ORIGINAL

Synthesis of (–)-Ambrox® from (–)-Levopimaric Acid*

Yasutaka NISHI and Hiroichi ISHIIHARA

Harima Chemicals, Inc. Central Research Laboratory

(671-4 Noguchi-cho, Kakogawa-shi, 〒675)

(–)-Ambrox (1) and (+)-8-demethylisoambrox (2), which give out a strong ambergris-type odor, were efficiently synthesized from (–)-levopimaric acid (3). The keto diester (8) was obtained by ozonolysis of methyl levopimarate. By the Wittig reaction, followed by epoxidation and reduction, the methyl and hydroxyl groups at C-8 were introduced. The triol (15) was converted to the 8 α , 12-epoxy mesylate (16) by dehydration with methanesulfonyl chloride. The reduction of 16 with sodium iodide and zinc dust gave (–)-ambrox (1).

1 Introduction

Ambergris, an internal concretion of the sperm whale, has long been prized by perfumers for its unique fragrance properties. The diminishing availability of ambergris has necessitated a search for synthetic substitutes. (–)-Ambrox (1) known to possess a strong ambergris-type odor was synthesized from manool (4) and sclareol (5)¹⁾. Recently, (+)-8-demethylisoambrox (2) was synthesized from (+)-podocarpic acid (6) by Cambie's group²⁾. This demethyl compound (2) was reported to have an ambergris-type odor.

Here, we wish to report an efficient synthesis of (–)-ambrox (1) and (+)-8-demethylisoambrox (2) from (–)-levopimaric acid (3). (–)-Levopimaric acid (3) is a major component of pine oleoresin, and can be purified easily³⁾. Pine oleoresin is obtained on an industrial scale from pine trees. (–)-Levopimaric acid (3) was considered to be a good chiral synthon for the elaboration of (–)-ambrox skeleton, since the four chiral carbons of 3 can be utilized into 1 by oxidative cleavage of ring C (as shown with a dotted line) and reduction of carboxylic acid function to a methyl group.

2 Results and Discussion

The synthesis of (+)-8-demethylisoambrox (2) was first completed in the following way

Scheme-1

(Scheme-1). The keto diester (8) was obtained from methyl levopimarate (7) by Pelletier's method⁴⁾. Ozonolysis of methyl levopimarate (7) in ethyl acetate at -70°C , followed by Jones oxidation and methylation with diazomethane, gave the keto diester (8). Reduction of the keto diester (8) with lithium aluminium hydride gave the triol (9). The hydroxyl group at C-8 was considered to be β -configuration since the attack of lithium aluminium hydride may occur from the α -side because of steric hindrance of the angular methyl group. Treatment of the triol (9) with

Ambrox® is the registered trade name of Firmenich SA (Switzerland).

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methanesulfonyl chloride in pyridine²⁾ effected direct cyclization to the 8 β ,12-epoxy mesylate (10) in an overall yield of 23 % from 8.

The remaining problem to complete the synthesis of 2 was the reduction of the mesyloxyl group to methyl group. Treatment of the mesylate (10) with lithium aluminium hydride afforded predominantly the 8 β ,12-epoxyalcohol (11). Reduction of the mesylate (10) with sodium iodide and zinc dust in *N,N*-dimethylformamide (DMF) (115°C, 6 h)⁵⁾ gave (+)-8-demethylisoambrox (2) (43 %) along with the starting material (10) (40 %).

Next, the keto diester (8) was successfully converted to (–)-ambrox (1) (Scheme-2). Introduction of methyl group at C-8 was a crucial step in this approach. Addition of methyl lithium was considered to give α -methyl group at C-8 predominantly. Therefore, we attempted to prepare the exocyclic methylene group at C-8 by Wittig reaction, followed by epoxidation and reduction. Bell and coworkers previously investigated about the methylation of C-8 ketone in podocarpane series, but they could not get any Wittig product⁶⁾. In the case of the keto diester (8), although the use of sodium methylsulfinylmethide or *n*-butyl lithium as the base in the Wittig reaction failed, the Wittig reaction of 8 with two equivalents of methyltriphenylphosphonium iodide and potassium *t*-butoxide in diisopropyl ether (68°C, 2 h)⁷⁾ gave the exocyclic methylene diester (12) (59 %). It is interesting to note that when more than three equivalents of phosphorane were used under these conditions, the keto diester (8) gave the diene (13)⁸⁾.

Epoxidation of the exocyclic methylene diester (12) with *m*-chloroperbenzoic acid (MCPBA) gave the α -epoxide (14) as a major product.

