New Syntheses of ($\pm$)-Ambrox, ($\pm$)-Ambra Oxide and Their Stereoisomers

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Received November 12, 1985

New and efficient syntheses of ($\pm$)-ambrox (**1a**), ($\pm$)-ambra oxide (**2a**) and their stereoisomers (**1b**, **2b~c**), amber-like odorous compounds, are described. Starting from dihydro β - and α -ionone (**5**, **12**), these substances were obtained in only a few steps *via* stereoselective acid-catalyzed cyclization of monocyclodienoic acid (**7a~b**, **11a~b**, **15a**).

Ambrox (8 α , 12-epoxy-13, 14, 15, 16-tetra-norlabdane, **1a**) and ambra oxide (8 α , 13-epoxy-14, 15, 16-trinorlabdane, **2a**) are well known as key substances with an amber-like odor.¹⁾ In particular, **1a** has been extensively utilized in the perfumery industry for more than 20 years. Much attention has been paid to the synthesis of the tricyclic ethers (**1a**, **2a**) and related compounds, including norambreinolide (**3a**) and ambreinolide (**4a**), because of their usefulness in the perfumery and tobacco industries, various synthetic studies of these compound having been reported.

The major approaches to **1a** and **2a** have been accomplished by the transformation of **3a** and **4a**, which were derived from the oxidative degradation²⁾ of naturally occurring sclareol, manool and ambrein, and the biogenetic-type cyclization³⁾ of homofarnesic acid, farnesylacetic acid and their analogues.

We describe here a new and efficient synthesis of **1a**, **2a** and their stereoisomers (**1b**, **2b~c**) *via* monocyclodienoic acids (**7a~b**, **11a~b**, **15a**) and their cyclization products (**3a~b**, **4a~c**), and also report the olfactory properties of **1a~b** and **2a~c**.

a) Synthesis of ($\pm$)-ambrox (**1a**) and ($\pm$)-9-epi-ambrox (**1b**)

In order to prepare β -monocyclohomofar-

nesic acids (**7a~b**), elongation of the side chain of dihydro- β -ionone (**5**) was tried by employing Darzen's condensation and subsequent malonic acid condensation. Condensation of **5** with ethyl chloroacetate was carried out in the presence of NaOEt at 5°C and then decarboxylation of the resulting glycidic acid with a catalytic amount of AcONa at 200°C under a reduced pressure gave an aldehyde (**6**) in a 55% yield from **5**. Successively, treatment of **6** with malonic acid in the presence of NEt₃ under reflux afforded a mixture of *trans*- β -monocyclohomofarnesic acid (**7a**) and a *cis* isomer (**7b**) in an 87% yield (*ca.* 1:1). The acid mixture of **7a** and **7b** was esterified by TiCl₄/EtOH to give an ester mix-

Fig. 1

SCHEME 1.

ture (**8a~b**), which was separated to each pure ester⁴⁾ by fractional distillation, and followed by hydrolyzing to each pure acid (**7a**, **7b**) by 15% KOH in EtOH.

Recently, Saito *et al.*^{3a)} reported an excellent stereoselective cyclization of **7a** and **7b** in the presence of SnCl₄ to yield (±)-norambreinolide (**3a**) and the (±)-9-epimer (**3b**), respectively. We studied a modification of this cyclization in the presence of SnCl₄ under various conditions. Treatment of **7a** and **7b** with CF₃COOH at 0°C for 2 hr stereoselectively gave **3a** and **3b** as main products in 64 and 65% yields, respectively. These results were almost the same yield and stereoselectivity as those reported. Subsequently, reduction of **3a** and **3b** with Vitride [NaAlH₂(OCH₂CH₂OCH₃)₂] at 60°C, followed by treatment TsCl/pyridine at 0°C yielded (±)-ambrox (**1a**) and the (±)-9-epimer (**1b**) in 69 and 74% yields.

