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Synthesis of *Ambrox*® from (-)-sclareol and (+)-*cis*-abienol

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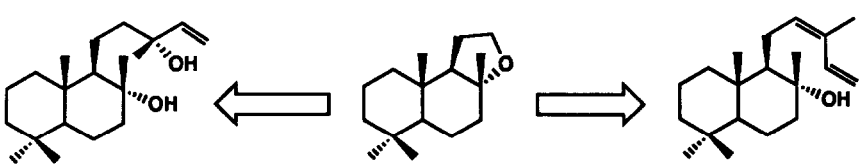
Abstract: Short and efficient syntheses of (-)-*Ambrox*® **(12)** from (-)-sclareol **(1)** and (+)- *cis*-abienol **(11)** are described. In contrast to previously described procedures, the transformation of **1** to **12**, involving in the key step, an oxidative degradation by catalytic osmium tetroxide, in the presence of sodium periodate, has the advantage of using the more suitable sodium borohydride, as the reducing agent. The isolation and characterization of some reaction intermediates allowed us to confirm the degradation mechanism.

INTRODUCTION

Commercially Ambrox® **(12)** constitutes the most important substitute for ambergris,[1] due to its unique olfactive and fixative properties. It occurs naturally in trace amounts and has been isolated from ambergris,[2] the essential oils of *Salvia sclarea* L,[1a] *Cistus labdaniferus* L,[1] *Cupressus sempervivens* L[3] and in the absolute of *Nicotiana tabacum* .[4] This lack of abundance has encouraged chemical synthesis. Several syntheses of (-)-ambrox **(12)** have been developed since the first preparation in 1950.[5] Most of them have started from naturally occuring sesqui- or diterpenes such as (-)-drimenol,[6] (+)-manool,[7] manoyl oxide,[8] (-)-labdanolic acid,[9] (+)-abietic acid[10] and (-)-levopimaric acid.[11] Furthermore, some total syntheses of **12** have been reported.[12]

In this paper we report a new synthesis of (-)-ambrox **(12)** from (-)-sclareol **(1)**,[13] the main constituent of the flowerheads of *Salvia sclarea* L[14] (scheme 1). Syntheses starting from **1** are of increasing interest, due to recent developments in methods of isolation of this diterpene from tissue cultures.[15] The procedure outlined here provides a good overall yield and has the advantage of using the more suitable sodium borohydride, as the reducing agent.[16] Furthermore, the isolation of some reaction intermediates allows us to confirm the degradation mechanism, previously hypothesized for this type of oxidation.[13e]

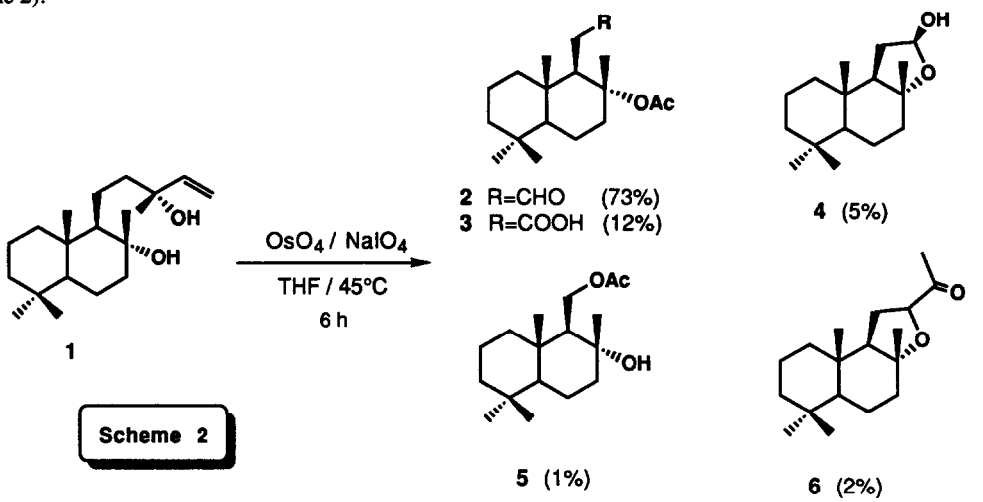


1 **Scheme 1** **12** Ambrox ® **11**

We also report on a novel two-step synthesis of (-)-ambrox (**12**) from (+)-*cis*-abienol (**11**), the major diterpene constituent from the resin of Abies species[17] (scheme 1).

