

THE PREPARATION OF OXYGENATED DERIVATIVES OF AMBROX AND ISOAMBROX FROM DRIMENOL

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ABSTRACT

The preparation of oxygenated derivatives of ambrox and isoambrox is described. The compounds 7 α -hydroxy-isoambrox, 7 β -hydroxy-isoambrox, 7 α -hydroxy-ambrox, 7 β -hydroxy-ambrox, 7-oxo-isoambrox and 7-oxo-ambrox have been synthesized from (-)-drimenol, readily available from the bark of *Drimys winteri*. The structures of the products were determined mainly by spectroscopic methods.

Key words: Ambrox, Isoambrox, Ambergris

INTRODUCTION

Ambergris is one of the most valuable animal perfumes, like civet, musk and castoreum.^{1,2} This substance is a metabolic product of the blue whale (*Physeter macrocephalus*) sperm that accumulates in the gut of the animal. It has been used for centuries because of its unique fragrance and fixative properties,³ but is now commercially banned or taken off the market thanks to the Marine Mammals Protection Act. Extensive reviews with detailed studies correlating their structure with smell, synthetic efforts, etc., are available.⁴

The most important equivalent of this scarce natural source is the norlabdane oxide Ambrox® (1) (trade name of Firmenich SA). The growing demand for ambergris-type odorants has stimulated an intense search for substitutes. For this reason various synthetic routes to Ambrox and Isoambrox have been developed.⁵⁻¹⁰

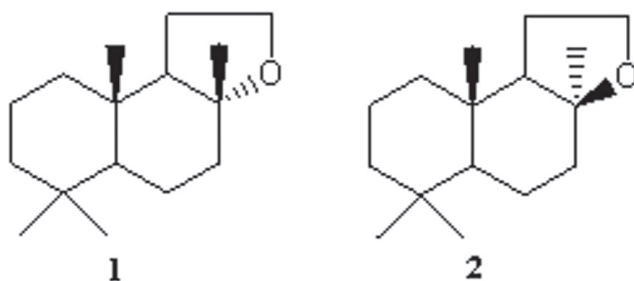


Figure 1. Structures of Ambrox (1) and Isoambrox (2)

Using the framework of our studies of natural sesquiterpenes to provide materials for the preparation of various ambergris type compounds,¹¹⁻¹³ we are now describing the formal synthesis of the oxygenated derivatives of Ambrox and Isoambrox 3, 4, 5, 6, 7 and 8. The starting material was the sesquiterpene (-)-drimenol, readily available from the bark of *Drimys winteri*.¹⁴

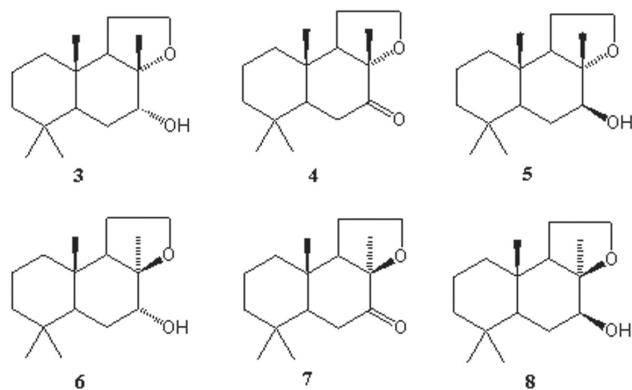


Figure 2. Structures of oxygenated derivatives of Ambrox and Isoambrox 3 - 8

EXPERIMENTAL

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. Optical rotations were obtained for chloroform solutions on a Perkin-Elmer 241 polarimeter, and their concentrations are expressed in g/100 mL. ¹H NMR and ¹³C NMR spectra were recorded on a Varian XL and a Bruker AW-80 spectrometers. Chemical shifts are expressed in ppm downfield relative to TMS (δ scale) in CDCl₃ solutions, and coupling constants (*J*) are reported in Hz. Carbon multiplicity was established by a DEPT pulse sequence. IR spectra were recorded as KBr disks on a Bruker FT-IR 1FS 25 spectrometer and frequencies are in cm⁻¹. Mass spectrometry measurements were made on a Finnigan 3300 and a Hewlett Packard 5930A spectrometers at an ionizing voltage of 70 eV.

