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A SHORT SYNTHESIS OF AMBROX® FROM SCLAREOL†

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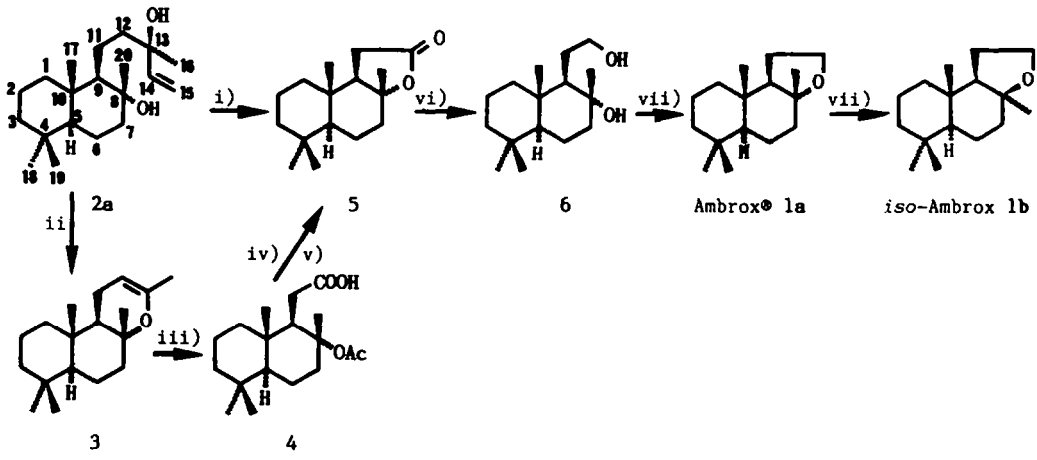
Abstract - A two-step transformation of sclareol into Ambrox® (overall yield 11-12%) *via* β-cleavage of an alkoxy radical intermediate is described.

Introduction - Ambrox® **(1a)**[1], one of the most important ambergris fragrance chemicals [1], was discovered by Hinder and Stoll in 1950 [2a, b]. It is still manufactured by a tedious degradation process (producing Cr^{III} or Mn^{II} waste, maximum overall yield 52%) of natural sclareol **(2)**,[2,3]

Scheme 1



Reagents: i) CrO_3/AcOH; ii) $KMnO_4$; iii) O_3/Δ; iv) KOH. then HCl;
v) 150°/vacuum; vi) $LiAlH_4$/ether; vii) β-naphthtalenesulfonic acid

† Dedicated to Professor George Büchi on the occasion of his 65th birthday.

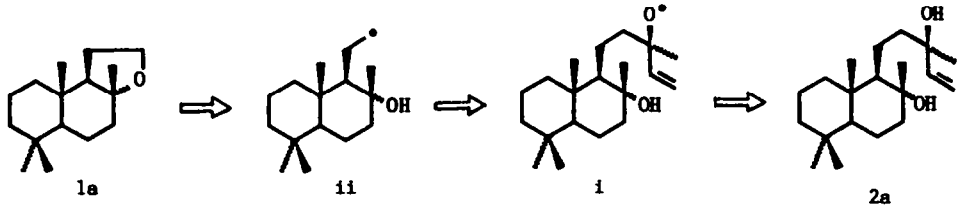
1) Trade name of Firmenich SA for an ambergris fragrance chemical, whose *Chem. Abstr.* name is: naphtho[2,1-*b*]furan, dodecahydro-3a,6,6,9a-tetramethyl-, [3a*R*-(3aα,5aβ,9aα,9bβ)].

2) *Chem. Abstr.* names: 1-naphthalenepropanol, α-ethenyldecahydro-2-hydroxy-α,2,5,5,8a-pentamethyl-, [1*R*-(1α(*R**),2β,4aβ,8aα)], and (13*R*)-labd-14-ene-8,13-diol.

