A Convenient Preparation of Ambergris Odorants from Copalic Acid

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Descrevemos neste trabalho as sinteses de odoríferos de âmbar gris: ent-epi-8-ambracetal (7), ent-ambrox (10) e dois óxidos 13 e 14, a partir do ácido copalico (2a).

The syntheses of the ambergris odorants ent-epi-8-ambraketal (7), ent-ambrox (10), and two oxides 13 and 14 starting from copalic acid (2a) are described.

Keywords: copalic acid, ambergris odorant, ent-ambrox, ent-epi-8-ambraketal

Introduction

Ambergris is a metabolic product of the sperm whale (Physeter macrocephallum) and is considered one of the most valuable animal perfumes besides civet, musk and castoreum. 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, which is more commonly known under the trade names Ambrox (Firmenich), Amberlyn (Quest) and Ambroxan (Henkel).

The great interest and importance of ambergris derivatives nowadays can be demonstrated by the increasing number of recent publications on this topic.

Many of the total syntheses have been developed either in a racemic or optically active form, although the most successful asymmetric syntheses have started from naturally occurring sesqui or diterpenes such as (-)-drimmenol, (-)-levopimaric acid, (-)-labdanolic acid, (-)-abietic acid, (-)-communnic acid, (+)-cis-abienol, (+)-manool, manoyl oxide, and (-)-sclareol. Continuing a program to develop our project, where resinic acid was used as the chiral starting material for stereo-controlled synthesis of the optically active compounds, we undertook the synthesis of ent-ambrox (10), ent-epi-8-ambraketal (7) and two oxides 13 and 14 starting from copalic acid (2a).

Results and Discussion

As can be seen in Scheme 1 and Scheme 2, the epoxyketone 6 is the key intermediate for the synthesis of 7, 10, 13 and 14. This intermediate could be prepared in two steps following the known procedure, i.e., KMN₄ oxidative degradation of the side chain of 2a, followed by stereospecific epoxidation of the exocyclic methylene double bond of 3 with MCPBA. In our case, the best results obtained...
was 25% overall yield, and although it has not been previously mentioned in the literature, the diketone 4 was always isolated in an approximately 15% yield, along with unreacted starting material (10-15%). Thus, to avoid further oxidation of the exocyclic methylene group, methyl copalate (2b) was first epoxidized with mCPBA (Scheme 1), followed by ozonolysis of the resulting epoxide 5 in methylene chloride at -78 °C, to afford 6 in a ~37% overall yield. In the next step, a benzene solution of 6 was treated with p-TsOH affording the expected ent-epi-8-ambraketal 7 in a 54% yield.

In order to begin the synthesis of ent-ambrox (10) (Scheme 1), the epoxy-ketone 6 was submitted to the Baeyer-Villiger reaction with mCPBA. The progress of the reaction was monitored by TLC, and after 7 days, the epoxy-acetate 8 was obtained in a 32% yield along with recovered starting material (30%). Following the sequence, the reduction of 8 with LiAlH4 in THF furnished the diol 9 in a 97% yield, which was treated with MsCl and pyridine in benzene, affording the ent-ambrox (10) in a 66% yield.

For the synthesis of oxides 13 and 14 (Scheme 2) the epoxy-ketone 6 was reduced with LiAlH4 in THF, leading to a C-13 epimeric mixture of diols 11 and 12. The mixture was easily separated by silica-gel column chromatography to furnish 11 and 12 in 40% and 43% yields, respectively. The stereochemistry at C-13 of the diols 11 and 12 was established by the comparison of the physical and spectral data with those reported for their enantiomers, and also by analysis of the 1H- and 13C-NMR data of the oxides 13 and 14. Finally, using the same conditions employed for the cyclization of 9 to 10, the diols 11 and 12 were converted separately to the oxides 13 and 14 in 61% and 66% yields, respectively. The physical constants and spectral data of these oxides are in good agreement with

Scheme 1: (a) m-CPBA, CH2Cl2; (b) O3, CH2Cl2 then Me2S; (c) TsOH, Bz; (d) m-CPBA, CH2Cl2; (e) LiAlH4, THF; (f) MsCl, Py, Bz.

Scheme 2: (a) LiAlH4, THF; (b) MsCl, Py, Bz.
those reported for their respective enantiomers\(^5\). Taking into account that cyclization of diols 11 and 12 with MeCl-pyridine proceeds through an Sn2 mechanism, the stereochemistry of 13 and 14 at C-13 should be assigned as depicted in the structure.

