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The synthesis of (−)-Ambrox® starting from labdanolic acid

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Abstract—Iododecarboxylation of labdanolic acid (**1**), followed by dehydrohalogenation led to alkenes **4** and **12**. Both compounds were converted into (1*R*,2*R*,4a*S*,8a*S*)-1-(2-hydroxyethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenol (**8**), which was transformed via cyclization into (−)-Ambrox® (**9**). © 2001 Elsevier Science Ltd. All rights reserved.

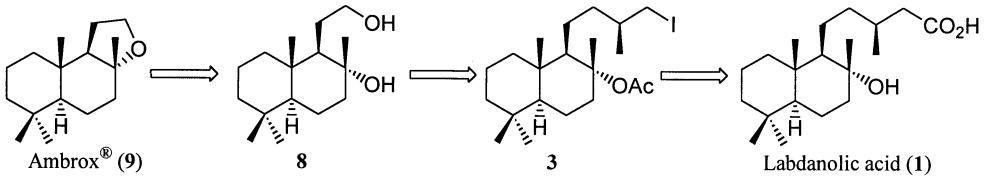
1. Introduction

Since ancient times, ambergris has been one of the most highly valued perfumery materials.[1] Ambergris is a metabolic product of the spermwhale (*Physeter macrocephalus L.*) which accumulates as concretions in the gut. (−)-Ambrox® (**9**), the commercially most important constituent of the scarce natural ambergris, is recognized as the prototype of all ambergris odorants[2] and the release of ambergris scent proved to be strongly related to structural elements of the tetra-*nor*-labdane skeleton.[3] Several synthetic routes to (−)-Ambrox® and its racemate have been developed[4] and many are based on naturally occuring sesqui-[5] or diterpenes[6] as starting material. Nowadays (−)-sclareol is the industrially used starting material for the preparation of (−)-Ambrox®.[7] The price of (−)-Ambrox® is relatively high, which induces an ongoing search for new syntheses starting from cheap, abundantly available labdanes. Labdanolic acid (**1**) is one of the labdanes that has the potential to fulfill this role because it is easily available from Nature[8]. Labdanolic acid (**1**) is the main component (ca. 40%) in the acidic fraction of the *n*-hexane extract of *Cistus ladaniferus L.* ('Rock-rose')[8b–9] and after oxidative degradation of the C(9) side chain of labdanolic acid suitable synthons for the synthesis of (−)-Ambrox® become available.

The degradation of labdanolic acid is not an easy task because the carboxyl group is the only available functional group in the side chain. Several studies to break down the side chain of labdanolic acid (**1**) or its methyl ester have been reported in the literature.[10a] Lead tetraacetate is mostly used as decarboxylating reagent[10b,c] and acetates are obtained in rather irreproducible yields.[11] We now report on the iododecarboxylation of labdanolic acid as the key step in the synthesis of (−)-Ambrox® (Scheme 1).

2. Results and discussion

The commercial extract from *C. ladaniferus L.*,[12] is obtained by steam distillation of the twigs and leaves of the plants, or by treatment of the plant material with hot water or aqueous base. These conditions may cause elimination of the tertiary hydroxyl group which results in formation of a mixture of labdenic acids. To prevent this dehydration the air dried twigs and leaves of the *C. ladaniferus L.* were soaked with *n*-hexane and evaporation of the solvent gave rise to a sticky labdanum gum. Partial purification was performed by extracting the acid from an etheral solution into water by base and upon acidification crude labdanolic acid (**1**) was obtained. Further purification of this crude labdanolic acid (**1**) appeared to be difficult, but after conversion of the C(8) tertiary hydroxyl group in its acetate, the purification of the acetate **2** proved to be relatively easy, and pure acetate **2**



Ambrox® (**9**) **8** **3** Labdanolic acid (**1**)

Keywords: Ambrox®; labdanolic acid; iododecarboxylation.