For analytical TLC, Merck silica gel 60 in 0.26 mm layer was used. Chromatographic separations were carried out by conventional column on Merck silica gel 60 (230-400 Mesh) using hexane-EtOAc gradients of increasing polarity.

All reactions were routinely run under an N₂ atmosphere. All organic extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure at a temperature below 65 °C.

(-)-Drimenol was obtained from a light petroleum extract of the bark of *Drimys winteri*.⁵

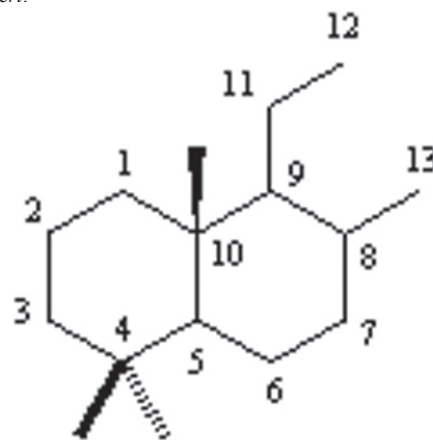


Figure 3. Compound numbering

8 β -Methyl-7 α ,8 α -epoxy-12-acetoxydrimane (10)

To a solution of 8-methyl-12-acetoxy-7,8-drimene (9) (370 mg, 1.33 mmol) in CH₂Cl₂, mCPBA (647 mg, 5.4 mmol) was added. The resulting solution was stirred for 1 h at 0 °C, and it was diluted with CH₂Cl₂ (20 mL), washed with saturated NaHCO₃ (3 x 25 mL), water (50 mL), dried, and evaporated. The crude was column chromatographed on silica gel (hexane-EtOAc). Evaporation of the more polar fraction yielded 8 β -methyl-7 α ,8 α -epoxy-12-acetoxydrimane (10) (270 mg, 69%) as a white solid: m.p 48 – 49 °C (Hexane); [α]_D²⁰ = +24.6° (c = 2.59; CHCl₃). IR ν_{\max} cm⁻¹ 2950 - 2860 (C-H), 1732 (C=O), 1360 (C-H), 1240 (C-O). ¹H-NMR (200 MHz): δ 4.11 (m, 2H, H-12); 2.96 (m, W₁₂ 7 Hz,

1H, H-7), 2.04 (s, 3H, AcO), 1.32 (s, 3H, 10-Me); 0.85 (s, 6H, 4-Me- α + 8-Me- β); 0.74 (s, 3H, 4-Me- β). ¹³C-RMN (50 MHz): δ 170.5 (AcO), 65.0 (C-12); 60.5 (C-7); 57.9 (C-8); 51.2 (C-5); 45.3 (C-9); 41.7 (C-3); 38.4 (C-1); 35.4 (C-10); 32.6 (C-4); 32.4 (4-Me- β); 24.9 (C-11); 22.7 (10-Me); 22.6 (C-6); 21.6 (4-Me- α); 20.6 (AcO); 18.3 (C-2); 13.8 (8-Me- β).

The less polar fraction yielded 8 α -Methyl-7 β ,8 β -epoxy-12-acetoxydrimane (121.3 mg, 31%) as a white oil. $[\alpha]_D^{20} = -11.3^\circ$ (c = 2.11; CHCl₃). IR $\nu_{\max} \text{ cm}^{-1}$ 2950 - 2860 (C-H), 1732 (C=O), 1360 (C-H), 1240 (C-O). ¹H-NMR (200 MHz): δ 4.15 (m, 2H, H-12); 3.01 (m, W_{1/2} 11 Hz, 1H, H-7), 2.05 (s, 3H, AcO), 1.28 (s, 3H, 10-Me); 0.88 (s, 3H, 8-Me- β); 0.84 (s, 6H, 4-Me- α + 4-Me- β). ¹³C-RMN (50 MHz): δ 170.8 (AcO), 65.1 (C-12); 61.6 (C-7); 59.7 (C-8); 50.1 (C-9); 49.9 (C-5); 42.1 (C-3); 40.5 (C-1); 36.6 (C-10); 33.4 (4-Me- α); 32.8 (C-4); 25.8 (C-11); 22.7 (10-Me); 21.9 (C-6); 21.6 (4-Me- α); 20.8 (AcO); 17.9 (C-2); 14.9 (8-Me- α).

