

Synthesis of ambergris odorant *ent*-ambrox

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Dedicated to Prof. Dr. Edmundo A. Rúveda on the occasion of his 70th anniversary

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Abstract

A synthesis of the ambergris odorant *ent*-ambrox starting from (-)-ozic acid is described.

Keywords: Ambergris odorant, *ent*-ambrox, ozic acid, diterpene

Introduction

Ambergris is a metabolic product of the sperm whale (*Physeter macrocephalus*) and is considered one of the most valuable animal perfumes besides civet, musk and castoroleum.¹ Due to enforced whale protection, the use of ambergris in perfumery has been abolished, thus encouraging chemists to search for new synthetic substitutes. (-)-Tetranorlabdane oxide (**1**) is one of the commercially important products, synthesized for the first time by Stoll and Hinder in 1950,² and is commonly known under the trade names Ambrox[®] (Firmenich), Amberlyn[®] (Quest) and Ambroxan[®] (Henkel).³

Nowadays, an increasing number of publications on this topic demonstrates the great interest and importance of ambergris derivatives.⁴ Many racemic⁵ and chiral syntheses have been described in the literature. Among the chiral syntheses, several used naturally occurring terpenes as starting materials, for example, monoterpenes such as (+)-carvone⁶ and thujone,^{7,8} sesquiterpenes such as (-)-drimenol⁹ or diterpenes such as (-)-labdanolic acid,^{4a,10} (+)-larixol,¹¹ (+)-*cis*-abienol,¹² (-)-levopimaric acid,¹³ (-)-abiatic acid,¹⁴ (-)-communic acid,¹⁵ (+)-manoyl oxide,¹⁶ and (-)-sclareol.¹⁷ More recently, polyenes such as geranylacetone¹⁸ and homofarnesol^{4b,19} have been used for the synthesis of Ambrox[®] and enzymatic reactions have been employed for the resolution.²⁰ As part of our current interest on the synthesis of terpenoids and analogues starting from readily available natural resinic acids, we had synthesized the enantiomer, *ent*-ambrox (**2**), with 46% ee starting from (-)-copalic acid.²¹ Continuing our

research program and in order to obtain pure *ent*-ambrox, we undertook the synthesis of **2** starting from (-)-ozic acid (**3a**) (Figure 1). This acid is the main component of the seed pod extract of *Hymenaea courbaril* var. *altissima*²² and can be obtained readily as the methyl ester **3b**, after esterification with diazomethane.

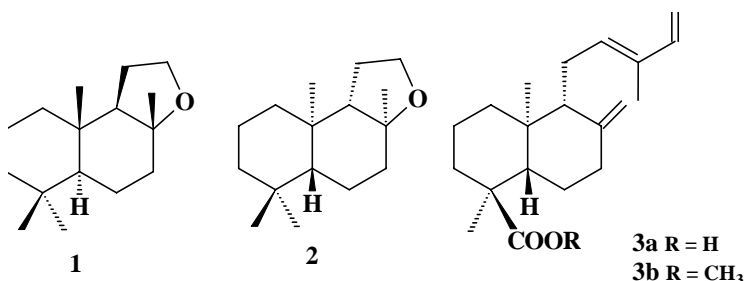
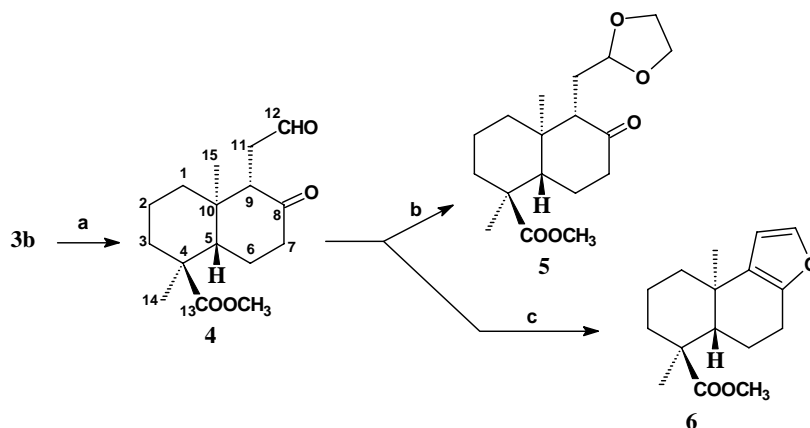


