Electrochemical Synthesis of Sobrerol *O*-Derivatives

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(±)-α-Pinene **(1)** has been converted electrochemically to (±)-*cis/trans*-sobrerol [(5-(1-hydroxy-1-methylethyl)-2-methyl-2-cyclohexen-1-ol] dimethyl ether **(2a/2b)** and (±)-*trans*-sobrerol diacetate **(3)**, which can be hydrolyzed to (±)-*trans*-sobrerol **(5)** or its monoacetate **(4)**.

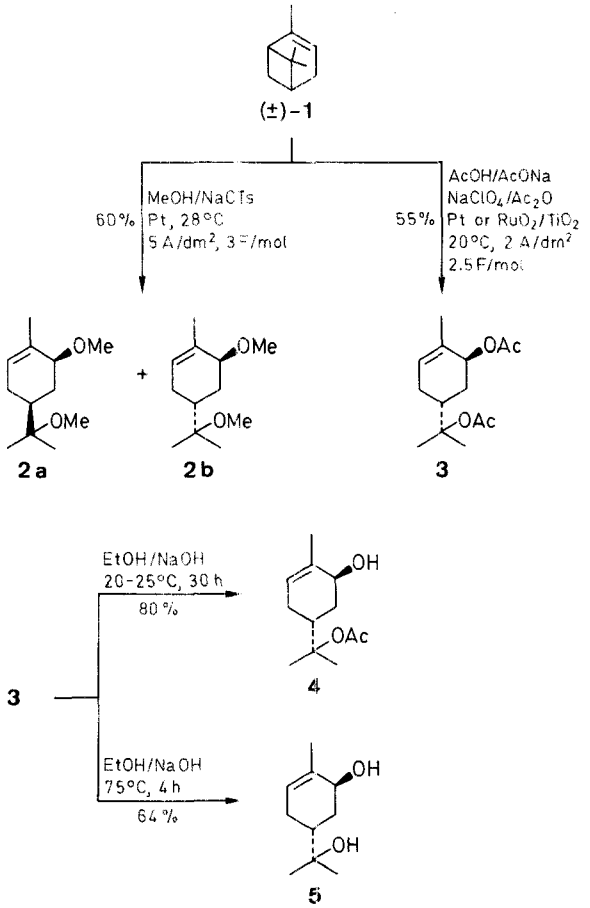
Sobrerol (5-(1-hydroxy-1-methylethyl)-2-methy-2-cyclohexen-1-ol). **(5)** is a well-known mucolytic agent.[1] Some of its derivatives also reveal pharmacological activities.[2]Recently, a mention has been made of the application of sobrerol **(5)** as an intermediate in pheromone synthesis.[3]

The synthesis of sobrerol is usually a multi-step process.[4-7] Hence, research aimed at finding more efficient methods for the synthesis of this compound have been carried out.[8] Recent literature describes a possible direct electrochemical transformation of (±)-α-pinene **(1)** into (±)-*trans*-sobrerol **(5)**,[9] however, the yield is low (21 %).

In continuation of our investigations on the electrocatalytical transformations of terpenoids,[10] we wish to present a simple and

efficient method for the synthesis of sobrerol dimethyl ether (**2**) and sobrerol diacetate (**3**) from (±)-α-pinene (**1**). The diacetate **3** can be easily hydrolyzed to (±)-sobrerol (**5**) or its monoacetate (**4**). Previously, Shono et al[11] had obtained *O*-derivatives of sobrerol in poor yield from α-pinene (**1**) by an electrochemical method using carbon electrodes.

The synthesis of sobrerol dimethyl ethers (**2a, b**) was carried out by electrochemical methoxylation of α-pinene (**1**) with methanol on a platinum electrode in the presence of sodium *p*-toluenesulfonate as the supporting electrolyte. The main reaction product (60%) was a mixture of dimethyl ethers of (±)-*cis*- and (±)-*trans*-sobrerol (**2a** and **2b**) in a ratio of 25:75. These isomers were separated by column chromatography and their structures were determined using ^{1}H-NMR data (Table).



It was found that if α-pinene (**1**) is electrolyzed on a platinum or titanium electrode covered with titanium dioxide/ruthenium dioxide in acetic acid in the presence of sodium perchlorate and sodium acetate, 55% yield of (±)-*trans*-sobrerol diacetate (**3**) with ca 3–4% of the *cis*-isomer is obtained.

Sobrerol acetate (**3**) obtained electrochemically is a convenient substrate for the synthesis of sobrerol (**5**, alkaline hydrolysis at elevated temperature) or 8-acetoxydihydrocarbeole (**4**, alkaline hydrolysis at room temperature). The selective elimination of acetic acid, which takes place due to prolonged heating with acetic anhydride and sodium acetate, leads to carveyl acetate.

Apparatus:[10] Typical three-electrode electrolyzer. The anode is placed centrally between the Pt cathodes at a distance 0.3 cm.

Electrolyte: a) For the ether **2**; Pt anode and sodium *p*-toluenesulfonate (0.5 g) in MeOH (28 mL, 0.7 mol). b) For the ester **3**; Pt or RuO_2/TiO_2 anode and NaOAc (0.25 mol), and $NaClO_4$ (0.1 mol) in a mixture of AcOH (1 mL) and Ac_2O (0.1 mol).