The spectral data of synthetic **1a** and **1b** were identical with those reported.⁵⁾

Thus, a short and efficient synthesis of **1a** and **1b** was accomplished.

b) *Synthesis of (±)-ambra oxide (2a), (±)-9-epi-ambra oxide (2b) and (±)-epi-ambra oxide (2c)*

Claisen rearrangement of β- and α-monocyclonerolidol (**9**, **13**) from **5** and **12** was applied to obtain β-monocyclofarnesylacetic acids (**11a~b**) and the α-forms (**15~b**). Grignard reactions of **5** and **12** with vinyl magnesium bromide in THF gave **9** and **13** in 80% and 90% yields, respectively. Then, treatment of **9** with ethyl orthoacetate in the presence of propionic acid at 120°C for 12 hr with continuous removal of the resulting EtOH afforded a mixture of ethyl *trans*-β-

monocyclofarnesylacetate (**10a**) and a *cis* isomer (**10b**) in a 72% yield (*ca.* 1:1), which were separated by fractional distillation. In the same manner, pure ethyl *trans*-α-monocyclofarnesylacetate (**14a**) and the *cis* isomer (**14b**) were obtained by the separation of their compounds, prepared from **13** in an 81% yield (*ca.* 1:1). The structures of **10a~b** and **14a~b** were confirmed by ¹H-NMR and ¹³C-NMR spectra. Hydrolysis of **10a~b** and **14a~b** with KOH/EtOH gave the corresponding acids (**11a~b**, **15a~b**) in quantitative yields.

Acid-catalyzed cyclization of *trans*-β-monocyclofarnesylacetic acid (**11a**) to (±)-ambreinolide (**4a**), and *trans*-α-monocyclofarnesylacetic acid (**15a**) to **4a** and (±)-9-epi-ambreinolide (**4b**) had been reported by Stork *et al.*,^{3b)} although their yields were quite low. In order to improve the yield and stereoselectivity, cyclization of the *trans* acids (**11a**, **15a**) and *cis* acids (**11b**, **15b**) with CF₃COOH and SnCl₄ were examined under various conditions, the results being shown in Table I.

Cyclization of **11a**, **11b** and **15a** with CF₃COOH at 0°C for 2 hr gave **4a**, **4b** and the (±)-10-epi-ambreinolide (**4c**) as main products in 22, 17 and 46% isolated yields (Nos. 1~3). On the other hand, treatment of **15a** at a higher temperature predominantly afforded **4a** (Nos. 4, 5). However, reaction of **15b** with CF₃COOH and SnCl₄ did not yield the desired tricyclic lactones, but complicated products. The spectral data of synthetic **4a** were identical to those reported.⁶⁾ The structures of **4b** and **4c** were assigned to the 9-epimer and 10-epimer by comparing their ¹H-NMR and ¹³C-NMR spectra with those of **3b** and **3c**.^{3a,4)} Thus, stereoselective cyclization of **11a**, **11b** and **15a** to **4a**, **4b** and **4c** was achieved in moderate yields.

TABLE I. CYCLIZATION OF **11a~b** AND **15a** TO **4a~c**

No.	Acid	Catalyst (solvent)	Temp. (°C)	Time (hr)	Yield (%)	Ratio of products (%)		
						4a	4b	4c
1	11a	CF ₃ COOH	0	2	22	53	21	19
2	11b	CF ₃ COOH	0	2	17	6	62	4
3	15a	CF ₃ COOH	0	2	46	13	5	75
4	15a	SnCl ₄ (C ₆ H ₆)	25	2	23	64	6	14
5	15a	SnCl ₄ (CH ₂ Cl ₂)	45	1	11	70	—	—

The ratio of products was estimated by peak area measurement of the GLC trace (PEG 20M glass capillary column, ϕ 0.25 mm $\times$ 10 m).

SCHEME 2.

In the same manner, **4a**, **4b** and **4c** were converted to the (±)-ambra oxide (**2a**), (±)-9-epimer (**2b**) and (±)-10-epimer (**2c**) in 63, 65, 79% yields, respectively. Further reduction of **4a** and **4c** with diborane (NaBH₄/BF₃-etherate) at 0°C gave **2a** and **2c** in 63 and 76% yields for one step.