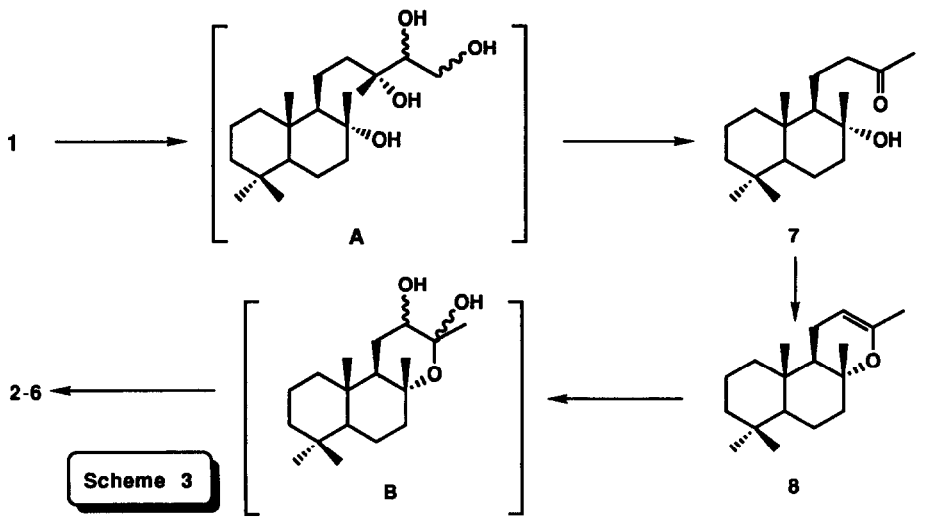
RESULTS AND DISCUSSION

The critical step in the preparation of (-)-ambrox (**12**) from (-)-sclareol (**1**) involves an oxidative degradation of the side chain of **1**, which can be efficiently accomplished by using a modification of Corey's procedure.[18] Treatment of **1** with osmium tetroxide-sodium periodate in tetrahydrofuran solution at 45°C afforded the acetoxyaldehyde **2**, the acetoxyacid **3** and the hemiacetal **4** along with the minor products **5** and **6** (scheme 2).



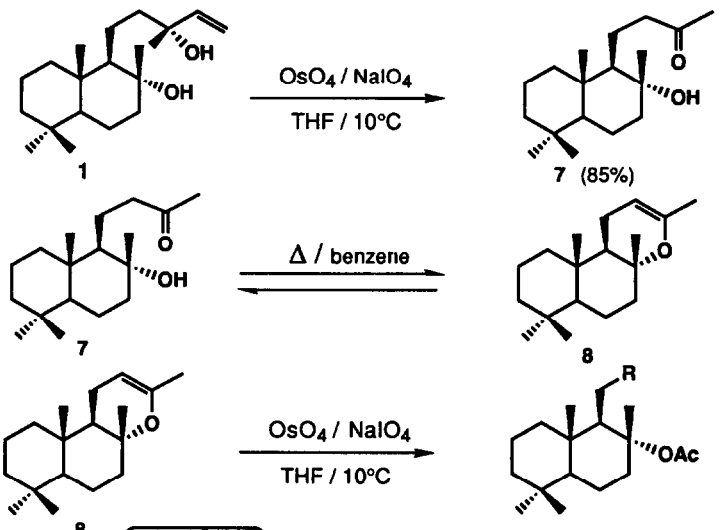
Scheme 2

In the course of our research we have isolated some reaction intermediates, which allowed us to confirm the previously proposed mechanism for this type of oxidation[13e] (scheme 3).