Figure 1

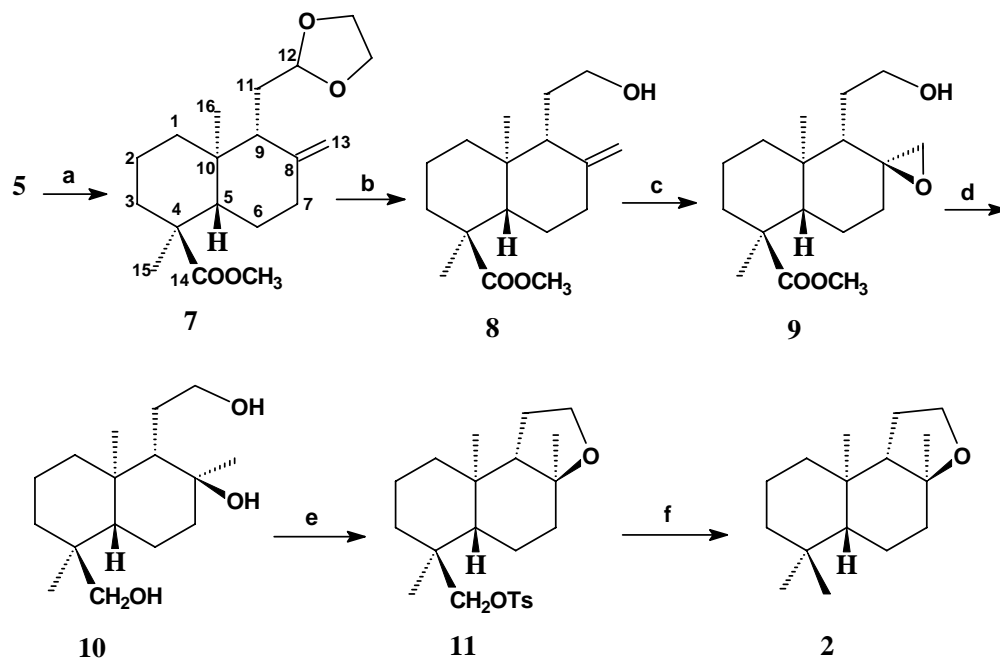
Results and Discussion

The reaction of **3b** with a stream of ozone followed by treatment with PPh_3 furnished the corresponding keto-aldehyde **4** in 85% yield (Scheme 1). In order to selectively protect the carbonyl group of the aldehyde, treatment of **4** with ethylene glycol in benzene using camphorsulfonic acid as catalyst gave the desired compound **5** in 90% yield. When *p*-TsOH was used as the catalyst, the furan derivative **6** was obtained as the sole product, in 48% yield, instead of the desired **5**. Compound **6** was characterized through NMR spectroscopic analysis. The presence of two olefinic hydrogens at δ 6.08 (d, 1H, $J = 2.20$) and at δ 7.11 (d, 1H, $J = 2.2$ Hz) in the ^1H NMR spectra and four sp^2 carbons at δ 106.7 (CH), 129.8 (C), 140.7 (CH) and at δ 148.3 (C) in the ^{13}C NMR spectra indicates clearly that we had a furan unit in the molecule.



Scheme 1. a) i. O_3 , CH_2Cl_2 , -78°C , ii. PPh_3 , rt, 85%; b) camphorsulfonic acid, benzene, reflux, 90%, c) *p*-TsOH, benzene, reflux, 48%.

Following the synthetic sequence, the intermediate **5** was submitted to the Wittig reaction using methyltriphenylphosphonium bromide and *n*-BuLi as the base. However, this met with failure and starting material was recovered. After some attempts, we obtained the olefination product by treating **5** with $\text{CH}_2\text{Br}_2/\text{Zn}/\text{TiCl}_4$ in CH_2Cl_2 , following the Lombardo's protocol,²³ where **7** was obtained in 73% yield (Scheme 2).



Scheme 2. (a) Zn, TiCl_4 , CH_2Br_2 , CH_2Cl_2 , rt, 73%; (b) i. THF, HCl 1%, rt; ii. NaBH_4 , MeOH, rt, 81%; (c) *m*CPBA, CH_2Cl_2 , rt, 90%; (d) LiAlH_4 , THF, reflux, 86%; (e) TsCl, Py, rt, 62%; (f) i. NaI, Zn, DMF, 120°C ; ii. *m*CPBA, CH_2Cl_2 , rt, 58% (two steps).