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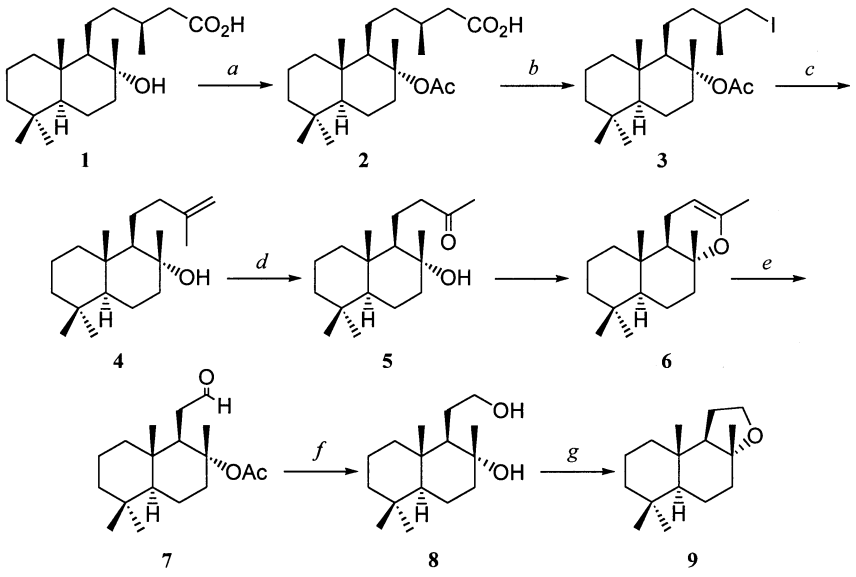


Scheme 2. *Reagents and conditions*: (a) AcCl, *N*,*N*-dimethylaniline; (b) IBDA, I_2, CCl_4, $h\nu$, Δ, 76%; (c) *t*BuOK, THF, 74%; (d) O_3, $MeOH/CH_2Cl_2$ 1:5, −78°C, PPh_3, 44%; (e) O_3, CH_2Cl_2, py, −78°C; (f) $LiAlH_4$, THF, 60%; (g) *p*TsOH, CH_3NO_2, 87%.

could be obtained in 35–45% based upon crude acidic material.

The iododecarboxylation[13] of acetate **2** with iodobenzenediacetate (IBDA) and iodine could be achieved under irradiation with a 100 W tungsten lamp and the iodide **3** was obtained in 76% yield. Because this iodide **3** proved to be a rather unstable compound and because it was contaminated with iodobenzene, the product was treated immediately with potassium *tert*-butoxide (*t*BuOK) in THF at room temperature to give dehydroiodination and hydrolysis of the acetate group to compound **4** in 74% yield.

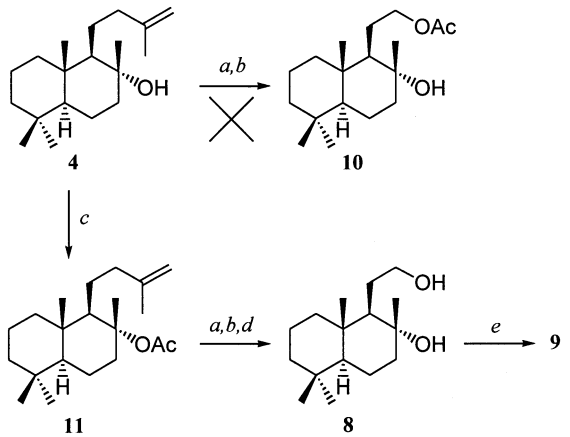
Ozonolysis of the double bond of compound **4** and reduction of the intermediate ozonides gave the methyl ketone which immediately cyclized into sclareol oxide (**6**). The irreproducible yield of 45–90% in the conversion of **4** to sclareol oxide (**6**) is due to the fact that this compound is fairly unstable. Therefore, the enol ether in sclareol oxide (**6**) was ozonolyzed immediately, and reduction of the aldehyde and acetate group in intermediate **7** afforded the diol **8** in 60% overall yield starting from **4**. Stirring of this diol **8** in nitromethane in the presence of *p*-toluenesulfonic acid gave the cylized product (−)-Ambrox® (**9**) in 87% yield (Scheme 2).[14]

An obvious way to circumvent the unstable sclareol oxide was the synthesis of acetate ester **10** via a Criegee rearrangement[15] of the ozonide of alkene **4**, but this approach was unsuccessful. The rearranged product **10** was not observed upon treatment of the ozonide under the usual Criegee conditions (acetic anhydride, triethylamine, and *N*,*N*-dimethylaminopyridine), probably because an unfavourable seven membered ring intermediate cannot be formed, and the reaction gave the *normal* ozonolysis product **5** which cyclized as before to sclareol oxide.

