178. Configuration-Odor Relationships in 5β-Ambrox

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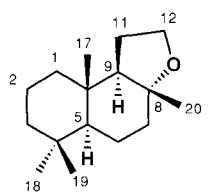
The four possible A/B *cis*-fused diastereoisomers of *Ambrox*® have been synthesized and their configurations and conformations established by X-ray and NMR analysis. Only 5β-ambrox (= 1,2,3a,4,5,5aβ,6,7,8,9,9a,9bα-dodecahydro-3aβ,6,6,9aβ-tetramethylnaphtho[2,1-*b*]furan; **5**) has an odor quality comparable to *Ambrox*®. The 1,3-synperiplanar/diaxial conformation of the substituents at C(8) (= C(3a)) and C(10) (= C(9a)) has thus been confirmed to be a compulsory structure element for the particular odor.

Introduction. – *Ambrox*®[1]), the prototype of ambergris odorants, occurs in three diastereoisomeric forms **1**, **2**, and **4** with regard to the C-atoms 8 and 9. Conformational considerations make the existence of the highly strained fourth diastereoisomer **3** unlikely. All three tricyclic ethers obey the 'triaxial rule' of odor sensation [1–3]. Continuing



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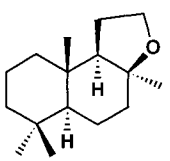

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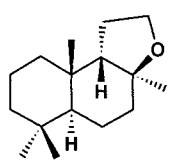

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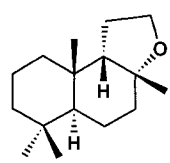

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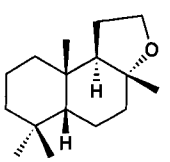

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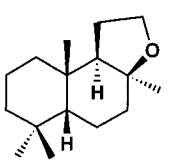

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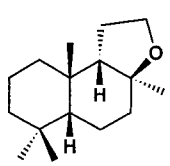

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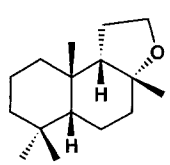

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interest in this field stimulated preparation and sensory evaluation of A/B *cis*-fused *Ambrox*®, and in this paper, we report the synthesis, conformation, and olfactory properties of the four existing 5β-diastereoisomers **5**–**8**[2]).

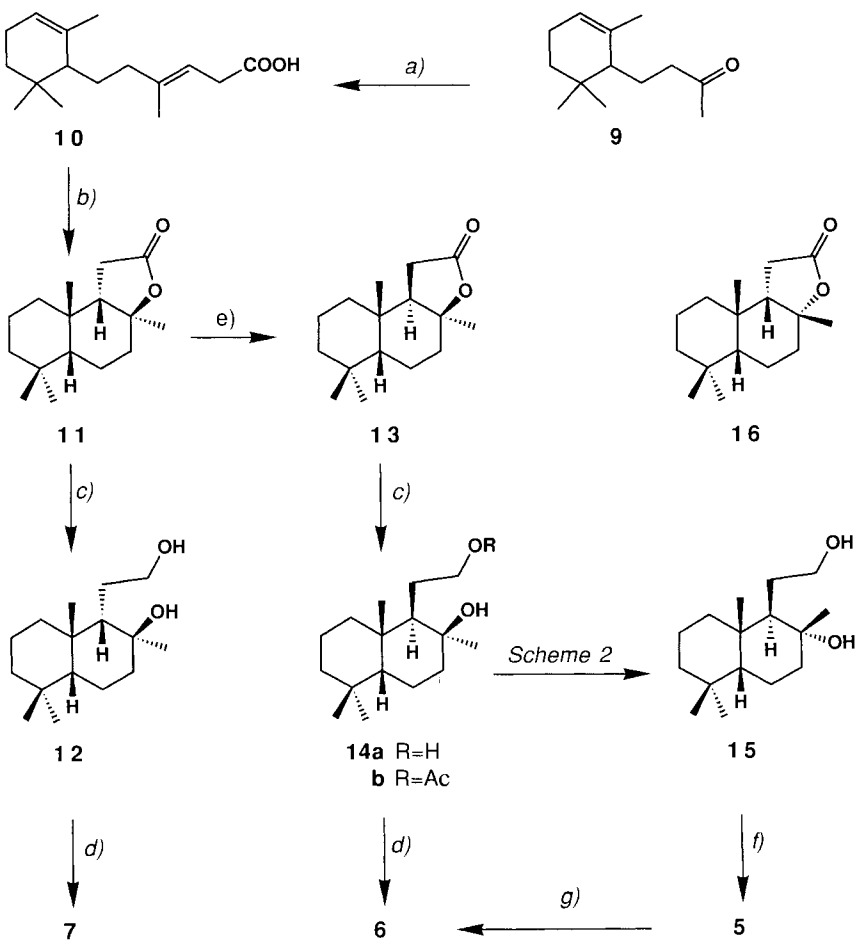
[1]) Trade name of *Firmenich SA*.

[2]) All compounds synthesized in this work are racemic.

Syntheses. – Racemic 5β,8α,9β-sclareolide (**11**) represents an ideal starting material for the target molecules **5**–**7**. Thanks to extensive studies on cyclization of monocyclohomofarnesic acid and related compounds by *Saito* and coworkers [4] [5], lactone **11** is readily available from α-dihydroionone **9** through acid-catalyzed cyclization of (*E*)-α-monocyclohomofarnesic acid **10** (*Scheme 1*). The structure of **11** has been fully corroborated by X-ray diffraction analysis [4][3]). Reduction of **11** with $LiAlH_4$ and cyclization of the resulting diol **12** by means of $POCl_3$ in pyridine provided 5β,8α,9β-ambrox (**7**).

In analogy to the well known isomerization of sclareolide [6] [7], lactone **11** was treated with $HCOOH/H_2SO_4$ at 90° for several h, whereby a new lactone was formed (*Scheme 1*). The ^{13}C-NMR spectrum of this lactone was identical with the spectrum of

Scheme 1



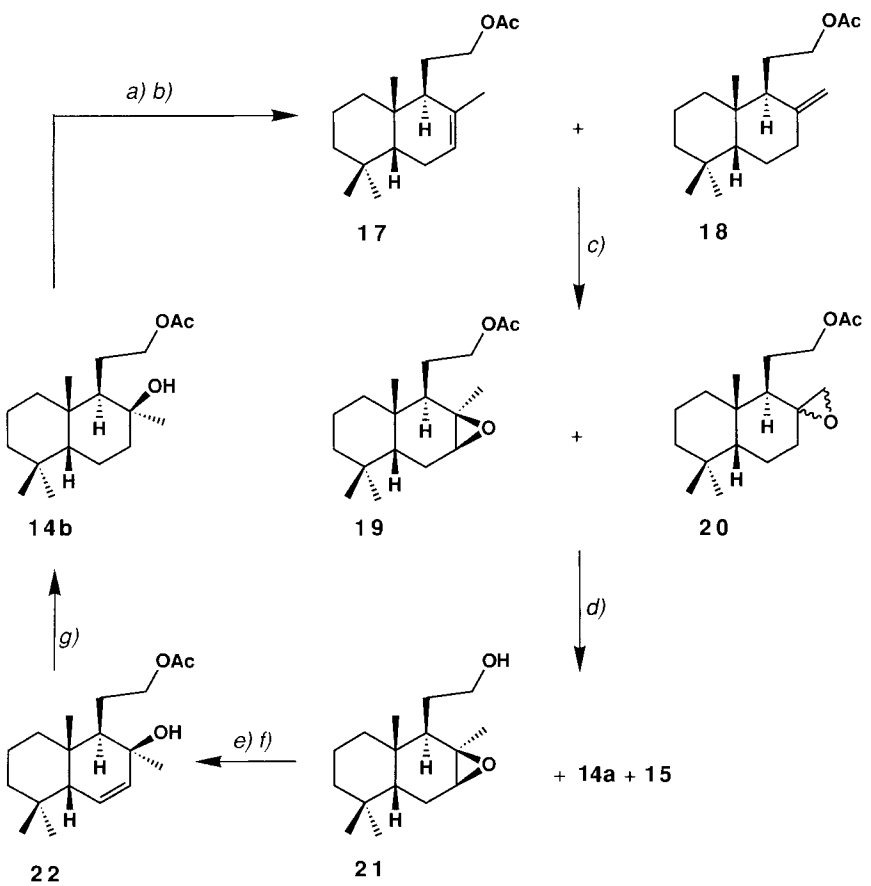
a) Horner-Wittig reaction. *b*) $SnCl_4$, CH_2Cl_2, −75°. *c*) $LiAlH_4$. *d*) $POCl_3$, Py. *e*) HCOOH, H_2SO_4. *f*) TsCl, Py. *g*) TsOH, $MeNO_2$.