Next, the deprotection of the ketal using 1% HCl in THF furnished an unstable aldehyde which decomposed during purification. Thus, after deprotection, the crude material was treated with NaBH_4 in MeOH to furnish the corresponding hydroxy ester **8** in 81% yield. Epoxidation of **8** with *m*CPBA in CH_2Cl_2 followed by reduction of the epoxide **9** with LiAlH_4 , furnished the triol **10** in 77% overall yield. Since it is known that treatment of hydroxy groups at C-8 and C-12 with 1.0 equivalent of MsCl^{21} leads to tetrahydrofuran derivatives, triol **10** was treated with 2.0 equivalent of TsCl in pyridine. As expected, monotosylate **11** was obtained in 62% yield. Finally, treatment of **11** with NaI and activated Zn in DMF at 120°C furnished *ent*-ambrox (**2**) together with an inseparable mixture of isomeric olefins. The presence of unsaturated compounds was detected by ^1H NMR spectral analysis, which showed signals between δ 4.0 and 5.2, characteristic of olefinic hydrogens and also by ^{13}C NMR spectra which showed signals of sp^2 carbons between δ 120 and 140. Analysis by GC/MS showed the presence of at least 4 compounds with masses 2 Daltons less than the expected product. Based on these data, it was

possible to infer that unexpected rearrangement products were obtained during the reduction reaction. Due to the difficulty observed in purification of the desired product, the crude mixture was treated with *m*CPBA and after purification using silica gel column chromatography, *ent*-ambrox (**2**) was obtained in a 58% overall yield. All spectroscopic data were in good agreement with those reported previously.^{21,24}

Experimental Section

General Procedures. Melting points were determined on a Micro-Química MQAPF-31 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FTIR or on a BOMEM MB-100 instrument. ¹H NMR and ¹³C NMR spectra were recorded on a Varian Gemini 2000 spectrometer at 300 MHz and 75 MHz, respectively, or on a Varian Inova 500 spectrometer at 500 MHz and 125 MHz, respectively, with CDCl₃ as solvent and TMS as internal standard. GC/MS analyses were carried out using a HP-5990/5970 system equipped with J&W Scientific DB-5 [fused silica capillary column (30m×0.25mm×0.25μm)] and using helium as the carrier gas. High resolution mass spectra were obtained on a VG Autospec-Micromass instrument. Elemental analyses were performed with a Perkin-Elmer 2400 CHN analyzer. Optical rotations were measured with a Carl Zeiss photoelectric polarimeter.

Keto-aldehyde 4. To a solution of (-)-methyl ozate (**3b**) (2.4 g, 7.59 mmol) in 50 mL of CH₂Cl₂ at -78°C, was bubbled a stream of ozone (200 mL/min) over 5 h until a blue color persisted. The excess of ozone was eliminated by flushing nitrogen through mixture and then PPh₃ (7.5 g, 28.6 mmol) was added and the mixture was stirred for 12 h at room temperature. After removal of the solvent under reduced pressure and purification of the residue by column chromatography (silica gel, petroleum ether:EtOAc, 85:15) **4** (1.8 g, 85%) was obtained as colorless crystals; mp. 74-76°C; [α]_D²⁰ +54.2 (c = 2.5, CHCl₃); IR (KBr) ν_{max} : 2935, 2820, 2722, 1724, 1440, 1387, 1249, 1190, 1168, 1147, 1116, 964, 677 cm⁻¹; NMR (500 MHz, CDCl₃) δ : 0.78 (3H, s, H-15), 1.22 (3H, s, H-14), 1.33 (1H, dd, *J* = 4.8, 12.9 Hz, H-1), 1.58-1.63 (3H, m, H-1', H-2), 1.64-1.67 (1H, m, H-6), 1.69 (1H, dt, *J* = 1.7, 2.9 Hz, H-3), 1.71-1.82 (2H, m, H-3', H-6'), 2.23-2.29 (1H, m, H-7) 2.45-2.50 (3H, m, H-5, H-11), 2.96 (1H, bs, H-9), 2.97 (1H, dq, *J* = 9.5 Hz; *J* = 1.0 Hz, H-7'), 3.72 (3H, s, OCH₃), 9.83 (1H, s, H-12); ¹³C NMR (125 MHz, CDCl₃) δ : 15.6 (C-15), 16.9 (C-14), 17.8 (C-2), 25.5 (C-6), 37.1 (C-3), 37.1 (C-7), 38.5 (C-1), 40.6 (C-10), 41.3 (C-11), 47.4 (C-4), 48.1 (C-5), 52.5 (-OCH₃), 58.4 (C-9), 178.8 (C-13), 201.2 (C-12), 209.8 (C-8); MS (70 eV) *m/z* (relative intensity): 224 (39), 252 (19), 281 (16) 123 (100); Anal. Calcd. for C₁₆H₂₄O₄: C, 68.55; H, 8.63. Found: C, 68.66; H, 8.65.