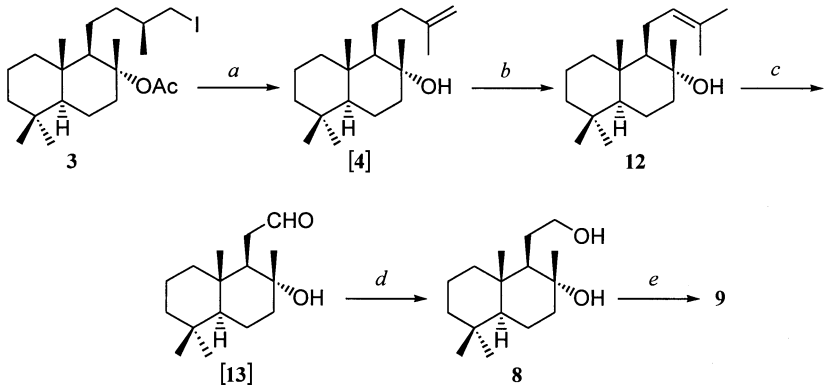
Another way to circumvent the formation of sclareol oxide was to apply the Criegee rearrangement but to prevent the interference of the hydroxyl group at C(8) during the ozonolysis. So the tertiary hydroxyl group of **4** was protected again as its acetate and the ozonolysis product of **11** was subjected to Criegee rearrangement. After reduction of the obtained intermediate with lithium aluminum hydride ($LiAlH_4$) compound **8** was obtained in 89% overall yield from compound **11** (Scheme 3). This diol was transformed into (−)-Ambrox® **9** as shown in Scheme 2.

In the first route it was shown that treatment of **3** with *t*BuOK at room temperature afforded compound **4**. When this dehydroiodonation was performed using the same base in refluxing THF (or in DMSO at room temperature), the intermediate **4** was in situ isomerized to **12** (Scheme 4). Ozonolysis of the double bond and reduction with sodium borohydride ($NaBH_4$) of the intermediate ozonides gave diol **8** in 92% overall yield and this diol again was transformed into (−)-Ambrox® **9** according to Scheme 2.

The results of these three synthetic routes of acetate **2** to (−)-Ambrox® are summarized in Table 1. From this table, it is clear that (−)-Ambrox® (**9**) can be obtained in a short



Scheme 3. *Reagents and conditions*: (a) O_3, $MeOH/CH_2Cl_2$ 1:5, −78°C; (b) Ac_2O, NEt_3, DMAP; (c) AcCl, *N*,*N*-dimethylaniline, 83%; (d) $LiAlH_4$, THF, 89%; (e) CH_3NO_2, *p*TsOH, 87%.



Scheme 4. *Reagents and conditions*: (a) *t*BuOK, THF; (b) Δ, 78%; (c) O_3, MeOH/CH_2Cl_2 3:1, −78°C; (d) $NaBH_4$, 92%; (e) *p*TsOH, CH_3NO_2, 87%.

Table 1. Synthesis of (−)-Ambrox®, starting from 8-acetoxy-labdanolic acid (**2**)

Route depicted in Schemes	Steps	Overall yield (%)	Average step yield (%)
2	5	13	65
3	5	36	80
4	4	47	85

four-step procedure in 47% overall yield starting from the acetate of labdanolic acid **2**. The main drawback of the method is the application of IBDA and iodine in the decarboxylation reaction. When a cheaper procedure can be found for this reaction, labdanolic acid (**1**) will become a good alternative as starting material for the industrial preparation of (−)-Ambrox® (**9**).