3) The relative and absolute configuration of sclareol **(2a)** (and 13-*epi*-sclareol) is drawn as given in [3a, b], and has been confirmed by X-ray crystallography [3c].

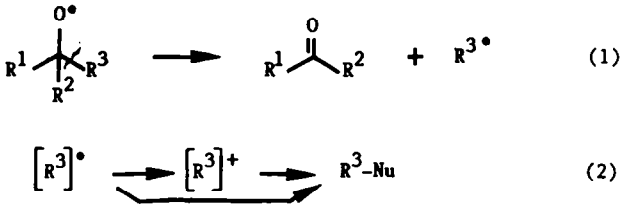
the principal source of which is clary sage (*Salvia sclarea* L.). Accordingly, sclareol (**2a**) is degraded to lactone 5 either directly using chromium trioxide [4], or indirectly using a sequence of reactions comprising permanganate to give sclareol oxide (**3**), ozone to yield the acetoxy acid 4, and acid, which cyclizes 4 to lactone 5 [5]. Lactone 5 is finally transformed in two steps ($LiAlH_4$ reduction and acid-catalyzed cyclization [2]) *via* diol 6 into Ambrox (**1a**). Although these routes produce the intermediates 5 and 6 with the correct stereochemistry, the final acid-catalyzed cyclization of 6 to 1a needs special care since Ambrox (**1a**) isomerizes readily under acid conditions to the more stable, but olfactively much weaker [6] *iso*-Ambrox (**1b**) together with other compounds [7].

Scheme 2. Retrosynthetic analysis



This publication describes a fragmentative degradation process of sclareol (**2a**), presumably *via* its oxygen-centred radical i, giving in two steps stereochemically pure Ambrox (**1a**) (*cf.* scheme 2: retrosynthetic analysis). There is ample literature on the fragmentation of tertiary alkoxy radicals (β-cleavage) into ketones and alkyl radicals [8] [9]. With non-identical alkyl groups being attached to the oxygen-carrying carbon atom ($R^1 \neq R^2 \neq R^3$), the selectivity of the β-cleavage is such as to favour the formation of the most stable alkyl radical [9g, h, i] (scheme 3, eqn. (1)). This alkyl radical needs to be oxidized further under the reaction conditions to give ultimately an alkyl halide , an alkyl ether, or an alcohol etc., depending on the nucleophile present (scheme 3, eqn. (2)); an olefin is sometimes also obtained.

Scheme 3



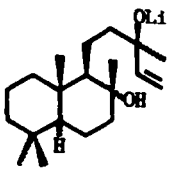
The oxidation of a carbon-centred radical is best carried out by Cu^{II} although other metal oxidants may be used instead [10].

Results and discussion

1. *Attempted direct oxidation of sclareol* (**2a**)

For simplicity, a series of direct oxidations of sclareol (**2a**) likely to generate the oxygen-centred radical i were tried first. Ce^{IV} [11], $Cu^{II}/S_2O_8^{2-}$ [12], $Pb(OAc)_4$ [13], and air (in this case on lithium alcoholate 7[4]) gave no useful results; starting material and/or complicated mixtures were isolated only.

[4] Selectively formed by treatment of 2a with BuLi [7].



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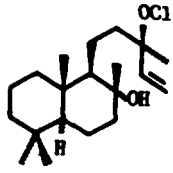