[3]) Prof. *Saito* kindly provided us with the X-ray diffraction data of lactone **11**.

lactone **16** reported by *Saito* and coworkers [4]. However, chemical transformations and a detailed ^{1}H- and ^{13}C-NMR analysis led us to revise this structure to be as in formula **13**. Lactone **13** was reduced to diol **14a** which was cyclized to noncrystalline 5β,8α-ambrox (**6**).

Inversion of configuration at C(8) of diol **14a** was achieved as shown in *Scheme 2*, albeit in low yield. Thus, the monoacetate **14b** was dehydrated by treatment with *p*-toluenesulfonyl isocyanate (TsNCO) and pyrolysis of the intermediate urethane [8] to a 9:1 mixture of endo- and exocyclic olefin **17** and **18**, respectively. Other methods to bring about dehydration ($POCl_3$, mesyl chloride, dinitrobenzoyl chloride) yielded the same isomeric ratio. Epoxidation of **17**/**18** produced one epoxide **19** derived from **17** and the diastereoisomeric mixture **20** in a ratio of 1:1 derived from **18**. Reduction of **19**/**20** with $LiAlH_4$ in refluxing THF afforded a 1:1 mixture of diols **14a** and **15** (10% of the reaction mixture), whereas the triply substituted epoxide function of compound **19**, which repre-

Scheme 2

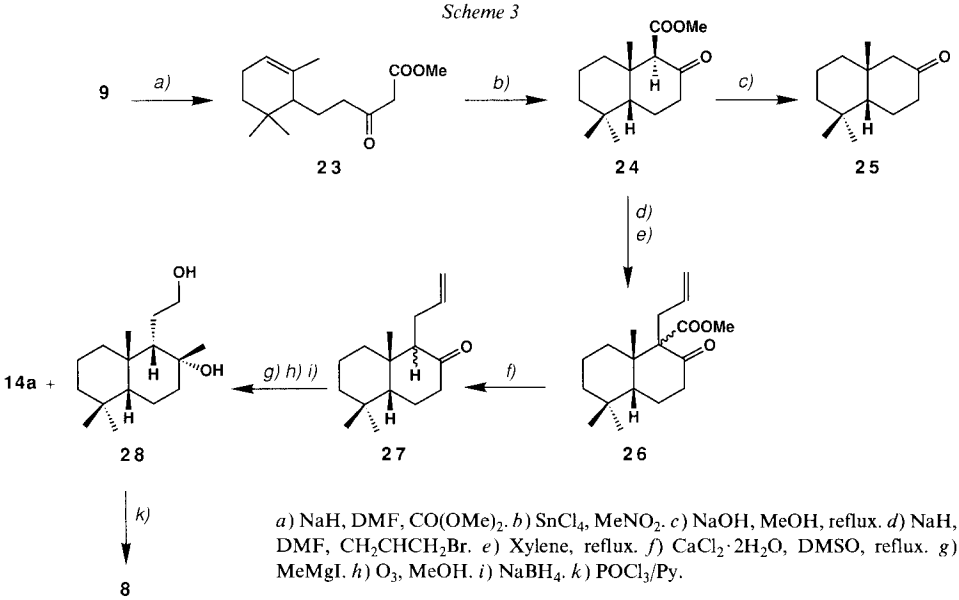


a) TsNCO. *b*) *Δ*. *c*) 3-$ClC_6H_4CO_3H$. *d*) $LiAlH_4$. *e*) LDA. *f*) Ac_2O, Py. *g*) H_2, PtO_2.

sented some 90% of the epoxide mixture, was not reduced under these conditions, yielding only epoxy alcohol **21**. The relative configuration at C(8) of **19** was found to be unaffected; treatment of the corresponding alcohol **21** with lithium diisopropylamide (LDA) yielded, upon acetylation, allylic alcohol **22** which was hydrogenated to give the starting **14b**. Pure diol **15** was isolated from the reaction mixture **14a**/**15**/**21** by chromatography on silica gel and was cyclized in the presence TsCl in pyridine (*Scheme 1*). The resulting 5β-ambrox (**5**) was crystalline, and its chromatographic and spectral data (^{1}H-NMR, MS) were in full agreement with those of (−)-**5** the structure of which had been established unambiguously both by chemical correlation [9] and X-ray diffraction analysis (see below). The relative configuration of **14a** and concomitantly also of lactone **13** has thus been settled by chemical correlation with 5β-ambrox (**5**). Furthermore, **5** was isomerized to **6** when exposed to a trace of TsOH in hot nitromethane (*Scheme 1*).

The fourth and last of the 5β-ambrox diastereoisomers, **8**, was prepared along the lines of a recent publication by *Büchi* and *Wüest* [10] (*Scheme 3*). Thus, keto ester **24** which is readily available from α-dihydroionone **9** and which on demethoxycarbonylation gives the known *cis*-decalone **25** [11] was alkylated (NaH in DMF, allyl bromide). The intermediate enol ether rearranged in refluxing xylene to give **26** as a mixture of C(1) epimers.

Scheme 3



a) NaH, DMF, $CO(OMe)_2$. *b*) $SnCl_4$, $MeNO_2$. *c*) NaOH, MeOH, reflux. *d*) NaH, DMF, CH_2CHCH_2Br. *e*) Xylene, reflux. *f*) $CaCl_2 \cdot 2H_2O$, DMSO, reflux. *g*) MeMgI. *h*) O_3, MeOH. *i*) $NaBH_4$. *k*) $POCl_3$/Py.

Without separation, these keto esters were demethoxycarbonylated ($CaCl_2 \cdot 2H_2O$ in DMSO) to decalone **27** (C(1) epimeric mixture). *Grignard* addition of MeMgI produced two tertiary alcohols which were ozonized and reduced to a mixture of two diols, the major one being identical with **14a**. The minor diol **28** was converted ($POCl_3$ in pyridine) to an oily 5β-ambrox which differed from **6** and **7** and, therefore, must be **8**. In retrospect, it is rather surprising to find that *Grignard* addition to **27** had occurred highly stereospecifically and had given rise to only one diastereoisomer from either one of the two decalones.