3. Experimental

3.1. General information and instrumentation

All reagents used were purchased from Aldrich or Acros Chimica and used without further purification, unless otherwise stated. Reactions under dry conditions were performed under a steady stream of dry nitrogen or argon with glassware pre-dried at 140°C. Sonication experiments were performed using a 35 KHz Bandelin Sonorex TK 52 apparatus. Melting points were determined on a C. Reichert, Vienna, hot stage apparatus and are not corrected. Infrared spectra were recorded on a FT-IR, Biorad FTS-7 spectrometer and only characteristic absorptions are reported. ^1H and ^{13}C NMR spectra were, unless otherwise stated, recorded at 200 and 50 MHz on a Bruker AC-E 200 spectrometer, respectively, using $CDCl_3$ as solvent. The chemical shift values are expressed in ppm (parts per million) (δ) relative to the residual $CHCl_3$ at 7.24 (^1H) and 77.00 (^{13}C) as internal standard. The multiplicity of the ^1H signals are expressed as: s=singlet, d=doublet, t=triplet, q=quartet, br s=broad singlet, m=multiplet. The multiplicity of the ^{13}C signals were determined with the DEPT technique, q=quartet, t=triplet, d=doublet, s=singlet. GC-MS data were determined at 70 eV on a Hewlett Packard 5890B series Mass Selective Detector, coupled with a Hewlett Packard 5973 GC provided with a DB-17 fused silica capillary column, 30 m×0.25 mm i.d., film thickness 0.25 μm with helium as the carrier gas. The ratios *m/e* and relative intensities (%) are indicated for the significant peaks. MS and HRMS data were obtained with a Finnigan MAT 95 spectrometer. The ratios *m/z* and relative intensities (%) are indicated for significant peaks. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter at 20°C for chloroform solutions and concentrations are specified in units of g/100 mL. Gas chromatography was performed on a 5890 Series II Hewlett Packard gas chromatograph using a DB-17 fused silica bonded capillary column (30 m×0.25 mm i.d.), programmed from 100–250°C at a rate of 10°C/min. For flash chromatography, ICN Biomedicals silica gel mean pore size 60 (32–63 μm) was used with mixtures of distilled light petroleum ether (bp 40–60°C) (PE) and EtOAc (EA) as eluents unless reported otherwise. Solvents were dried and freshly distilled by common practice. Usual work up refers to washing of the extract with brine, drying over anhydrous $MgSO_4$, filtration and evaporation of the solvent under reduced pressure. Reactions were monitored by GC or by TLC on Merck silica gel $60F_{254}$ plastic sheets plates. Compounds on TLC were visualized by UV detection and by spraying with basic $KMnO_4$ or with an acidic anisaldehyde solution or with a molybdate solution and subsequent heating.

3.1.1. (−)-(3*S*)-5-((1*R*,2*R*,4a*S*,8a*S*)-2-Hydroxy-2,5,5,8a-tetramethyldecahydro-1-naphthalenyl)-3-methylpentanoic acid (labdanolic acid (1)). The air dried twigs and leaves of *C. ladaniferus L.* (300 g) were soaked with *n*-hexane (5 L) at room temperature for three days. The solution was separated from the solid material and the solvent was evaporated to give a sticky labdanum gum. The gum was stirred with ether and the etheral solution was washed with a 4 M aqueous NaOH solution. The basic solution was acidified with aqueous 4 M HCl solution, extracted with ether and dried. After evaporation of the solvent a crude acidic fraction (30 g) was obtained. A sample of the crude product was purified by column chromatography (eluent CH_2Cl_2/MeOH 9:1) to give pure labdanolic acid (**1**) as a sticky solid compound. Mp 80–82°C (lit.[10a]: 82–83°C); $[\alpha]_D$=−6.9 (*c* 0.9) (lit.[10a]: −7.2); IR (KBr) ν_{max} 3431, 2924, 1710 cm^{-1}; ^1H NMR ($CDCl_3$/CD_3OD) δ 0.62 (s, 3H), 0.69 (s, 3H), 0.77 (d, *J*=5.0 Hz, 3H), 1.01 (s, 3H), 1.08 (s, 3H), 1.10–1.84 (m, 17H), 2.06 (m, 2H), 4.37 (br s, 2H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 15.1 (q), 18.1 (t), 19.4 (q), 20.1 (t), 21.1 (q), 22.7 (t), 23.1 (q), 29.3 (t),

30.9 (d), 31.0 (s), 32.9 (q), 38.8 (s), 39.4 (t), 40.3 (t), 41.6 (t), 43.3 (t), 55.8 (d), 61.7 (d), 73.9 (s), 176.7 (s); HRMS: M^+, found 324.2661. $C_{20}H_{36}O_3$ requires 324.2664; MS *m/e* (%) 324 (M^+, 38), 312 (58), 235 (47), 177 (65), 171 (100), 148 (84), 123 (64), 109 (62), 69 (86); Anal. found C, 73.50; H, 11.27%. $C_{20}H_{36}O_3$ requires C, 74.02; H, 11.18%.