Scheme 3

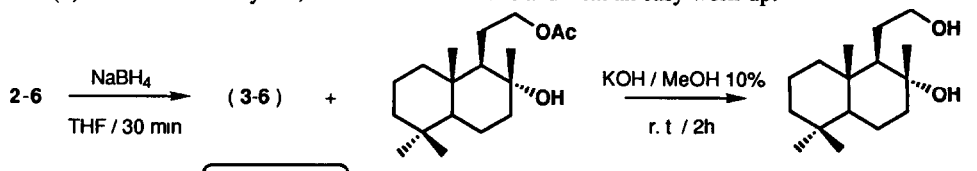
The most significants results are shown in the scheme 4. Thus, the methylketone **7** was the sole product isolated, when the oxidation of **1** was carried out at 10°C. An equilibrium mixture of **7** and the enol ether **8** was obtained by heating the ketone **7** in an inert solvent; the isolation of pure **8** could be achieved by azeotropic distillation of water. Treatment of **8** with osmium tetroxide - sodium periodate in tetrahydrofuran at 10°C yielded a mixture of **2** and **3**. Likewise, the minor products were in accordance with the proposed mechanism. Thus, **4** and **6** could be formed from the postulated intermediate B. The formation of drimane **5** can take place by radical decarbonylation of the aldehyde **2**, due to atmospheric oxygen, via a hydroperoxide-type intermediate.[19]



Scheme 4

2 R=CHO (70%)
3 R=COOH (10%)

Reduction of the mixture containing **2**(73%) and **3**(12%), the major products of the oxidative degradation of (-)-sclareol (**1**), with lithium aluminium hydride afforded a high yield of the diol **10**, which was quantitatively cyclized into (-)-ambrox (**12**), by using tosyl chloride in pyridine (72% overall yield from **1**). An alternative route, which involves the more appropriate sodium borohydride, consists of the treatment of the crude oxidation products with this reducing agent, and the subsequent saponification of the resulting acetoxyalcohol **9**, giving **10** in an 80% overall yield from **2** (scheme 5). In tetrahydrofuran solution, a ready migration of the acetyl group from O-C_8 to O-C_{12} takes place, affording **9**, which was smoothly hydrolyzed. Moreover, the unaltered acetoxyacid **3** could easily be removed in the work-up under these basic conditions, favoring the isolation and purification of the diol **10**. This procedure enabled us to obtain (-)-ambrox (**12**) from (-)-sclareol (**1**) in a 58% overall yield, under mild conditions and with an easy work-up.[16]

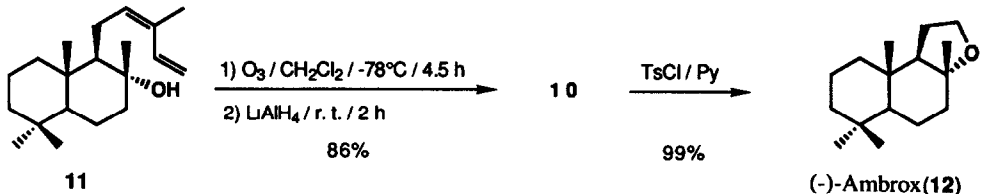


Scheme 5

9

10
(80% from **2**)

We have also studied the transformation of (+)-*cis*-abienol (**11**) into (-)-ambrox (**12**). The starting diterpene was prepared from a commercial sample of Canadian balsam. Ozonolysis of **11**, and the subsequent treatment with lithium aluminum hydride, afforded **10** in high yield.[16] Cyclization of **10** into **12** was carried out, as previously described, using tosyl chloride in pyridine (84% overall yield from **1**)(scheme 6).



11 (-)-Ambrox(**12**)