7 α -Hydroxy-isoambrox (6)

To a stirred suspension of LiAlH₄ (57 mg, 1.5 mmol) in dry THF (20 mL), a solution of 8 β -methyl-7 α ,8 α -epoxy-12-acetoxydrimane (**10**) (220 mg, 0.75 mmol) in dry THF (10 mL) was added, and the reaction mixture was stirred under nitrogen at 0 °C for 2 h. The excess reagent was decomposed by addition of EtOAc and aqueous 10% HCl solution. The mixture was then extracted with EtOAc (3 x 25 mL), and the organic phase was washed with saturated NaHCO₃ (25 mL), water (25 mL), dried, and evaporated. The solid obtained was column chromatographed on silica gel (hexane-EtOAc). Evaporation of the less polar fraction yielded Ambrox. The intermediate polar fraction yielded 7 α -hydroxy-isoambrox (**6**) (44 mg, 23.3%) as a white solid: m.p. 98 - 99 °C (hexane-CHCl₃); $[\alpha]_D^{20} = -38.3^\circ$ (c = 1.05; CHCl₃). IR $\nu_{\max} \text{ cm}^{-1}$ 3450 (OH), 2980 - 2830 (C-H), 1380 (C-H), 1020 (C-O). ¹H-NMR (200 MHz): δ 4.11-3.66 (m, 3H, H-7 + H-12); 1.20 (s, 3H, 10-Me); 0.93, 0.88, 0.87 (3s, 9H, 4-Me- β , 4-Me- α , 8-Me- α). ¹³C-RMN (50 MHz): δ 85.4 (C-8); 70.4 (C-7); 65.7 (C-12); 59.7 (C-5); 48.1 (C-9); 43.3 (C-3); 42.0 (C-1); 36.9 (C-10); 33.1 (C-4); 32.6 (4-Me- β); 27.5 (C-6); 26.9 (C-11); 22.4 (10-Me); 21.3 (4-Me- α); 18.3 (C-2); 16.9 (8-Me- α).

8 β -Methyl-7 α ,8 α ,12-drimantriol (**13**) and 8 α -methyl-7 β ,8 β ,12-drimantriol (**14**)

A solution of a mixture of *N*-methylmorpholine *N*-oxide 1.40 g (11.95 mmol), 3 mL of H₂O, 15 mL of acetone, and 1 mL (0.10 mmol) of OsO₄ dissolved to 2.5% in *t*-butyl alcohol was added to compound **9** (1.73 g, 6.22 mmol) in acetone (5 mL). The mixture was stirred for 4 days, then poured into water (10 mL) and extracted with EtOAc (4 x 30 mL). The combined organic layers were washed with Na₂SO₃ (5%) and water (50 mL). The major fraction (1.90 g), dissolved in 20 mL of EtOH and NaOH (200 mg) was added. The resulting solution was stirred for 1 h at room temperature and extracted with EtOAc (6 x 25 mL), and the organic phase was washed with saturated NaHCO₃ (25 mL), water (25 mL), dried, and evaporated. The solid obtained was column chromatographed on silica gel (hexane-EtOAc). Evaporation of the less polar fraction yielded compound **13** as a white solid: m.p. 152 - 153 °C, (EtOH - hexane); $[\alpha]_D^{20} = -32.5^\circ$ (c = 0.83; MeOH). IR $\nu_{\max} \text{ cm}^{-1}$ 3300 (OH), 2950 - 2840 (C-H), 1465, 1425, 1380 (C-H), 1050 (C-O). ¹H-NMR (200 MHz): δ 3.80 - 3.30 (m, 3H, H-7 + H-12); 1.18 (s, 3H, H-20); 0.89 (s, 3H, CH₃); 0.80 (s, 6H, 2 x CH₃).

