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Synthesis of *ent*-ambrox® from (−)-nidorellol

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ABSTRACT

Using ozonolysis of the acid-catalyzed cyclized products of (−)-nidorellol and air-autoxidation as the key steps, (+)-ambrox was obtained in 53% overall yield. In the course of our synthesis, we discovered that (−)-nidorellol provided (+)-ambrox instead of the expected product, (−)-ambrox. Thus the absolute configuration of (−)-nidorellol was proved to be *trans*-(5*R**,7*R**,8*R**,9*S**,10*R**)-labda-12,14-diene-7α,8β-diol, which is opposite to that illustrated in a previous report.

(−)-Ambrox® (Fig. 1) is an oxidatively degraded compound from ambergris [a secretion of the sperm whale *Physeter catodon* (*P. macrocephalus* L.)].[1] As it has a very strong ambergris-like odor and fixative property, it has become a highly valued fine fragrant ingredient.[2] In fact, several routes to synthesize ambrox® have been developed starting from naturally occurring diterpenes.[3]

Among those diterpenes, labdane-type diterpenes are considered suitable synthons for ambrox synthesis due to their structural features and ease of availability.

(−)-Nidorellol (**2**), a labdane-type diterpene, was first isolated from *Nidorella auriculata*[4] and later from *Stevia sarensis*.[5] In 1978, its configuration was established by Bohlmann and Fritz as *trans*-(5*S*,7*S*,8*S*,9*R*,10*S*)-labda-12,14-diene-7β,8α-diol **2′** (Fig. 1).[4]

Recently, we isolated **2** from *Croton oblongifolius* barks as a white solid in 0.42% yield based on 380 g of powdered air-dried bark. On the basis of spectroscopic data, including IR, 1D and 2D NMR, and MS, the structure of **2** was established. Careful analysis of the NOESY spectra showed an *E*-configuration of the conjugated diene. Since the specific rotation of **2** was $[\alpha]_D^{20} = -23.2$ (Lit. $[\alpha]_D^{24} = -21.0$),[4] its stereochemistry was that of (−)-nidorellol as reported by Bohlmann and Fritz,[4] and thus is a suitable synthon for the synthesis of (−)-ambrox®. However, it was unstable and decomposed to many compounds at ambient temperature. Fortunately, it was easily cyclized under acid conditions to provide more stable products. Therefore, the synthesis of ambrox® was performed via two routes, as summarized in Scheme 1.

The key steps of the first route involve the acid-promoted cyclization of **2**, ozonolysis of the cyclized product and air-autoxidation, and dehydroxylation at C-7, while the second route involves ozonolysis of **2** and dehydroxylation at C-7.

In the course of this seven-step synthesis an unexpected configuration of ambrox, that is *ent*-ambrox, which is the opposite to that previously reported,[4] was discovered. Thus, the configuration of each compound in each step was carefully investigated. We found that all the products retained their configurations, thereby confirming the absolute configuration of (−)-nidorellol as *trans*-(5*R*,7*R*,8*R*,9*S*,10*R*)-labda-12,14-diene-7α,8β-diol **2** (Fig. 1). We

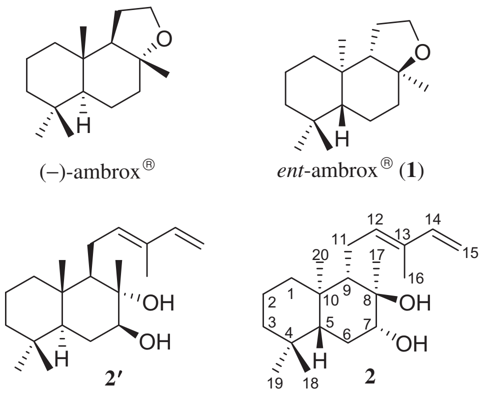

Figure 1. (−)-Ambrox®, (+)-ambrox® (**1**), the previous configuration of (−)-nidorellol (**2′**)[4] and absolute configuration of (−)-nidorellol (**2**).

