Synthesis of (±)-Ambrox from (E)-nerolidol and β-ionone via Allylic Alcohol [2,3]
Sigmatropic Rearrangement

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Ambregris is a metabolite of sperm whales (Phystero macrocephalus L.) which accumulates as concretions in the gut of the animal.1 After several years of aging, as a result of the action of sunlight, air, and water, the final ambregris combines a unique odor with fixative properties particularly prized by perfumers. Release of the ambregris fragrance is related principally to the presence of (−)-sclareol,3,5 (−)-sclareol,15 (−)-manoyl oxide,6 (−)-abietic acid,7 (−)-levopimaric acid8 and (−)-labdanolic acid,9 and recently, from the monoterpenes (−)-carvone10 and thujone.11 With respect to the racemic (−)-ambrox, diverse total syntheses have been performed based on biogenetic-type cyclizations from farnesic acid, monoylofarnesic acid, or derivatives of these.12 Among the cyclization agents employed in these processes are SnCl4,13 Sn(OiPr)4,14 BF3·Et2O,15 CF3COOH,16 HCOOH−H2SO4,17 and more recently the “superciders” FSO3H,12c and CISO3H.19

The present authors have recently described the synthesis of levo (−)-ambrox from the labdane-type diterpenes (−)-sclareol,20 (−)-cis-abienol,20,21 and (−)-abienol,21 which is the stereospecific formation of the diastereomer (−)-9-epi-ambrox (2) was also carried out. Compound (−)-2 was prepared from (−)-sclareolide2 and also through a stereocontrolled enantioselective process based on the anionic oxy-Cope rearrangement.24 The racemate (±)-2 was obtained in superacid cyclizations of hydroxypolyenes.12c

In our approach to (±)-ambrox (1) from (±)-(E)-nerolidol (3) and β-ionone (11) the key step is the [2,3] sigmatropic rearrangement of an allylic alcohol to the homologous amide promoted by heating the corresponding alcohol with N,N-dimethylformamide dimethyl acetate.

References


With this reaction the carbon required to complete the C16-skeleton of ambrox is directly incorporated into either the nerolidol molecule (3) or into the monocyclic alcohol analog 15a, the latter having been prepared from \( \beta \)-ionone in adequate yield. Thus, the refluxing of a mixture of (+)-\( E \)-nerolidol (3) and DMFDMA in xylene for 13 h yielded an \( E/Z \) mixture of the \( \beta,\gamma \)-unsaturated amides 4a and 4b (2.2:1) in 79% yield (Scheme 1). The easy separation of both amides by column chromatography allowed us to record their spectroscopic data separately and to perform the reduction of 4a with Li\( \text{BEt}_3 \)H in THF at –78 °C to give the alcohol 5 (75% yield). The cyclization of 5 was carried out with the superacid Cl\( \text{SO}_3 \)H in 1-nitropropane at –78 °C, giving a diastereomeric mixture formed mainly of (+)-1 (41% yield) and (+)-9-epi-ambrox (2) (34% yield).26 Besides these, other minor compounds with a cis A/B ring junction (6–10) were also analyzed by GC-MS and identified by comparison with authentic samples (Table 1; entry 1).27

In the synthesis from \( \beta \)-ionone (11) the precursor of (+)-1 is (E)-monocyclohomofarnesol (15a), prepared by reducing the (E)-amide 14a, which is obtained through the same \[2,3\] sigmatropic rearrangement developed in the nerolidol approach, now produced from monocyclo-nerolidol (13) (Scheme 2). The preliminary preparation of allylic alcohol 13 was accomplished in two steps: (a) the selective \( \Delta^3 \) hydrogenation of \( \beta \)-ionone (11) using tri-n-butyltin hydride together with azoisobutyronitrile as a source of free radicals28 to give 12 in 91% yield, and (b) the reaction of 12 with vinylmagnesium bromide in THF at 10 °C to give 13 in 96% yield. The treatment of 15a with Cl\( \text{SO}_3 \)H under the same conditions as before led to a mixture of (+)-1 (43%) and (+)-2 (34%), similar in composition to that obtained from the acyclic analog 5.