Scheme 6

EXPERIMENTAL

Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter with a 1 dm microcell, using $CHCl_3$ as solvent (concentration expressed in $cg \cdot cm^{-3}$). IR spectra were obtained on Perkin-Elmer Models 782 and 983G spectrometers with samples between sodium chloride plates or as potassium bromide pellets. ^1H NMR spectra were recorded on Bruker WP 80 SY (80 MHz) and Bruker AM 300 (300 MHz) spectrometers using $CDCl_3$ as solvent and TMS or residual protic solvent $CHCl_3$ (δ_H=7.25 ppm) as internal reference. ^{13}C NMR spectra were run at 20 MHz and 75 MHz on Bruker WP 80 SY and Bruker AM 300 instruments. Chemical shifts are in ppm (δ scale) and the coupling constants are in Hertz. Carbon substitution degrees were established by DEPT pulse sequence. MS were recorded on a Hewlett-Packard 5988A spectrometer using an ionizing voltage of 70 eV. For analytical TLC Merck silica gel 60G in 0.25 mm thick layers was used. Chromatographic separations were carried out by conventional column on Merck silica gel 60 (70-230 mesh) and by flash column on Merck silica gel 60 (230-400 mesh) using hexane-MeO^{t}Bu (H-E) mixtures of increasing polarity. Ozonization reactions were carried out with a mixture of ozone-oxygen provided by an oxygen-feed Fischer apparatus (8.3 mmol of O_3 in 10 litres of O_2/h). Compound **1** was isolated from flowerheads of *Salvia sclarea* L.[15] Compound **5** was isolated from the resin of Abies species.[17]

Reaction of 1 with OsO_4-$NaIO_4$

To a stirred solution of **1** (2 g, 6.5 mmol), THF (40 ml) and H_2O (7.5 ml), 7.7 g (36.3 mmol) of $NaIO_4$ and 8.2 ml (0.065 mmol) of 0.2% OsO_4 aq. solution were added for 5 min. The mixture was further stirred for 6 h at 45° C. After filtering and removing the solvent, the crude was diluted in MeO^{t}Bu (50 ml) and washed with H_2O (3 x 50 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to afford a crude (1.87 g) that by column chromatography yielded **2** (1.4 g, 73%, 7:3 H-E), **3** (242 mg, 12%, 3:7 H-E), **4** (82 mg, 5%, 1:1 H-E), **5** (18 mg, 1%, 4:6 H-E) and **6** (39 mg, 2%, 6:4 H-E).

8α-acetoxy-13,14,15,16-tetranor-12-labdanal (**2**): oil; $[\alpha]_D$ -30.7°, (*c*, 0.09); IR (neat): ν 2870, 1724, 1246, 937; ^1H NMR (300 MHz): δ 0.77 (3H, *s*, Me-10), 0.83 (3H, *s*, Meβ-4), 0.86 (3H, *s*, Meα-4), 1.48 (3H, *s*, Meβ-8), 1.85 (3H, *s*, AcO-8), 9.64 (1H, *dd*, 1.8, 3.4, H-12); ^{13}C NMR (75 MHz): δ 39.81 (C-1), 18.27 (C-2), 41.82 (C-3), 33.11 (C-4), 55.59 (C-5), 19.73 (C-6), 40.28 (C-7), 86.08 (C-8), 53.59 (C-9), 38.44 (C-

10), 28.95 (C-11), 202.42 (C-12), 22.52 (C-17), 33.25 (C-18), 21.31 (C-19), 15.88 (C-20), 169.66 (C-21), 20.06 (C-22); MS m/z (rel. int.): 295 ($M+1^+$, 1), 251 (M-MeCO$^-$, 100), 235 (45), 191 (78).

8α-acetoxy-13,14,15,16-tetranor-12-labdanoic acid (**3**): oil; IR (neat): ν 3450, 1727, 1703, 1240, 941; ^{1}H NMR (300 MHz): δ 0.78 (3H, *s*, Me-10), 0.82 (3H, *s*, Meβ-4), 0.87 (3H, *s*, Meα-4), 1.50 (3H, *s*, Meβ-8), 1.86 (3H, *s*, AcO-8); ^{13}C NMR (75 MHz): δ 39.07 (C-1), 18.27 (C-2), 41.60 (C-3), 33.11 (C-4), 55.35 (C-5), 19.78 (C-6), 38.85 (C-7), 86.27 (C-8), 55.35 (C-9), 38.62 (C-10), 30.26 (C-11), 180.10 (C-12), 22.46 (C-17), 33.27 (C-18), 21.34 (C-19), 15.65 (C-20), 169.88 (C-21), 19.87 (C-22); MS m/z (rel. int.): 295 ($M+1^+$, 0.4), 251 (M-MeCO$^-$, 100), 191 (21.8).