Reduction of the α -epoxide (14) with lithium aluminium hydride afforded the triol (15). The methyl group at C-8 was β -configuration. The triol (15) was converted into the 8 α ,12-epoxy mesylate (16) by dehydration with methanesulfonyl chloride in an overall yield of 35 % from 12. Reduction of the 8 α ,12-epoxy mesylate (16) with sodium iodide and zinc dust gave (–)-ambrox (1) (44 %) along with the starting material (16) (38 %).

(–)-Ambrox (1) and (+)-8-demethylisoambrox (2) synthesized here possessed an ambergris-type odor, and these spectral data were identical with those published^{1),2),9)}.

3 Experimental

All melting points were uncorrected. IR spectra were measured as films for oils or KBr discs for solids on a Hitachi 270-30 spectrometer. ¹H and ¹³C-NMR spectra were recorded with JEOL FX-60 spectrometer in CDCl₃ with TMS as an internal standard.

8 β ,12-Epoxy-13,14,15,16,17-pentanorlabdan-18-yl methanesulfonate (10)

A solution of the keto diester (8) (13.0 g, 41.9 mmol) in THF (30 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (5.2 g, 133 mmol) in THF (300 mL) under a nitrogen atmosphere with cooling in an ice-water bath. The mixture was refluxed for 2 h and the reaction was quenched with saturated sodium sulfate solution. The mixture was filtered. The residue was washed with hot THF. The filtrate was evaporated, and gave the crude triol (9) (10.4 g, 40.6 mmol). The crude 9 was used without further purification in the following reaction.

9: IR 3320 cm⁻¹ 1050 cm⁻¹; ¹³C-NMR δ (DMSO-d₆) = 16.3(10-Me) 17.7(4-Me) 59.8(C-12) 65.7(C-8) 70.1(4-CH₂OH); ¹H-NMR δ (DMSO-d₆) = 0.68(3 H, s) 1.36(3 H, s)

Methanesulfonyl chloride (15.0 g, 131 mmol) was added to a cooled solution of the crude triol (9) (10.4 g, 40.6 mmol) in dry pyridine (300 mL). The mixture was kept at room temperature for 16 h. Water was added. The mixture was extracted with ether. The extracts were washed with diluted hydrochloric acid and brine, then dried over sodium sulfate. Removal of solvent under reduced pressure gave an oil which was

chromatographed on silica gel. Elution with hexane-ethyl acetate (3:1) gave the 8 β , 12-epoxy mesylate (10) (3.0 g, 9.5 mmol) in an overall yield of 23 % from 8.

10 : Oil; IR 1350 cm⁻¹ 1175 cm⁻¹; ¹³C-NMR δ = 15.9(10-Me) 17.2 17.5(4-Me and 1C) 27.1 27.9 35.5(C-4 and 1C) 36.8(C-10) 37.0 (SO₂Me) 40.0 45.9(C-5) 52.4(C-9) 66.2(C-12) 77.3(C-8) 77.7(4-CH₂O); ¹H-NMR δ = 0.91 (3 H, s) 0.96(3 H, s) 3.0(3 H, s)

8 β , 12-Epoxy-13, 14, 15, 16, 17-pentanorlabdan-18-ol (11)

A solution of the 8 β , 12-epoxy mesylate (10) (200 mg, 0.63 mmol) in THF (2 mL) was added to a stirred suspension of lithium aluminium hydride (100 mg, 2.57 mmol) in THF (5 mL) under a nitrogen atmosphere. The mixture was refluxed for 5 h. After the same work-up as described for the preparation of 9, elution with benzene-ethyl acetate (3:1) on a silica gel column chromatography gave the 8 β , 12-epoxy-alcohol (11) (128 mg, 0.54 mmol, 85.0 %).

11 : mp 109~110°C; IR 3470 cm⁻¹ 1040 cm⁻¹; ¹³C-NMR δ = 16.1(10-Me) 17.3 17.6(4-Me) 18.1 27.1 28.0 35.4(C-4) 35.5 37.4 40.4 45.5 (C-5) 52.4(C-9) 66.3(C-12) 71.5(4-CH₂OH) 77.8(C-8); ¹H-NMR δ = 0.82(3 H, s) 0.98(3 H, s)

8 β , 12-Epoxy-13, 14, 15, 16, 17-pentanorlabdan-2)((+)-8-demethylisoambrox)

A stirred mixture of the 8 β , 12-epoxy mesylate (10) (7.0 g, 22.2 mmol), sodium iodide (11.0 g), and zinc powder (7.0 g) in DMF (50 mL) was heated at 115°C for 6 h. The mixture was cooled, diluted with ethyl acetate, and then filtered. The filtrate was washed with aqueous sodium thiosulfate and brine. After drying over sodium sulfate, the solution was evaporated. The residue was chromatographed on silica gel using hexane-ethyl acetate (20:1) as the eluent to give (+)-8-demethylisoambrox (2) (2.1 g, 9.5 mmol, 43 %). Elution with hexane-ethyl acetate (3:1) gave 10 (2.8 g, 8.9 mmol, 40 %).