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(4a:4b 2.2:1)
\]

**Table 1. Acid-Catalyzed Reactions of Alcohols 5 and 15**

<table>
<thead>
<tr>
<th>entry</th>
<th>starting material</th>
<th>cyclization agent</th>
<th>product distribution (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>Cl( \text{SO}_3 )H</td>
<td>45.1 36.5 1.0 0.6 2.9 – –</td>
</tr>
<tr>
<td>2</td>
<td>15a</td>
<td>Cl( \text{SO}_3 )H</td>
<td>47.8 37.7 2.6 0.8 7.0 – –</td>
</tr>
<tr>
<td>3</td>
<td>15b</td>
<td>Cl( \text{SO}_3 )H</td>
<td>0.8 82.9 – 13.2 1.7 2.2 –</td>
</tr>
<tr>
<td>4</td>
<td>15a</td>
<td>p-TsOH</td>
<td>0.9 &lt;0.2 – – – – 81.2</td>
</tr>
<tr>
<td>5</td>
<td>15a</td>
<td>SnCl(_4)</td>
<td>12.3 11.6 – 4.7 4.5 1.7 17.3</td>
</tr>
<tr>
<td>6</td>
<td>15a</td>
<td>H(_2)SO(_4)</td>
<td>42.3 26.5 – 2.7 5.0 2.4 13.0</td>
</tr>
</tbody>
</table>

a GC analysis of crude reaction.

(26) These yields were calculated taking into account the percentages recorded by the GC analysis of the crude reaction (Table 1; entry 1) and the loss of weight of cyclized crude material with respect to the starting material 5.
(27) A copy of the original mass spectral charts of compounds 2, 6–10 were kindly provided by Roger L. Snowden (Firmenich SA, Geneva, Switzerland). For spectral characterization see refs 2 and 23.
The action of ClSO\textsubscript{3}H on 5 and 15\text{a} is parallel to that observed with the other superacid FSO\textsubscript{3}H on the same alcohols,\textsuperscript{12c} which means that both reagents induce biomimetic acid-mediated cyclizations with an internal nucleophilic termination by a hydroxyl group through the same reaction mechanism.\textsuperscript{12c} In contrast to the behavior of alcohol 15\text{a}, the reaction of (Z)-monocyclohomofarnesol (15\text{b}) with ClSO\textsubscript{3}H (Table 1; entry 3) yielded a crude product basically composed of (±)-2 (only traces of 1 were detected) which means that cyclization of 15\text{a} to 1 competes with its isomerization to 15\text{b}, whose cyclization to 2 is more rapid in the superacid medium. In order to compare results, different cyclization agents, such as p-TsOH, SnCl\textsubscript{4} or H\textsubscript{2}SO\textsubscript{4}, were also tested with 15\text{a}. Whereas the use of p-TsOH (entry 4) yields principally the monocyclized compound 10, and SnCl\textsubscript{4} (entry 5) does not yield a synthetically useful result, it is worth noting that the use of simple commercial sulfuric acid (entry 6) yielded a crude product with a very similar composition to that obtained with the superacid (entry 2).

In conclusion, a new straightforward approach to the preparation of racemic ambrox starting from β-ionone and (E)-nerolidol has been developed. This is based on the utilization of the rarely employed [2,3] sigmatropic rearrangement for creating β,γ-unsaturated dimethylamides and hence the alcohols to be cyclized.

**Experimental Section**

Gas chromatography (GC) was performed on a fused-silica capillary column (25 m × 0.2 mm) coated with methylsilicone using nitrogen as carrier (25 mL min\textsuperscript{-1}) where the temperature program was from 50 °C to 220 °C (rate 5 °C min\textsuperscript{-1}) and from 220 °C to 280 °C (rate 3 °C min\textsuperscript{-1}). The retention times (t\textsubscript{R}) are expressed in minutes. Thin-layer chromatography (TLC) was performed on precoated 0.25 mm-thick Merck plates of silica gel 60 F\textsubscript{254}. Gravity column chromatography was carried out on Merck silica gel 60 (70–230 mesh) and low-pressure column chromatography on Merck silica gel 60 (230–400 mesh). All chromatographic separations were performed using hexane/Et\textsubscript{2}O or hexane/Me\textsubscript{3}Si mixtures of increasing polarity and monitored by TLC and/or GC. 1R spectra were obtained in liquid film between NaCl plates. 1H NMR spectra were recorded from CDCl\textsubscript{3} solutions at 300 or 400 MHz and 13C NMR spectra at 75 or 100 MHz. Chemical shifts are reported in parts per million (δ) relative to TMS (δ 0.00) and coupling constants (J) are in hertz. Carbon substitution degrees were established by DEPT multipulse sequence. Mass spectra (MS) were recorded using an ionizing voltage of 70 eV.