(12S)-13,14,15,16-tetranor-8α,12-epoxy-12-labdanol (**4**): oil; $[\alpha]_D$ +66.3°, (*c*, 0.64); IR (neat): ν 3595, 1072, 943; ^{1}H NMR (300 MHz): δ 0.80 (3H, *s*, Me-10), 0.84 (6H, *s*, Meβ, Meα-4), 1.21 (3H, *s*, Meβ-8), 5.41 (1H, *t*, 5.64, H-12); ^{13}C NMR (75 MHz): δ 39.71 (C-1), 18.33 (C-2), 42.42 (C-3), 33.05 (C-4), 57.00 (C-5), 20.46 (C-6), 39.95 (C-7), 81.18 (C-8), 60.20 (C-9), 36.03 (C-10), 30.82 (C-11), 101.83 (C-12), 23.48 (C-17), 33.45 (C-18), 21.03 (C-19), 15.16 (C-20); MS m/z (rel. int.): 252 (M^+, 15), 237 (25), 191 (78), 177 (15), 137 (35), 109 (44), 69 (76), 43 (55).

11-acetoxy-8α-drimanol (**5**): oil; IR (neat): ν 3458, 1736, 1242, 940; ^{1}H NMR (300 MHz): δ 0.79 (3H, *s*, Me-10), 0.85 (3H, *s*, Meβ-4), 0.87 (3H, *s*, Meα-4), 1.17 (3H, *s*, Meβ-8), 2.03 (3H, *s*, AcO-8), 4.23 (1H, *dd*, 5.33, 11.77, H-11), 4.33 (1H, *dd*, 4.42, 11.77, H'-11); ^{13}C NMR (75 MHz): δ 39.71 (C-1), 18.36 (C-2), 41.70 (C-3), 33.17 (C-4), 55.70 (C-5), 20.26 (C-6), 43.93 (C-7), 72.63 (C-8), 59.94 (C-9), 38.08 (C-10), 62.55 (C-11), 24.55 (C-12), 33.43 (C-13), 21.12 (C-14), 15.78 (C-15), 171.31(C-16), 21.26 (C-17); MS m/z (rel. int.): 283 ($M+1^+$, 1), 205 (100), 85 (60.2), 51 (100).

14,15-dinor-8α,12-epoxy-13-labdanone (**6**): oil; ^{1}H NMR (80 MHz): δ 0.85 (6H, *s*, Me-10, Meβ), 0.90 (3H, *s*, Meα-4), 1.18 (3H, *s*, Meβ-8), 1.98 (3H, *s*, Ac-12), 4.39 (1H, *dd*, 4, 10, H-12).

14,15-dinor-8α-hydroxy-13-labdanone (7)

To a stirred solution of **1** (120 mg, 0.39 mmol) THF (2 ml) and H_2O (0.5 ml), 417 mg (1.95 mmol) of $NaIO_4$ and 0.5 ml (0.0039 mmol) of 0.2% OsO_4 aq. solution were added. The mixture was then stirred for 6 h at 10°C. After working-up as described for oxidation of **1**, **7** (92.8 mg, 85%) was the only product obtained: oil; $[\alpha]_D$ +6.7, (*c*, 1); IR (neat): ν 3489, 1774, 1048; ^{1}H NMR (300 MHz): δ 0.75 (3H, *s*, Me-10), 0.77 (3H,*s*, Meβ-4), 0.83 (3H, *s*, Meα-4), 1.12 (3H, *s*, Meβ-8), 1.83 (1H, *dt*, 3.1, 12.2, H_{eq}-7), 2.10 (3H, *s*, Me-13), 2.54 (1H, *ddd*, 5.7, 7.8, 17.8, H-12), 2.66 (1H, *dd*, 7.8, 17.8, H'-12); ^{13}C NMR (75 MHz): δ 39.98 (C-1), 18.68 (C-2), 41.82 (C-3), 33.14 (C-4), 55.97 (C-5), 20.41 (C-6), 44.43 (C-7), 73.79 (C-8), 60.53 (C-9), 39.21 (C-10), 18.36 (C-11), 46.19 (C-12), 210.56 (C-13), 29.94 (C-16), 24.03 (C-17), 33.34 (C-18), 21.44 (C-19), 15.13 (C-20); MS m/z (rel. int.): 280 (M^+, 0.7), 262 (M^+-H_2O, 3.2), 191 (5.1), 177 (6.5), 135 (5.5), 109 (19.7), 43 (100).