5-(1-Hydroxy-1-methylethyl)-2-methyl-2-cyclohexen-1-ol *cis*- and *trans*-Dimethyl Ether (2a, b):

(±)-α-Pinene (**1**; 3.41 g, 0.025 mol) is added to the cell, and the mixture is electrolyzed at 28°C until 3F/mol has been delivered (current density 5.0 A/dm²). The excess MeOH is evaporated *in vacuo*, and the product is extracted with Et_2O (3 × 20 mL). The extract is washed with water (20 mL), dried ($MgSO_4$), and the solvent is evaporated. The residue is fractionally distilled under reduced pressure to give the ether **2** as a mixture of racemic *cis*/*trans*-isomers **2a, b**; yield: 2.98 g (60%). The *cis*/*trans*-mixture is separated by column chromatography on silica gel [petroleum ether (bp 36–40°)/ether, 96:4].

Racemic 5-(1-Hydroxy-1-methyethyl)-2-methyl-2-cyclohexen-1-ol Diacetate (3):

(±)-α-Pinene (**1**; 115.8 g, 0.85 mol) is added to the cell, and the mixture is electrolyzed at 20°C until 2.5 F/mol has been delivered (current density 2.0 A/dm²). Excess of AcOH is evaporated (68–70°C) *in vacuo* (27 mbar), and the product is extracted with Et_2O (3 × 200 mL). The extract is washed with 5% $NaHCO_3$ solution, dried ($MgSO_4$), and the solvent is evaporated. The residue is fractionally distilled in the presence of a small amount of K_2CO_3 to give the racemic diacetate **3**; yield: 119 g (55%); bp 116–121°C/0.5 mbar.

Racemic 5(-1-Hydroxy-1-methylethyl)-2-methyl-2-cyclohexen-1-ol 1-Monoacetate (4):

A mixture of diacetate **3** (25.44 g, 0.1 mol) and NaOH (8.4 g, 0.21 mol) in EtOH (100 mL) is allowed to stand for 30 h at room temperature. The solvent is distilled out under vacuum, and the product is extracted with Et_2O (3 × 100 mL). The combined ether layer is washed with water (80 mL), ($MgSO_4$), and the solvent is evaporated. Distillation of the residue affords pure **4**; yield: 16.99 g (80%); bp 112–117/0.3 mbar.

(±)-*trans*-Sobrerol (5):

A mixture of diacetate **3** (25.44 g, 0.1 mol) and NaOH (12 g, 0.3 mol) in EtOH (200 mL) is refluxed for 4 h. Then EtOH is evaporated *in vacuo*,

Table. Sobrerol *O*-Derivatives **2–4** Prepared

Product	Yield (%)	bp (°C)/mbar	n_D^{20}	Molecular Formula[a]	IR (neat)[b] ν(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS)[c] δ
2a (*cis*)	60[d]	130–133/27[d]	1.4669	$C_{12}H_{22}O_2$ (198.3)	1140, 1115, 1095, 1075, 910, 805	1.12 (s, 6H); 1.25–2.40 (m, 5H); 1.68 (br s, 3H); 3.17 (s, 3H); 3.33 (s, 3H); 3.77 (m, 1H, H-1); 5.43 (m, 1H)
2b (*trans*)	60[d]	130–133/27[d]	1.4684	$C_{12}H_{22}O_2$ (198.3)	1140, 1095, 1075, 910, 805	1.12 (s, 6H); 1.20–2.30 (m, 5H); 1.77 (br s, 3H); 3.17 (s, 3H); 3.37 (s, 3H); 3.43 (m, 1H, H-1); 5.50 (m, 1H)
3 (*trans*)	55	116–121/0.5	1.4660	$C_{14}H_{22}O_4$ (254.3)	1735, 1240, 1135, 1030, 1015, 790	1.41 (s, 6H); 1.50–2.45 (m, 5H); 1.67 (m, 3H) 1.90 (s, 3H); 2.00 (s, 3H); 5.10 (m, 1H); 5.65 (m 1H)
4 (*trans*)	80	112–117/0.3	1.4865	$C_{12}H_{20}O_3$ (212.3)	3400, 1735, 1600, 1255, 1135, 1050, 1035	1.40 (s, 6H); 1.55–2.50 (m, 5H); 1.73 (m, 3H) 1.90 (s, 3H); 3.87 (m, 1H, H-1); 5.45 (m, 1H)

[a] Satisfactory microanalyses obtained: C ±0.23, H ±0.03.
[b] Recorded on a Specord 71 IR spectrophotometer.
[c] Obtained on a Varian EM 360 spectrometer (60 MHz).
[d] These values refer to *cis*/*trans* mixture of **2a**/**2b**.

and the product is extracted with EtOAc (3 × 150 mL). The combined extract is washed with brine (50 mL), and the solvent is evaporated. The residue is recrystallized from $CHCl_3$ (40 mL); yield: 11 g (64%); mp 128–130°C (Lit.[4] mp 131–131.5°C); IR and ^{1}H-NMR data correspond to literature data.[3]

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