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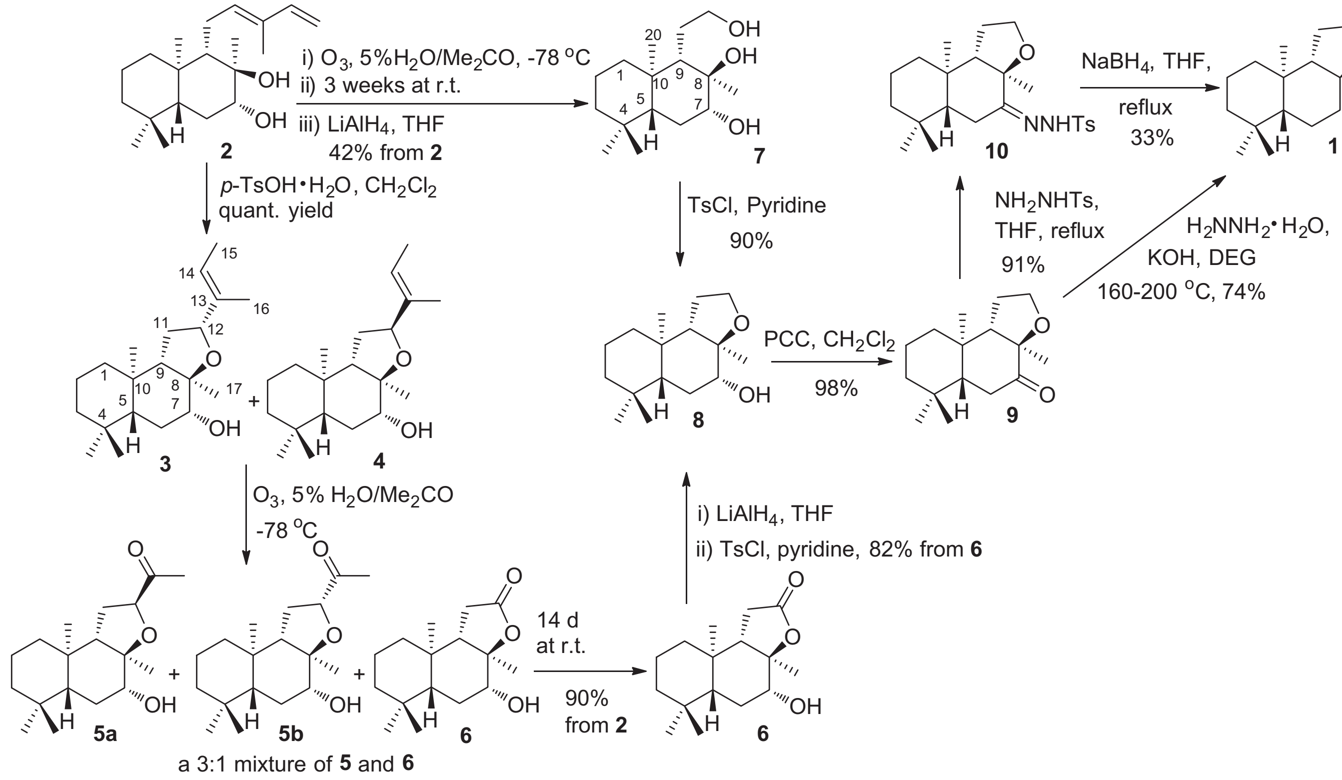

Scheme 1. Synthesis of (+)-ambrox® from (−)-nidorellol; DEG = diethylene glycol.

now describe the synthesis of (+)-ambrox® from (−)-nidorellol and report the absolute configuration of (−)-nidorellol.

Acid-promoted cyclization of **2** with 20% mol *p*-TsOH·H_2O in CH_2Cl_2 over 3 h at room temperature gave a mixture of **3** and **4**. ^1H NMR data and the masses of the products obtained showed that a 3:1 mixture of **3** and **4** had formed in quantitative yield. However, after their separation and isolation by silica gel column chromatography their yields were only 14% for **3** and 8% for **4**, presumably due to their decomposition during purification. Thus, the mixture of **3** and **4** was used directly in the ozonolysis step.