It is interesting to note that lactone **13**, which is formed as a minor product by acid-catalyzed cyclization of (*E*)-monocyclohomofarnesic acid **10** [4] and of related compounds [5] or as a major product from acid-catalyzed isomerization of **11**, corresponds most probably to 'lactone XVIII' (m.p. 100°) described by *Lucius* [12] (= 'lactone XII' in [13]). It had been obtained among other lactones from **10** under vigorous cyclization conditions (HCOOH, H_2SO_4, 40–60°). The configuration of this lactone was not established at that time although it was assumed to belong to the *cis*-decalin series [12] [13] [7]. The diol which was derived from the lactone in question had m.p. 138°, the same value as we recorded for diol **14a**, whereas the reported data of the tricyclic ether (n_D, density, b.p.) do not permit configurational comparison with the oily compound **6**.

A second comment concerns 8α,9β-sclareolide and 8α,9β-ambrox described by *Ohloff* (see [14], therein *Formulae* **19** and **23**, resp.). Since the two compounds had been obtained following the experimental procedure of *Lucius* [12] [13], their structures should be revised to **13** and **6**, respectively.

Conformational Analysis. – *cis*-Fused decalins may exist in either steroid or non-steroid conformation or consist of a rapidly equilibrating mixture of the two conformations. Conformation has a profound impact on the spatial arrangement of the substituents at C(8) and C(10) which play an important role in the case of ambergris odorants with respect to hydrophobic interaction with the receptor site [3]. Particular attention was thus given to establish the conformation of the four 5β-ambrox diastereoisomers **5**–**8**. To this end, we were in the comfortable situation of having available three X-ray diffraction

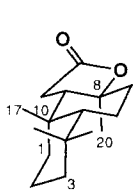
Table 1. *^{13}C-NMR Chemical Shifts* (ppm) *and Assignments for Compounds* **5**–**8** *and* **11**–**15**

	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C(11)	C(12)	C(17)	C(18)	C(19)	C(20)
11	29.2	18.6	35.2	34.1	51.9	24.4	37.8	85.7	57.3	37.2	26.9	176.7	29.4	32.6	31.2	21.1
12	26.7	19.1	35.4	34.1	53.2	23.7	43.1	72.3	57.2	40.8	28.4	64.5	27.9	33.7	31.5	24.3
7	27.1	19.0	35.5	34.1	52.5	23.4	38.7	78.9	58.6	37.7	25.1	64.4	29.7	33.3	31.4	20.6
13	33.9	19.0	35.5	33.8	46.7	21.7	33.3	85.6	54.6	36.7	34.3	175.8	28.6	32.5	31.0	26.9
14a	39.8	18.8	44.5	34.8	49.7	18.1	37.3	72.7	41.7	37.7	29.4	64.8	27.9	27.3	34.0	31.8
14b	39.8	18.9	44.7	34.9	49.8	18.1	37.5	72.7	42.1	37.8	25.1	66.3	27.9	27.3	34.0	31.9
6	34.0	19.2	36.2	33.8	47.0	22.4	33.0	80.1	56.2	36.6	29.2	63.3	29.2	32.2	31.2	26.9
15	39.8	18.5	44.2	34.8	49.0	20.4	39.3	73.2	46.3	38.8	28.8	63.7	28.1	27.2	34.1	25.7
5	41.2	18.3	42.6	33.2	48.7	21.4	36.4	80.2	49.2	36.2	23.6	64.1	25.9	28.0	34.5	22.1
8	27.5	18.8	34.8	[a])	52.4	19.9	35.8	80.9	55.3	[a])	28.6	65.0	30.4	31.8	31.2	28.2

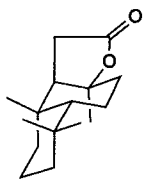
[a]) Not detectable.

analyses and a virtually complete set of ^{13}C-NMR data (*Table 1*). The conformation of lactone **11** had been established by X-ray diffraction analysis [4][3]) to be steroidal (*i.e.* CH_3(17) equatorial with respect to ring B). The constancy of the ^{13}C-NMR data of lactone **11**, of diol **12**, and of ether **7** clearly shows that the conformation remains steroidal throughout this series. The bonds C(8)–O and C(9)–C(11) are diequatorial, the conformation necessary to bring about *trans*-fusion of the five-membered lactone and ether moieties.

Fig. 1 shows the X-ray structure of 5β-ambrox (**5**) as determined on (–)-**5** [9]. The non-steroid conformation (*i.e.* CH_3(17) axial with respect to ring B) of this compound equally holds for diol **15**, the ^{13}C-NMR spectra of the two compounds being very similar.



11 [a] [4]



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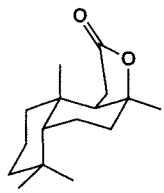

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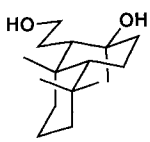

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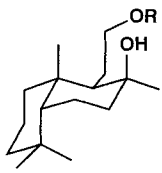
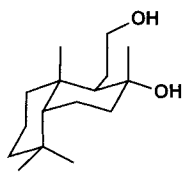


14 [a]



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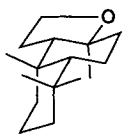

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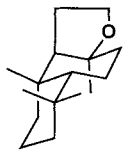

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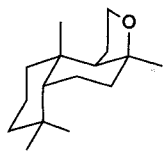

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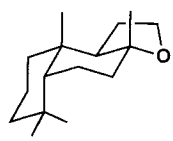

5 [a]

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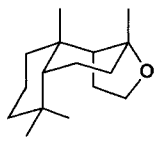

8'

[a]) From X-ray diffraction analysis.

The chemical shift of C(3) proved to be diagnostically useful for this type of conformational analysis: C(3) of the non-steroid-like conformers **15** and **5** resonate at *ca.* 45 ppm, the steroid ones **11**, **12**, and **7** at *ca.* 35 ppm. The difference in δ(C(3)) clearly indicates that the compounds derived from 5β,8α-sclareolide **13** belong to two different conformational series: δ(C(3)) of **13** and **6** are observed at *ca.* 36 ppm, whereas δ(C(3)) of **14** is found at 45 ppm. Lactone **13** as well as ether **6** may assume steroid or non-steroid conformation as both arrangements allow the five-membered ring to close axially-equatorially. On the basis of δ(C(3)), we attributed **13** and **6** to steroid and diol **14a** to non-steroid conformation. Other C-atoms, namely C(9), C(11), and C(20), show the expected relative shifts when comparing, *e.g.*, **6** with **7** or **14a** with **15**, whereas $\Delta\delta$(C(1))

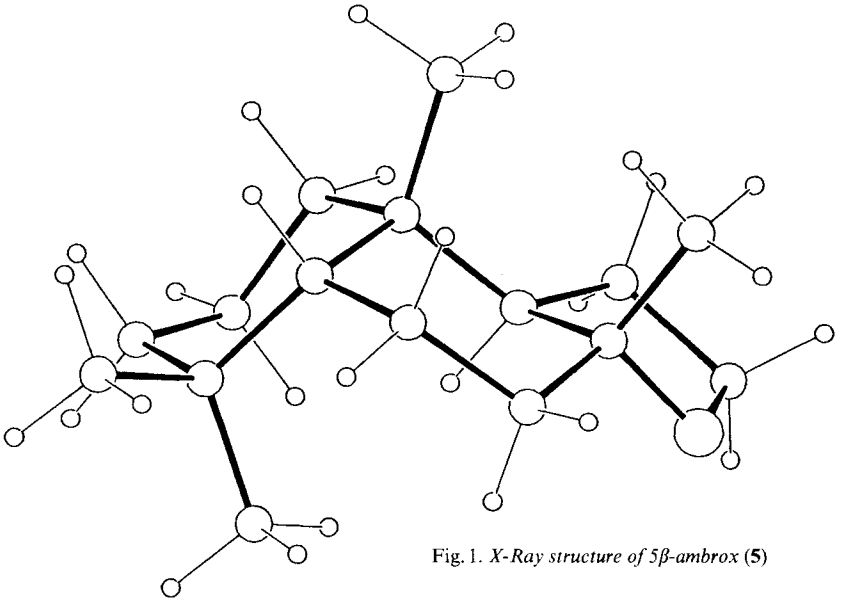

Fig. 1. *X-Ray structure of 5β-ambrox* (**5**)

does not follow simple additive rules [15]. The coupling constants of H–C(5) of compound **6** were calculated to be 3.6 and 12.4 Hz assuming steroid conformation and 1.3 and 4.5 Hz assuming non-steroid conformation. The former data correlate well with the observed values (*dd*, $J = 4$ and 10 Hz)[4]).