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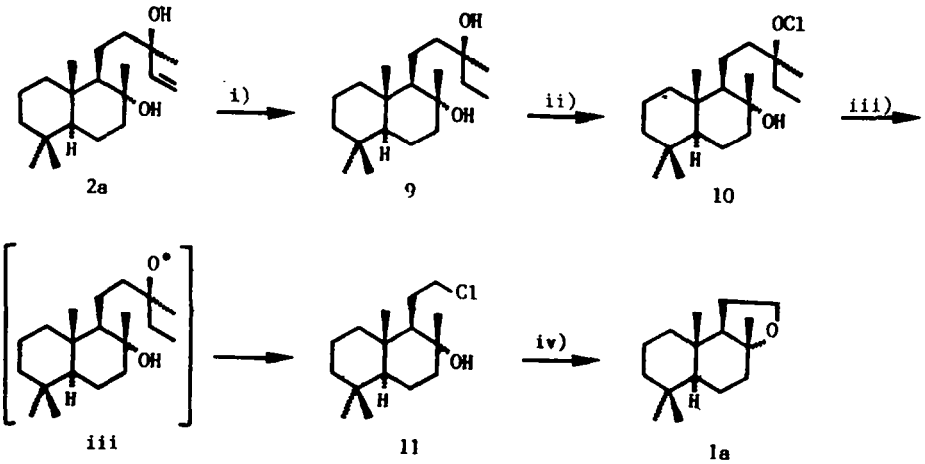
2. *Ambrox* (**1a**) *from dihydrosclareol* (9) via *decomposition of its hypochlorite* 10.
A second approach to radical i was offered by the well documented decomposition of tertiary hypochlorites [9g, h]. However, the necessary hypochlorite 8 proved to be inaccessible: chlorinating agents, such as sodium hypochlorite and *tert*-butyl hypochlorite, preferentially attacked the vinyl double bond. On the other hand, chlorination of the saturated alcohol 9 [4] to give the hypothetical intermediate 10, followed by thermal decomposition and base treatment (*via* chloride 11?) led to ≈0.5% of Ambrox (**1a**) together with a multitude of unknown decomposition products (scheme 4). Alkyl nitrite homolysis (AlkO–N=O/I_2/hν, AlkO–N=O/heat [14]) did not give Ambrox (**1a**) either.

Scheme 4

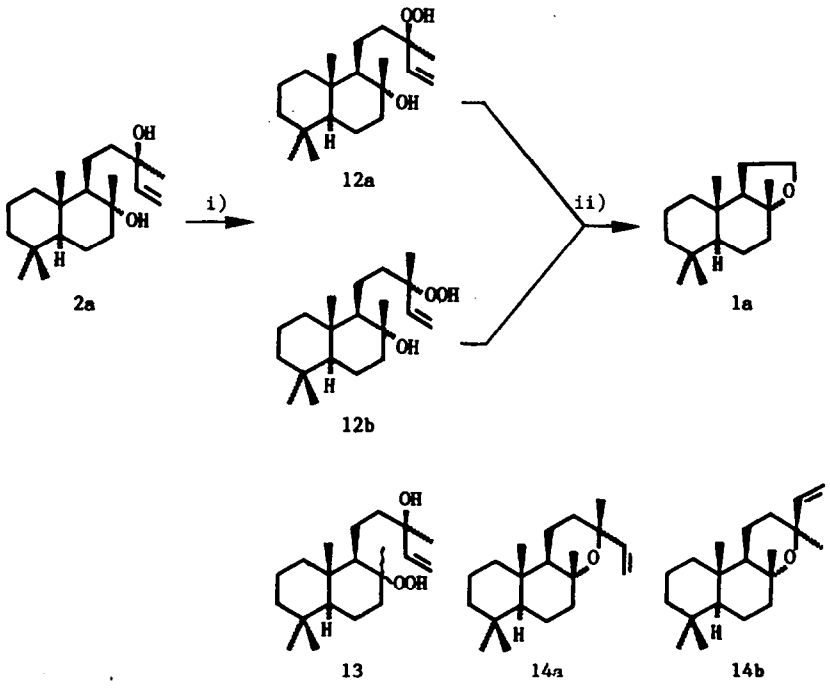


Reagents: i) 5% Pd-C/EtOH; ii) aqueous NaOCl/CCl_4; iii) 30–35°/3h;
iv) NaH/THF, 3h reflux.