Ketal 5. To a solution of aldehyde **4** (500 mg, 1.78 mmol) in dry benzene (30.0 mL) was added ethylene glycol (0.12 mL, 2.14 mmol) and a catalytic amount of camphorsulfonic acid (2 mg). After refluxing for 1 h using a Dean-Stark apparatus filled with benzene, the mixture was cooled to room temperature and the solution was washed with 5% aqueous NaHCO₃ solution and brine,

dried with anhydrous MgSO_4 and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (petroleum ether:EtOAc, 85:15) to give **5** (500 mg, 90%) as colorless crystals; mp. 118-119°C; $[\alpha]_D^{20} +43.2$ ($c = 2.6$, CHCl_3); IR (KBr) ν_{max} : 2950, 2886, 1722, 1471, 1429, 1410, 1389, 1247, 1189, 1168, 1143, 1115, 1050, 1014, 979, 959, 855 cm^{-1} ; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ : 0.71 (3H, s, H-15), 1.17 (3H, s, H-14), 1.32 (1H, dt, $J = 4.2, 12.9$ Hz, H-1), 1.43 (1H, dd, $J = 6.8, 13.4$ Hz, H-11), 1.49-1.68 (4H, m, H-2, H-2', H-3, H-6), 1.69-1.79 (3H, m, H-1', H-3, H-6), 2.28 (1H, ddd, $J = 2.9, 10.0, 16.4$ Hz, H-11'), 2.37-2.44 (4H, m, H-5, H-7, H-7', H-9), 3.68 (3H, s, $-\text{OCH}_3$), 3.76-3.82 (2H, m, $-\text{OCH}_2-$), 3.87-3.95 (2H, m, $-\text{OCH}_2-$), 4.80 (1H, dd, $J = 2.9, 6.8$ Hz, H-12); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ : 14.9 (C-15), 16.5 (C-14), 17.7 (C-2), 25.8 (C-6), 25.9 (C-11), 36.9 (C-3), 37.9 (C-1), 41.2 (C-4), 41.8 (C-7), 47.3 (C-10), 48.2 (C-5), 52.1 ($-\text{OCH}_3$), 58.8 (C-9), 64.6 ($-\text{OCH}_2-$), 64.7 ($-\text{OCH}_2-$), 103.4 (C-12), 178.7 (C-13), 210.5 (C-8); MS (70 eV) m/z (relative intensity): 324 (5), 265 (9), 163 (12), 121 (6), 87 (100), 73 (59); HRMS m/z 324.19367, calcd. for $\text{C}_{18}\text{H}_{28}\text{O}_5$ 324.19366.

Furan 6. To a solution of aldehyde **4** (20.0 mg, 0.07 mmol) in dry benzene (10.0 mL) was added ethylene glycol (0.1 mL, 1.7 mmol) and a catalytic amount of *p*-TsOH (1 mg). After refluxing for 30 min. using a Dean-Stark apparatus filled with benzene, the mixture was cooled to room temperature and the solution was washed with 5% aqueous NaHCO_3 solution, brine and dried with anhydrous MgSO_4 and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (petroleum ether:EtOAc, 95:5) to give a product proposed as **6** (9 mg, 48%) as a yellowish oil. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 1.07 (3H, s, H-15), 1.15 (3H, s, H-14), 1.30-1.39 (2H, m, H-1, H-6), 1.50-1.78 (5H, m, H-2, H-2', H-3, H-3', H-6'), 1.82-1.86 (1H, m, H-1'), 2.06 (1H, dd, $J = 1.8, 12.1$, H-5), 2.51-2.56 (2H, m, H-7, H-7'), 3.58 (3H, s, $-\text{OCH}_3$), 6.08 (1H, d, $J = 2.2$ Hz, H-11), 7.11 (1H, d, $J = 2.2$ Hz, H-12); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ : 16.1 (C-14), 18.0 (C-2), 21.7 (C-6), 23.6 (C-15), 24.1 (C-7), 33.8 (10), 36.9 (C-3) 37.4 (C-1), 46.5 (C-5), 47.2 (C-4), 51.9 ($-\text{OCH}_3$), 106.7 (C-11), 129.8 (C-9), 140.7 (C-12), 148.3 (C-8), 179.0 (C-13); MS (m/z) 262 (M^+).