The more polar fraction yielded compound **14** as a white solid: m.p. 109 - 110 °C (hexane - EtOH), $[\alpha]_D^{20} = -12.3^\circ$ (c = 0.75; MeOH). IR $\nu_{\max} \text{ cm}^{-1}$ 3310 (OH), 2940 - 2825 (C-H), 1450, 1380, 1355 (C-H), 1040 (C-O). ¹H-NMR (200 MHz): δ 3.82 - 3.47 (m, 3H, H-7 + H-12); 1.22 (s, 3H, H-20); 0.97 (s, 3H, CH₃); 0.88 (s, 3H, CH₃); 0.84 (s, 3H, CH₃).

7 β -Hydroxy-isoambrox (8)

To 250 mg (0.93 mmol) of 8 α -methyl-7 β ,8 β ,12-drimantriol (**14**) in 10 mL of dry pyridine was added 106 mg (0.93 mmol) of mesyl chloride. The mixture was stirred under nitrogen at 0 °C for 16 h, then poured into water (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with HCl (5%), saturated NaHCO₃, and water, dried (Na₂SO₄) and concentrated in vacuo. The crude product was purified by column chromatography to yield 7 β -hydroxy-isoambrox (**8**) (83.7 mg, 36%) as a white solid: m.p. 84 °C (hexane-CHCl₃); $[\alpha]_D^{20} = -40.9^\circ$ (c = 1.05; CHCl₃). IR $\nu_{\max} \text{ cm}^{-1}$ 3500 (OH), 2980 - 2840 (C-H), 1360 (C-H), 1020 (C-O). ¹H-NMR (200 MHz): δ 3.76 (m, 2H, H-12); 3.31 (m, W_{1/2} 24 Hz, 1H, H-7); 1.20 (s, 3H, 10-Me) 0.90, 0.87 (2 x s, 9H, 4-Me- β , 4-Me- α , 8-Me- α). ¹³C-RMN (50 MHz): δ 86.1 (C-8); 76.2 (C-7); 64.5 (C-12); 57.8 (C-5); 50.5 (C-9); 41.6 (C-3); 41.3 (C-1); 36.2 (C-10); 33.4 (4-Me- β); 32.7 (C-4); 28.1 (C-6); 26.5 (C-11); 24.0 (10-Me); 22.2 (4-Me- α); 18.1 (C-2);

14.9 (8-Me- α). MS *m/z* (rel. int.): 252 [M⁺, C₁₆H₂₈O₃] (55); 237 (7); 137 (100); 124 (40); 123 (5); 109 (26); 107 (5); 96 (1); 95 (7); 84 (7); 83 (10); 82 (7); 81 (11); 44 (45); 81 (17); 41 (31).

7-Oxo-isoambrox (7)

To a stirred solution of 7 β -hydroxy-isoambrox (**8**) (40 mg, 0.16 mmol) in 10 mL of CH₂Cl₂, PCC reagent 150 mg (0.70 mmol) was added dropwise at room temperature. The reaction was monitored by TLC until disappearance of the starting material. The residue was filtered through silica gel and purified by column chromatography to provide 7-oxo-isoambrox (**7**) as a white solid: m.p. 64 - 67 °C (hexane-CHCl₃); $[\alpha]_D^{20} = +9.5^\circ$ (c = 0.48; CHCl₃). IR $\nu_{\max} \text{ cm}^{-1}$ 2960 - 2840 (C-H), 1715 (C=O), 1350 (C-H), 1085 (C-O). ¹H-NMR (200 MHz): δ 3.85 - 3.40 (m, 2H, H-12); 2.52 - 2.32 (m, 2H, H-6); 1.37 (s, 3H, 10-Me) 0.94, 0.90, 0.72 (2 x s, 9H, 4-Me- β , 4-Me- α , 8-Me- α). ¹³C-RMN (50 MHz): δ 213.2 (C-7); 85.8 (C-8); 66.6 (C-12); 61.8 (C-5); 49.1 (C-9); 41.6 (C-3); 41.3 (C-1); 37.0 (C-10); 35.3 (C-6); 33.0 (C-4); 32.5 (C-19); 26.8 (C-11); 26.4 (C-20); 21.3 (C-18); 18.1 (C-2); 14.9 (C-17).