3. *Synthesis and decomposition of hydroperoxide* **12a/b**: *a viable route to Ambrox* (**1a**) (Scheme 5).
A major difficulty in the oxidation and chlorination reactions discussed so far seems to be the lack of selectivity for the allylic as opposed to the non-allylic tertiary alcohol. Similarly, acetylation of sclareol gave a 1:1 mixture of the two positional monoacetates [7]. On the other hand the allylic alcohol in sclareol should undergo nucleophilic displacement with hydrogen peroxide much faster than the corresponding non-allylic alcohol and therefore selectively give the hydroperoxides **12a/b** rather than peroxide 13. Hydroperoxides readily give oxygen-centred radicals when either treated with transition metals such as Fe^{II}, Ti^{III}, and V^{III} [9i, k] or pyrolyzed.

Reaction of sclareol (**2a/b**, 9:1) with 70% aqueous H_2O_2 in the presence of a catalytic amount of *p*-toluenesulphonic acid at room temperature gave in 38% isolated yield the two epimeric hydroperoxides **12a** and **12b** (2:1) together with a little of the undesired hydroperoxide 13 and the manoyl oxides **14a** and **14b** (7:3) [15]. Chromatography and crystallization allowed the isolation of 95% pure **12a** (m.p. 114°) and 90% pure 13. The new peroxides were characterized by a) iodometric

Scheme 5



Reagents: i) 70% aqueous H_2O_2/*p*-TsOH/CH_2Cl_2;
ii) $Cu(OAc)_2.2H_2O/FeSO_4.7\ H_2O/CH_3OH$, 2h/50°

titration and b) ^{13}C-NMR (Table) of the mixtures obtained. The hydroperoxy function as opposed to the hydroxy function exhibits a typical and diagnostically valuable shift on the neighbouring α and β-carbon atoms allowing localization of the position of the hydroperoxide function exactly by using the known reference pair *tert*-butyl hydroperoxide/*tert*-butanol. The shift differences Δδ observed between the C-13 epimers **2a/2b** for the atoms C-9, C-13, C-14, C-15, and C-16 parallel (or match) the corresponding Δδ-values of the two hydroperoxides **12a** and **12b** which are also epimeric at C-13. For all the other carbon atoms of the C-13 epimeric pairs **12a/b** and **2a/b** no shift difference could be detected. This suggests that the major hydroperoxide **12a** has sclareol configuration and the minor hydroperoxide **12b** 13-*epi*-sclareol configuration. Chemical transformation of **12a** back into **2a** (reduction by triphenylphosphine) corroborated this assignment. Structure of by-product **13** (without stereochemical assignment) was evident from ^{13}C and ^{1}H-NMR spectra and the two manoyl oxides (**14a/b**) were identified by comparison of their ^{13}C-NMR values with the reported values [15].

When the mixture of the two hydroperoxides **12a/b** (2:1) reacted with the redox couple Fe^{II}/Cu^{II} [17] Ambrox (**1a**) (≈30% isolated yield) was directly formed (scheme 5). Thermal decomposition (250°, contact time ≈10s) led only to traces of Ambrox (**1a**) and a multitude of unknown products.

Mechanistically, the catalytic decomposition of **12a/b** might be rationalized as outlined in scheme 6 in analogy to known, related reactions [7a] [8a] [9a, i] [10] [17].

In step (1) Fe^{II} cleaves the hydroperoxide to give the radical intermediate i together with Fe^{III}. In step (2) the free radical i fragments into the radical intermediate ii

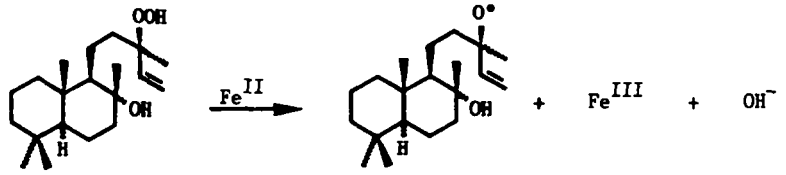
Table. ^{13}*C-NMR shift values (ppm from internal* Me_4Si*) of* **2a**, **2b**, **12a**, **12b**, **13**, **14a**, **14b** *(≈0.2M in* $CDCl_3$*)*[a) b)]