Olefin 7. To a suspension of activated zinc dust (900 mg, 13.8 mmol) in dry THF (8.0 mL), containing CH_2Br_2 (0.32 mL, 4.56 mmol) at -40°C , was added dropwise, TiCl_4 (0.40 mL, 2.32 mmol) with vigorous stirring. The cooling bath was then removed and the temperature was left to rise to 5°C . After stirring the mixture for 3 days, the solution was diluted with CH_2Cl_2 (1.6 mL), cooled to 0°C and a solution of ketal **5** (750 mg, 2.32 mmol) in dry CH_2Cl_2 (1.6 mL) was added. The cooling bath was then removed and after stirring the reaction for 1.5 h at room temperature, the mixture was diluted with *n*-pentane (10 mL) and a saturated NaHCO_3 solution (2 mL) was added carefully. The organic phase was separated and the aqueous phase was extracted with *n*-pentane (2 x 15 mL). The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4 and filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (petroleum ether:EtOAc, 95:5) to give **7** (540 mg, 73%) as colorless a solid; mp. 115-116°C; $[\alpha]_D^{20} -21.7$ ($c = 2.1$, CHCl_3); IR (KBr) ν_{max} : 2949, 2887, 2865, 1713, 1644, 1437, 1411, 1388, 1243, 1129, 1104, 1049 cm^{-1} ; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ : 0.70 (3H, s, H-16), 1.15 (3H, s, H-15), 1.20-1.24 (2H, m, H-1, H-6), 1.45 (1H, dq, $J =$

4.3, 12.8 Hz, H-6'), 1.55-1.61 (2H, m, H-2, H-2'), 1.66-1.80 (4H, m, H-1', H-3, H-3', H-11), 1.89 (1H, dt, $J = 2.1, 12.7$ Hz, H-11'), 2.00-2.07 (2H, m, H-5, H-9), 2.09 (1H, dd, $J = 4.3, 12.8$ Hz, H-7), 2.35 (1H, ddd, $J = 2.1, 4.3, 12.8$ Hz, H-7'), 3.66 (3H, s, -OCH₃), 3.81-3.84 (2H, m, -OCH₂-), 3.95-3.98 (2H, m, -OCH₂-), 4.61 (1H, bs, H-13), 4.86 (1H, bs, H-13), 4.86-4.89 (1H, m, H-12); ¹³C NMR (125 MHz, CDCl₃) δ : 14.6 (C-16), 16.5 (C-15), 18.4 (C-2), 26.6 (C-6), 28.5 (C-11), 36.9 (C-3), 37.6 (C-7), 37.9 (C-1), 38.5 (C-4), 47.7 (C-10), 49.5 (C-5), 51.8 (-OCH₃), 52.0 (C-9), 64.6 (-OCH₂-), 64.7 (-OCH₂-), 103.9 (C-12), 107.3 (C-13), 147.9 (C-8), 179.1 (C-14); HRMS m/z 322.21458, calcd. for C₁₉H₃₀O₄ 322.21441.

Hydroxy-olefin 8. To a solution of **7** (100 mg, 0.31 mmol) in THF (6 mL) at 0°C was added, drop by drop, an aqueous 1% HCl solution (2 mL). After removal of the cooling bath, the mixture was stirred for 12 h and then was neutralized by adding 5% aqueous NaHCO₃ solution and extracted with Et₂O. The organic layer was dried with anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The crude material, without any purification, was dissolved in MeOH (12 mL) and NaBH₄ (30 mg, 0.79 mmol) was added. After stirring the mixture at room temperature for 2 h, the solvent was removed under reduced pressure and the residue was dissolved in CH₂Cl₂ (20 mL). The organic phase was washed with a saturated aqueous solution of NH₄Cl and dried with anhydrous Na₂SO₄. The solvent was removed under reduced pressure. The residue was then chromatographed on silica gel (petroleum ether:EtOAc, 85:15) to give **8** (77 mg, 89%) as a colorless oil; $[\alpha]_D^{20}$ -15.3 ($c = 6.2$, CHCl₃); IR (film) ν_{\max} : 3383, 3079, 2930, 2866, 1726, 1643, 1445, 1387, 1245, 1197, 1173, 1129, 1046, 981, 892, 737 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ : 0.72 (3H, s, H-16), 1.15 (3H, s, H-15), 1.19-1.26 (2H, m, H-1, H-6), 1.37 (1H, bs, -OH), 1.46 (1H, dq, $J = 4.4, 12.8$ Hz, H-6'), 1.54-1.87 (8H, m, H-1', H-2, H-2', H-3, H-3', H-9, H-11, H-11'), 1.99 (1H, dd, $J = 2.9, 12.5$ Hz, H-5), 2.05 (1H, dt, $J = 5.1, 12.8$ Hz, H-7), 2.35 (1H, ddd, $J = 2.2, 4.4, 12.8$ Hz, H-7'), 3.49-3.58 (1H, m, H-12), 3.67 (3H, s, OCH₃), 3.70-3.78 (1H, m, H-12), 4.57 (1H, bs, H-13), 4.84 (1H, bs, H-13'); ¹³C NMR (75 MHz, CDCl₃) δ : 15.4 (C-16), 17.2 (C-15), 19.1 (C-2), 27.3 (C-6), 27.5 (C-11), 37.5 (C-3), 38.3 (C-7), 38.6 (C-1), 39.3 (C-4), 48.3 (C-10), 50.3 (C-5), 52.5 (-OCH₃), 53.3 (C-9), 62.9 (C-12), 107.5 (C-13), 148.4 (C-8), 179.6 (C-14); HRMS m/z 280.20346, calcd. for C₁₇H₂₈O₃ 280.20385.