The relative configurations of **3** were determined by NOE analysis. Due to the absence of any NOE between H-12 [δ_H 4.27 (dd, *J* = 6.4, 9.2 Hz)] and the protons of C-17, the methyl protons of C-17 are proposed to be on the opposite face to H-12. The observed NOEs between H-12 and H-9, H-9 and H-7, and H-7 and H-5 indicated that these protons occupied the same face. Due to the observation of an NOE between the methyl protons of C-15 and C-16, the configuration of the double bond was confirmed as *E*. The relative configuration of **3** was determined and confirmed by X-ray crystallographic analysis,[6] as that shown in Figure 2. The ^1H and ^{13}C NMR spectra of **4** indicated that its structure was closely related to **3**. Moreover, the observed NOE in **4** between H-12 [δ_H 4.42 (dd, *J* = 2.0, 9.2 Hz)] and the methyl protons of C-17 suggested that H-12 occupied the same face as the methyl protons of C-17. Thus, compound **4** was an epimer of **3**.

Oxidative cleavage of **3** and **4** with ozone in 5% water in acetone[7] at −78 °C for 3 h gave a 3:1 mixture of **5** and **6**, as shown in Figure 3a. Isolation of the mixture by silica gel column chromatography [EtOAc-hexane (4:6)] gave **5a**, **5b**, and **6** in yields of 15%, 14%, and 19%, respectively. Surprisingly, we found that the ratio of **5** and **6** changed when the viscous mixture of **5** and **6** was stored and exposed to air at ambient temperature. Monitoring the viscous

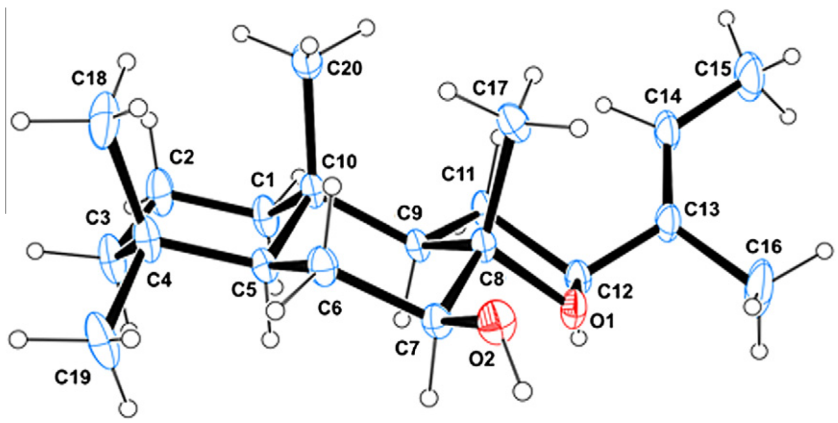

Figure 2. The ORTEP drawing of **3**.

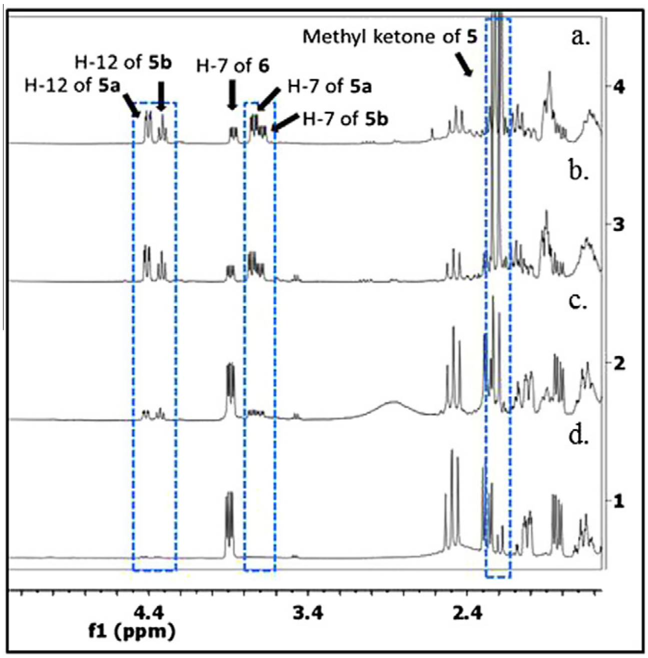

Figure 3. ^{1}H NMR spectra of the products from ozonolysis of a 3:1 mixture of **3** and **4**: (a) after work-up; (b) under no O_2 (stored in a desiccator with a GasPak) for 3 days; (c) exposed to air for 3 days, and (d) exposed to air for 14 days.