Carbon Compound	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
2a	39.7	18.5	42.0	33.2	56.1	20.5	44.1	74.7	61.7	39.3	18.9	45.1	73.5	146.6	110.8	26.5	15.4	33.4	21.5	24.2
2b									61.9				73.9	144.9	111.8	29.5				
9	39.6	18.5	42.0	33.2	56.1	20.5	44.0	74.6	62.1	39.3	18.8	44.1	73.2	36.1	8.3	25.2	15.4	33.4	21.5	24.2
12a	39.6	18.4	42.0	33.2	56.0	20.5	44.0	75.3	62.6	38.9	17.5	39.2	84.0	142.8	113.8	21.2	15.5	33.3	21.4	24.2
12b									62.5				84.5	140.2	114.8	23.2				
13	40.1	18.5	42.0	33.1	55.6	20.2	36.8	86.4	55.4	39.4	18.1	43.7	74.1	145.9	111.2	26.3	15.6	33.4	21.5	19.7
14a	39.1	18.6	42.2	33.3	56.5	20.0	43.3	75.0	55.8	37.0	15.4	35.8	73.2	148.0	110.2	28.6	15.5	33.4	21.4	25.6
14b	39.5	18.7	42.2	33.4	56.5	20.0	43.2	76.0	58.6	39.5	16.2	34.9	73.2	147.8	109.5	32.8	16.0	33.3	21.3	23.9

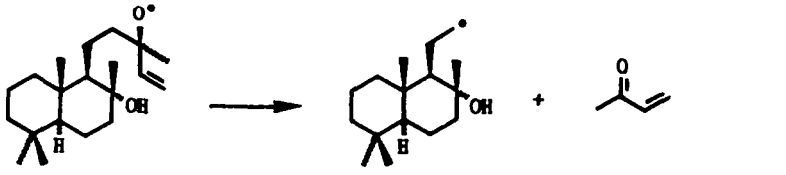
a) For ^{13}C-NMR-shift reference values of **2a** and **12a** and **12b**, see [15].

b) For ^{13}C-NMR-shift differences between alcohols and hydroperoxides, see *e.g.*: *tert*-butanol (CH_3 31.3, C-OH 69.0) and *tert*-butyl hydroperoxide (CH_3 25.9, C-OOH 81.0).

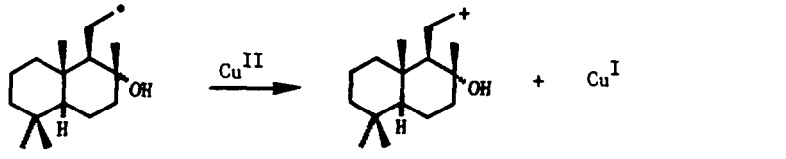
Scheme 6



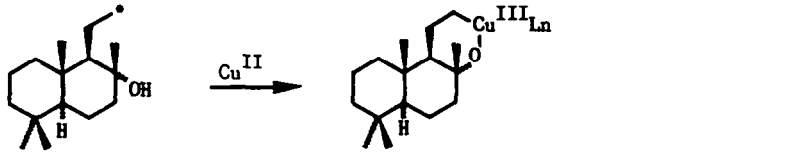
12a i (1)



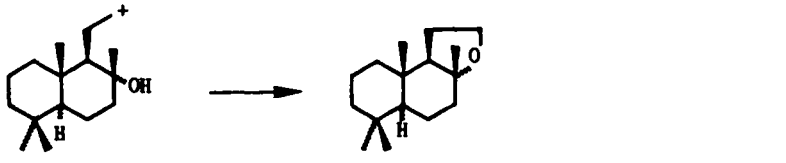
i ii (2)