Epoxy-alcohol 9. To a stirred solution of **8** (70 mg, 0.25 mmol) in dry CH₂Cl₂ (5 mL) at 0°C was added 50% *m*CPBA (86 mg, 0.5 mmol). After stirring for 3 h, the mixture was diluted with CH₂Cl₂ (20 mL) and washed successively with aqueous Na₂S₂O₅ and NaHCO₃ solutions. The organic phase was then dried with anhydrous Na₂SO₄, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether:EtOAc, 85:15 to 75:25) to give a product proposed as **9** (67 mg, 90%) as colorless crystals; mp. 51-53°C; $[\alpha]_D^{20}$ +12.2 ($c = 2.5$, CHCl₃); IR (film) ν_{\max} : 3428, 2942, 2869, 1449, 1388, 1248, 1174, 1151, 1134, 1104, 1048, 978, 736 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ : 0.82 (3H, s, H-16), 0.94-1.01 (1H, m, H-11), 1.10-1.14 (1H, m, H-1), 1.16 (3H, s, H-15), 1.29-1.38 (2H, m, H-6, H-7), 1.50-1.60 (5H, m, H-2, H-2', H-3, H-6', H-11'), 1.69-1.77 (4H, m, H-1', H-3', H-9, -OH), 1.90 (1H, dd, $J = 2.4, 12.5$ Hz, H-5), 1.96 (1H, ddt, $J = 2.1, 4.6, 12.5$ Hz, H-7'), 2.57 (1H, d, $J = 4.0$ Hz, H-13), 2.86 (1H, dd, $J = 2.1, 4.0$ Hz, H-13'), 3.46 (1H, ddd, $J = 5.2, 8.6, 10.4$ Hz, H-12), 3.63 (1H, dt, $J = 5.5,$

10.4 Hz, H-12'), 3.66 (3H, s, -OCH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 14.9 (C-16), 16.4 (C-15), 17.6 (C-2), 24.1 (C-6), 25.1 (C-11), 35.8 (C-7), 36.7 (C-3), 37.7 (C-1), 39.4 (C-4), 47.4 (C-10), 49.1 (C-5), 50.7 (-OCH₃), 51.9 (C-13), 52.5 (C-9), 59.2 (C-8), 63.5 (C-12), 178.9 (C-14); MS (*m/z*) 296 (M⁺).

Triol 10. To a suspension of LiAlH₄ (37 mg, 1.0 mmol) in dry THF (25 mL) was added a solution of **9** (110 mg, 0.34 mmol) in dry THF (25 mL) and the mixture was refluxed for 3 h. After cooling to room temperature, the excess hydride was destroyed by the careful additions of 15% aqueous NaOH solution. The solid was removed by filtration through a Celite pad and the organic phase was washed with brine, dried with anhydrous MgSO₄, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (silica gel, CH₂Cl₂:MeOH, 95) to give triol **10** (78 mg, 86%) as colorless crystals; mp. 129-130°C; IR (KBr) ν_{\max} : 3330, 2928, 2861, 1477, 1450, 1076, 1051, 1031, 1000, 920 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 0.73 (3H, s, H-16), 0.83 (3H, s, H-15), 0.90-0.99 (1H, m, H-1), 1.19 (3H, s, H-13), 1.11-1.34 (5H, m, H-3, H-3', H-5, H-6, H-9), 1.40-1.71 (6H, m, H-1', H-2, H-2', H-6', H-11, H-11'), 1.80-1.97 (2H, m, H-7, H-7'), 2.20 (1H, bs, -OH), 2.66 (1H, bs, -OH), 2.82 (1H, bs, -OH), 3.07 (1H, d, *J* = 11.0 Hz, H-14), 3.44 (1H, d, *J* = 11.0 Hz, H-14'), 3.68 (2H, bt, *J* = 5.5 Hz, H-12, H12'); ¹³C NMR (75 MHz, CDCl₃) δ: 15.7 (C-16), 17.5 (C-15), 17.8 (C-2), 20.2 (C-6), 24.6 (C-13), 27.9 (C-11), 35.1 (C-3), 37.7 (C-4), 38.9 (C-1), 38.9 (C-10), 43.8 (C-7), 48.8 (C-5), 59.2 (C-9), 62.7 (C-12), 71.6 (C-14), 72.9 (C-8); HRMS *m/z* 270.21946, calcd. for C₁₆H₃₀O₃ 270.21950.