The physical data of synthetic **2a** were identical with those reported,⁶⁾ and the spectral data of synthetic **2b** and **2c** supported their structures.

Thus, a new and short synthesis of **2a**, **2b** and **2c** was established.

The tricyclic lactones (**3a~b**, **4a~c**) were practically odorless, while the corresponding tricyclic ethers (**1a~b**, **2a~c**) had a pronounced amber-like odor. Among them, the most intense odorous compound was **1a**, the second was **2a**, and the odor intensity of their epimers (**1b**, **2b~c**) was less.

EXPERIMENTAL

All boiling points (bp) and melting points (mp) were uncorrected. IR were determined on a JASCO-2 spectrometer. ¹H-NMR and ¹³C-NMR spectra were measured with JEOL JNM FX 90Q and Hitachi R-24A (60) spectrometers. MS spectra were obtained on a Hitachi RMU-5M GC-MS spectrometer.

4-(2,6,6-Trimethyl-1-cyclohexenyl)-2-methyl butanal (6). To a stirred suspension of NaOEt, prepared from NaH (58 g of a 60% mineral oil dispersion) and abs. EtOH (76 g) in dry toluene (1.4 liters) was added dropwise a mixture of **5** (194 g) and ethyl monochloroacetate (185 g) during 1 hr at 5°C. After stirring at room temperature for a further 3 hr, a solution of KOH (84 g) in EtOH (500 ml) was added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into water. The aqueous layer was acidified with 10% HCl aq. and extracted with ether, before the extract was washed with brine, dried over MgSO₄ and concentrated. The residue was distilled to give **6** (114.5 g, 55%), bp 106~111°C/2 mmHg. IR $\nu_{\max}^{\text{film}}$ cm⁻¹: 1730. ¹H-NMR $\delta_{\text{Me}_4\text{Si}}$: 0.98 (6H,

s), 1.14 (3H, d, $J=7$ Hz), 1.59 (3H, s), 1.4~2.5 (11H), 9.62 (1H, d, $J=2$ Hz). MS m/z : 208 (M^+ , 26), 193 (24), 123 (99), 95 (89), 41 (100).

trans- and cis- β -Monocyclohomofarnesic acids (7a~b). A mixture of **6** (52 g), malonic acid (100 g) and triethylamine (151.5 g) was refluxed for 8 hr. To this mixture, malonic acid (50 g) was added. After refluxing for 4 hr, the reaction mixture was concentrated, poured into cold dil. HCl and then extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was distilled *in vacuo* to give the recovered **6** (7 g), **7a** and **7b** (47 g, 87% based on the recovery of **6**). The mixture of **7a~b** (45 g) and $TiCl_4$ (1.5 ml) in EtOH (71 g) was stirred at room temperature for 12 hr. After the usual work-up, the residue was distilled to give mixture of **8a** and **8b** (45 g, 90%). The mixture was separated by a spinning band-type distillation to give pure **8a** (15 g) and pure **8b** (18 g). A mixture of **8a** (11 g) and 15% KOH in EtOH (35 g) was stirred at room temperature for 2 hr. The reaction mixture was acidified with 3N HCl, extracted with ether, washed with brine, dried over $MgSO_4$ and concentrated to give **7a** (9.5 g, 95%). In the same manner, **8b** (12.5 g) gave **7b** (10.5 g, 93%).

8a: bp 131~133°C/0.5 mmHg. IR ν_{max}^{film} cm^{-1} : 1740. 1H -NMR $\delta_{Me_4Si}^{CDCl_3}$: 0.99 (6H, s), 1.25 (3H, t, $J=7$ Hz), 1.59 (3H, s), 1.5~2.0 (6H), 1.67 (3H, s), 2.07 (4H, s), 3.00 (2H, d, $J=7$ Hz), 4.13 (2H, q, $J=7$ Hz), 5.32 (1H, t, $J=7$ Hz). MS m/z : 278 (M^+ , 4), 137 (100), 95 (43), 81 (32), 69 (18).