2 : mp 51~52°C (lit²⁾. 54~55°C); [α]_D²⁰ + 6.7° (c = 0.9, CHCl₃) [lit²⁾. [α]_D¹⁹ + 7.6° (c = 0.34)]; IR 1455 cm⁻¹ 1040 cm⁻¹; ¹³C-NMR δ = 15.5 (10-Me) 17.7 18.3 22.2(4-Me) 27.3 28.6 33.1 (C-4) 33.8(4-Me) 35.8(C-10) 41.0 42.3 52.8 (C-9) 53.1(C-5) 66.4(C-12) 77.8(C-8); ¹H-NMR δ = 0.87(3 H, s) 0.89(3 H, s) 0.93

(3 H, s)(lit²⁾. 0.88 0.90 0.93)

Dimethyl 13, 14, 15, 16-tetranorlabda-8(17)-ene-12, 19-dioate (12)

Methyltriphenylphosphonium iodide (7.6 g, 18.8 mmol) and potassium *t*-butoxide (2.1 g, 18.7 mmol) were suspended in diisopropyl ether (70 mL) at 60°C under a nitrogen atmosphere for 30 min. The keto diester (8) (2.8 g, 9.0 mmol) was added, and refluxed for 2 h. After cooling, 50 mL of water was added. The mixture was stirred for 30 min. The organic layer was washed with brine and dried over sodium sulfate. Removal of solvent under reduced pressure gave an oil, which was chromatographed on silica gel. Elution with hexane-ethyl acetate (8:1) gave the exocyclic methylene diester (12) (1.65 g, 5.4 mmol, 59 %).

12 : mp 65~68°C; IR 1730 cm⁻¹; ¹³C-NMR δ = 14.8(10-Me) 16.7(4-Me) 18.5 26.3 30.7 37.0 (2 C) 38.0 38.3(C-10) 47.7(C-4) 49.5(C-5) 51.6(-OMe) 51.9(-OMe) 52.6(C-9) 107.0(=CH₂) 148.4(C-8) 174.2(C-12) 178.9(4-CO₂); ¹H-NMR δ = 0.72(3 H, s) 1.15(3 H, s) 3.66 (6 H, s) 4.51(1 H, s) 4.71(1 H, s)

Methyl 12-methyl-14, 15, 16-trinorlabda-12, 8(17)-diene-19-oate (13)

Methyltriphenylphosphonium iodide (1.45 g, 3.6 mmol) and potassium *t*-butoxide (0.45 g, 4.0 mmol) were suspended in diisopropyl ether (30 mL) at 60°C under a nitrogen atmosphere for 30 min. The keto diester (8) (290 mg, 0.94 mmol) was added, and refluxed for 2 h. After the treatment by a method similar to that for 12, elution with hexane-ethyl acetate (9:1) on a silica gel column chromatography gave the diene (13) (120 mg, 0.41 mmol, 44 %).

13 : Oil; IR 1720 cm⁻¹; ¹³C-NMR δ = 14.6 (10-Me) 16.6(4-Me) 18.5 22.9(12-Me) 26.6 31.8 37.0 37.5 38.0 38.8(C-10) 47.7(C-4) 50.0 (C-5) 51.8(-OMe) 53.4(C-9) 107.9(8=CH₂) 110.4(12=CH₂) 145.0(C-12) 147.7(C-8) 179.2 (4-CO₂); ¹H-NMR δ = 0.72(3 H, s) 1.15(3 H, s) 1.42(3 H, s) 3.66(3 H, s)

8 α , 12-Epoxy-13, 14, 15, 16-tetranorlabdan-18-yl methanesulfonate (16)

A solution of *m*-chloroperbenzoic acid (1.0 g, 5.8 mmol) in chloroform (5 mL) was added at room temperature to a solution of the exocyclic methylene diester (12) (1.45 g, 4.7 mmol) in chloroform (10 mL). The mixture was allowed to

stand for 16 h. The mixture was washed with aqueous potassium iodide, sodium thiosulfate, sodium hydrogen carbonate, brine, and dried over sodium sulfate. Removal of solvent under reduced pressure gave the crude α -epoxide (14) (1.54 g, 4.7 mmol). The crude 14 was used without further purification in the following reaction.