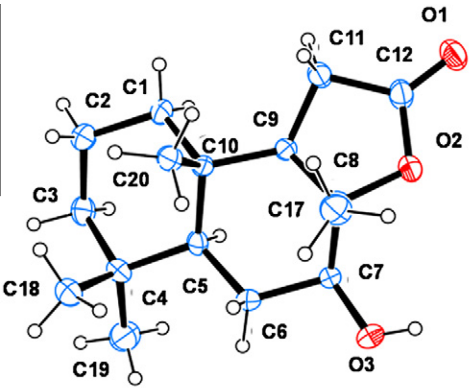

Figure 4. The ORTEP drawing of **6**.

mixture of **5** and **6** by ^{1}H NMR spectroscopy (Fig. 3), revealed that the mixture of **5a** and **5b** was slowly transformed into **6**, and compound **6** crystallized after 14 days. Recrystallization from acetone in the presence of a small amount of water gave lactone **6** as colorless crystals in 90% yield. The structure of **6** was characterized by 1D and 2D NMR, and its relative configurations were determined by NOESY analysis and further confirmed by X-ray crystallographic analysis[8] (Fig. 4).

To understand how ketones **5a** and **5b** were converted into lactone **6**, they were examined by ^{1}H NMR spectroscopy during storage under aerobic and anaerobic conditions. The results (Fig. 3b and 3c) revealed that both ketones were transformed into **6** under atmospheric air but remained unchanged under anaerobic conditions. Thus, both diastereomers could be converted into **6** by air-autoxidation. We also found that compounds **3** and **4** underwent air oxidative degradation to give **6**, but the degradation of **3** and **4** was slower than that of ketone **5**. As compounds **3** and **4** could be converted into **6**, this encouraged us to investigate the direct oxidative degradation of the conjugated diene of **2** under the same conditions. Using ^{1}H NMR analysis, we established signals due to aldehyde protons (δ_H 9.60–10.42 ppm), olefinic protons (δ_H 5.10–5.67 ppm), and a small H-7 signal due to compound **6** (Fig. 5a). Attempts to isolate the reaction mixture were unsuccessful because the product of the oxidative degradation consisted of many seemingly unstable compounds. However, the magnitude of the H-7 signal of **6** in the ^{1}H NMR spectrum increased when the reaction mixture from the ozonolysis of **2** was stored under atmospheric air and the ^{1}H signals were unchanged after three weeks (Fig. 5b). This suggested that the product from ozonolysis of **2** also underwent air-autoxidation. Isolation of the air-autoxidation mixture using silica gel column chromatography gave lactone **6** in a low yield (47%).

The mechanism of air-autoxidation of ketones **5a** and **5b** was investigated by GC/MS analysis of the gaseous products using the

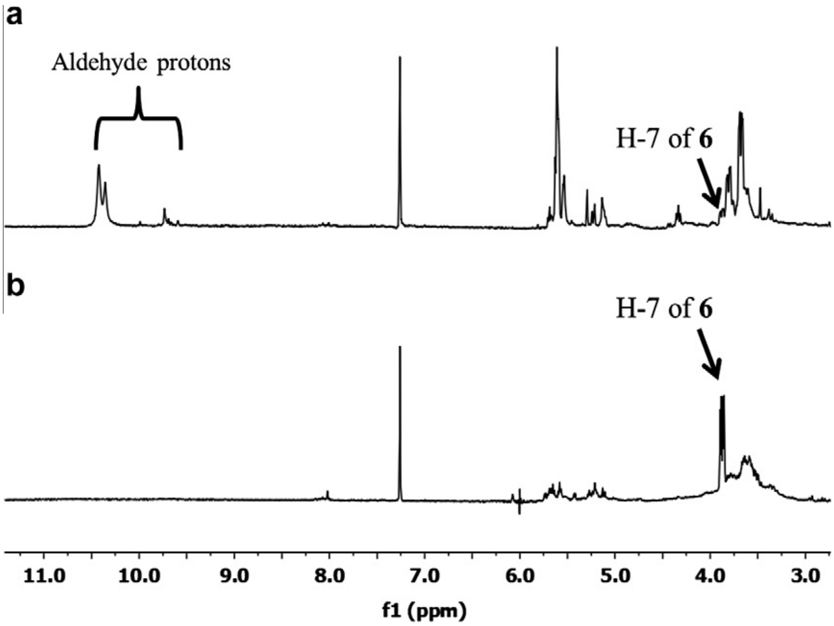

Figure 5. ^{1}H NMR spectra of the products from ozonolysis of (−)-nidorellol: (a) after work-up; (b) exposure to air for 3 weeks.

head space technique. Since the presence of acetic acid was detected, the mechanism of air-autoxidation likely takes place by substitution of an O_2 molecule at C-12 of **5** and degradation of the corresponding hydroperoxide to yield lactone **6** and acetic acid as the products.