7a: IR ν_{max}^{film} cm^{-1} : 3400~2400, 1720.

8b: bp 126~128°C/0.5 mmHg. IR ν_{max}^{film} cm^{-1} : 1740. 1H -NMR $\delta_{Me_4Si}^{CDCl_3}$: 1.01 (6H, s), 1.25 (3H, t, $J=7$ Hz), 1.64 (3H, s), 1.5~2.0 (6H), 1.79 (3H, s), 2.05 (4H, s), 3.03 (2H, d, $J=7$ Hz), 4.13 (2H, q, $J=7$ Hz), 5.28 (1H, t, $J=7$ Hz). MS m/z : 278 (M^+ , 5), 137 (100), 95 (44), 81 (35), 69 (23).

7b: IR ν_{max}^{film} cm^{-1} : 3400~2400, 1720.

($\pm$)-Norambreinolide (3a). A solution of **7a** (2.2 g) in CH_2Cl_2 (2.2 ml) was added to CF_3COOH (16 ml) at 0°C. After stirring for 2 hr at 0°C, the mixture was poured into water and extracted with CH_2Cl_2 . The extract was washed with brine and $NaHCO_3$ aq., dried over $MgSO_4$ and concentrated. The residue on SiO_2 chromatography eluted with ether-pentane-cyclohexane (4:1:1) gave **4a** (1.4 g, 64%), mp 119~121°C (recrystallized from *n*-hexane). IR ν_{max}^{film} cm^{-1} : 1770. 1H -NMR $\delta_{Me_4Si}^{CDCl_3}$: 0.84 (3H, s), 0.89 (3H, s), 0.91 (3H, s), 1.34 (3H, s), 2.2~2.5 (2H, m). ^{13}C -NMR ($CDCl_3$): 15.1 (q), 18.2 (t), 20.6 (t), 21.0 (q), 21.6 (q), 28.8 (t), 33.2 (q), 33.2 (s), 36.2 (s), 38.9 (t), 39.7 (t), 42.3 (t), 56.8 (d), 59.3 (d), 86.3 (s), 176.8 (s). MS m/z : 250 (M^+ , 0.7), 235 (18), 207 (13), 206 (13), 147 (22), 133 (58), 95 (53), 82 (58), 81 (49), 69 (58), 55 (56), 43 (100), 41 (78).

($\pm$)-9-Epi-norambreinolide (3b). In the same manner as that just described, **7b** was treated to give **3b** (1.1 g, 65%), mp 93~95°C (recrystallized from *n*-hexane). IR ν_{max}^{film}

cm^{-1} : 1770. 1H -NMR $\delta_{Me_4Si}^{CDCl_3}$: 0.84 (3H, s), 0.92 (3H, s), 1.12 (3H, s), 1.56 (3H, s), 2.4~2.7 (2H, m). ^{13}C -NMR ($CDCl_3$): 18.2 (t), 19.3 (t), 21.8 (q), 22.8 (q), 27.4 (q), 32.6 (t), 32.8 (s), 33.4 (q), 36.0 (s), 37.2 (t), 38.3 (t), 42.0 (t), 46.6 (d), 56.8 (d), 85.8 (s), 175.3 (s). MS m/z : 250 (M^+ , 7), 235 (22), 207 (5), 147 (53), 146 (57), 134 (67), 133 (59), 95 (51), 81 (88), 69 (76), 55 (65), 43 (100), 41 (88). These physical data for synthetic **3b** are identical with those reported.⁴⁾