3.1.2. (−)-(3*S*)-5-((1*R*,2*R*,4a*S*,8a*S*)-2-(Acetyloxy)-2,5,5,8a-tetramethyldecahydro-1-naphthalenyl)-3-methylpentanoic acid (2). To a stirred solution of crude labdanolic acid (**1**) (10 g) in *N*,*N*-dimethylaniline (40 mL) was added acetyl chloride (15 mL; 16.56 g; 210.9 mmol) and the solution was left overnight. Dilute sulfuric acid was carefully added to the blue reaction mixture till the color had disappeared. The mixture was extracted with ether and the ethereal solution was washed with aqueous 1 M sulfuric acid (150 mL), and worked up as usual. The residue was purified by flash column chromatography on silica gel (eluent PE/EA 7:1) to yield **2** (4.66 g; 12.73 mmol; 47%, based upon the crude acidic fraction) as a light yellow sticky gum. $[\alpha]_D$=−18.1 (*c* 1.8); IR (KBr) ν_{max} 3449, 2925, 2852, 1734, 1643, 1287 cm^{-1}; ^1H NMR δ 0.75 (s, 3H), 0.80 (s, 3H), 0.96 (d, *J*=6.6 Hz, 3H), 1.20 (s, 3H), 1.90 (s, 3H), 0.65–2.38 (m, 20H), 2.62 (dt, *J*=3.0, 12.4 Hz, 1H), 4.38 (br s, 2H); ^{13}C NMR δ 15.7 (q), 18.3 (t), 19.7 (q), 19.9 (t), 20.3 (q), 21.4 (q), 22.8 (q), 23.1 (t), 29.7 (t), 30.8 (d), 33.0 (s), 33.3 (q), 38.7 (t), 39.3 (s), 39.5 (t), 39.8 (t), 41.6 (t), 55.5 (d), 59.0 (d), 88.0 (s), 170.4 (s), 179.7 (s); HRMS: (M^+−60), found 306.2557. $C_{20}H_{34}O_2$ requires 306.2559; MS *m/e* (%) 366 (M^+, 1), 307 (29), 306 (100), 291 (66), 191 (98), 182 (65), 137 (40), 109 (42), 95 (33), 69 (36); Anal. found C, 72.51; H, 10.49%. $C_{22}H_{38}O_4$ requires C, 72.09; H, 10.45%.

3.1.3. (1*R*,2*R*,4a*S*,8a*S*)-1-((3*S*)-4-Iodo-3-methylbutyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenyl acetate (3). A solution of **2** (1.5 g; 4.10 mmol) in carbon tetrachloride (40 mL) containing iodobenzene diacetate (IBDA) (0.72 g; 2.25 mmol) and iodine (0.52 g; 2.05 mmol) was irradiated with a 100 W tungsten filament lamp for 45 min at reflux temperature. Then another portion of IBDA (0.72 g; 2.25 mmol) and iodine (0.52 g; 2.05 mmol) was added, and the irradiation at reflux temperature was continued for 45 min. The reaction mixture was cooled to room temperature and was washed with aqueous 1 M sodium thiosulfate solution (100 mL), water and brine. Flash column chromatography of the residue (eluent PE/EA 9:1) on silica gel gave the iodo compound **3** (1.40 g; 3.12 mmol; 76%) as an oil contaminated with iodobenzene in a 1:1 molar ratio, determined via ^1H NMR. ^1H NMR δ 0.76 (s, 3H), 0.81 (s, 3H), 0.85 (s, 3H), 0.97 (d, *J*=6.4 Hz, 3H), 1.05–1.81 (m, 19H), 1.96 (s, 3H), 2.63 (dt, *J*=2.7, 12.3 Hz, 1H), 3.18 (d, *J*=5.2 Hz, 2H); ^{13}C NMR δ 15.7 (q), 17.8 (t), 18.4 (t), 20.0 (t), 20.4 (q), 20.8 (q), 21.5 (q), 23.2 (t), 23.3 (q), 29.7 (s), 33.1 (s), 33.4 (q), 35.7 (d), 38.8 (t), 39.4 (t), 39.6 (t), 41.9 (t), 55.6 (d), 58.9 (t), 87.8 (s), 170.3 (s); HRMS: M^+, found 448.1844. $C_{21}H_{37}O_2I$ requires 448.1838; MS *m/e* (%) 448 (M^+, 1), 389 (25), 388 (100), 373 (37), 264 (44), 191 (60), 137 (33), 95 (28), 69 (31), 43 (29).