Tosylate 11. To a solution of **10** (70 mg, 0.26 mmol) in dry pyridine (5 mL) was added TsCl (100 mg, 0.52 mmol) and the mixture was stirred at room temperature for 12 h. The mixture was diluted with EtOAc (10 mL) and washed successively with 5% aqueous HCl solution, 5% aqueous NaHCO₃ solution and brine. The organic phase was dried with anhydrous MgSO₄, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether:EtOAc, 9:1) to give **11** (74 mg, 62%) as white crystals; mp. 160-161°C; IR (KBr) ν_{\max} : 2928, 2877, 1597, 1475, 1450, 1359, 1189, 1174, 1097, 960, 856, 812 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 0.79 (3H, s, H-16), 0.83 (3H, s, H-15), 0.99-1.09 (1H, m, H-1), 1.05 (3H, s, H-13), 1.18-1.59 (9H, m, H-1', H-2, H2', H-3, H-3', H-5, H-6, H-6', H-9), 1.64-1.82 (4H, m, H-7, H-7', H-11, H-11'), 2.46 (3H, s, Ph-CH₃), 3.55 (1H, d, *J* = 9.2 Hz, H-14), 3.70 (1H, d, *J* = 9.2, H-14'), 3.78-3.94 (2H, m, H-12, H-12'), 7.35 (2H, d, *J* = 8.1 Hz, Ph-H), 7.78 (2H, d, *J* = 8.4 Hz, Ph-H'); ¹³C NMR (75 MHz, CDCl₃) δ: 15.4 (C-16), 16.8 (C-15), 17.5 (C-2), 20.3 (C-6), 21.2 (C-13), 21.7 (Ph-CH₃), 22.7 (C-11), 35.6 (C-3), 36.2 (C-4), 36.8 (C-10), 39.1 (C-1), 39.3 (C-7), 50.2 (C-5), 59.9 (C-9), 64.9 (C-12), 77.8 (C-14), 79.4 (C-8), 127.8 (Ph-ortho), 129.7 (Ph-meta), 132.8 (Ph-para), 144.6 (Ph-*ipso*); HRMS *m/z* 406.21758, calcd. for C₂₃H₃₄O₄S 406.21778.

ent-Ambrox 2. To a suspension of NaI (280 mg, 1.87 mmol) and activated zinc dust (240 mg, 3.69 mmol) in dry DMF (18 mL) was added a solution of **11** (75 mg, 0.18 mmol) and the mixture was heated at 110°C for 12 h. After cooling the mixture to room temperature, the solution was diluted with *n*-pentane (20 mL) and filtered. The organic phase was then washed successively with 5% aqueous HCl solution, 2% aqueous Na₂S₂O₃ solution, brine, and dried with anhydrous

MgSO₄. The solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (5 mL) at room temperature and treated with 50% *m*CPBA (50 mg). After stirring for 3 h, the mixture was diluted with CH₂Cl₂ (15 mL) and washed with 10% aqueous Na₂S₂O₅ solution, brine and the organic phase was dried with anhydrous Na₂SO₄. After removing the solvent under reduced pressure, the residue was chromatographed on silica gel (petroleum ether:EtOAc, 95:5) to give *ent*-ambrox (**2**) (95 mg, 58%, two steps) as colorless crystals; mp. 75-76°C, {lit.²¹ mp. 69-70°; lit.²⁴ for enantiomer mp. 77-77.5°}; [α]_D²⁰ +27.0 (c = 1.0, CHCl₃), {lit.²⁴ [α]_D²⁰ +21.7}; IR (KBr) ν_{max}: 2921, 2869, 2841, 1765, 1456, 1378, 1274, 1218, 1160, 1084, 1068, 1025, 1007, 979, 955, 943 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 0.84 (3H, s, H-16), 0.85 (3H, s, H-15), 0.88 (3H, s, H-14), 0.94-1.05 (3H, m, H-1, H-2, H-5), 1.10 (3H, s, H-13), 1.36-1.51 (7H, m, H-2, H-1', H-6, H-7, H-7', H-9, H-11), 1.59-1.79 (3H, m, H-3, H-6', H-11'), 1.92-1.98 (1H, m, H-7), 3.79-3.96 (2H, m, H-12, H-12'); ¹³C NMR (75 MHz, CDCl₃) δ: 15.1 (C-16), 18.5 (C-2), 20.7 (C-6), 21.2 (C-15), 21.2 (C-13), 22.7 (C-11), 33.1 (C-4), 33.6 (C-14), 36.2 (C-10), 39.8 (C-7), 40.0 (C-1), 42.5 (C-3), 57.3 (C-5), 60.1 (C-9), 65.0 (C-12), 79.9 (C-8); MS (m/z) 236 (M⁺). Anal. Calcd. for C₁₆H₂₈O₂: C, 81.29; H, 11.94. Found: C, 81.24; H, 11.65.