7 α -Hydroxy-ambrox (3)

To 350 mg (1.30 mmol) of 8 β -methyl-7 α ,8 α ,12-drimantriol (**13**) in 10 mL of dry pyridine, 149 mg (1.30 mmol) of mesylchloride were added. The mixture was stirred under nitrogen at 0 °C for 24 h, then poured into water (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with HCl (5%), saturated NaHCO₃ solution, and water, dried (Na₂SO₄) and concentrated in vacuo. The solid obtained was purified by column chromatography to yield 7 α -hydroxy-ambrox (**3**) (310 mg, 95%) as a white solid, m.p. 62 - 63 °C (CHCl₃ - hexane); $[\alpha]_D^{20} = -66.0^\circ$ (c = 0.89; CHCl₃). IR $\nu_{\max} \text{ cm}^{-1}$ 3410 (OH), 2980 - 2830 (C-H), 1380 (C-H), 1065 (C-O), 1010 (C-O). ¹H-NMR (200 MHz): δ 3.98-3.77 (m, 3H, H-7 + H-12); 2.56 (bs 1H, OH); 1.09 (s, 3H, 10-Me); 0.88, 0.84 (2 x s, 9H, 4-Me- β , 4-Me- α , 8-Me- β). ¹³C-RMN (50 MHz): δ 81.4 (C-8); 71.2 (C-7); 65.4 (C-12); 51.8 (C-9); 48.7 (C-5); 42.3 (C-3); 39.6 (C-1); 36.0 (C-10); 33.2 (4-Me- β); 32.5 (C-4); 26.1 (C-6); 22.1 (C-11); 21.2 (10-Me); 21.1 (4-Me- α); 18.3 (C-2); 14.6 (8-Me- β). MS *m/z* (rel. int.): 252 [M⁺, C₁₆H₂₈O₃] (52); 237 (10); 219 (2); 137 (100); 124 (8); 109 (25); 107 (4); 99 (2); 96 (1); 95 (4); 84 (8); 83 (8); 82 (6); 81 (12); 44 (81); 41 (31).

7-Oxo-ambrox (4)

To a stirred solution of 7 α -hydroxy-ambrox (**3**), 260 mg (1.03 mmol) in 15 mL of CH₂Cl₂, PCC reagent 600 mg (2.78 mmol) was added dropwise at room temperature. The reaction was monitored by TLC until disappearance of the starting material. The residue was filtered through silica gel and purified by column chromatography to yield 7-oxo-ambrox **4** as a white solid m.p. 133 - 134 °C (CHCl₃-hexane); $[\alpha]_D^{20} = -146.8^\circ$ (c = 0.98; CHCl₃). IR $\nu_{\max} \text{ cm}^{-1}$ 2980 - 2870 (C-H), 1720 (C=O), 1380 (C-H), 1010 (C-O). ¹H-NMR (200 MHz): δ 3.97 - 3.68 (m, 2H, H-12); 2.69-2.25 (m, 2H, H-6); 1.28 (s, 3H, 10-Me); 1.02, 0.83 (2 x s, 9H, 4-Me- β , 4-Me- α , 8-Me- β). ¹³C-RMN (50 MHz): δ 208.8 (C-7); 85.8 (C-8); 65.0 (C-12); 60.4 (C-9); 58.9 (C-5); 41.6 (C-3); 39.3 (C-1); 35.8 (C-6); 33.5 (C-4); 32.8 (4-Me- β); 21.7 (C-11); 20.5 (4-Me- α); 19.8 (10-Me); 17.9 (C-2); 14.4 (10-Me- β). MS *m/z* (rel. int.): 250 [M⁺, C₁₆H₂₆O₃] (15); 222 (32); 138 (7); 137 (100); 124 (54); 127 (27); 109 (24); 108 (1); 107 (2); 96 (1); 95 (10); 84 (20); 83 (20); 82 (5); 81 (17); 41 (39).