An X-ray diffraction analysis was performed on one member of the 5β,8α-series in order to have an independent control. As can be seen from *Fig. 2*, monoacetate **14b** and consequently also diol **14a** have non-steroid conformation. On the other hand, the steroid conformation of **13** and **6** is thus confirmed.

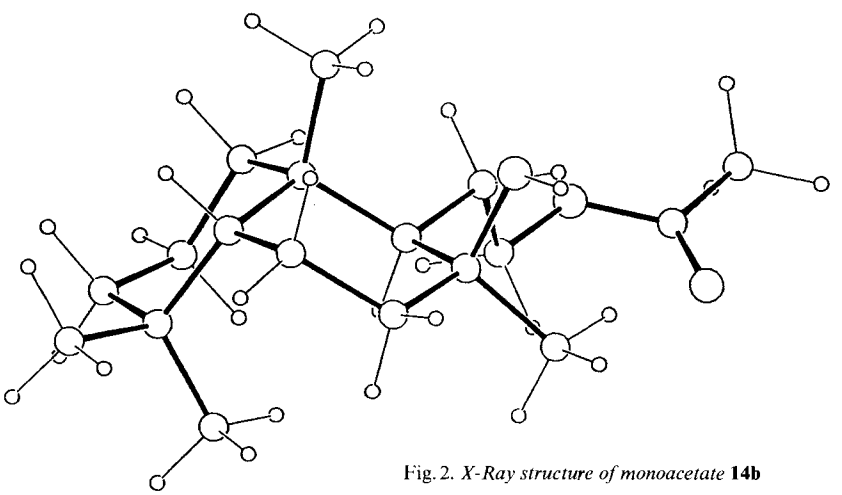

Fig. 2. *X-Ray structure of monoacetate* **14b**

[4]) We thank Dr. *A. Boschung, Firmenich SA*, for the calculations [16].

The 5β-ambrox diastereoisomer **8**, for which we have no X-ray support, is very likely to be a steroid conformer, the chemical shift δ(C(3)) of 34.5 ppm being the main argument. Furthermore, calculated and observed coupling constants for H–C(5) are in good agreement. We conclude that 5β-ambrox (**5**) is the only A/B *cis*-fused tricyclic ether which possesses non-steroid conformation and thus has the groups CH_3(17) and CH_3(20) 1,3-synperiplanar/diaxial with respect to ring B. The other 5β-diastereoisomers **6**–**8** have steroid-like conformations with CH_3(17) equatorial with respect to ring B.

Qualitative Sensory Testing of Compounds 1, 2, and 4–8. – *Ambrox*® (**1**) is recognized as prototype of all ambergris odorants, both structurally and organoleptically [3]. The dominating exotic woody note of strong warm animal tonality in **1** is accompanied by an undesired earthy subnote of potato-cellar in 8α-ambrox **2**. Besides this qualitative difference between **1** and **2**, a reduction of the odor strength in **2** by a factor of one hundred has been determined [3]. The odor of the diastereoisomeric ether **4** is of similar strength than the one of **1**, and it differs only slightly from the rich and complex bouquet of **1**. Out of the four 5β-ethers **5**–**8**, but **5** has an odor quality comparable to prototype **1**. The odor threshold value of **5** is 11 ppb[5]), thus *ca.* 20 times higher than the one of racemic **1** (0.6 ppb). The tricyclic ethers **6** and **8** are very weak odorants of woody-camphoraceous tonality with hardly discernable ambergris notes. In **7**, the weak ambergris-like tone is masked by a dirty-sweaty malodor. The qualitative and quantitative data of the sensory evaluation obtained are not surprising with regard to the structural features necessary for the release of an ambergris fragrance. Only the shape of 5β-ambrox (**5**) fulfills the 'triaxial rule' of odor sensation [3] perfectly well. Hence, the 1,3-synperiplanar/diaxial conformation of the substituents at C(8) and C(10) in the tricyclic ethers **1**, **2**, **4**, and **5** has been recognized as the active element for the particular odor release. The lack of this structural feature in diastereoisomers **6**–**8** prevents the corresponding molecules from a distinct receptor event.

We are indepted to Mr. *W. Thommen* and Mr. *R. Brauchli* for the NMR measurements. We also wish to thank Mrs. *B. Mayor-Frei* for her valuable technical assistance.

Experimental Part

General. If not stated otherwise, org. extracts were washed to neutral reaction with aq. soln. of H_2SO_4 and/or $NaHCO_3$ and NaCl, dried ($MgSO_4$), and evaporated. TLC: silica-gel plates. Medium-pressure chromatography (MPLC): silica gel *60* (particle size 0.040–0.063 mm, *Merck*) or prepacked *Lobar*® columns (*Merck*). Low-pressure chromatography (LPLC): silica gel *60* (particle size < 0.230 mm, *Merck*). Anal. GC: fused silica capillary columns (*Supelcowax*®*10*, 60 m × 0.25 mm; *DB WAX*, 15 m × 0.53 mm; *CP-Sil 5-CB*, 10 m × 0.25 mm). Prep. GC: 5% *SP-1000* (polyethylene glycol) on *Chromosorb G, AW-DMCS*, 80–100 mesh, 2.5 m × 3 mm, 10% *Carbowax 20M* (polyethylene glycol) on *Chromosorb W*, 80–100 mesh, 3 m × 4 mm; 4% *SOMB* (methyl silicone) on *Chromosorb G, AW-DMCS*, 80–100 mesh, 2.5 m × 3 mm. M.p.: not corrected. ^{1}H-NMR (360 MHz) and ^{13}C-NMR (90.5 MHz): *Bruker-WH-360* instrument; in $CDCl_3$ solns. with TMS (= 0.00 ppm) as internal standard; *J* in Hz. MS: *Finnigan-MAT* quadrupole instrument coupled with a GC; electron energy *ca.* 70 eV; fragment ions *m/z* in % of the most abundant peak.

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[5]) The threshold values were determined by the method of *Guadagni* and coworkers [17]. We thank Mr. *A. Furrer, Firmenich SA*, for the measurements.