Reduction of lactone **6** followed by cyclization gave **8** in 82% yield (Scheme 1). After cyclization of **7**, oxidation of **8** with PCC gave **9** in 98% yield. Reduction of the carbonyl group of **9** to a methylene was performed by Wolff-Kishner reduction,[9] via heating with hydrazine hydrate in the presence of KOH in diethylene glycol (DEG) to give compound **1** in 74% yield (after chromatographic separation), from **9**. Also, reduction of the carbonyl group of **9** was performed by treatment with tosylhydrazine followed by reduction with $NaBH_3CN$[3o] or with $NaBH_4$[10] to give **1** in yields of 15% and 33%, respectively. Using 1D and 2D NMR analysis, the structure of **1** was identified as ambrox®, but its specific rotation ($[\alpha]_D^{20}$ +23.0) was in good agreement with that of (+)-ambrox® synthesized by Giacomini.[3n] This indicated that the synthesis of ambrox® from (−)-nidorellol (**2**) gave the *ent*-ambrox® configuration instead of the expected product, (−)-ambrox® ($[\alpha]_D^{20}$ -28.8)[3o] and so the absolute configuration of (−)-nidorellol has been shown to be opposite to that previously reported.[4] Therefore, the correct absolute configuration of (−)-nidorellol is established here to be *trans*-(5*R**,7*R**,8*R**,9*S**,10*R**)-labda-12,14-diene-7α,8β-diol.

In conclusion, the synthesis of (+)-ambrox® (*ent*-**1**) was achieved in 53% overall yield in seven steps. The absolute configuration of (−)-nidorellol (**2**) was established and the structure identified as an *ent*-labdane-type diterpene.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, spectroscopic data, X-ray crystallographic data of **4** and **6** and GC/MS spectra following the air-autoxidation of compounds **5a** and **5b**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.120.

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6. Crystal data for **3** were obtained using a BRUKER SMART CCD diffractometer, MoK$_\alpha$ radiation (λ = 0.71073 Å), graphite monochromator, $C_{20}H_{34}O_2$, monoclinic, space group P21/c, a = 12.0921(6) Å, b = 11.7469(6) Å, c = 13.6286(7) Å, V = 1863.68(16) Å^3, Z = 4, D_c = 1.092 mg/m^3, crystal size 0.30 × 0.25 × 0.18 mm, F(000) = 680, μ = 0.068 mm^{-1}. Data were collected at 293(2) K using ω–2θ scans in the ranges θ = 1.75–34.82°. A total of 14997 reflections were collected, 5648 were unique (R_{int} = 0.0307). The structure was refined by full-matrix least-squares on F^2. The final refinement [$I > 2\sigma(I)$] gave R_1 = 0.0905, wR_2 = 0.2542. Crystallographic data for the structure of **3** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number 823857. Copies of this information may be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; email: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).
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8. Crystal data for **6** were obtained using a BRUKER SMART CCD diffractometer, MoK$_\alpha$ radiation (λ = 0.71073 Å), graphite monochromator, $C_{16}H_{25}O_3$, monoclinic, space group P2(1), a = 6.2810(5) Å, b = 35.810(4) Å, c = 7.3289(9) Å, V = 14925(3) Å^3, Z = 4, D_c = 1.181 mg/m^3, crystal size 0.18 × 0.20 × 0.30 mm, F(000) = 580, μ = 0.080 mm^{-1}. Data were collected at 293(2) K using ω–2θ scans in the ranges θ = 2.27–26.40°. A total of 11060 reflections were collected, 5864 were unique (R_{int} = 0.0714). The structure was refined by full-matrix least-squares on F^2. The final refinement [$I > 2\sigma(I)$] gave R_1 = 0.1077, wR_2 = 0.2957. Crystallographic data for the structure of **6** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number 820557. Copies of this information may be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; email: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).
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