3.1.4. (+)-(1*R*,2*R*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-1-(3-methyl-3-butenyl)-decahydro-2-naphthalenol (4). To a solution of **3** (1.61 g; 3.6 mmol) in THF (20 mL) under nitrogen was added *t*BuOK (2.02 g; 18 mmol). After stirring overnight at room temperature the mixture was quenched with an aqueous saturated solution of NH_4Cl, and worked up as usual. The residue was purified by flash column chromatography (eluent PE/EA 5:1) and **4** (0.74 g; 2.66 mmol; 74%) was obtained as a sticky solid compound. $[\alpha]_D$=+0.6 (*c* 1.6); IR (liquid film) ν_{max} 3420, 3072, 2927, 2868, 1457 cm^{-1}; ^1H NMR δ 0.76 (s, 3H), 0.78 (s, 3H), 0.84 (s, 3H), 1.11 (s, 3H), 1.71 (s, 3H), 0.87–2.36 (m, 17H), 4.67 (s, 2H); ^{13}C NMR δ 15.5 (q), 18.5 (t), 20.6 (t), 21.5 (q), 22.6 (q), 23.6 (t), 23.9 (q),, 33.3 (s), 33.4 (q), 39.2 (s), 39.7 (t), 41.3 (t), 42.0 (t), 44.6 (t), 56.1 (d), 61.5 (d), 74.1 (s), 109.7 (t), 147.1 (s); HRMS: M^+, found 278.2605. $C_{19}H_{34}O$ requires 278.2610; MS *m/e* (%) 278 (M^+, 6), 245 (36), 192 (100), 191 (71), 177 (75), 123 (39), 109 (45), 95 (50), 69 (58), 43 (32); Anal. found C, 82.18; H, 12.62%. $C_{19}H_{34}O$ requires C, 81.95; H, 12.31%.

3.1.5. (+)-(4a*R*,6a*S*,10a*S*)-3,4a,7,7,10a-Pentamethyl-4a,5,6,6a,7,8,9,10,10a,10b-decahydro-1*H*-benzo[*f*]chromene (sclareol oxide (6)). A stirred solution of **4** (0.30 g; 1.08 mmol) in a mixture of MeOH and CH_2Cl_2 1:5 (20 mL) was purged through with ozone at −78°C until a pale blue color appeared. The excess ozone was expelled and PPh_3 (0.57 g; 2.17 mmol) was added at −78°C. The mixture was allowed to warm to room temperature. After stirring overnight the solvent was evaporated. The residue was purified by flash column chromatography (eluent PE/EA 6:1) to yield sclareol oxide (**6**) (0.124 g; 0.47 mmol; 44%) as a light yellow oil. $[\alpha]_D$=+4.9 (*c* 1.3) (lit.[16]: $[\alpha]_D$=+5.7, *c* 1.6); IR (liquid film) ν_{max} 3055, 2950, 2900, 2890, 1687, 1470, 1390, 1342, 1000 cm^{-1}; ^1H NMR δ 0.74 (s, 3H), 0.75 (s, 3H), 0.81 (s, 3H), 1.25 (s, 3H), 1.61 (s, 3H), 1.76–1.83 (m, 13H), 1.87 (dt, *J*=4.3, 14.6 Hz, 1H), 4.30 (br s, 1H); ^{13}C NMR δ 19.3 (q), 18.2 (q), 18.6 (t), 19.8 (t), 20.7 (q), 21.0 (q), 26.6 (q), 28.6 (q), 33.1 (s), 36.7 (s), 39.3 (t), 41.1 (t), 41.9 (t), 52.4 (d), 55.2 (d), 76.2 (s), 94.6 (d), 147.8 (s); MS *m/e* (%) 262 (M^+, 100), 191 (81), 177 (39), 123 (46), 109 (97), 95 (64), 81 (72), 43 (78).

3.1.6. (−)-(1*R*,2*R*,4a*S*,8a*S*)-1-(2-Hydroxyethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenol (8). A solution of sclareol oxide (**6**) (0.124 g; 0.47 mmol) in CH_2Cl_2 (35 mL) and pyridine (0.35 mL) was ozonolyzed at −78°C. The excess of ozone was expelled and the mixture was allowed to come to room temperature. The mixture was acidified with an aqueous 1 M hydrochloric acid solution and worked up as usual. The residue was dissolved in THF (20 mL), cooled to 0°C and $LiAlH_4$ (137 mg; 3.60 mmol) was added in portions. After stirring overnight at room temperature the mixture was carefully acidified with 1 M HCl. The aqueous layer was extracted three times with ethyl acetate and worked up as usual. The crude oil was purified by flash column chromatography (eluent PE/EA 1:1) to give **8** (72 mg; 0.28 mmol; 60%) as a white crystalline solid. Mp 128–130°C; $[\alpha]_D$=−13.8 (*c* 1.1); IR (KBr) ν_{max} 3410, 2926, 2894, 1458, 1243, 1051 cm^{-1}; ^1H NMR δ 0.80 (s, 6H), 0.89 (s, 3H), 1.16 (s, 3H), 0.92–1.70 (m, 13H), 1.92 (dt, *J*=4.5, 11.9 Hz, 1H), 2.67 (br s, 2H), 3.48 (dt, *J*=6.5, 10.0 Hz, 1H), 3.81 (dt, *J*=4.3, 10.0 Hz, 1H); ^{13}C NMR δ 15.3 (q), 18.4 (t), 20.5 (t), 21.5 (q), 24.7 (q), 27.9 (t), 33.3 (s), 33.4 (q), 39.0 (s), 39.3 (t), 41.9 (t), 44.3 (t), 56.0 (d), 59.1

