



Enantioselective preparation of 1-hydroxy neoisopulegol and 1-hydroxy neoisomenthol

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Abstract: A enantioselective procedure is described for the preparation of (1*R*,3*R*,4*R*)-1-hydroxy isopulegol **3** and (1*R*,3*S*,4*R*)-1-hydroxy neoisopulegol **4** in 4 steps starting from geraniol. Their enantiomers (1*S*,3*S*,4*S*)-1-hydroxy isopulegol **5** and (1*R*,3*S*,4*R*)-1-hydroxy neoisopulegol **5** were prepared analogously. These compounds were converted to 1-hydroxy neoisomenthol **7**, **8** and 1-hydroxy isomenthol **9**, **10**. Most of these compounds possess an organoleptic property. © 1997 Elsevier Science Ltd

Introduction

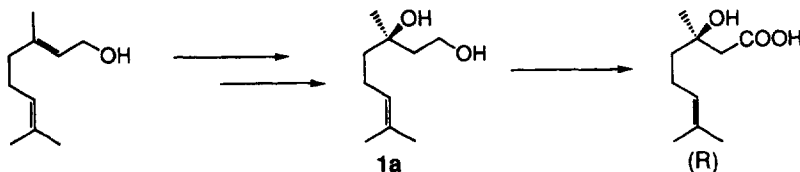
Monoterpenoids are widespread in the plant kingdom as essential oils and used as perfumes, drugs, paint plasticizers and starting materials for organic synthesis. Recently, some interest has been shown for the preparation and biological study of hydroxy menthol¹⁻³. Asakawa *et al.* reported a simple method for introducing a hydroxy group at a non activated carbon of (-)-menthol or neomenthol by *m*-chloroperbenzoic acid, dry ozonisation¹ or biotransformation using micro organisms such as *Aspergillus* species^{2,3}. All these non regioselective methods gave, with low yield, a mixture of at least three products which are difficult to separate. In this paper we report a new, highly enantioselective, method for the preparation of 1-hydroxy isopulegol and 1-hydroxy neoisopulegol in four steps starting from geraniol. These compounds were converted to 1-hydroxy isomenthol and 1-hydroxy neoisomenthol. Their tastes were evaluated in comparison to menthol.

Result and discussion

The key intermediate for this synthesis is the enantioselective preparation of (3*R*)-3-hydroxy citronellal **2a** and (3*S*)-3-hydroxy citronellal **2b**.

These compounds has been isolated from the essential oil of *Eucalyptus citriodora*⁴ and a brief description of its preparation from citral epoxide has been reported⁵.

In a previous work⁶, we described a enantioselective preparation of a new natural monoterpene (3-hydroxy citronellal acid) from geraniol in three steps (Scheme 1).



Scheme 1.

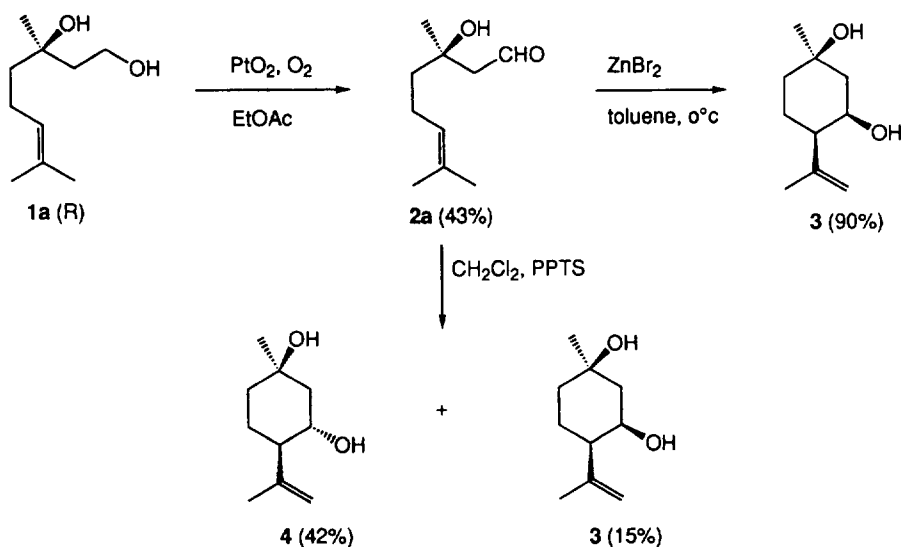
In the last step, the direct oxidation of diols **1a** and **1b** to the acids was accomplished by a catalytic amount of platinum in an oxygen atmosphere in water. The 3-hydroxy citronellal **2a** and **2b** were obtained as intermediate products. This reaction performed in ethyl acetate, instead of water, afford

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the latter compound as major product with 42% yield, 30% of the starting material was recovered and the acid was obtained as by-product.

