First Synthesis of (+)-γ-Coronal

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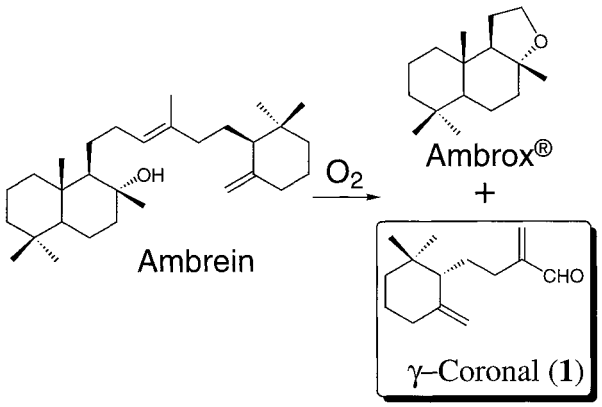
Abstract: Enantiomerically pure (+)-γ-Coronal (ambra aldehyde) was synthesized from easily prepared (+)-γ-cyclogeraniol.

Ambergris, a metabolite of the sperm whale, is one of the most important animal perfumes. (+)-Ambrein, the major constituent of ambergris, is decomposed by exposure to air and sunlight to produce some odorous compounds (Scheme 1).[1] The unique fragrance properties are related principally to (-)-Ambrox®. We have reported useful asymmetric syntheses[2] of (-)-Ambrox® and a total synthesis[3] of (+)-ambrein itself via lipase catalyzed kinetic resolution. In 1977 Ohloff *et al.*[4a,4b] and Mookherjee *et al.*[5] found (+)-γ-coronal (ambra aldehyde) (**1**) in ambergris odorants formed under oxygen degradation of (+)-ambrein.

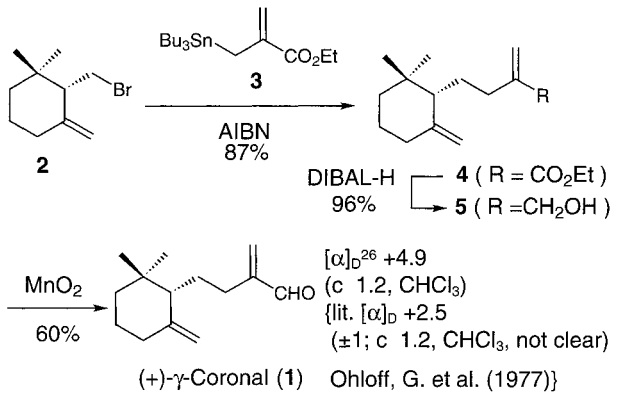
In spite of the long history of research on ambergris, no publication has appeared on the synthesis of (+)-γ-coronal (**1**), which is a marine-ozone type fragrance. It is worthy of note, however, that (±)-γ-coronal was synthesized from (±)-γ-ionone in the patent of Hasegawa T Co., Ltd.[6] In this paper we report an efficient synthesis of (+)-γ-coronal (**1**) from easily prepared enantiomerically pure γ-cyclogeranyl bromide **2** used for the synthesis of (+)-ambrein.[3]



Scheme 1. Air degradation of Ambrein (1)

Scheme 2 shows the synthetic route leading to (+)-γ-coronal (**1**). We found the formation of carbon skeleton of (+)-γ-coronal can be synthesized efficiently by coupling γ-cyclogeranyl bromide **2** with the stannane **3.** The stannane **3**[9] was synthesized by Baldwin's method[7] from easily prepared ethyl α-bromomethylacrylate.[8] The coupling reaction of **2** (362 mg, 1.67 mmol) with **3** (1.01 g, 2.51 mmol) in the presence of AIBN (35 mg) in boiling benzene (20 mL) for 30 h gave the acrylate **4**[10] (364 mg, 87.2%). The compound **4** was reduced with DIBAL-H to give allyl alcohol **5**[11] which was converted to (+)-γ-coronal (**1**)[12] according to literature.[6] Although the IR, ^{1}H NMR and MS spectra of **1** were identical with those of known data, the optical rotation value {$[\alpha]_D^{26}$ +4.9 (*c* 1.2, $CHCl_3$} was higher than that reported.[4a] {lit.[4a] {$[\alpha]_D$ +2.5 (*c* 1.2, $CHCl_3$, not clear)}.