14,15-dinor-8α,13-epoxy-12-labdene (8)

A solution of **7** (200 mg, 0.71 mmol) in benzene (1 ml) was refluxed for 1 h with water removal. After evaporating the solvent, **8** (187 mg, quantitative) was obtained: oil; $[\alpha]_D$ +5.7, (*c*, 1.6); IR (neat): ν 3053, 1681; ^{1}H NMR (300 MHz): δ 0.79 (6H, *s*, Me-10, Meβ-4), 0.86 (3H, *s*, Meα-4), 1.13 (3H, *s*, Meβ-8), 1.66 (3H, *br s*, Me-13), 1.91 (1H, *dt*, 3.2, 12.3, H_{eq}-7), 4.41 (1H, *m*, H-12); ^{13}C NMR (75 MHz): δ 39.29 (C-1), 18.56 (C-2), 41.12 (C-3), 33.14 (C-4), 55.17 (C-5), 19.74 (C-6), 41.91 (C-7), 76.19 (C-8), 52.44 (C-9),

36.67 (C-10), 18.24 (C-11), 94.57 (C-12), 147.84 (C-13), 20.43 (C-16), 24.07 (C-17), 33.42 (C-18), 21.55 (C-19), 15.00 (C-20); MS m/z (rel. int.): 262 (M^+, 19.6), 237 (40.7), 191 (29.5), 135 (23.2), 109 (84.5), 43 (100).

13,14,15,16-tetranor-12-acetoxy-8α-labdanol (9)

To a stirred solution of **2-6** (1.8 g, 78% of **2**) in THF (40 ml), 2.3 g (60.5 mmol) of $NaBH_4$ were added. The reaction mixture was then stirred for 30 min. at room temperature. The solvent was evaporated and the residue solved in MeO^tBu (50 ml) and washed with H_2O (3 x 50 ml). Combined organic phases were dried over anh. Na_2SO_4, filtered and evaporated to dryness to afford **9** (1.4 g, 99.5%): oil; IR (neat): ν 3453, 1735, 1243, 1072, 1030, 940; ^1H NMR (300 MHz): δ 0.77 (6H, *s*, Me-10, Meβ-4), 0.85 (3H, *s*, Meα-4), 1.13 (3H, *s*, Meβ-8), 1.87 (1H, *dt*, 3.18, 12.2, H_{eq}-7), 2.00 (3H, *s*, AcO-8), 4.06 (1H, *m*, H-12), 4.13 (1H, *m*, H'-12); ^{13}C NMR (75 MHz): δ 39.56 (C-1), 18.36 (C-2), 41.85 (C-3), 33.23 (C-4), 56.02 (C-5), 20.44 (C-6), 44.33 (C-7), 73.52 (C-8), 57.98 (C-9), 38.71 (C-10), 24.44 (C-11), 66.59 (C-12), 23.90 (C-17), 33.34 (C-18), 21.43 (C-19), 15.28 (C-20), 171.14 (C-21), 21.10 (C-22).

13,14,15,16-tetranor-8α,12-labdanediol (10)