(d), 64.2 (t), 73.2 (s); HRMS: M^+, found 254.2249. $C_{16}H_{30}O_2$ requires 254.2250; MS *m/e* (%) 254 (M^+, 9), 221 (73), 195 (100), 177 (64), 151 (65), 109 (81), 95 (76), 69 (87), 43 (48); Anal. found C, 75.98; H, 12.27%. $C_{16}H_{30}O_2$ requires C, 75.53; H, 11.89%.

3.1.7. (−)-(1*R*,2*R*,4a*S*,8a*S*)-1-(2-Hydroxyethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenol (8). A stirred solution of **11** (0.25 g; 0.78 mmol) in a mixture of MeOH and CH_2Cl_2 1:5 (20 mL) was purged through with ozone at −78°C until a pale blue color appeared, then the solution was purged with nitrogen to remove the excess of ozone. This mixture was treated with acetic anhydride (1.16 mL; 10.5 mmol), triethylamine (0.53 mL; 7.16 mmol) and 4-*N*,*N*-dimethylaminopyridine (DMAP) (25 mg; 0.20 mmol). The reaction mixture was allowed to come to room temperature and stirred overnight. The solution was poured into an aqueous 1 M HCl solution and extracted with ethyl acetate and worked up as usual. The residue was dissolved in THF (10 mL), and cooled to 0°C and $LiAlH_4$ (84 mg; 2.22 mmol) was added. After stirring for 1 h at room temperature the mixture was carefully diluted with ethyl acetate, and treated with aqueous 1 M HCl solution. The aqueous layer was extracted with ethyl acetate and worked up as usual. The crude oil was purified by flash column chromatography (PE/EA 1:1) to give **8** (0.17 g; 0.65 mmol; 89%) as a white crystalline solid. For analytical data see the foregoing experiment.

3.1.8. (−)-(1*R*,2*R*,4a*S*,8a*S*)-1-(2-Hydroxyethyl)-2,5,5,8a-tetramethyldecahydro-2-naphthalenol (8). A solution of **12** (0.2 g; 0.72 mmol) in a mixture of MeOH and CH_2Cl_2 3:1 (30 mL) was ozonized at −78°C. The excess ozone was expelled and $NaBH_4$ (0.22 g; 5.79 mmol) was added at −78°C. The mixture was alllowed to warm to room temperature. The excess of $NaBH_4$ was destroyed with a 1 M aqueous HCl solution and diluted with water. The mixture was extracted with ethyl acetate and worked up as usual. The residue was purified by flash column chromatography (eluent PE/EA 2:1) to yield **8** (0.17 g; 0.66 mmol; 92%) as a white crystalline solid. The analytical data were as mentioned before.

3.1.9. (−)-(3a*R*,5a*S*,9a*S*,9b*R*)-3a,6,6,9a-Tetramethyldodecahydronaphtho[2,1-*b*]furan ((−)-Ambrox® (9)). A mixture of **8** (0.10 g; 0.39 mmol) and *p*-toluenesulfonic acid (0.04 g; 0.19 mmol) in nitromethane (7 mL) was stirred at room temperature for 3 h. Ether was added and the mixture was washed with a saturated aqueous sodium bicarbonate solution and brine, dried and evaporated. Flash column chromatography (eluent PE/EA 6:1) gave Ambrox® (**9**) (0.08 g; 0.34 mmol; 87%) as white crystals. Mp 74–75°C (lit.[6a]: 74–76°C); $[\alpha]_D$=−23.8 (*c* 1.3) (lit.[6a]: −22.1, *c* 0.7); IR (KBr) ν_{max} 3441, 2922, 2884, 1130, 1120, 1005 cm^{-1}; ^1H NMR δ 0.82 (s, 6H), 0.86 (s, 3H), 1.07 (s, 3H), 0.92–1.92 (m, 14H), 3.85 (m, 2H); ^{13}C NMR δ 15.1 (q), 18.4 (t), 20.7 (t), 21.2 (q), 21.3 (q), 22.6 (t), 33.1 (s), 33.6 (q), 36.2 (s), 39.7 (t), 40.0 (t), 42.4 (t), 57.3 (d), 60.1 (d), 65.0 (t), 79.9 (s); HRMS: M^+, found 236.2143. $C_{16}H_{28}O$ requires 236.2140; MS *m/e* (%) 236 (M^+, 3), 221 (100), 137 (15), 97 (10), 95 (4), 81 (4), 69 (5), 55 (4), 43 (4); Anal. found C, 81.10; H, 11.95%. $C_{16}H_{28}O$ requires C, 81.29; H, 11.94%.