($\pm$)-Ambrox (1a). To a mixture of **3a** (1.2 g) and dry toluene (6 ml) was added dropwise $NaAlH_2(OCH_2CH_2OCH_3)_2$ (2.4 ml at 70% in toluene) during 10 min at 50°C, and the mixture was stirred for 2 hr at the same temperature. The reaction mixture was washed with 5% NaOH aq., brine, AcOH aq. and $NaHCO_3$ aq., dried over $MgSO_4$ and concentrated. To a solution of the resulting crystal in pyridine (30 ml) was added $TsCl$ (1.5 g) at 0°C. The mixture was stirred for 12 hr at room temperature, poured into ice-cooled water and extracted with ether. The extract was washed with $CuSO_4$ aq. and brine, dried over $MgSO_4$ and concentrated. The residue on SiO_2 chromatography eluted with ether-pentane-cyclohexane (4:1:2) gave **1a** (780 mg, 69%). IR ν_{max}^{KBr} cm^{-1} : 1000. 1H -NMR $\delta_{Me_4Si}^{CDCl_3}$: 0.84 (6H, s), 0.88 (3H, s), 1.09 (3H, s), 3.7~4.0 (2H, m). MS m/z : 236 (M^+ , 3), 221 (100), 137 (39), 97 (44), 95 (21), 81 (23), 69 (26), 67 (21), 55 (24), 43 (21), 41 (24). These physical data for synthetic **1a** are identical with those reported.⁵⁾

($\pm$)-9-Epi-ambrox (1b). In the same manner, **4b** (900 mg) gave **2b** (630 mg, 74%). IR ν_{max}^{KBr} cm^{-1} : 1050. 1H -NMR $\delta_{Me_4Si}^{CDCl_3}$: 0.79 (3H, s), 0.87 (3H, s), 1.07 (3H, s), 1.35 (3H, s), 3.6~4.0 (2H, m). MS m/z : 236 (M^+ , 16), 221 (64), 137 (100), 109 (24), 97 (33), 95 (29), 81 (33), 69 (36), 67 (24), 55 (40), 43 (78), 41 (67). These physical data for synthetic **1b** are identical with those reported.⁵⁾

β -Monocyclonerolidol (9). To a solution of Grignard reagent, prepared from vinyl bromide (128 g) and Mg (27 g) in dry THF (400 ml), was added dropwise a solution of dihydro- β -ionone (**5**, 194 g) in dry THF (400 ml) at 10°C over 1 hr, stirring being continued for 2 hr. The reaction mixture was poured into NH_4Cl solution and extracted with ether. The extract was washed with brine and $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated. The residue was distilled to give **9** (178 g, 80%), bp 110~112°C/2 mmHg. IR ν_{max}^{film} cm^{-1} : 3400, 3070, 1640, 920. 1H -NMR $\delta_{Me_4Si}^{CDCl_3}$: 0.99 (6H, s), 1.30 (3H, s), 1.59 (3H, s), 1.4~2.2 (10H), 5.07 (1H, dd, $J=2$, 10 Hz), 5.24 (1H, dd, $J=2$, 16 Hz), 6.03 (1H, dd, $J=10$, 16 Hz). MS m/z : 222 (M^+ , 6), 204 (6), 189 (24), 123 (52), 121 (55), 95 (100), 93 (40), 81 (50), 71 (43), 55 (43), 43 (45), 41 (48).

α -Monocyclonerolidol (13). In the same manner, **12** (80 g) was converted to **13** (82 g, 90%), bp 102~104°C/2 mmHg. IR ν_{max}^{film} cm^{-1} : 3400, 3070, 1640, 920. 1H -NMR $\delta_{Me_4Si}^{CDCl_3}$: 0.85 (3H, s), 0.91 (3H, s), 1.26 (3H, s), 1.45 (3H, d,

$J=2$ Hz), 1.2~2.2 (9H), 5.02 (1H, dd, $J=2$, 10 Hz), 5.15 (1H, dd, $J=2$, 16 Hz), 5.25 (1H, s), 5.92 (1H, dd, $J=10$, 16 Hz). MS m/z : 204 (4), 136 (100), 123 (39), 121 (40), 93 (40), 81 (40), 80 (49), 71 (50), 43 (41), 41 (37).