Crystallographic Data for Compounds **5** *and* **14b**. Cell parameters and reflection intensities were measured at r.t. on a *Philips-PW1100* diffractometer with graphite-monochromated Mo*Kα* radiation. A summary of crystal data, intensity measurements, and structure refinements is given in *Table 2*. The structures were solved by direct methods (MULTAN-80) [18] and refined by least-square analysis with the XRAY-76 [19] program. Crystallographic data have been deposited with the *Cambridge Crystallographic Data Center*, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

1. *Compound* **7**. 1.1. *(±)-13,14,15,16-Tetranor-5β,9β-labdane-8β,12-diol* (= *2-(1,2,3,4,4aβ,5,6,7,8,8a-Decahydro-2β-hydroxy-2,5,5,8aβ-tetramethyl-1α-naphthyl)ethanol*; **12**). A soln. of **11**[6]) (4.3 g, 17.2 mmol) in anh. Et_2O (50 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (400 mg, 10.5 mmol) in a few ml of Et_2O. The mixture was refluxed for 2 h, then cooled and hydrolyzed by addition of H_2O (0.4 ml), 15% aq. NaOH soln. (0.4 ml), and H_2O (1.2 ml). The precipitate was filtered and the filtrate evaporated: 3.5 g (80.7%) of **12**. An anal. sample was recrystallized several times from petroleum ether (80–100°)/EtOH. M.p. 145–146°. ^{1}H-NMR: 0.89 (*s*, 3 H); 1.10 (*s*, 3 H); 1.16 (*s*, 3 H); 1.24 (*s*, 3 H–C(20)); 3.47 (*m*, 1 H–C(12)); 3.82 (*m*, 1 H–C(12)). ^{13}C-NMR: *Table 1*. MS: 254 (0, $M^{+\cdot}$), 239 (2), 236 (2), 221 (10), 195 (7), 177 (7), 151 (41), 137 (17), 123 (31), 109 (100), 95 (77), 81 (68), 69 (93), 55 (51), 43 (52).

1.2. *(±)-5β,8α,9β-Ambrox* (= *1,2,3a,4,5,5aβ,6,7,8,9,9a,9bβ-Dodecahydro-3aα,6,6,9aβ-tetramethylnaphtho[2,1-b]furan*; **7**). Diol **12** (1.0 g, 3.9 mmol) was dissolved in anh. pyridine (5 ml) and treated slowly with ten drops of $POCl_3$. After 1 h (TLC: no **12** left), the mixture was diluted with Et_2O and hydrolyzed cautiously with ice. Usual workup and bulb-to-bulb distillation of the crude product at 150°/0.2 Torr afforded pure **7** (700 mg, 76%). ^{1}H-NMR: 0.89 (*s*, 3 H); 1.14 (*s*, 3 H); 1.155 (*s*, 3 H); 1.18 (*s*, 3 H); 3.81 (*ddd*, J = 8.6, 1 H–C(12)); 3.88 (*ddd*, J = 8.6, 8.6, 3.6, 1 H–C(12)). ^{13}C-NMR: *Table 1*. MS: 236 (1, $M^{+\cdot}$), 221 (67), 203 (3), 177 (5), 137 (39), 121 (13), 109 (21), 97 (100), 81 (36), 69 (35), 55 (31), 43 (37).

2. *Compound* **6**. 2.1. *(±)-5β,8α-Sclareolide* (= *3a,4,5,5aβ,6,7,8,9,9a,9bα-Decahydro-3aα,6,6,9aβ-tetramethylnaphtho[2,1-b]furan-2(1H)-one*; **13**). Lactone **11** (3.2 g, *ca.* 90%, 11.5 mmol) was dissolved in HCOOH (50 ml) and conc. H_2SO_4 (5 ml) and stirred under Ar at 90° for 5 h. The mixture was poured onto ice and the org. material extracted with several portions of Et_2O. The combined extracts were treated in the usual way to give 3.0 g of crude material which consisted of **13** (37%) and **11** (8%) besides several undefined side products (*Supelcowax®10*). One recrystallization from petroleum ether (80–100°) raised the purity of **13** to 92% (980 mg, 31%). An anal. sample was recrystallized several times from the same solvent. M.p. 96–96.5° ([4] (non-revised structure): 99–100°). ^{1}H-NMR: 0.93 (*s*, 3 H); 1.085 (*s*, 3 H); 1.105 (*s*, 3 H); 1.525 (*s*, CH_3(20)); 2.475 (*dd*, J = 18, 7, 1 H–C(11)); 2.62 (*dd*, J = 18, 7, 1 H–C(11)). ^{13}C-NMR: *Table 1*. MS: 250 (2, $M^{+\cdot}$), 235 (33), 207 (12), 190 (8), 175 (9), 167 (22), 136 (71), 121 (77), 109 (79), 95 (62), 81 (100), 69 (75), 55 (73), 43 (90).

2.2. *(±)-13,14,15,16-Tetranor-5β-labdane-8β,12-diol* (= *2-(1,2,3,4,4aβ,5,6,7,8,8a-Decahydro-2β-hydroxy-2,5,5,8aβ-tetramethyl-1β-naphthyl)ethanol*; **14a**). Reduction of **13** (1.0 g, 4 mmol) with $LiAlH_4$ (200 mg, 5.3 mmol) in anh. Et_2O (100 ml) was carried out as described above: 1.0 g (98%) of **14a**. An anal. sample was recrystallized from petroleum ether (80–100°). M.p. 138.5–139°. ^{1}H-NMR[7]): 0.91 (*s*, CH_3(19)); 1.00 (*s*, CH_3(18)); 1.06 (*s*, CH_3(17)); 1.16 (*s*, CH_3(20)); 3.60 (*dd*, J = 7, 2 H–C(12)). ^{13}C-NMR: *Table 1*. MS: 254 (1, $M^{+\cdot}$), 236 (3), 221 (56), 195 (6), 177 (12), 165 (6), 151 (22), 137 (36), 123 (27), 109 (100), 95 (70), 81 (76), 69 (82), 55 (69), 43 (66).

2.3. *(±)-5β,8α-Ambrox* (= *1,2,3a,4,5,5aβ,6,7,8,9,9a,9bα-Dodecahydro-3aα,6,6,9aβ-tetramethylnaphtho[2,1-b]furan*; **6**). Diol **14a** (1.0 g, 3.9 mmol) was converted to **6** as described above. The crude product was bulb-to-bulb distilled at 150°/0.1 Torr to give 0.8 g (87%) of pure **6** as an oil. ^{1}H-NMR: 0.89 (*s*, 3 H); 1.075 (*s*, 3 H); 1.095 (*s*, 3 H); 1.305 (*s*, CH_3(20)); 3.75 (*m*, 2 H–C(12)). ^{13}C-NMR: *Table 1*. MS: 236 (1, $M^{+\cdot}$), 221 (67), 203 (2), 177 (7), 137 (41), 121 (18), 109 (32), 97 (100), 81 (44), 69 (40), 55 (41), 43 (48).

3. *Compound* **5**. 3.1. *(±)-8β-Hydroxy-13,14,15,16-tetranor-5β-labdan-12-yl Acetate* (= *2-(1,2,3,4,4aβ,5,6,7,8,8a-Decahydro-2β-hydroxy-2,5,5,8aβ-tetramethyl-1β-naphthyl)ethyl Acetate*; **14b**). Diol **14a** (20 mg, 0.78 mmol) was acetylated in a mixture of Ac_2O (0.1 ml) and pyridine (1.0 ml) at r.t. overnight. Upon evaporation and recrystallization from pentane, pure **14b** was obtained as prisms. M.p. 78–79°. ^{1}H-NMR: 0.94 (*s*, 3 H); 1.03 (*s*, 3 H); 1.07 (*s*, 3 H); 1.20 (*s*, CH_3(20)); 2.02 (*s*, CH_3CO); 4.06 (*m*, 2 H–C(12)). ^{13}C-NMR: *Table 1*. MS: 296 (0, $M^{+\cdot}$), 281 (< 1), 236 (1), 221 (5), 203 (3), 195 (7), 177 (5), 165 (8), 151 (56), 131 (21), 123 (22), 109 (78), 95 (100), 81 (60), 69 (80), 55 (49), 43 (93). Crystal data: see *Table 2*.