To a stirred solution of **9** (1.4 g, 4.7 mmol) in MeOH (14 ml), 14 ml of 10% methanolic KOH were added. The resulting solution was kept at room temperature for 2 h. After evaporation, the crude was solved in Me^tBuO (20 ml) and washed successively with 2N ClH solution (2 x 20 ml), sat. $NaHCO_3$ (2 x 20 ml) and H_2O (20 ml). The organic phase was dried over anh. Na_2SO_4 and evaporated to afford a crude reaction(1.2 g) that by column chromatography yielded **10** (967 mg, 80% from **9**): white crystals; $[\alpha]_D$ -15°, (*c*, 1); IR (nujol): ν 3244, 1052; ^1H NMR (300 MHz): δ 0.77 (6H, *s*, Me-10, Meβ-4), 0.85 (3H, *s*, Meα-4), 1.16 (3H, *s*, Meβ-8), 1.87 (1H, *dt*, 3.20, 12.2, H_{eq}-7), 3.42 (1H, *dt*, 6.9, 10.3, H-12), 3.75 (1H, *dt*, 4.3, 10.3, H'-12); ^{13}C NMR (75 MHz): δ 39.31 (C-1), 18.38 (C-2), 41.87 (C-3), 33.24 (C-4), 55.99 (C-5), 20.42 (C-6), 44.15 (C-7), 72.94 (C-8), 59.22 (C-9), 38.93 (C-10), 27.85 (C-11), 63.98 (C-12), 24.56 (C-17), 33.38 (C-18), 21.48 (C-19), 15.29 (C-20); MS m/z (rel. int.): 254 (M^+, 0.41), 236 (M^+-H_2O, 25), 177 (26.3), 151 (18.1), 95 (48.8), 43 (100).

Isolation of (+)-*cis*-abienol (11)

A solution of Canadian balsam (48 g) in Et_2O (500 ml) was successively washed with 2% NaOH solution (4 x 200 ml) and water (3 x 50 ml). The organic phase was dried over anh. $NaSO_4$ and evaporated to afford a residue (18.4 g) that by vacuum distillation yielded almost pure **11** (7.8 g, 48%; 23-36°C / 0.4-0.1 mmHg).

Ozonolysis of (+)-*cis*-abienol (11)

A solution of **11** (980 mg, 338 mmol) in CH_2Cl_2 (100 ml) was slowly bubbled with a O_3/O_2 mixture at -78°C for 4.5 h. The solution was flushed with argon and the solvent evaporated under vacuum at room temperature. The residue was solved in THF (70ml) and $LiAlH_4$ (1.5 g, 39.47 mmol) was added. The mixture was allowed to stir for 2 h at room temperature, then it was diluted with Et_2O (50 ml) and washed successively with 10% HCl (2 x 30 ml), sat. $NaHCO_3$ solution (2 x 30 ml) and water (30 ml). The organic phase was dried over anh. Na_2SO_4 and evaporated to yield a crude reaction (1.39 g) which was crystallized from hexane to afford **10** (0.74 g, 86.6%).

Cyclization of 10 to give Ambrox (12)

A stirred mixture of **10** (500 mg, 1.97 mmol), Py (4 ml) and ClTs (375 mg, 1.97 mmol) was kept at room temperature for 1 h. Then H_2O (1 ml) was added and the separed solid filtered. This residue was solved in Me^{t}BuO (5 ml) and successively washed with 2N ClH solution (2 x 5 ml), sat. $NaHCO_3$ solution (2 x 5 ml) and H_2O (10 ml). The organic phase was dried over anh. Na_2SO_4 and evaporated to afford 460 mg (99%) of Ambrox (**12**): white cristals; $[\alpha]_D$ -22.1° (*c*, 0.68); IR (KBr): ν 1083, 1006, 978, 915 (ether); ^{1}H NMR (300 MHz): δ 0.81 (3H, *s*, Meβ-4 or Me-10), 0.82 (3H, *s*, Me-10 or Meβ-4), 0.86 (3H, *s*, Meα-4), 1.07 (3H, *s*, Me-8), 3.81 (1H, *q*, 8.3, H-12), 3.90 (1H, *td*, 8.3, 4.3, H'-12); ^{13}C NMR (75 MHz): δ 39.95* (C-1), 18.39 (C-2), 42.43 (C-3), 33.06 (C-4), 57.25 (C-5), 20.64 (C-6), 39.73 (C-7)*, 79.91 (C-8), 60.11 (C-9), 36.18 (C-10), 22.62 (C-11), 64.97 (C-12), 21.13 (C-17), 33.58 (C-18), 21.13 (C-19), 15.03 (C-20); MS *m/z* (rel. int.): 236 (M^+, 2%), 221 (M^+-CH_3, 100), 205 (5), 203 (4), 177 (3), 137 ($C_{10}H_{17}^+$, 15), 109 (5), 97 (13), 81 (7), 67 (6), 55 (5), 43 (8).

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