**Materials.** β-ionone (99% purity) was provided by Destilaciones Garcia de la Fuente (Granada), and (±)-(E)-nerolidol (65% purity) was isolated from the essential oil of Inula viscosa L. THF was freshly distilled from Na(benzophenone) under argon. Other reagents and solvents were purchased from Aldrich Chemical Co. or Merck and were used as received.

**Reaction of 3 with N,N-Dimethylformamide Dimethyl Acetal.** A mixture of (+)-(E)-nerolidol (3) (1.30 g, 65% purity, 3.80 mmol), DMFDMA (3.80 g, 31.93 mmol), and xylene (10 mL) was refluxed for 13 h under continuous removal of methanol (Dean–Stark device). The mixture was directly concentrated in vacuo yielding a residue (1.47 g) which, after silica gel column chromatography, yielded Δ\textsuperscript{22}-amide 4\text{a} (575 mg, 54.6%, hexane: Et\textsubscript{2}O 1:1, 1:4) and Δ\textsuperscript{22}-amide 4\text{b} (258 mg, 24.4%, hexane:Et\textsubscript{2}O 1:1).

(E,E)-4,8,12-Trimethyl-3,7,11-tridecatrienoic acid N,N-dimethylamide (4\text{a}): t\textsubscript{R} 37.95; IR 1R 1648 (CONMe\textsubscript{2}) cm\textsuperscript{-1}; 1H NMR (400 MHz) δ 1.57 (br s, 6H), 1.63 (s, 3H), 1.65 (s, 3H), 2.91, 2.97 (2 s, 6H), 3.05 (d, 6.7, 2H), 5.04 – 5.10 (m, 2H), 5.30 (td, 6.7, 1.1, 1H); 13C NMR (100 MHz) δ 15.95, 16.41, 17.63, 25.64, 34.46, 37.31 (CH\textsubscript{3}), 26.41, 26.67, 33.73, 39.55, 39.65 (CH\textsubscript{2}), 116.82,
123.87, 124.27 (CH3), 128 (46), 121 (44), 119 (60), 109 (43), 107 (12), 104 (72), 78 (57), 55 (41), 43 (29).

Reaction of 13 with N,N-Dimethylformamide Dimethyl Acetal. Alcohol (135 mg, 0.49 mmol) was treated with DMF (90 mg, 1.30 mmol) in xylene (10 mL) under the same conditions described for 3 to yield a residue (1.1 g) which, after silica gel column chromatography, afforded (E)-amide 14a (594 mg, 50.1%). 

(E)-4-Methyl-6-(2,6,6-trimethylcyclohex-1-enyl)-3-hydroxy acid N,N-dimethylamide (14a): 

1H NMR (400 MHz): δ 1.50 (s, 3H), 1.70 (s, 3H), 1.89 (t, 6.7, 1H), 1.95 (d, 6.7, 2H), 2.07 (d, 6.7, 2H), 2.29 (s, 6H), 2.58 (d, 6.7, 1H), 2.60 (s, 6H), 2.91, 2.97 (2 s, 3H), 2.97 (s, 3H), 3.06 (m, 4H), 3.27 (m, 4H), 5.09 (br t, 7.3, 1H), 13C NMR (100 MHz): δ 19.81, 27.54, 51.17, 62.76, 121.03, 125.81, 127.03, 127.94, 136.82, 138.88, 172.06 (C); MS m/z (rel int) 236 (M+1, 1), 221 (M–H2O, 1), 203 (M–CH3, 1), 190 (5.1), 177 (3.9), 163 (3.8), 142 (2.9), 129 (2.1), 117 (2.5), 105 (2.3), 93 (2.0), 81 (2.0), 79 (2.0), 77 (2.0), 65 (2.0), 53 (2.0).

Notes


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Supporting Information Available: Spectral assignments and copies of 1H NMR and 13C NMR spectra of compounds 4a, 4b, 5, 12–15 (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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