New Synthesis of $\gamma$-Homocyclogeranial, $\gamma$-Dihydroionone and Their Derivatives

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A new and efficient synthesis of $\gamma$-homocyclogeranial (4), $\gamma$-dihydroionone (3) and their derivatives, 5, 6, 7 and 8, volatile components of ambergris, is described. Their compounds were synthesized via Claisen rearrangement of (3,3-dimethylcyclohexenyl)methyl vinyl ether (14).

Ambergris, an intestinal concretion of spermwhale, is extensively utilized in the perfumery industry for its characteristic odor and fixative power. A major component of ambergris is the odorless triterpene alcohol, ambrein (1), oxidative degradation of which produces many odorous substances. Oxidation of the central trans double bond of 1 results in an ambreinolide (2) group and $\gamma$-dihydroionone (3) group. The oxidative substances belonging to the latter, $\gamma$-homocyclogeranial (4), $\gamma$-homocyclogeraniol (5), $\gamma$-homocyclogeranyl acetate (6), $\gamma$-homocyclogeranyl chloride (7), and $\alpha$-ambrinol (8), have already been found in ambergris and contributed importantly to the ambergris odor. Since these compounds are not readily available from natural sources, much attention has been paid to the synthesis of 2~8. In particular, various synthesis of 3~8 from such different starting materials as geranyl acetone, $\alpha$-ionone and 3-methyl-2-cyclohexenone have been reported.

Here we wish to describe a new and efficient synthesis of 3 and 4 via the same intermediate, allylic alcohol (13), and their conversion to 5~7 and 8. Claisen rearrangement of the vinyl ether (14) from 13 was applied to prepare 4, which was transformed to 3 by employing Darzen’s condensation and subsequent decarboxylation.
Table

<table>
<thead>
<tr>
<th>No.</th>
<th>Substrate</th>
<th>E.V.E.</th>
<th>Cat.</th>
<th>Temp. (°C)</th>
<th>Time (hr)</th>
<th>Yield (%) 4</th>
<th>Yield (%) 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>—</td>
<td>—</td>
<td>200</td>
<td>2</td>
<td>88</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>2.0 eq</td>
<td>H₃PO₄ (0.2 eq)</td>
<td>200</td>
<td>3</td>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>2.0</td>
<td>AcOH (0.5)</td>
<td>220</td>
<td>2</td>
<td>Trace</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>2.0</td>
<td>t-Bu-COOH (0.1)</td>
<td>220</td>
<td>3</td>
<td>46</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>2.0</td>
<td>t-Bu-COOH (0.2)</td>
<td>220</td>
<td>3</td>
<td>79</td>
<td>—</td>
</tr>
</tbody>
</table>

- The starting material, hydroxymethylene cyclohexanone (10), was prepared from 2-methyl cyclohexanone (9) by an improved method of Bailey’s procedure. Protection of the hydroxy group of 10 was achieved by treating 10 with ethyl vinyl ether in the presence of H₃PO₄ at room temperature to give the acetal (11) in a quantitative yield. Reduction of 11 with NaBH₄ in EtOH, followed by treatment with 20% aqueous H₂SO₄, yielded the aldehyde (12), which was reduced with NaBH₄ in EtOH at 10°C to give the key intermediate, allylic alcohol (13), in an 85% yield from 11.

- Subsequently, in order to obtain the aldehyde (4), Claisen rearrangement was examined, the results of which are shown in the table. Refluxing of 13 with ethyl vinyl ether in the presence of Hg(OAc)₂ gave the vinyl ether (14) in a 91% yield, which was then rearranged at 200°C for 2 hr in an autoclave to afford the desired aldehyde (4) in an 88% yield. Further heating of 13 with ethyl vinyl ether in the presence of pivalic acid at 220°C for 3 hr in an autoclave directly afforded 4 in a 79% yield. However, the reaction 13 with ethyl vinyl ether in the presence of H₃PO₄ and AcOH yielded the acetal (15) as a major product.

- Reduction of 4 with NaBH₄ in EtOH at room temperature gave the alcohol 5 in a 92% yield, which was then acetylated with Ac₂O–pyridine at room temperature to give the acetate (6) in a 88% yield. Furthermore, chlorination of 5 with SOCl₂–pyridine at 70°C for 2 hr gave the chloride (7) in a 65% yield.

- In order to elongate the side chain of 4, Darzen’s condensation was employed, and the intermediate (16) was selected for the synthesis of 3. Condensation of 4 with ethyl α-bromo-propionate was carried out in the presence of NaOEt at 5°C and then decarboxylated with a catalytic amount of AcONa at 200°C under a reduced pressure to afforded the ketone (3) as a pure product in a 65% yield from 4.