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[6]) Lactone **11** was prepared from dihydro-α-ionone **9** according to [20]: m.p. 103–104° ([4]: 103–104°).

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

Table 2. *Crystal Data, Intensity Measurement, and Structure Refinement for 5β-Ambrox* (**5**) *and Monoacetate* **14b**

	5	**14b**
Formula	$C_{16}H_{28}O$	$C_{18}H_{32}O_3$
Molecular weight	236.4	296.5
Crystal system	orthorhombic	triclinic
Space group	$P2_12_12_1$	$P\bar{1}$
Crystal size [mm]	0.22 × 0.25 × 0.28	0.20 × 0.25 × 0.38
a [Å]	8.185(2)	7.5499(15)
b [Å]	10.436(3)	7.5831(9)
c [Å]	16.875(5)	16.105(12)
α [°]	90.0	78.83(5)
β [°]	90.0	79.74(6)
γ [°]	90.0	75.54(2)
V [Å^3]	1441.4(7)	867.7(7)
Z	4	2
F_{000}	528	328
D_c [gr·cm^{-3}]	1.09	1.14
μ [mm^{-1}]	0.061	0.070
$\sin(\theta/\lambda)_{max}$ [Å^{-1}]	0.60	0.51
No. measured reflections	1499	1864
No. observed reflections	943	1472
Criterion for observed	$\|F_o\| > 4\sigma(F_o)$	$\|F_o\| > 4\sigma(F_o)$
Refinement (on F)	full-matrix	full-matrix
No. of parameters	154	190
Weighting scheme	$\omega = 1$	$\omega = 1$
Max. and average Δ/σ	0.0002, 0.0001	0.014, 0.004
Max. and min. $\Delta\varrho$ [e·Å^{-3}]	0.35, −0.35	0.25, −0.41
R ($= \omega R$) [%]	7.2	6.5

3.2. *(±)-13,14,15,16-Tetranor-5β-labd-7-en-12-yl and -8(20)-en-12-yl Acetate* (= *2-(1,4,4aβ,5,6,7,8,8a-Octahydro-2,5,5,8aβ-tetramethyl-1β-naphthyl)ethyl Acetate* and *2-(1,2,3,4,4aβ,5,6,7,8,8a-Decahydro-5,5,8aβ-trimethyl-2-methylidene-1β-naphthyl)ethyl Acetate*, resp.; **17** and **18**, resp.). The procedure was adapted from [8]: To a soln. of **14a** (4.97 g, 16.8 mmol) in benzene (17 ml) was added TsNCO (2.8 ml, 18.4 mmol). After stirring at r.t. for 2 h, the solvent was evaporated. The intermediate urethane was heated at 160° under stirring, until CO_2 evolution had ceased (15 min). The crude olefin mixture was purified by MPLC (*Lobar*® column, size *C*; hexane/AcOEt 8:2): thick oil (4.19 g, 89%) which contained 87% of **17** and 12% of **18**. On *SP-1000* and *SOMB GC* columns, **17** preceded **18**. Anal. samples were collected by prep. GC. *Data of* **17**. ^{1}H-NMR: 0.81 (*s*, 3 H); 0.84 (*s*, 3 H); 0.87 (*s*, 3 H); 1.69 (br. *s*, CH_3(20)); 2.06 (*s*, CH_3CO); 4.02 (*m*, 1 H–C(12)); 4.26 (*m*, 1 H–C(12)); 5.35 (*d*, J = 4.3, 1 H–C(7)). MS: 278 (< 1, M^+), 218 (3), 203 (1), 190 (1), 124 (7), 109 (61), 94 (100), 79 (44), 43 (17).

Data of **18**. ^{1}H-NMR: 0.89 (*s*, 3 H); 1.03 (*s*, 3 H); 1.06 (*s*, 3 H); 2.03 (*s*, CH_3CO); 3.86 (*m*, 1 H–C(12)); 4.02 (*m*, 1 H–C(12)); 4.52 (*s*, 1 H–C(20)); 4.74 (*s*, 1 H–C(20)). MS: 278 (< 1, M^+), 218 (8), 203 (11), 190 (2), 162 (4), 137 (66), 123 (33), 109 (37), 95 (70), 81 (100), 69 (61), 43 (60).

3.3. *(±)-7β,8- and 8,20-Epoxy-13,14,15,16-tetranor-5β-labdan-12-yl Acetate* (= *2-(2β,3β-Epoxy-1,2,3,4,4aβ,5,6,7,8,8a-decahydro-5,5,8aβ-trimethyl-1β-naphthyl)ethyl Acetate* and *2-(3,4,4aβ,5,6,7,8,8a-Octahydro-5,5,8aβ-trimethylspiro[naphthalene-2(1H),2′-oxiran]-1β-yl)ethyl Acetate*, resp.; **19** and **20** resp.). To a slightly cooled soln. of **17**/**18** (4.19 g, 15.1 mmol) in anh. CH_2Cl_2 (165 ml) was added 3-chloroperbenzoic acid (*Aldrich*; *ca.* 85%, 3.41 g, 16.8 mmol) in small portions. After stirring at r.t. for 5 h (TLC: no **17**/**18** left), the soln. was washed with 10% aq. $NaHSO_3$ and $NaHCO_3$ solns., dried ($MgSO_4$), and evaporated: 4.62 g (100%) of crude product as a thick oil. GC/MS (*Supelcowax*®*10*): 3 isomers, *ca.* 87:6:6. The major isomer was isolated in pure form by prep. GC (*SP-1000*). The two minor isomers were coeluted under these conditions.

Major Isomer **19**. ^{1}H-NMR: 0.87 (*s*, 3 H); 0.89 (*s*, 3 H); 0.93 (*s*, 3 H); 1.31 (*s*, CH_3(20)); 2.06 (*s*, CH_3CO); 2.94 (*d*, J = 7.2, H–C(7)); 4.13 (*m*, 1 H–C(12)); 4.26 (*m*, 1 H–C(12)). MS: 294 (< 1, M^+), 279 (3), 234 (3), 219 (10), 161 (9), 149 (9), 135 (12), 124 (24), 109 (64), 95 (52) 81 (47), 69 (56), 55 (42), 43 (100).

Minor Isomers **20**. ^{1}H-NMR: 2.53, 2.58 (2*m*, H–C(20)); 4.04 (*m*, H–C(12)). MS (isomer 1): 294 (0, $M^{+\cdot}$), 279 (2), 234 (4), 219 (11), 180 (5), 156 (11), 136 (22), 121 (31), 109 (75), 95 (65), 81 (72), 69 (96), 55 (77), 43 (100). MS (isomer 2): 294 (0, $M^{+\cdot}$), 279 (2), 234 (3), 219 (4), 180 (5), 156 (12), 136 (22), 123 (29), 109 (74), 95 (72), 81 (75), 69 (89), 55 (68), 43 (100).