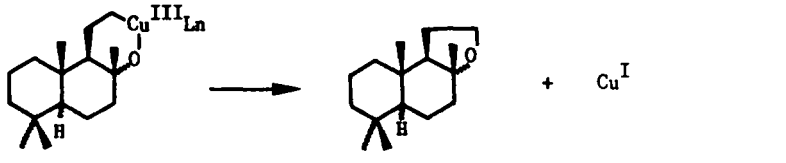
ii iv (3a)



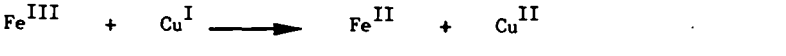
ii v (3b)



iv la (4a)



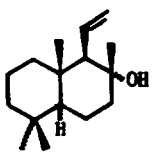
v la (4b)



(5)

and methyl vinyl ketone.

The carbon-centred primary radical ii is oxidized by Cu^{II} to the carbonium ion iv (an electron transfer process, step (3a)) which then cyclizes to Ambrox (1a) (step (4a)). Alternatively, the ring-closing step of radical ii might involve the cyclic, transient organocopper(III) species v which upon reductive elimination of Cu^{I} would give Ambrox (1a) (a ligand transfer process, steps (3b) and (4b)). Finally, (step (5)), Fe^{II} and Cu^{II} are regenerated making the whole sequence catalytic in iron and copper. It is noteworthy that neither olefin 15 nor chloride 11 could be isolated, in contrast to similar cases [9a] [10].



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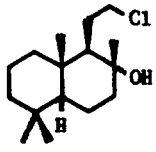

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Acknowledgements.
The authors are indebted to Dr. B. Maurer for helpful discussions.

Experimental Part

Generalities
NMR spectra are measured in $CDCl_3$ on a *Bruker* WH 360 instrument. Chemical shifts are expressed in ppm (δ scale) downfield from tetramethylsilane as internal standard; abbreviations: *s* singlet, *d* doublet, *t* triplet, *q* quadruplet, *J* spin-spin coupling constant (Hz); the assignments of methyl groups in ^{1}H-NMR spectra were based on ^{13}C-NMR/^{1}H-NMR correlation. Gas chromatography (GC) was carried out on a *Hewlett-Packard* series 5890A instrument using Methyl Silicone 530 mμ x 5m. Column chromatography was performed on silica gel *Merck* (particle size 0.063–0.200mm). All reactions were carried out under argon. Pure solvents and reagents were purchased from *Fluka* (CH 9470 Buchs) or *Siegfried* (CH 4800 - Zofingen).

The sclareol used (of Russian origin), m.p. 99–100°, $[\alpha]^{20}$ -2.17° (*c* = 1.45, $CHCl_3$), consisted of 90% sclareol + 10% 13-*epi*-sclareol (^{13}C-NMR). It was not possible to increase the sclareol content further by recrystallization and/or column chromatography.

1. *Ambrox* **(1a)** *from dihydrosclareol* **(9)** via *decomposition of its hypochlorite* **10.**
1.1 **Dihydrosclareol (9)** [4]. Sclareol (77 g, 0.25 mol) dissolved in pure ethanol (600 ml) was hydrogenated over 5% Pd on carbon (0.6 g) at room temperature and atmospheric pressure. After filtration, concentration, and crystallization (petroleum ether 80–100°) 64 g (83% yield) of crystalline (m.p. 107°) dihydrosclareol (9) was obtained.- ^{1}H-NMR-360 MHz spectrum: 0.77, 0.78, 0.85 (3*s*, 3H each, respectively H_3C-19, -17, -18); 0.88 (*t*, *J* = 7, H_3C-15); 1.13 (*s*, H_3C-16); 1.15 (*s*, H_3C-20); 1.46 (*q*, *J* = 7, H_2C-14).