3.1.10. (−)-(1*R*,2*R*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-1-(3-methyl-3-butenyl)-decahydro-2-naphthalenyl acetate (11). To a stirred solution of **4** (0.53 g; 1.91 mmol) in *N*,*N*-dimethylaniline (30 mL) was added acetyl chloride (8 mL; 8.83 g; 112.5 mmol) and left overnight. An aqueous 1 M sulfuric acid solution was added carefully to the blue reaction mixture till the color had disappeared. The mixture was extracted with ether and worked up as usual. The residue was purified by flash column chromatography on silica gel (eluent PE/EA 10:1) to yield **11** (0.53 g; 1.58 mmol; 83%) as a white crystalline solid. Mp 64–66°C; $[\alpha]_D$=−23.1 (*c* 1.2); IR (KBr) ν_{max} 3431, 2926, 2852, 1728, 1253 cm^{-1}; ^1H NMR δ 0.76 (s, 3H), 0.81 (s, 3H), 0.84 (s, 3H), 1.91 (s, 3H), 1.05–2.03 (m, 21H), 2.61 (dt, *J*=3.0, 12.4 Hz, 1H), 4.65 (s, 2H); ^{13}C NMR δ 15.7 (q), 18.3 (t), 20.4 (q), 21.4 (q), 22.5 (q), 22.9 (q), 24.5 (t), 29.7 (t), 33.1 (s), 33.3 (q), 38.7 (t), 39.3 (s), 39.4 (t), 41.1 (t), 41.9 (t), 55.6 (d), 58.6 (d), 88.0 (s), 109.3 (t), 146.9 (s), 170.1 (s); HRMS: M^+, found 320.2715. $C_{21}H_{36}O_2$ requires 320.2715; MS *m/e* (%) 320 (M^+, 4), 245 (30), 192 (100), 191 (57), 177 (55), 123 (31), 109 (32), 95 (33), 81 (34), 69 (36), 43 (33); Anal. found C, 78.63; H, 11.45%. $C_{21}H_{36}O_2$ requires C, 78.69; H, 11.32%.

3.1.11. (+)-(1*R*,2*R*,4a*S*,8a*S*)-2,5,5,8a-Tetramethyl-1-(3-methyl-2-butenyl)-decahydro-2-naphthalenol (12). Under an atmosphere of nitrogen iodide, **3** (0.56 g; 1.24 mmol) was dissolved in DMSO (20 mL) and *t*BuOK (1.39 g; 12.4 mmol) was added. After stirring overnight at room temperature the mixture was quenched with saturated NH_4Cl and worked up as usual. The residue was purified by flash column chromatography (eluent PE/EA 5:1) and **12** (0.27 g; 0.97 mmol; 78%) was obtained as a yellow oil. $[\alpha]_D$=+14.7 (*c* 1.6); IR (liquid film) ν_{max} 3446, 2924, 2867, 1457, 1387, 1083 cm^{-1}; ^1H NMR δ 0.72 (s, 3H), 0.75 (s, 3H), 0.80 (s, 3H), 1.12 (s, 3H), 1.60 (s, 6H), 0.83–2.26 (m, 15H), 5.18 (t, *J*=4.5 Hz, 1H); ^{13}C NMR δ 15.4 (q), 17.9 (q), 18.6 (t), 20.2 (t), 21.6 (q), 23.7 (t), 24.7 (q), 25.9 (q), 33.3 (s), 33.5 (q), 38.7 (s), 40.0 (t), 41.9 (t), 56.1 (d), 61.6 (d), 74.3 (s), 127.2 (d), 130.8 (s); HRMS: (M^+−18), found 260.2500. $C_{19}H_{32}$ requires 260.2504; HRMS: (M^+−15), found 263.2377. $C_{18}H_{31}O$ requires 263.2374; MS *m/e* (%) 278 (M^+, 1), 263 (2), 260 (13), 178 (11), 136 (9), 122 (100), 109 (11), 107 (19), 95 (10), 69 (19), 43 (9).

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