In summary, we have described a two-step synthesis of the epoxy-ketone 6, starting from copallic acid (2a), an important intermediate for the synthesis of the ambergris odorant derivatives 7, 10, 13 and 14. It is worth mentioning that compounds 7 and 10, which belong to the ent-labdane series, are known to have characteristic olfactory properties\(^20,22\).

**Experimental Details**

\(^1\)H- and \(^{13}\)C-NMR spectra were recorded in a CDCl\(_3\) solution at 300 MHz and 75.5 MHz, respectively, with a Bruker spectrometer. IR spectra of neat samples were obtained with a Perkin-Elmer 1600 series FT-IR. Elemental analyses were performed with a Perkin-Elmer 2400 CHN analyzer. Melting points were determined on a Reichert-Kofler hot stage and are uncorrected. Optical rotations were measured with a Carl Zeiss photoelectric polarimeter.

**Methyl 8β,17-epoxy-copale (5)**

\(m\)-Chloroperoxybenzoic acid (50%, 420 mg, 1.21 mmol) was added to a stirred solution of 2b (320.0 mg, 1.0 mmol) in dry dichloromethane. After the mixture was stirred overnight at room temperature, it was diluted with adding dichloromethane (30 mL), washed with 10% aqueous sodium hydrogen carbonate solution (3 x 30 mL), followed by saturated aqueous sodium chloride, dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica-gel chromatography [n-hexane/ethyl ether (7:3)] to give 5 (237.0 mg, 70%): [\(\alpha\)]\(_D\)\(^{22}\) -101.5 (c 0.8, CHCl\(_3\)). - IR (film) 1720, 1649, 1224, 1148 cm\(^{-1}\); \(^1\)H-NMR δ 0.80 (s, 3H), 0.83 (s, 3H), 0.90 (s, 3H), 2.13 (s, 3H), 2.50 (d, \(J = 4.32\) Hz, 1H), 2.70 (d, \(J = 4.32\) Hz, 1H), 3.68 (s, 3H), 5.65 (s, 1H); \(^{13}\)C-NMR (Table 1).

**Table 1.** \(^{13}\)C-NMR data of compounds 2b, 5-14 (δ, CDCl\(_3\), 75.5 MHz)\(^9\).

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| a) Assignments were supported by DEPT NMR experiments.
| b) Assignments within a column may be interchanged.
Ent-14,15-dinor-8a,17-epoxy-labdane (6)

A stirred solution of 5 (820.0 mg, 0.24 mmol) in dry dichloromethane (20.0 mL) was slowly bubbled with a O$_2$/O$_2$ mixture at -78 °C until the solution became light blue. The excess of ozone was eliminated by bubbling nitrogen and the ozonide was reduced by adding an excess of dimethylsulfide (0.2 mL, 2.7 mmol), and the mixture was being stirred at room temperature for 3 h. The mixture was diluted with dichloromethane (20 mL) and washed with saturated aqueous sodium chloride solution (3 x 30 mL), dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica-gel chromatography [n-hexane/ethyl ether (93:7)] to afford epoxy-ketone 6 (36.8 mg, 54%): [α]$_D$ = -19.5 (c 4.4, CHCl$_3$), [lit.$^{23}$ for enantiomer [α]$_D$ +9.0]; IR (film) 1716, 967, 893, 833 cm$^{-1}$; $^1$H-NMR δ 0.82 (s, 3H), 0.83 (s, 3H), 0.89 (s, 3H), 2.09 (s, 3H), 2.49 (d, J = 4.5 Hz, 1H), 2.82 (d, J = 4.5 Hz, 1H); $^{13}$C-NMR (see Table 1); MS m/z (rel.int.) 278 (M$^+$, 4), 137(31), 175(32), 218(58), 43(100). Anal. Calcd. for C$_{18}$H$_{30}$O$_2$: C, 77.65; H, 10.86. Found: 77.66; H, 10.46.

Ent-14,15-dinor-13(R),8β,13,17-dioxido-labdane (ent-epi-8-ambra-ketal) (7)

A catalytic amount of p-toluenesulfonic acid (1.3 mg) was added to a stirred solution of 6 (21.1 mg, 0.08 mmol) in dry benzene (3 mL), at room temperature. After the reaction mixture was stirred for 5 h, it was diluted with dichloromethane (30 mL) and washed with 10% aqueous sodium bicarbonate solution (3 x 30 mL), followed by saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica-gel chromatography [n-hexane/ethyl ether (7:3)] to give 7 (11.3 mg, 54%) as a colorless crystal: m.p. 103-105°C; [α]$_D$ = -3.7 (c 2.3, CHCl$_3$), [lit.$^{22a}$ m.p. 123-124 °C; [α]$_D$ = +5.7]; IR (KBr) 1385, 1364, 1231, 1213, 1145, 1113, 1035, 1025 cm$^{-1}$; $^1$H-NMR δ 0.87 (s, 3H), 0.88 (s, 3H), 1.09 (s, 3H), 1.42 (s, 3H), 3.32 (d, J = 6.9 Hz, 1H), 3.77 (d, J = 6.9 Hz, 1H); $^{13}$C-NMR (Table 1). Anal. Calcd. for C$_{18}$H$_{30}$O$_2$: C, 77.65; H, 10.86. Found: C, 77.67; H, 10.70.