1.2 **Ambrox (1a).** A mixture of 2.8 molar aqueous sodium hypochlorite (30 ml), 84 mmol), prepared according to [9h], dihydrosclareol (9, 9.3 g, 30 mmol), acetic acid (3.6 g, 60 mmol), and CCl_4 (30 ml) was stirred at 0° for 3h. The organic layer was separated, washed (H_2O), and filtered. It weighed 82.3 g and contained 46.7 mmol hypochlorite by iodometric titration, and was immediately used. Of this solution 74 g were stirred at 30–35° for 3h. A slightly exothermic reaction occurred and no more active chlorine was present at the end (by titration). The reaction solution was concentrated (11.1 g), dissolved in anhydrous THF (20 ml), and poured onto a stirred slurry of 80% NaH dispersion (0.81 g, 29 mmol) in anhydrous THF (20 ml). The mixture was heated at reflux temperature for 3h, poured onto ice and extracted with ether. After concentration, the crude material (7.8 g) was chromatographed on silica gel (100 g) using hexane/ether 4:1. Fraction 2 gave 0.37 g of 10% pure Ambrox **(1a)** (yield based on dihydrosclareol **(9)** ≈0.5%).

2. *Ambrox* **(1a)** via *the hydroperoxides* **12a/b.**
2.1 **Hydroperoxides 12a/12b.** A mixture of sclareol (30.8 g, 0.1 mol), CH_2Cl_2 (200 ml), 70% aqueous hydrogen peroxide (100 ml), and *p*-toluenesulphonic acid (0.2 g) was vigorously stirred at room temperature for 7 days. The organic layer was separated, washed (H_2O), dried ($MgSO_4$), and concentrated with a Rotavapor (below 25°) to give 35 g of crude material which was chromatographed on

silica gel (*Merck* 0.2-0.063; 350 g) with cyclohexane/ether (7:3 to 0:1). The first fraction (6.9 g) consisted mainly of manoyl oxides **14a/b** (7:3). Fraction 2 (19.7 g) contained the peroxides **12a**, **12b**, **13**, and unknown impurities (40%, 20%, 20%, 20%) as determined by ^{13}C-NMR (-CH=CH_2) and the chromatographic separation described below. Yield of **12a/b**: ≈38% based on sclareol. Fraction 3 (1.7 g) consisted of sclareol.

Fraction 2 (1 g) was chromatographed using two commercially available *Merck*-columns connected in series [Lobar®-Fertigsäule, Grosse B (310-23 mm), filled with LiChroprep® Si 60 (40-63 µm), Art.n° 10401]. Solvent: cyclohexane/ethyl acetate 7:3; solvent pressure ≈20 psi. The epimers **12a/b** (629 mg) were eluted first (98% peroxide by iodometric titration [19]) followed directly by **13** (205 mg, epimeric mixture). The mixture **12a/b** was recrystallized from hexane (+25° to -20°) to give 95% pure sample of **12a** (m.p. 113-114°). It so became possible to run ^{13}C-NMR spectra and attribute chemical shift values to the hydroperoxides **12a**, **12b**, and **13**, and to the manoyl oxides **14a/b** (see table).

12a ^{1}H-NMR-360 MHz-spectrum: 0.80, 0.81, 0.87 (3*s*, 3H each, respectively H_3C-19, -17, -18); 1.19 (*s*, H_3C-16); 1.22 (*s*, H_3C-20); 5.13 (*dd*, *J* = 11 and 2, HC-15); 5.19 (*dd*, *J* = 18 and 2, HC-15); 6.04 (*dd*, *J* = 11 and 18, HC-14).

12b ^{1}H-NMR-360 MHz spectrum: 0.78, 0.79, 0.87 (3*s*, 3H each, respectively H_3C-19, -17, -18); 1.20 (*s*, H_3C-20); 1.34 (*s*, H_3C-16); 5.14 (*dd*, *J* = 11 and 2, HC-15); 5.19 (*dd*, *J* = 18 and 2, HC-15); 5.81 (*dd*, *J* = 11 and 18, HC-14).