7 β -Hydroxy-ambrox (5)

To a suspension of (t-BuO)₃AlH (40 mg, 0.11 mmol) in dry THF (10 mL), a solution of 7-oxo-ambrox (**4**) (40 mg, 0.16 mmol) solution in THF (10 mL) was added dropwise. The reaction mixture was refluxed for 2 h, then EtOAc (10 mL) and 1N HCl (10 mL) were successively added to decompose the excess (t-BuO)₃AlH. After extraction with EtOAc (3 x 25 mL) the combined organic extracts were washed with NaHCO₃ solution, water, dried, and concentrated. The crude product was purified by column chromatography to yield 36.2 mg (22%) of 7 α -hydroxy-ambrox **3** (the less polar fraction). The more polar fraction yielded 7 β -hydroxy-ambrox (**5**), (62 mg, 61.5%) as a white solid: m.p. 149 - 150 °C (hexane-CHCl₃); $[\alpha]_D^{20} = -34.6^\circ$ (c = 0.61; CHCl₃). IR $\nu_{\max} \text{ cm}^{-1}$ 3420 (OH), 2980 - 2860 (C-H), 1380 (C-H), 1030 (C-O). ¹H-NMR (200 MHz): δ 3.98-3.50 (m, 3H, H-7 + H-12); 1.09 (s, 3H, 10-Me); 0.89, 0.84 (2 x s, 9H, 4-Me- β , 4-Me- α , 8-Me- β). ¹³C-RMN (50 MHz): δ 83.8 (C-8); 78.5 (C-7); 65.2 (C-12); 58.4 (C-9); 55.9 (C-5); 42.1 (C-3); 39.6 (C-1); 35.7 (C-10); 33.5 (4-Me- β); 33.0 (C-4); 28.8 (C-6); 22.3 (C-11); 21.0 (4-Me- α); 18.3 (C-2); 15.7 (10-Me); 15.0 (10-Me- β). MS *m/z* (rel. int.): 252 [M⁺, C₁₆H₂₈O₃] (55); 237 (7); 137 (100); 124 (40); 123 (5); 109 (26); 107 (5); 96 (1); 95 (7); 84 (7); 83 (10); 82 (7); 81 (11); 44 (45); 81 (17); 41 (31).

RESULTS AND DISCUSSION

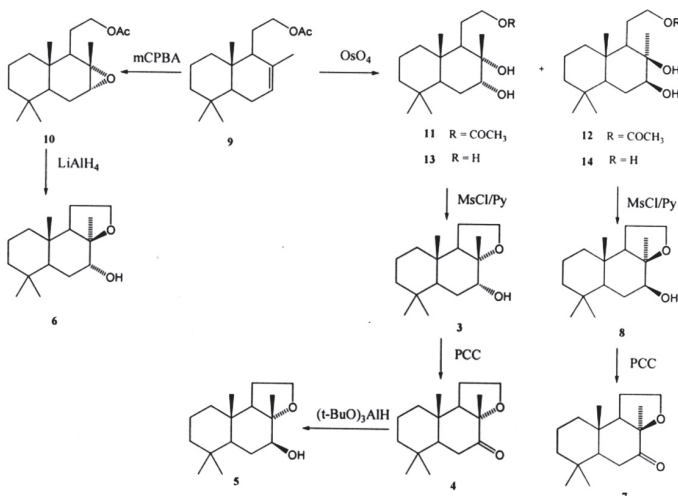
Following our studies on the transformation of the main component of *Drimys winteri* to obtain compounds with ambergris-like odours,¹²⁻¹⁴ we now describe a formal synthesis of the oxygenated derivatives of Ambrox and Isoambrox, **3**, **4**, **5**, **6**, **7** and **8**, which involves an alternative access to **9**, the direct precursor of **3**, **4**, **5**, **6**, **7** and **8**. The starting material was the sesquiterpene (-)-drimenol readily available from the bark of *D. winteri*.