Ent-13,14,15,16-tetranor-12-acetoxy-8a,17-epoxy-labdane (8)

NaHCO$_3$ (316 mg, 3.76 mmol) and mCPBA (60%, 216 mg, 3.76 mmol) was added to a solution of 6 (522.5 mg, 1.48 mmol) in dry dichloromethane (10 mL), and the reaction was left to stand in the dark at room temperature. The reaction was monitored by TLC and progress was stabilized after seven days. The reaction mixture was then diluted with dichloromethane (30 mL), washed with 10% aqueous sodium bicarbonate solution (3 x 30 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica-gel chromatography [n-hexane/ethyl ether (7:3)] to recover the starting material (158 mg, 30%) and to afford 8 (122 mg, 32% based on reacted material): [α]$_D$ = -3.0 (c 2.8, CHCl$_3$); IR (film) 1736, 1246, 1038 cm$^{-1}$; $^1$H-NMR δ 0.81 (s, 3H), 0.83 (s, 3H), 0.90 (s, 3H), 2.03 (s, 3H), 2.51 (d, J = 4.5 Hz, 1H), 2.75 (d, J = 4.5 Hz, 1H), 4.02 (m, 2H); $^{13}$C-NMR (Table 1). Anal. Calcd. for C$_{18}$H$_{30}$O$_3$: C, 73.43; H, 10.27. Found: C, 73.55; H, 9.87.

Ent-13,14,15,16-tetranor-8a,12-labdanediol (9)

A solution of 8 (60.5 mg, 0.2 mmol) in dry tetrahydrofuran (3 mL) was added by drops to a stirred suspension of LiAlH$_4$ (16.0 mg, 0.4 mmol) in dry tetrahydrofuran (5 mL), at room temperature under argon. The reaction was then refluxed for 12 h, and after cooling at room temperature, the excess of hydride was destroyed by the careful addition of 15% aqueous sodium hydroxide solution. The solid was removed by filtration through a Celite pad, the organic phase was dried with anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica-gel chromatography [n-hexane/ethyl acetate (7:3)] to give diol 9 (47.4 mg, 97%): m.p. 112-113 °C, [α]$_D$ = +5.1 (c 3.3, CHCl$_3$), [lit.$^{17}$ for enantiomer m.p. 130-131 °C; [α]$_D$ = -17.0]; IR (KBr) 3242, 1386, 1083, 1053 cm$^{-1}$; $^1$H-NMR δ 0.79 (s, 6H), 0.87 (s, 3H), 1.19 (s, 3H), 3.47 (m, 1H), 3.74-3.79 (m, 1H); $^{13}$C-NMR (Table 1). Anal. Calcd. for C$_{18}$H$_{30}$O$_2$: C, 75.54, H, 11.89. Found: C, 75.93, H, 11.51.

Ent-13,14,15,16-tetranor-8a,12-epoxy-labdane (ent-ambrox) (10)

Methanesulfonyl chloride (0.05 mL) was added to a stirred solution of 9 (68.6 mg, 0.29 mmol) in dry benzene (1.4 mL) and pyridine (0.3 mL) under argon. The reaction mixture was refluxed for 12 h, and after cooling it was poured into water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic phase was washed with 2 N aqueous hydrochloric solution (3 x 30 mL), followed by saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica-gel chromatography [n-hexane/ethyl acetate (9:1)] to give ent-ambrox (10) (45.3 mg, 66%), m.p. 69-70°C; [α]$_D$ = +8.5 (c 2.0, CHCl$_3$), [lit.$^{20}$ [α]$_D$ = +21.7; [lit.$^{29}$ for enantiomer m.p. 75-76°C; [α]$_D$ = -26.0]; IR (KBr) 1458, 1380, 1129, 1007, 978 cm$^{-1}$; $^1$H-NMR δ 0.83 (s, 3H), 0.84 (s, 3H), 0.87 (s, 3H), 1.08 (s, 3H), 3.78-3.95 (m, 2H); $^{13}$C-NMR (Table 1). Anal. Calcd. for C$_{18}$H$_{30}$O$_2$: C, 81.29, H, 11.94. Found: C, 81.24, H, 11.65.
Ent-14,15-dinor-8a,13(S,R)-labdanediols (11 and 12)