The aldehyde **2a** was cyclized to 1-hydroxy neoisopulegol (1*R*,3*R*,4*R*) using Lewis acid (ZnBr₂), with a high stereoselectivity with 90% yield. The other diastereoisomers were only present in trace amounts⁷.

This cyclization is less stereoselective when performed in aprotic solvent (CH₂Cl₂) in the presence of pyridinium *para*-toluene sulfonate (PPTS). The major product was (1*R*,3*S*,4*R*)-1-hydroxy isopulegol **4** (42% yield) and (1*R*,3*R*,4*R*)-1-hydroxy neoisopulegol **3** was obtained as by-product (15% yield) (Scheme 2).



Scheme 2.

The stereochemistry of these unknown compounds was confirmed by analogy with isopulegol and by high resolution NMR. However, a single crystal X-ray analysis^{8,10} of **3** revealed the absolute stereochemistry to be 1*R*,3*R*,4*R* (Scheme 3). In that the absolute stereochemistry of the starting hydroxy citronellal was known, the absolute stereochemistry at the C-3 and C-4 stereogenic centers in **3** was automatically established by the X-ray analysis. Both hydroxy groups are present in the axial position, and X-ray analysis clearly showed intramolecular and intermolecular hydrogen bonding⁹.

The enantiomeric (3*S*) aldehyde **2b** was cyclized under the conditions described above. The (1*S*,3*S*,4*S*)-1-hydroxy neoisopulegol **5** was the exclusive product in the presence of Lewis acid (ZnBr₂). The (1*S*,3*R*,4*S*)-1-hydroxy isopulegol **6** was the major product in the presence of Brønsted acid (Scheme 4).

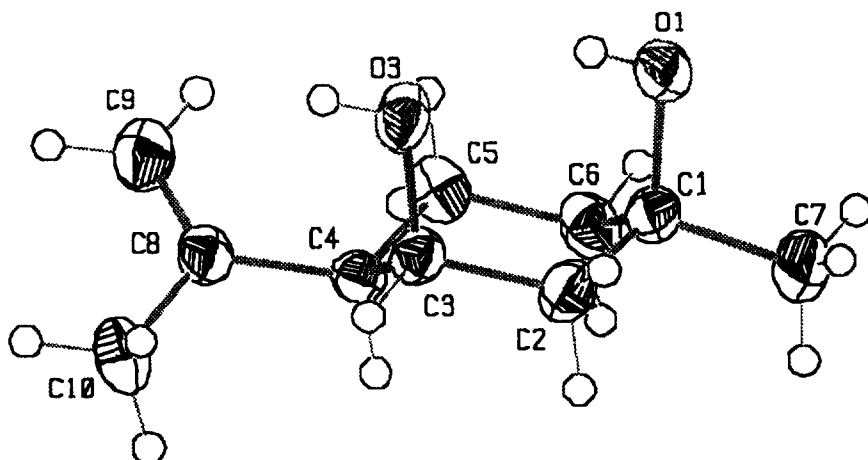
The stereoisomers **3**, **4**, **5**, **6** were then efficiently converted respectively into the corresponding 1-hydroxy neoisomenthol **7**, **8** and 1-hydroxy isomenthol **9**, **10** through hydrogenation in the presence of palladized carbon (Scheme 5).

These compounds **3**–**10** were tested at 5 ppm in water, and were compared to Brazilian menthol. They are less refreshing than menthol but possess a very pure and clear effect without any annex taste except for compound **5** which have a unpleasant and grassy taste.