13 (main isomer only) ^{1}H-NMR-360 MHz spectrum: 0.82, 0.84, 0.88 (3*s*, 3H each, respectively H_3C-19, -17, -18); 1.08 (*s*, H_3C-20); 1.29 (*s*, H_3C-16); 5.01 (*dd*, *J* = 11 and 2, HC-15); 5.21 (*dd*, *J* = 18 and 2, HC-15); 5.93 (*dd*, *J* = 11 and 18, HC-14).

14a ^{1}H-NMR-360 MHz spectrum (*cf.* [15]): 0.79, 0.80, 0.86 (3*s*, 3H each, respectively H_3C-17, -18, -19); 1.28, 1.30 (2*s*, 3H each, H_3C-16 and H_3C-20); 4.91 (*dd*, *J* = 11 and 2, HC-15); 5.14 (*dd*, *J* = 18 and 2, HC-15); 5.87 (*dd*, *J* = 18 and 11, HC-14).

14b ^{1}H-NMR-360 MHz spectrum (*cf.* [15]): 0.73, 0.79, 0.86 (3*s*, 3H each, respectively H_3C-17, -18, -19); 1.14, 1.23 (2*s*, 3H each, H_3C-16 and H_3C-20); 4.89 (*d*, *J* = 11, HC-15); 4.95 (*d*, *J* = 18, HC-15); 6.01 (*dd*, *J* = 18 and 11, HC-14).

2.2 **Sclareol (2a) from peroxide 12a.** Peroxides **12a/b** (95:5; 6 mg, 0.018 mmol), diluted in anhydrous ether (5 ml) was treated with triphenylphosphine (9.4 mg, 0.036 mmol) at 20° during 24h. The reaction mixture was concentrated and directly analyzed by ^{1}H-360 NMR. The spectrum obtained was identical with the spectrum of authentic sclareol **2a/b** (≈95:5).

2.3 **Ambrox (1a) from the hydroperoxides 12a/b using the Fe(II)/Cu(II) redox couple.** The peroxide mixture **12a/b** (2:1, 98% pure by iodometric titration; 0.47 g, 1.45 mmol) was dissolved in pure methanol (5 ml) and treated with $Cu(OAc)_2$. 2 H_2O (0.435 g, 2 mmol) and $FeSO_4$. 7 H_2O (0.417 g, 1.5 mmol). The resulting suspension was stirred at 50° for 2h. The reaction mixture was concentrated (below 25°), diluted with water, and extracted with ether. The extract was washed (H_2O, dried ($MgSO_4$), concentrated, and filtered through ≈1 g of silica gel with ether to give 0.355 g of crude material containing 60% Ambrox (**1a**) (by capillary GC without internal standard). Chromatography of the crude product (0.3 g) on silica gel (20 g) using cyclohexane/ether 9:1 gave 87 mg (30% yield) of crystalline Ambrox (**1a**), m.p. 70-73° (cyclohexane), $[\alpha]_D^{20}$ -23.6°. The missing material consisted mainly of polymers.

A second experiment, using 6.2 mmol of **12a/b** (2:1), 10 mmol of $Cu(OAc)_2$. 2 H_2O, 7 mmol of $FeSO_4$. 7 H_2O, 20 ml of methanol for 3h at 50° gave a 33% isolated yield of Ambrox (**1a**).

2.4 **Ambrox (1a) from the hydroperoxides 12a/b using thermal decomposition only.** Fraction 2 of experiment 2.1 (50 mg containing 0.095 mmol of peroxides **12a/b** (2:1)) was dissolved in cyclohexane (0.5 ml) and passed through a heated, empty Pyrex tube (8 mm x 5 m) at a rate of approximately 1 ml/min. Three experiments at different temperatures (200°, 250°, 300°) were performed. In all cases terrible mixtures resulted, 250° giving the best yield of Ambrox (**1a**) (<<5% by GC).

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