trans- and cis-β-Monocyclofarnesylacetic acids (11a~b). A mixture of **9** (100 g), ethyl orthoacetate (520 g) and propionic acid (6 g) was refluxed for 12 hr with continuous removal of the EtOH. The reaction mixture was distilled to give a mixture of **10a** and **10b** (94 g, 72%) bp 147~152°C/2 mmHg. The ratio of **10a** to **10b** was *ca.* 1:1 by GLC (PEG 20M, 3 mm×2 m). The mixture (50 g) of **10a** and **10b** was distilled by using a spinning band-type apparatus to give pure **10a** (21 g) and **10b** (17 g). A mixture of **10a** (10 g) or **10b** (10 g) and KOH (5 g) in EtOH (30 ml) was stirred at room temperature for 12 hr. After the usual work-up, the residue was concentrated *in vacuo* to give **11a** (9 g, 99%) or **11b** (8.5 g, 94%).

10a: bp 120~122°C/0.1 mmHg. IR $\nu_{\max}^{\text{film}}$ cm^{-1} : 1740. $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.02 (6H, s), 1.24 (3H, t, $J=7$ Hz), 1.65 (3H, s), 1.74 (3H, s), 1.4~2.0 (6H), 2.05 (4H, s), 2.2~2.4 (4H), 4.16 (2H, q, $J=7$ Hz), 5.10 (1H, br. s).

$^{13}\text{C-NMR}$ (CDCl_3): 14.2, 16.0, 19.6, 19.8, 23.6, 27.8, 28.6 (two carbons), 32.8, 34.6, 34.9, 40.0, 40.3, 60.0, 121.7, 126.9, 137.1, 137.5, 173.2. MS m/z : 292 (M^+ , 1.5), 137 (100), 136 (41), 95 (37), 81 (29), 69 (12), 41 (13).

11a: IR $\nu_{\max}^{\text{film}}$ cm^{-1} : 3600~2400, 1715.

10b: bp 115~118°C/0.1 mmHg. IR $\nu_{\max}^{\text{film}}$ cm^{-1} : 1740. $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.02 (6H, s), 1.24 (3H, t, $J=7$ Hz), 1.65 (3H, s), 1.74 (3H, s), 1.4~2.0 (6H), 2.05 (4H, s), 2.2~2.4 (4H), 4.16 (2H, q, $J=7$ Hz), 5.10 (1H, br. s). $^{13}\text{C-NMR}$ (CDCl_3): 14.2, 19.6, 19.8, 23.2 (q), 23.6 (t), 27.3, 28.7 (two carbons), 32.6, 32.8 (two carbons), 34.9, 39.9, 60.0, 122.7, 127.2, 137.1, 137.4, 173.1. MS m/z : 292 (M^+ , 2.1), 137 (100), 136 (46), 95 (50), 81 (39), 69 (17), 41 (19).

11b: IR $\nu_{\max}^{\text{film}}$ cm^{-1} : 3600~2400, 1715.

trans- and cis-α-Monocyclofarnesylacetic acids (15a~b). In the same manner as that just described, **13** (50 g) was treated to give a mixture of **14a~b** (53 g, 81%). The mixture (50 g) of **14a~b** (*ca.* 1:1) was separated to give pure **14a** (18 g) and **14b** (17 g). Respectively, **14a** and **14b** were hydrolyzed by KOH-EtOH to give **15a** and **15b**.

14a: bp 110~113°C/0.1 mmHg. IR $\nu_{\max}^{\text{film}}$ cm^{-1} : 1735. $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.88 (3H, s), 0.95 (3H, s), 1.27 (3H, t, $J=7$ Hz), 1.65 (3H, s), 1.70 (3H, s), 1.0~2.2 (9H), 2.2~2.5 (4H), 4.19 (2H, q, $J=7$ Hz), 5.18 (1H, br. s), 5.36 (1H, br. s). $^{13}\text{C-NMR}$ (CDCl_3): 14.2, 16.0, 23.0, 23.4, 23.6, 27.4, 27.6, 29.8, 31.7, 32.6, 34.6, 40.5, 49.1, 60.1, 119.9, 122.2, 136.7, 137.3, 173.3. MS m/z : 292 (M^+ , 4), 168 (50), 136 (100), 123 (37), 131 (55), 109 (46), 95 (54), 81 (98), 41 (55).