A solution of 6 (408.4 mg, 1.46 mmol) in dry tetrahydrofuran (10 mL) was added by drops to a stirred suspension of LiAlH₄ (111.4 mg, 2.94 mmol) in dry tetrahydrofuran (40 mL) at room temperature under argon. The mixture was refluxed for 12 h, and after cooling at room temperature, the excess of hydride was destroyed by the careful addition of 15% aqueous sodium hydroxide solution. The solid was removed by filtration through a Celite pad, and the ether solution was dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography to give 11 [165.8 mg, 40%; n-hexane/ethyl acetate (7:3)] and 12 [179.7 mg, 43%; n-hexane/ethyl acetate (1:1)]. Ent-14,15-dinor-8a,13(R)-labdanediol 11. m.p. 118-119°C; [α] +11.0 (c 2.3, CHCl₃), (lit.⁹ for enantiomer m.p. 102-103°C; [α] 38.6); IR (film) 3319, 1385, 1133, 1088, 939, 912, 740 cm⁻¹; ¹H-NMR δ 0.79 (s, 3H), 0.81 (s, 3H), 0.87 (s, 3H), 1.16 (s, 3H), 1.18 (d, J = 6.30 Hz, 3H), 2.56 (bs, 2H), 3.92 (m, 1H); ¹³C-NMR (see Table 1); ent-14,15-dinor-8a,13(S)-labdanediol 12. m.p. 123-124°C; [α]ₚ +3.4 (c 2.5, CHCl₃), (lit.⁹ for enantiomer m.p. 112-113°C; [α] 6.4); IR (film) 3355, 1459, 1388, 1130, 1082, 938, 740 cm⁻¹; ¹H-NMR δ 0.78 (s, 6H), 0.86 (s, 3H), 1.15 (s, 3H), 1.16 (d, J = 6.0 Hz, 3H), 3.05 (bs, 2H), 3.78 (m, 1H); ¹³C-NMR (Table 1).

Ent-14,15-dinor-8a,13(S)-epoxy-labdane (13)

Diol 11 (93.5 mg, 0.33 mmol) was cyclized according to the previous experiment for ent-anthrox, to give oxide 13 (53.1 mg, 61%). m.p. 56-58 °C; [α] 33 -3.4 (c 2.5, CHCl₃), (lit.⁹ for enantiomer m.p. 78-79°C; [α] 0 -9.0; lit.⁹ [α] 9.5); IR (KBr) 1456, 1384, 1098, 958 cm⁻¹; ¹H-NMR δ 0.74 (s, 3H), 0.80 (s, 3H), 0.86 (s, 3H), 1.08 (d, J = 6.30 Hz, 3H), 1.24 (s, 3H), 3.72 (m, 1H); ¹³C-NMR (Table 1); Anal. Calcld. for C₁₈H₂₀O: C, 81.75; H, 12.20. Found: C, 81.92, H, 12.33.

Ent-14,15-dinor-8a,13(R)-epoxy-labdane (14)

Following the same procedure, diol 12 (134.8 mg, 0.48 mmol) was cyclized to give oxide 14 (57.4 mg, 66%). [α] 20 -7.4 (c 2.1, CHCl₃), (lit.⁹ for enantiomer [α] 20 +19.0; lit.⁹ [α] +18.0); IR (film) 1458, 1376, 1075, 975 cm⁻¹; ¹H-NMR δ 0.80 (s, 6H), 0.86 (s, 3H), 1.14 (d, J = 6.60 Hz, 3H), 1.22 (s, 3H); 3.97 (m, 1H); ¹³C-NMR (Table 1); Anal. Calcld. for C₁₈H₂₀O: C, 81.75; H, 12.20. Found: C, 81.95, H, 12.31.

Acknowledgments

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References

11. (a) Barrero, A.F.; Altarejos, J.; Manzaneke, E.J.A.; Ramos, J.M.; Salido, S. Tetrahedron 1993, 49, 9525; (b) ibid, 6251.


16. The optical purity of methyl copalate (2b) [α]D 23 -12.9° (c 2.3, CHCl3) used in this work was evaluated to be −46% e.e.; {lit. 22 [α]D20 -28.3° (c 0.98, CHCl3)}.


18. Although not attempted, we believe that the overall yield of 6 can be improved by optimizing the ozonolysis step.

19. An interesting ketalization process for the enantiomer of 6 has been recently described in ref. 4(b).


21. When 6 was reduced in Et2O, only the C-13 epimeric mixture of the epoxy-alcohols was obtained.


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