- Finally, conversion of 3 to α-ambrinol (8) was achieved by treating with 20% aqueous sulfuric acid–THF in a 78% yield. Thus a short and efficient synthesis of the several important constituents in ambergris, 3~8, was established.

EXPERIMENTAL

All bps were uncorrected. IR were determined on a JASCO-2 spectrometer. NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer. MS spectra were obtained on a Hitachi RMU-5M GC-MS spectrometer.

2,2-Dimethyl-6-hydroxymethylene cyclohexanone (10). To a stirred suspension of NaH (58 g of 60% mineral oil dispersion) in dry toluene (1.8 liters) was added dropwise 2-methyl cyclohexanone (135 g) during 2 hr at 100°C, the mixture being stirred throughout this period. To this was
added dropwise Mel (206 g) during 2 hr at 60°C, and the mixture was stirred for a further 2 hr at 60°C. After cooling, a mixture of NaOMe (110 g) and HCO₂Me (163 g) was added to the mixture at 5°C, and the reaction mixture stirred for a further 12 hr at room temperature before being poured into ice cooled water. The aqueous layer was acidified with 10% HCl aq. and extracted with ether. The extract was washed with brine, dried over MgSO₄ and concentrated. The residue was distilled to give 10 (95 g, 51%): bp 85~87°C/15mmHg. IR ν_mar cm⁻¹: 3150, 1625, 1580, 895. NMR (CDCl₃) δ: 1.18 (6H, s), 1.5~2.4 (6H), 8.54 (1H, s), 14.40 (1H, broad s). MS m/z: 154 (M⁺, 27), 111 (65), 70 (44), 69 (100), 55 (51), 43 (42), 41 (82).

2,2-Dimethyl-6-(1-ethoxy ethoxy) methane cyclohexanone (11). To a mixture of ethyl vinyl ether (250 g) and 10 (100 g) was added H₂PO₄ (3 g). After stirring for 12 hr at room temperature, the reaction mixture was poured into NaHCO₃ aq. and extracted with ether. The extract was washed with brine, dried over MgSO₄ and concentrated to yield crude 11 (145 g, 99%): IR ν_mar cm⁻¹: 1670, 1378, 1340, 1110. NMR (CDCl₃) δ: 1.10 (6H, s), 1.20 (3H, t), J = 8 Hz), 1.40 (3H, d, J = 6 Hz), 1.6~2.7 (6H), 3.4~3.9 (2H, m), 5.20 (1H, q, J = 6 Hz), 7.61 (1H, t, J = 2 Hz).

3,3-Dimethyl-1-hydroxymethyl-1-cyclohexene (13). To a stirred suspension of NaBH₄ (25 g) in 95% EtOH (40 ml) was added dropwise a solution of 4 (20 g) in 95% EtOH (40 ml) during 1 hr at 10°C, the mixture being stirred for a further 1 hr at room temperature. After the usual work-up as above, the residue was distilled to give 15 (6.4 g, 85%): NMR (CDCl₃) δ: 0.98 (6H, s), 1.21 (3H, t, J = 7 Hz), 1.30 (3H, d, J = 6 Hz), 1.4~2.1 (6H), 3.3~3.8 (2H, m), 3.89 (2H, s), 4.68 (1H, q, J = 6 Hz), 5.40 (1H, s).

γ-Homocyclogeranyl chloride (7). To a stirred solution of NaBH₄ (4.5 g) in 95% EtOH (40 ml) was added dropwise a solution of 4 (20 g) in 95% EtOH (40 ml) during 1 hr at 10°C, the mixture being stirred for a further 1 hr at room temperature. After the usual work-up as above, the residue was distilled to give 7 (32.8 g, 88%): bp 78~82°C/2mmHg. IR ν_mar cm⁻¹: 3350, 1640, 1050, 895. NMR (CDCl₃) δ: 0.87 (3H, s), 0.93 (3H, s), 1.1~2.2 (9H), 2.90 (1H, s), 3.50 (2H, t, J = 7 Hz), 4.58 (1H, d, J = 2 Hz), 4.73 (1H, d, J = 2 Hz). MS m/z: 168 (M⁺, 1.3), 153 (15), 123 (23), 109 (46), 81 (47), 69 (100), 55 (25), 41 (60).