15a: IR $\nu_{\max}^{\text{film}}$ cm^{-1} : 3600~2400, 1715.

14b: bp 108~110°C/0.1 mmHg. IR $\nu_{\max}^{\text{film}}$ cm^{-1} : 1735. $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.90 (3H, s), 0.98 (3H, s), 1.27 (3H, t, $J=7$ Hz), 1.71 (6H, s), 1.0~2.2 (9H), 2.2~2.5 (4H), 4.20 (2H, q, $J=7$ Hz), 5.16 (1H, br. s), 5.41 (1H, br. s). $^{13}\text{C-NMR}$ (CDCl_3): 14.2, 23.0, 23.3, 23.6 (two carbons), 27.3,

27.5, 29.5, 31.8, 32.5, 32.8, 34.8, 49.6, 60.0, 120.0, 122.7, 136.3, 137.4, 173.0. MS m/z : 292 (M^+ , 4), 168 (46), 136 (66), 123 (52), 121 (46), 109 (42), 95 (57), 81 (100), 55 (37), 41 (42).

15b: IR $\nu_{\max}^{\text{film}}$ cm^{-1} : 3600~2400, 1715.

(±)-Ambreinolide (**4a**), (±)-9-epi-ambreinolide (**4b**) and (±)-10-epi-ambreinolide (**4c**).

a) In the same manner as that for **3a** from **7a**, **11a** (5 g), **11b** (6 g) and **15a** (10 g) were converted to **4a** (1.1 g, 22%), **4b** (1.0 g, 17%) and **4c** (4.6 g, 46%).

b) A solution of **15a** (10 g) in CH_2Cl_2 (100 ml) was added to SnCl_4 (400 ml) and CH_2Cl_2 (400 ml) at 45°C, the mixture being stirred for 1 hr at 45°C. The reaction mixture was poured into ice-cooled water, washed and separated by SiO_2 chromatography to give **4a** (1 g, 10%).

4a: mp 132~135°C (recrystallized from *n*-hexane). IR $\nu_{\max}^{\text{film}}$ cm^{-1} : 1730. $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.82 (3H, s), 0.85 (3H, s), 0.90 (3H, s), 1.39 (3H, s), 2.5~2.8 (2H, m). $^{13}\text{C-NMR}$ (CDCl_3): 15.1 (q), 16.0 (t), 18.5 (t), 19.8 (t), 21.5 (q), 23.0 (q), 29.1 (t), 33.4 (s), 33.4 (q), 37.4 (s), 39.3 (t), 41.4 (t), 41.9 (t), 53.8 (d), 56.2 (d), 83.8 (s), 171.6 (s). MS m/z : 264 (M^+ , 1.3), 249 (18), 192 (35), 177 (29), 137 (27), 136 (29), 109 (50), 95 (58), 82 (74), 81 (67), 69 (67), 67 (74), 55 (76), 43 (100), 41 (90).

4b: mp 125~127°C (recrystallized from *n*-hexane). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1730. $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.81 (3H, s), 0.87 (3H, s), 1.15 (3H, s), 1.62 (3H, s), 2.5~2.8 (2H, m). $^{13}\text{C-NMR}$ (CDCl_3): 18.6 (t), 19.4 (t), 20.6 (t), 21.7 (q), 24.3 (q), 30.6 (t), 31.3 (q), 33.1 (s), 33.1 (q), 36.8 (t), 37.5 (t), 38.0 (s), 42.1 (t), 47.1 (d), 54.0 (d), 87.7 (s), 170.7 (s). MS m/z : 264 (M^+ , 1.3), 249 (28), 192 (18), 177 (28), 137 (64), 136 (49), 109 (79), 95 (62), 82 (38), 81 (67), 69 (69), 67 (44), 55 (77), 43 (87), 41 (100).