14: IR 1720 cm^{-1} 1240 cm^{-1} ; ^{13}C -NMR δ =14.8(10-Me) 16.6(4-Me) 50.0(0- CH_2) 51.8(20-Me) 58.1(C-8) 173.7(C-12) 178.6(4- CO_2); ^1H -NMR δ =0.86(3 H, s) 1.21(3 H, s) 3.31(6 H, s)

A solution of the crude α -epoxide (14) (1.54 g, 4.7 mmol) in THF (5 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (0.55 g, 14.5 mmol) in THF (50 mL) under a nitrogen atmosphere with cooling in an ice-water bath. The mixture was refluxed for 2 h. After the same work-up as described for the preparation of 9, the crude triol (15) (1.20 g, 4.4 mmol) was obtained. The crude 15 was used without further purification in the following reaction.

15: IR 3390 cm^{-1} 1050 cm^{-1} ; ^{13}C -NMR δ (DMSO- d_6)=15.4(10-Me) 18.3(4-Me) 23.9(8-Me) 63.1(C-12) 70.0(4- CH_2OH) 71.4(C-8); ^1H -NMR δ (DMSO- d_6)=0.74(3 H, s) 1.05(3 H, s) 1.17(3 H, s)

Methanesulfonyl chloride (1.53 g, 13.3 mmol) was added to a cooled solution of crude triol (15) (1.20 g, 4.4 mmol) in dry pyridine (100 mL). The mixture was kept at room temperature for 16 hours. After the treatment by a method similar to that for 10, elution with hexane-ethyl acetate (3:1) on a silica gel column chromatography gave the 8 α ,12-epoxymesylate (16) (0.55 g, 1.7 mmol) in an overall yield of 35 % from 12.

16: mp 109~110°C; IR 1340 cm^{-1} 1180 cm^{-1} ; ^{13}C -NMR δ =15.3(10-Me) 16.6(4-Me) 17.5 20.5 21.1(8-Me) 22.6 35.8 36.2(C-4) 36.8(C-10) 37.1(- OSO_2Me) 39.3(2 C) 50.7(C-5) 60.1(C-9) 64.8(C-12) 77.6(4- CH_2O) 79.4(C-8); ^1H -NMR δ =0.89(6 H, s) 1.09(3 H, s) 3.00(3 H, s)

8 α , 12-Epoxy-13, 14, 15, 16-pentanorlabdane (1)[(-)-ambrox]

A stirred mixture of the 8 α ,12-epoxy mesylate (16) (180 mg, 0.55 mmol), sodium iodide (0.30 g), and zinc powder (0.30 g) in DMF (5 mL) was heated at 115°C for 6 h. After the

same work-up as described for the preparation for 2, the mixture was chromatographed on silica gel using hexane-ethyl acetate (20:1) as the eluent to give (-)-ambrox(1) (56 mg, 0.24 mmol, 44 %). Elution with hexane-ethyl acetate (3:1) gave 16(69 mg, 0.21 mmol, 38 %).

1: mp 73~74°C(lit¹⁾. 75~76°C); $[\alpha]_D^{20}$ -26.3° (c=0.9, C_6H_6) [lit^{1b)}. $[\alpha]_D^{23}$ -28.0°(C_6H_6)]; IR 1380 cm^{-1} 1010 cm^{-1} (identical IR spectrum^{1b)}); ^{13}C -NMR δ =15.0(10-Me) 18.4 20.7 21.1(4-Me and 8-Me) 22.6 33.0(C-4) 33.6(4-Me) 36.2(C-10) 39.7 40.0 42.4 57.3(C-5) 60.1(C-9) 64.8(C-12) 79.7(C-8)(lit⁹⁾. 15.2 21.2 33.8 64.9); ^1H -NMR δ =0.87(6 H, s) 0.89(3 H, s) 1.10(3 H, s)(lit⁹⁾. 0.84 0.88 1.09)

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(-)-レボピマル酸より(-)-

アンブロックスの合成

西 康隆・石原宏一

播磨化成工業株式会社中央研究所
(〒675 古古川市野口町水足 671-4)

アンバー香をもつ (-)-アンブロックス (1) と (+)-8-デメチルイソアンブロックス (2) を (-)-レボピマル酸 (3) より合成した。レボピマル酸メチルのオゾン分解によりケトジエステル (8) を得た。Wittig 反応, 続いてエポキシ化反応, 還元反応を行い, C-8位にメチル基とヒドロキシル基を付加した。トリオール (15) は塩化メタンスルホニルを用いた脱水反応により, 8 α ,12-エポキシメシレート (16) に変換した。ヨウ化メチルと亜鉛末を用いて 16 を還元し, (-)-アンブロックス (1) を合成した。