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References and Notes

1. Ohloff, G. The Fragrance of Ambergris. In *Fragrance Chemistry*, Theimer, E.T., Ed.; Academic Press: New York, 1982, pp 535.
2. Stoll, M.; Hinder, M. *Helv. Chim. Acta* 1950, 33, 1251 *ibid.* 1308.
3. Sell, C. *Chem. Ind.* 1990, 20, 516.
4. For recent publications see: (a) Castro, J.M.; Salido, S.; Altarejos, J.; Noguera, M.; Sánchez, A. *Tetrahedron* 2002, 58, 5941; (b) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* 2002, 124, 3647; (c) Bolster, M.G.; Lagnel, B.M.F.; Jansen, B.J.M.; Morin, C.; Groot, A. *Tetrahedron* 2001, 57, 8369; (d) Moulines, J.; Lamidey, A.M.; Desvergnès-Breuil, V. *Synth. Commun.* 2001, 749.
5. Zoretic, P.A.; Fang, H.; Ribeiro, A. A. *J. Org. Chem.* 1998, 63, 4779 and references cited therein.
6. Haksma, A. A. V. H.; Swarts, H. J.; Jansen, B. J. M.; Groot, A. *Tetrahedron* 1994, 50, 10073.
7. Kutney, J. P.; Chen, Y. H. *Can. J. Chem.* 1994, 72, 1570.
8. Kutney, J. P.; Cirera, C. *Can. J. Chem.* 1997, 75, 1136.

9. Gonzalez Sierra, M.; Rúveda, E.A.; López, J.T.; Cortés, M.J. *Heterocycles* 1987, 26, 2801.
10. Bolster, M.G.; Jansen, B.J.M.; Groot, A. *Tetrahedron* 2001, 57, 5657.
11. Bolster, M.G.; Jansen, B.J.M.; Groot, A. *Tetrahedron* 2001, 57, 5663.
12. Barrero, A.F.; Alvarez-Manzaneda, E.J.; Altarejos, J.; Salido, S.; Ramos, J.M. *Tetrahedron* 1993, 49, 10405.
13. Nishi, Y.; Ishihara, H. *Jpn. Oil Chem. Soc.* 1989, 38, 276.
14. Koyama, H.; Kaku, Y.; Ohno, M. *Tetrahedron Lett.* 1987, 28, 2863.
15. Barrero, A.F.; Altarejos, J.; Alvarez-Manzaneda, E.J.; Ramos, J.M.; Salido, S. *Tetrahedron* 1993, 49, 9525.
16. Cambie, R.C.; Joblin, K.N.; Preston, A.F. *Aust. J. Chem.* 1971, 24, 583.
17. Barton, D.H.R.; Parekh, S.I.; Taylor, D.K.; Tse, C. *Tetrahedron Lett.* 1994, 35, 5801 and references cited therein.
18. Snowden, R. L.; Eichenberger, J-C.; Linder, S. M.; Sonnay, P.; Vial, C.; Schulte-Elte, K. H. *J. Org. Chem.* 1992, 57, 955.
19. Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* 2000, 122, 8131 and references cited therein.
20. Akita, H.; Nozawa, M.; Shimizu, H. *Tetrahedron: Asymmetry* 1998, 9, 1789.
21. Nunes, F.M.N.; Imamura, P.M. *J. Braz. Chem. Soc.* 1996, 7, 181. The optical purity of methyl copalate used in this work was evaluated to be 46% ee based on its optical rotation.
22. Nogueira, R.T.; Giacomini, R.A.; Shepherd, G.; Imamura, P.M. *J. Braz. Chem. Soc.* 2002, 13, 389.
23. (a) Lombardo, L. *Org. Synth.* 1987, 65, 81. (b) Lombardo, L. *Tetrahedron Lett.* 1982, 23, 4293.
24. Ohloff, G.; Giersch, W.; Pickenhagen, W.; Furrer, A.; Frei, B. *Helv. Chim. Acta* 1985, 68, 2022.