Epoxidation of 8-methyl-12-acetoxy-7,8-drimene (**9**) with mCPBA in CH₂Cl₂ at 0° C gave the α -epoxide **10** (69% yield). The compound was characterized by ¹H NMR and ¹³C NMR spectra. The α -stereochemistry for the C-7 proton is indicated by the W_{1,2} value (7 Hz) of the signal at δ 2.96. These results led us to the conclusion that the reagent attacks from the less hindered α -face of the double bond, and the stereochemistry of the epoxide was consequently assigned as α . Surprisingly, treatment of **10** with LiAlH₄ led us to the 7 α -hydroxy-isoambrox (**6**) in 23% yield and produced a mixture of epimeric diols. Compound **6** was characterized by ¹H NMR spectroscopy, which showed multiplet at δ 3.66-4.11, which was assigned to H-7 + H-12. The INEPT ¹³C NMR spectrum showed the signal of C-12 at δ 65.7 (CH₂), the signal of C-7 at δ 70.4 (CH), and the signal of C-8 at δ 85.4 (C), confirming that it was joined to the oxygen. The stereochemistry of **6** has been established by comparing the spectrum of ambrox and isoambrox using Beierbeck and Saunders parameters.¹⁵ All other signals were in agreement with those found for drimane models.^{12,13} Besides, chemical support for the structure of compound **6** was obtained by (t-BuO)₃AlH reduction of **10**. Spectroscopic data were in agreement with the values reported for LiAlH₄ reduction.

Oxidation of **9** with OsO₄ and co-oxidant *N*-methylmorpholine *N*-Oxide in acetone, *t*-butyl alcohol and water gave the mixture of acetyl diols in 98% yield. Attempts to separating this mixture did not give acceptable results and it was decided to try saponification. After separation, the triols **13** and **14** were identified by ¹H NMR. Triols **13** and **14** were used as the starting materials for the synthesis of derivatives of ambrox and isoambrox.

The cyclization of **13** and **14** to give 7 α -hydroxy-ambrox (**3**) and 7 β -hydroxy-isoambrox (**8**) was carried out in 95% and 36% yields, respectively, using mesyl chloride in pyridine. The stereochemistry of the C-7 hydroxyl group in compound **8** is confirmed by the W_{1,2} value (24 Hz) of the signal at δ 3.31. Oxidation of 7 α -hydroxy-ambrox (**3**) and 7 β -hydroxy-isoambrox (**8**) with PCC reagent in CH₂Cl₂ gave the corresponding ketones **4** and **7** in 99% and 95% yields. These ketones were characterized by ¹³C NMR spectrum showed the chemical shifts of C-7 at δ 208.7 and 213.2 respectively, clearly deshielded when compared with C-7 of **3** and **8**. Chemical support for the stereochemistry of compound **3** was obtained by Huang-Milong reduction of **4**, which gave ambrox in 90% yield. Its spectroscopic data were in agreement with the values reported by Cortés.¹³

Finally, reduction of 7-oxo-ambrox (**4**) and 7-oxo-isoambrox (**7**) with (t-BuO)₃AlH gave 7 β -hydroxy-ambrox (**5**) and 7 α -hydroxy-isoambrox (**6**) in 50% and 61% yield, respectively.



Scheme 1. Chemical synthesis of oxygenated derivatives of Ambrox and Isoambrox.

CONCLUSION

In conclusion this work is an important contribution to a simple and inexpensive methodology for the preparation of new oxygenated derivatives in position 7 of ambrox and isoambrox from a readily available starting material. From a qualitative point of view these results are promising, and the new oxygenated derivatives will be submitted to evaluation by qualified perfumers because they may provide significantly to structure-odoriferous properties relations.

ACKNOWLEDGMENTS

We acknowledge with thanks the financial support of the Dirección de Investigación, Universidad Arturo Prat, and of the Pontificia Universidad Católica de Chile.

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