3.4. *(±)-13,14,15,16-Tetranor-5β-labdane-8α,12-diol* (= *2-(1,2,3,4,4aβ,5,6,7,8,8a-Decahydro-2α-hydroxy-2,5,5,8aβ-tetramethyl-1β-naphthyl)ethanol*; **15**). A suspension of anh. $AlCl_3$ (733 mg, 5.5 mmol) and $LiAlH_4$ (690 mg, 18.1 mmol) in anh. Et_2O (70 ml) was prepared at – 10° under Ar. A soln. of 4.60 g (*ca.* 15 mmol) of **19**/**20** in 60 ml of anh. Et_2O was added dropwise. The mixture was stirred at – 5 to 0° for 1 h, then at r.t. for 1 h. The reaction was quenched with MeOH (3.6 ml) and the mixture poured into cold sat. aq. NH_4Cl soln. The org. material was extracted into Et_2O and treated in the usual way. Separation of the crude product (4.20 g) into the pure components was achieved by MPLC (*Lobar*® column, size *C*; hexane/AcOEt 8:2). *(±)-7β,8-Epoxy-13,14,15,16-tetranor-5β-labdan-12-ol* (= *2-(2β,3β-epoxy-1,2,3,4,4aβ,5,6,7,8,8a-decahydro-5,5,8aβ-trimethyl-1β-naphthyl)ethanol*; **21**; 3.26 g, 86%) was eluted first. An anal. sample was recrystallized from hexane. M.p. 66–66.5°. ^{1}H-NMR: 0.88 (*s*, 3 H); 0.89 (*s*, 3 H); 0.94 (*s*, 3 H); 1.31 (*s*, CH_3(20)); 2.94 (*d*, *J* = 6.5, 1 H–C(7)); 3.70 (*m*, 1 H–C(12)); 3.83 (*m*, 1 H–C(12)). MS: 252 (1, $M^{+\cdot}$), 237 (19), 221 (10), 207 (2), 193 (2), 135 (15), 123 (40), 109 (100), 97 (77), 81 (70), 69 (78), 55 (59), 43 (70).

The next fractions contained 200 mg (5%) of **14a**. Diol **15** was eluted last (240 mg, 6%). It was recrystallized from AcOEt/hexane. M.p. 136–136.5°. ^{1}H-NMR[7]: 0.885 (*s*, CH_3(17)); 0.95 (*s*, CH_3(19)); 1.06 (*m*, H–C(5)); 1.13 (*s*, CH_3(18)); 1.27 (*s*, CH_3(20)); 3.47 (*m*, 1 H–C(12)); 3.79 (*m*, 1 H–C(12)). ^{13}C-NMR: *Table 1*. MS: 254 (0, $M^{+\cdot}$), 239 (1), 221 (3), 195 (7), 177 (11), 165 (7), 151 (15), 139 (11), 123 (22), 109 (70), 95 (77), 83 (74), 69 (10), 55 (52), 43 (50).

3.5. *(±)-5β-Ambrox* (= *1,2,3a,4,5,5aβ,6,7,8,9,9a,9bα-Dodecahydro-3aβ,6,6,9aβ-tetramethylnaphtho[2,1-b]furan*; **5**). A soln. of **15** (125 mg, 0.49 mmol) in anh. pyridine (1.5 ml) was cooled to 0°, and TsCl (210 mg, 1.1 mmol) was added. After stirring at 0° for 30 min, the mixture was abandoned in the refrigerator overnight. (TLC: no **15** left). The mixture was diluted with ice/H_2O, and extracted with several portions of Et_2O. The combined extracts were treated in the usual way: 120 mg of crude **5**. It was purified by MPLC (*Lobar*® column, size *B*; hexane/Et_2O 4:1): 100 mg (86%) of pure **5** which was bulb-to-bulb distilled at 100°/0.05 Torr and crystallized from hexane. M.p. 52–53°. ^{1}H-NMR[7]): 0.92 (*s*, CH_3(17)); 0.96 (*s*, CH_3(19)); 1.06 (*s*, CH_3(18)); 1.12 (*m*, H–C(5)); 1.14 (*s*, CH_3(20)); 1.94 (*dd*, *J* = 6.5, 13.0, H–C(9)); 3.80 (*ddd*, *J* = 7.9, 1 H–C(12)); 3.86 (*ddd*, *J* = 3.5, 7.9, 7.9, 1 H–C(12)). ^{13}C-NMR: *Table 1*. MS: 236 (6, $M^{+\cdot}$), 221 (57), 203 (3), 177 (5), 151 (7), 137 (46), 124 (22), 109 (27), 97 (100), 81 (41), 69 (33), 55 (32), 43 (40). Crystal data: see *Table 2*.

4. *Acid-Catalyzed Isomerization of* **5**. A soln. of 1 mg of **5** in 50 µl of nitromethane was heated in the presence of one crystal of TsOH at 60° for 1 h. A few mg of solid Na_2CO_3 were added, and the supernatant was analyzed by capillary GC (*Supelcowax®10*). Compound **5** had disappeared and besides a new unknown (67%), 27% of a product was observed, the retention time of which was identical with the one of 5β,8α-ambrox (**6**). Isomer **6** was eluted immediately after **5**.

5. *Correlation of Epoxide* **21** *with* **14b**. The procedure is adapted from [21]. To a soln. of LDA (5 mmol) in anh. Et_2O (63 ml) was added dropwise and at 0° a soln. of **21** (504 mg, 2 mmol) in 4 ml of Et_2O. The mixture was allowed to warm to r.t. and stirred overnight. It was poured onto ice and extracted with Et_2O. The crude product was acetylated with Ac_2O/pyridine 1:2 (3 ml) overnight. Excess reagent was removed by repeated evaporation in the presence of toluene. Thus, 560 mg of material were obtained which still contained much unreacted epoxide in the form of **19** as shown by TLC. The mixture was separated by MPLC (*Lobar*® column, size *B*; hexane/EtOAc 3:1): 420 mg (71%) of **19** and 120 mg (20%) of the more polar *(±)-8β-hydroxy-13,14,15,16-tetranor-5β-labd-6-en-12-yl acetate* (= *2-(1,2,4aβ,5,6,7,8,8a-octahydro-2β-hydroxy-2,5,5,8aβ-tetramethyl-1β-naphthyl)ethyl acetate*; **22**). After two recrystallizations from hexane, the m.p. was 64–65°. ^{1}H-NMR: 0.82 (*s*, 3 H); 0.94 (*s*, 3 H); 0.96 (*s*, 3 H); 1.22 (*s*, CH_3(20)); 2.06 (*s*, CH_3O); 4.13 (*m*, 2 H–C(12)); 5.69 (*d*, *J* = 9.7, H–C(7)); 5.80 (*dd*, *J* = 5.8, 9.7, H–C(6)). MS: 294 (0, $M^{+\cdot}$), 279 (2), 234 (2), 219 (30), 133 (55), 123 (30), 107 (35), 95 (41), 84 (72), 69 (69), 55 (36), 43 (100).

A soln. of **22** (120 mg, 0.47 mmol) in EtOH (2 ml) was hydrogenated in the presence of PtO_2 (10 mg) until H_2 uptake had ceased. The catalyst was filtered off and the filtrate concentrated to give **14b**. M.p., ^{1}H-NMR and chromatographic data, identical with those of starting **14b**.

6. *Compound* **8**. 6.1. *Methyl 1,2,3,4,4aβ,5,6,7,8,8a-Decahydro-5,5,8aβ-trimethyl-2-oxo-1β-naphthalenecarboxylate* (**24**). To an efficiently stirred soln. of **23** (4.7 g, 18.6 mmol; prepared from **9** according to [22]) in nitromethane (320 ml) was added dropwise stannic chloride (4 ml, 34.2 mmol) at r.t. under Ar. After 45 min (TLC: no **23** left after 15 min), the mixture was worked up in the usual way. The crude product was bulb-to-bulb distilled at 190°/0.1

Torr: 3.5 g of material containing 39% of **24** and of 26% of the corresponding known 4aα,8aβ-isomer [23] (*DB WAX*, *cis*-fused **24** preceded *trans*-fused isomer). Pure **24** was isolated by repetitive LPLC on silica gel (cyclohexane/Et_2O 95:5). ^{1}H-NMR: 1.04 (*s*, 3 H); 1.16 (*s*, 3 H); 1.18 (*s*, 3 H); 3.70 (*s*, CH_3O); 3.87 (*s*, H–C(1)). MS: 252 (2, M^+), 234 (9), 219 (12), 205 (33), 136 (100), 69 (98), 55 (83), 41 (73).