4c: mp 111~114°C (recrystallized from *n*-hexane). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1730. $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.91 (3H, s), 1.18 (3H, s), 1.20 (3H, s), 1.42 (3H, s), 2.4~2.8 (2H, m). $^{13}\text{C-NMR}$ (CDCl_3): 16.7 (t), 19.0 (t), 22.5 (q), 23.1 (t), 27.5 (t), 28.1 (q), 30.0 (t), 31.4 (q), 33.4 (q), 34.0 (s), 35.1 (t), 38.8 (s), 39.9 (t), 51.6 (d), 52.6 (d), 83.3 (s), 171.6 (s). MS m/z : 264 (M^+ , 4.5), 249 (23), 192 (56), 177 (38), 137 (42), 136 (33), 109 (47), 95 (54), 82 (61), 81 (59), 69 (61), 67 (68), 55 (77), 43 (100), 41 (94).

(±)-Ambra oxide (**2a**).

a) In the same manner as that for **1a** from **3a**, **4a** (0.6 g) was treated with $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ (1.2 ml at 70% in toluene) and TsCl (1.5 g) in pyridine (15 ml) to give **2a** (360 mg, 63%). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1090, 990. $^1\text{H-NMR}$ $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.75 (3H, s), 0.80 (3H, s), 0.87 (3H, s), 1.25 (3H, s), 3.5~3.8 (2H, m). MS m/z : 250 (M^+ , 4), 235 (100), 137 (25), 111 (32), 95 (21), 81 (23), 69 (26), 67 (20), 55 (32), 43 (45), 41 (43). These physical data of synthetic **2a** are identical with those reported.⁶⁾

b) To a stirred suspension of NaBH_4 (0.44 g) in diglyme (29 ml) was added dropwise a mixture of **3a** (1.5 g), BF_3 -etherate (24.5 g) and THF (58 g) during a 1 hr at 0°C. After

stirring for 2 hr at 5°C, the reaction mixture was poured into water and extracted with ether. The extract was washed with NaHCO₃ aq. and brine, dried over MgSO₄ and concentrated. The residue was chromatographed on SiO₂ with ether-pentane-cyclohexane (4:1:2) as the eluent to give **2a** (0.9 g, 63%).

(±)-9-Epi-ambra oxide (**2b**). In the same manner as that for **2a** from **4a** in the method of a), **4b** (360 mg) gave **2b** (220 mg, 65%). IR $\nu_{\text{max}}^{\text{film}}$ cm⁻¹: 1090, 990. ¹H-NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.80 (3H, s), 0.87 (3H, s), 1.12 (3H, s), 1.39 (3H, s), 3.5~3.8 (2H, m). MS m/z : 250 (M⁺, 26), 235 (70), 137 (100), 111 (48), 109 (61), 99 (30), 98 (30), 95 (57), 93 (26), 81 (65), 69 (61), 67 (48), 55 (83), 43 (100), 41 (100).

(±)-10-Epi-ambra oxide (**2c**). In the same manner as that for **2a** from **4a** in the method of a), **4c** (1.0 g) gave **2c** (0.75 g, 79%), and also in the method of b), **4c** (2.6 g) gave **2c** (1.9 g, 76%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1090, 990. ¹H-NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.88 (3H, s), 1.10 (3H, s), 1.17 (3H, s), 1.29 (3H, s), 3.5~3.8 (2H, m). MS m/z : 250 (M⁺, 4), 235 (100), 137 (19), 111 (50), 95 (25), 81 (29), 69 (33), 67 (28), 55 (42), 43 (50), 41 (48).

Acknowledgments. We are indebted to Dr. K.

Hayashi, the senior director of T. Hasegawa Co., Ltd. for his encouragement in this work. We thank Mr. T. Yanai and Dr. A. Fujita of T. Hasegawa Co., Ltd. for recording and measuring the MS and NMR spectra.

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