.5 (*q*, C(7′)); 30.5 (*t*, C(6′)); 30.8 (*q*, CH_3–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, $M^{+\cdot} - H_2O$), 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**. ^{1}H-NMR: 1.45 (*m*, H_{ax}–C(5′)); 1.48 (*s*, CH_3–C(2)); 1.62 (*m*, 1 H); 1.68 (br. *s*, CH_3(7′)); 1.75 (br. *s*, CH_3(10′)); 2.02 (*m*, CH_2(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, CH_2(9′)); 5.86 (*m*, H–C(2′)). ^{13}C-NMR: 22.4 (*t*, C(5′)); 22.8 (*q*, C(10′)); 23.6 (*q*, C(7′)); 30.8 (*t*, C(6′)); 31.2 (*q*, CH_3–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. *(3S,4aS,8aR)- and (3R,4aS,8aR)-3-Ethynyl-3,4,4a,7,8,8a-hexahydro-1,1,3,6-tetramethyl-1H-2-benzopyran* (**24** and **25**). To a stirred soln. of **22**/**23** (ratio 6:4; 4.8 g, 22 mmol) in CH_2Cl_2 (100 ml) was added at −20° with a syringe $SnCl_4$ (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 $SnCl_4$-pyridine complex. The soln. was washed with ice-cold 2N H_2SO_4 and sat. NaCl soln., dried ($MgSO_4$), 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/Et_2O 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:** $[\alpha]_D^{20} = +135°$ (*c* = 1.9). IR (neat): 3300*s*, 1095*s*, 1005*m*. ^{1}H-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*, CH_3–C(3)); 1.64 (br. *s*, CH_3–C(6)); 1.73 (*dd*, *J* = 14, 4, H_{eq}–C(4)); 1.97 (*m*, CH_2(7)); 2.36 (*s*, HC≡C); 2.78 (*m*, H–C(4a)); 5.40 (*m*, H–C(5)). ^{13}C-NMR: *Table*. MS: 218 (< 1, $M^{+\cdot}$), 203 (6), 145 (21), 117 (10), 105 (11), 94 (100), 93 (22), 91 (19), 79 (48), 43 (28).

25: $[\alpha]_D^{20} = +199.8°$ (*c* = 1.2). IR (neat): 3300*s*, 1375*s*, 1185*s*, 1165*s*, 1095*s*, 990*s*. ^{1}H-NMR: 1.28, 1.33 (2*s*, 3 H each, 2 CH_3–C(1)); 1.54 (*s*, CH_3–C(3)); 1.62 (*dd*, *J* = 14, 4, H_{eq}–C(4)); 1.66 (br. *s*, CH_3–C(6)); 1.87 (*t*, *J* = 14, H_{ax}–C(4)); 1.95 (*m*, CH_2(7)); 2.38 (*m*, H–C(4a)); 2.40 (*s*, CH≡C); 5.27 (*m*, H–C(5)). ^{13}C-NMR: *Table*. MS: 218 (1.5, $M^{+\cdot}$), 203 (12), 145 (13), 117 (9), 105 (10), 94 (100), 93 (19), 91 (17), 79 (50), 43 (23).

(1S,3R,5R,6R)-3-Ethynyl-6-isopropenyl-1,3-dimethyl-2-oxabicyclo[3.3.1]nonane (**26**). IR (neat): 3300*s*, 3095*w*, 1645*m*, 1455*s*, 1370*s*, 1240*s*, 1090*s*, 1060*m*, 1010*m*, 895*s*. ^{1}H-NMR: 1.28 (*s*, CH_3–C(1)); 1.48 (*s*, CH_3–C(3)); 1.73 (br. *s*, CH_3–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, CH_2=C). MS: 218 (< 1, $M^{+\cdot}$), 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. *(3S,4aS,8aR)-3,4,4a,7,8,8a-Hexahydro-1,1,3,6-tetramethyl-3-vinyl-1H-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 H_2 (0.4 mmol) was absorbed (*ca.* 3 h). The soln. was filtered, washed with aq. 2N HCl and sat. NaCl soln., dried ($MgSO_4$), 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 (^{1}H-NMR, MS, t_R) with natural **2**, except for $[\alpha]_D$. Colorless oil, $[\alpha]_D^{20} = +115.4°$ (*c* = 1.4). IR (neat): 3100*w*, 3075*w*, 1645*w*, 1455*m*, 1390*m*, 1375*m*, 1205*m*, 1095*s*, 1000*s*, 920*s*, 860*m*. ^{1}H-NMR: 1.14, 1.16 (2*s*, 3 H each, 2 CH_3–C(1)); 1.26 (*s*, CH_3–C(3)); 1.32 (*t*, *J* ≈ 14, overlapped, 1 H, H_{ax}–C(4)); 1.65 (br. *s*, CH_3–C(6)); 1.86 (*dd*, *J* = 14, 4, H_{eq}–C(4)); 1.98 (*m*, CH_2(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′)). ^{13}C-NMR: *Table*. MS: 220 (2, $M^{+\cdot}$), 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. *(3R,4aS,8aR)-3,4,4a,7,8,8a-Hexahydro-1,1,3,6-tetramethyl-3-vinyl-1H-2-benzopyran* (= Cabreuva Oxide D; *ent*-**4**). Prepared in 90% yield by catalytic hydrogenation of **25**, as described above for **2**. Oil, $[\alpha]_D^{20} = +178.5°$ (*c* = 0.9). The compound was identical with natural **4**, except for the $[\alpha]_D$. IR (neat): 3100*w*, 3070*w*, 1650*w*, 1390*m*, 1380*m*, 1190*m*, 1110*m*, 1050*m*, 1000*s*, 930*s*, 860*m*. ^{1}H-NMR: 1.17 (*s*, CH_{3eq}–C(1)); 1.32, 1.33 (2*s*, 3 H each, CH_{3ax}–C(1), CH_3–C(3)); 1.42 (*'d'*, *J* ≈ 9, CH_2(4)); 1.65 (br. *s*, CH_3–C(6)); 1.96 (*m*, CH_2(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′)). ^{13}C-NMR: *Table*. MS: 220 (4, $M^{+\cdot}$), 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.