6.2. *3,4,4aβ,5,6,7,8,8a-Octahydro-5,5,8aβ-trimethylnaphthalen-2(1H)-one* (**25**). An anal. sample of **24** was treated with NaOH in aq. MeOH at reflux temperature for 3 h. The soln. was acidified and worked up with Et_2O. Bulb-to-bulb distillation gave **25**. GC and NMR: identical with the ones of the authentic sample [11].

6.3. *Methyl 1,2,3,4,4aβ,5,6,7,8,8a-Decahydro-5,5,8aβ-trimethyl-2-oxo-1-(prop-2′-enyl)naphthalene-1-carboxylate* (**26**). Procedure according to [10]: A soln. of **24** (1.6 g, 6.3 mmol) in 15 ml of DMF was treated with NaH (6.3 mmol) and stirred at r.t. overnight. The mixture was cooled to 0° and allyl bromide (0.7 ml, 8.1 mmol) added dropwise. Stirring was continued at r.t. overnight. The mixture was poured onto ice and extracted with Et_2O. Evaporation left 1.1 g of enol ether of **24** which was heated at reflux temperature in 20 ml of xylene during 30 h. The soln. was evaporated and the crude **26** (18:57 epimeric mixture; *CP-Sil 5-CB*) was separated into the two components by LPLC (cyclohexane/EtOH 95:5).

Minor Epimer: less polar, 0.2 g. ^{1}H-NMR: 0.89 (*s*, 3 H); 1.18 (*s*, 3 H); 1.46 (*s*, 3 H); 3.61 (*s*, CH_3O); 4.93 (*d*, J = 10.8, 1 H); 5.00 (*d*, J = 16.2, 1 H); 5.75 (*m*, 1H). ^{13}C-NMR: 208.0 (C(2)); 171.3 (C=O); 136.4 (C(2′)); 116.5 (C(3′)); 69.1 (C(1)); 51.3 (CH_3O); 47.9 (C(8a)); 39.5 (C(8)); 34.5 (C(5)); 33.4 (CH_3–C(5)); 33.3 (C(3)); 32.9 (C(6)); 31.2 (CH_3–C(5)); 27.1 (C(1)); 26.3 (C(4)); 24.2 (CH_3–C(8a)); 18.6 (C(7)). MS: 292 (2, M^+), 259 (11), 233 (5), 169 (38), 141 (48), 137 (81), 123 (100), 114 (36), 109 (80), 95 (60), 81 (90), 67 (57), 55 (71), 41 (100).

Major Epimer: more polar 0.6 g. ^{1}H-NMR: 0.95 (*s*, 3 H); 1.11 (*s*, 3 H); 1.12 (*s*, 3 H); 3.71 (*s*, CH_3O); 4.97 (*d*, J = 10.8, 1 H); 4.05 (*d*, J = 16.2, 1 H); 5.61 (*m*, 1 H). ^{13}C-NMR: 207.7 (C(2)); 170.8 (C=O); 134.1 (C(2′)); 117.4 (C(3′)); 51.4 (CH_3O); 48.0 (C(4a)); 44.5 (C(1)); 38.7 (C(8)); 35.5 (C(6)); 34.5 (C(8a)); 33.4 (C(3)); 33.3 (C(5)); 31.3 (CH_3–C(5)); 28.7 (C(1′)); 25.0 (CH_3–C(8a)); 23.5 (C(4)); 18.6 (C(7)). MS: 292 (2, M^+), 260 (3), 233 (3), 169 (43), 136 (80), 123 (100), 114 (32), 109 (100), 95 (95), 81 (91), 69 (74), 55 (80), 41 (98).

6.4. *3,4,4a,5,6,7,8,8a-Octahydro-5,5,8aβ-trimethyl-1-(prop-2′-enyl)naphthalen-2(1H)-one* (**27**). A stirred mixture of **26** (major epimer; 500 mg, 1.71 mmol), $CaCl_2 \cdot 2H_2O$ (1 g), and DMSO (10 ml) was heated at reflux for 2 h. The mixture was then poured into H_2O and extracted with Et_2O. The crude product was bulb-to-bulb distilled at 140°/0.09 Torr: 400 mg (100%) of **27** (major epimer). ^{1}H-NMR: 0.82 (*s*, 3 H); 1.02 (*s*, 3 H); 1.21 (*s*, 3 H); 4.92 (*d*, J = 10.8, 1 H); 5.00 (*d*, J = 16.2, 1 H); 5.83 (*m*, 1 H). ^{13}C-NMR: 213.8 (C(2)); 138.7 (C(2′)); 115.0 (C(1)); 50.0 (C(4a)); 43.0 (C(8a)); 42.3 (C(6)); 39.9 (C(3)); 37.5 (C(8)); 34.8 (C(5)); 34.4 (C(1)); 33.9 (CH_3–C(5)); 26.3 (CH_3–C(8a)); 26.3 (CH_3–C(5)); 22.9 (C(4)); 18.5 (C(7)). MS: 234 (6, M^+), 219 (3), 201 (2), 109 (22), 96 (100), 69 (24), 55 (23), 41 (26).

6.5. When the epimeric mixture **26** (ratio 18:57; 3.7 g, 12.6 mmol) was demethoxycarbonylated under the same conditions, a 18:65 C(1)-epimeric mixture **27** (*CP-Sil 5-CB*) was obtained. The minor diastereoisomer was not isolated in pure form.

6.6. *(±)-5β,9β-Ambrox (= 1,2,3a,4,5,5aβ,6,7,8,9,9a,9bβ-Dodecahydro-3aβ,6,6,9aβ-tetramethylnaphtho[2,1-b]furan*; **8**). The mixture **27** (18:65; 1.0 g, 4.2 mmol) in Et_2O (10 ml) was added to the *Grignard* reagent prepared from Mg (1.0 g) and MeI (2 ml) in Et_2O (20 ml) and heated at reflux for 30 min. It was decomposed with aq. NH_4Cl soln. and extracted with Et_2O. The residue (1.1 g; 2 alcohols in the ratio of 18:65; *CP-Sil 5-CB*) was dissolved in AcOEt (20 ml) and ozonized at −70°. Upon addition of $NaBH_4$ (1.0 g), the mixture was allowed to warm to r.t. overnight. It was hydrolyzed (H_2O) and worked up with Et_2O, giving **28**/**14a** (1.1 g) in a ratio of *ca.* 18:65. The major isomer was identical with **14a** obtained above (by TLC and GC). The diol mixture was converted to **8**/**6** (18:65) by the method described above ($POCl_3$/pyridine). Separation was achieved by repetitive MPLC (*Lobar*® columns; cyclohexane/Et_2O 98:2). The major isomer was identical with **6** (*Supelcowax*® *10*) and eluted well after **8**. Compound **8** remained a thick oil. ^{1}H-NMR: 0.915 (*s*, 3 H); 1.055 (*s*, 3 H); 1.08 (*s*, 3 H); 1.10 (*s*, 3 H); 3.71 (*m*, 2 H–C(12)). ^{13}C-NMR: *Table 1*. MS: 236 (0, M^+), 221 (100), 203 (3), 137 (47), 97 (75), 81 (33), 69 (32), 55 (33), 41 (41).

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