γ-Homocyclogeranyl acetate (6). To a solution of Ac₂O (12.4 g) in pyridine (14 ml) was added dropwise 4 (10 g) during 30 min at 10°C, and the mixture was stirred at room temperature for 12 hr. After the usual work-up, the residue was distilled to give 6 (32.8 g, 88%): bp 58~62°C/2mmHg. IR ν_mar cm⁻¹: 1742, 1640, 895. NMR (CDCl₃) δ: 0.89 (3H, s), 0.93 (3H, s), 1.1~2.2 (9H), 2.02 (3H, s), 3.8~4.2 (2H, m), 4.65 (1H, s), 4.82 (1H, s). MS m/z: 150 (28), 135 (32), 107 (28), 81 (26), 79 (25), 69 (100), 43 (63), 41 (47).

γ-Homocyclogeranyl chloride (7). To a stirred solution of 5 (10 g) in pyridine (6.4 g) was added dropwise SOCl₂ (9.6 g) during 30 min at 15°C, the mixture being stirred for a further 2 hr at 70°C. The mixture was then cooled, diluted with water and extracted with ether. The extract was washed with brine and NaHCO₃ aq., dried over MgSO₄ and concentrated. The residue was distilled to give 7 (7.2 g, 65%): bp 58~60°C/1 mmHg. IR ν_mar cm⁻¹: 1642, 895, 660. NMR (CDCl₃) δ: 0.86 (3H, s), 0.94 (3H, s), 1.1~2.2 (9H), 3.2~3.7 (2H, m), 4.60 (1H, broad s), 4.80 (1H, broad s). MS m/z: 188 (M⁺, 1.3), 186 (M⁺, 3.9), 173 (27), 171 (8), 145 (6.7), 143 (20), 109 (12), 95 (11), 81 (29), 75 (43).
Ethyl 4-(2-methylene-6,6-dimethylcyclohexyl)-2-methyl-2,3-epoxybutyrate. To a stirred suspension of NaOEt, prepared from NaH (21 g, 60% mineral oil dispersion) and abs. EtOH (27 g) in dry toluene (500 ml), was added dropwise a mixture of 4 (60 g) and ethyl α-bromopropionate (97 g) during 1 hr at 5°C. After stirring at room temperature for a further 12 hr, the mixture was washed with water, dried over MgSO₄, and concentrated. The residue was distilled to give a mixture of cis/trans 16 (82 g, 86%) in a 1:1 ratio: bp 115~118°C/0.2 mmHg. IR ν_max cm⁻¹: 1742, 1730, 1640, 895. NMR (CDCl₃): δ: 0.85 (3H, s), 0.95 (3H, s), 1.1~2.3 (9H), 1.27 (3H, t, J=7 Hz), 1.50 (3H, s), 2.85 and 3.10 (1H, t, J=7 Hz), 4.0~4.4 (2H, m), 4.62 (1H, broad s), 4.80 (1H, broad s). MS m/z: 193 (11), 149 (23), 122 (22), 109 (30), 107 (30), 93 (30), 81 (34), 69 (67), 43 (100), 41 (57).

γ-Dihydroionone (3). A mixture of 4 (45 g) and 15% KOH in EtOH (100 g) was stirred at room temperature for 12 hr. To this, 6N HCl aq. (50 ml) was added dropwise during 30 min at room temperature. The reaction mixture was extracted with ether and the extract was washed with brine and 15% NaOAc aq., dried over MgSO₄, and concentrated. The residue was distilled in the presence of NaOAc (2 g) in vacuo to give 3 (25 g, 76%): bp 82~84°C/0.5 mmHg. IR ν_max cm⁻¹: 1720, 1642, 895. NMR (CDCl₃): δ: 0.88 (3H, s), 0.93 (3H, s), 1.1~2.6 (11H), 2.12 (3H, s), 4.55 (1H, broad s), 4.80 (1H, broad s). MS m/z: 194 (M⁺, 8), 176 (16), 161 (13), 136 (88), 121 (56), 105 (39), 95 (52), 71 (42), 43 (100), 41 (42). These data for synthetic 3 were identical with those of the authentic sample.

α-Ambrinol (8). To a stirred solution of 2N H₂SO₄ aq. (100 ml) in THF (60 ml) was added dropwise 3 (9 g) during 10 min at 20°C. After stirring for a further 2 hr at 40°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 distilled to give 8 (7 g, 78%): bp 81~82°C/0.8 mmHg. IR ν_max cm⁻¹: 3450. NMR (CDCl₃): δ: 0.87 (3H, s), 0.92 (3H, s), 1.21 (3H, s), 1.1~2.1 (11H), 1.84 (1H, s), 5.45 (1H, t, J=2 Hz). MS m/z: 194 (M⁺, 8), 176 (16), 161 (13), 136 (88), 121 (56), 105 (39), 95 (52), 71 (42), 43 (100), 41 (42). These data for synthetic 8 were identical with those of the authentic sample.

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REFERENCES