In summary, we have synthesized enantiomerically pure (+)-γ-coronal from easily prepared (+)-γ-cyclogeraniol. This will serve practical and academic purposes of ambergris.



Scheme 2. Synthetic route of (+)-γ-Coronal (1)

References and Notes

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9. Spectroscopic data for **3**: bp 90 °C (0.4 mmHg). IR (film) ν cm^{-1} 1710 (s, C=O), 1610 (m, C=C), 902 (w, $C=CH_2$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75-1.00 (9H, CH_3), 1.30 (3H, t, *J* = 7.2 Hz, CH_3CH_2O), 1.2-1.55 (18 H, m), 1.97 (2 H, s, CH_2Sn), 4.18 (2 H, q, *J* = 7.2 Hz, CH_3CH_2O), 5.27 (1 H, s, conj. C=CHH), 5.81 (1 H, d, *J*= 1.6 Hz, conj. C=CHH).
10. Spectroscopic data for **4**: $[\alpha]_D^{22}$ + 4.2 (*c* 2.0, $CHCl_3$). IR (film) ν cm^{-1} 3375 (br. s, OH), 3060 [w, (C=)C–H], 1720 (s, conj. C=O), 1630 (m, C=C), 940 (m, conj. $C=CH_2$), 885 (m, $C=CH_2$). ^{1}H NMR (300 MHz): δ 0.81 (3 H, CH_3), 0.91 (3 H, CH_3). 0.91 (3H, t, *J* = 7.1 Hz, CH_3CH_2O), 1.15-2.36 (11 H, m), 4.20 (2 H, q, *J* = 7.1 Hz, CH_3CH_2O), 4.58 (1 H, s, C=CHH), 4.78 (1 H, s, C=CHH), 5.50 (1 H, s, conj. C=CHH), 6.10 (1 H, s, conj. C=CHH). HREIms: Found: 250.1952. Calcd. for $C_{16}H_{26}O_2$ (M): 250.1933.
11. Spectroscopic data for **5:** $[\alpha]_D^{22}$ +5.2 (*c* 1.2, $CHCl_3$). IR (film) ν cm^{-1} 3325 (br. s, OH), 3070 [w, (C=)C–H], 1642 (m, C=C), 890 (s, $C=CH_2$). ^{1}H NMR (300 Mz): δ 0.86 (3 H, CH_3), 0.93 (3 H, CH_3), 1.19-2.10 (12 H, m), 4.08 (2 H, s, CH_2OH), 4.56 (1 H, s,

C=CHH), 4.78 (1 H, s, C=CHH), 4.88 (1 H, s, $C(CH_2OH)$=CHH), 5.02 (1 H, s, $C(CH_2OH)$=CHH).

12. Spectroscopic data for (+)-γ-coronal (**1**): $[\alpha]_D^{22}$ + 4.9 (c 1.2, $CHCl_3$). IR (film) ν cm^{-1} 3060 [w, (C=)C–H] , 1698 (s, CHO conj.), 1642 (w, C=C), 940 (m, conj. $C=CH_2$), 890 (m, $C=CH_2$). ^1H NMR (300 MHz): δ 0.83 (3 H, CH_3), 0.92 (3 H, CH_3), 1.18-2.28 (11 H, m), 4.59 (1 H, s, C=CHH), 4.80 (1 H, s, C=CHH), 5.98 (1 H, s, conj. C=CHH), 6.26 (1 H, s, conj. C=CHH), 9.54 (1 H, s, CHO). EIms m/z (relative intensity): 206 (M^+ 52), 188 (M^+–OH, 28), 173 (34), 95 (72), 81 (92), 69 (100), 41 (84). HREIms: Found: 206.1644. Całcd. for $C_{14}H_{22}O$ (M): 206.1670.