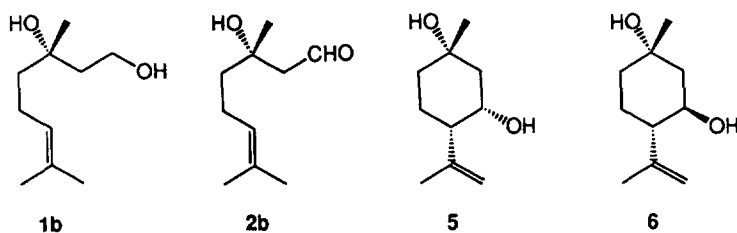
Experimental

General

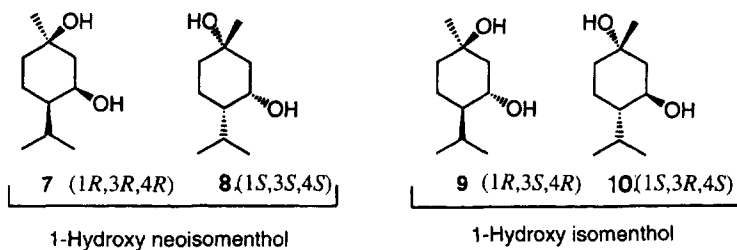
All commercially available chemical reagents were used without further purification. All reactions were followed by TLC: aluminium sheets silica gel 60 F 254 (Merck). Prep. column chromatography



Scheme 3.



Scheme 4.



Scheme 5.

(CC): silica gel (Merck 60, 0.063–0.200 mm). M.P.: Gallenkamp MFB-595-010M. FT-IR: Perkin–Elmer 1720X, KBr disks, unless otherwise indicated. $^1\text{H-NMR}$: Bruker AMX 400 δ in ppm, J in Hz. EI-MS: positive mode, Nermag-R-3010 spectrometer. Optical rotation: Jasco DIP 370.

(3*S*)-3-Hydroxy citronellal **2b**

A suspension of platinum oxide catalyst (200 mg) in EtOAc (5 ml) was reduced under a hydrogen atmosphere (40 bar) for 1 hour. The oxygen was replaced by air for 1 hour. Then (3*S*)-3-hydroxycitronellol **1b** (300 mg, 1.7 mmol) was added and the reaction mixture was oxidized under an oxygen atmosphere (40 bar) for 18 hours. Platinum oxide was filtered off and the residue was purified by column chromatography (eluent: AcOEt/hexane 1/4) to afford 126 mg of (3*S*)-hydroxycitronellal **2b** (42% yield), $[\alpha]_{\text{D}}^{25} = +3.05$ (c 0.72, CHCl_3). $^1\text{H-NMR}$ (CDCl_3); 9.87 (1H, t, $J=2.02$ Hz, CHO); 5.10 (1H, m, $J=7.1$ Hz, $J=1.38$ Hz, H-6); 2.60 (2H, dd, $J=16.4$ Hz, $J=2.1$ Hz, H-2); 2.40 (1H, br, OH); 2.05 (2H, m, H-5); 1.68 (3H, d, $J=1.1$ Hz, H-8); 1.62 (3H, s, H-9); 1.59 (2H, m, H-4); 1.30 (3H, s, H_{10}). $^{13}\text{C-NMR}$ (CDCl_3); 203.76 (C-1); 133.03 (C-7); 124.42 (C-6); 72.69 (C-3); 54.74 (C-

2); 43.04 (C-4); 27.99 (C-10); 26.36 (C-8 or C-9); 23.27 (C-5); 18.36 (C-8 or C-9). IR (neat); 3418, 2970, 2926, 2858, 2736, 1719, 1452, 1378, 1342, 1299, 1270, 1250, 1119, 1044, 935, 837, 781, 744, 492 cm^{-1} . Anal. calcd $\text{C}_{10}\text{H}_{18}\text{O}_2$: C, 70.55; H, 10.66. Found C, 70.34; H, 10.85.

The 3R isomer **2a** prepared analogously from (3R)-3-hydroxy citronellol **1a** (32% yield), showed identical properties, $[\alpha]_{\text{D}}^{25} = -4.89$ (c 1.09, CHCl_3).

(1R,3R,4R)-1-Hydroxy neoisopulegol **3**

To an ice-cooled and stirred solution of (3R)-3-hydroxy citronellal **2a** (60 mg, 0.35 mmol) in anhydrous toluene (2 ml), anhydrous powdered zinc bromide (100 mg, 0.49 mmol) was added carefully (in small portions), while the reaction temperature was kept at 5–10°C. After the reaction was complete (approx. 10 min), stirring was continued for 30 min at 5–10°C. The precipitated zinc bromide was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (eluent: AcOEt/hexane 1/4) and afford (1R,3R,4R)-1-hydroxy neoisopulegol **3**; 54 mg (90% yield), $[\alpha]_{\text{D}}^{25} = -22.3$ (c 0.72, CHCl_3). m.p.: 75–78°C. $^1\text{H-NMR}$ (CDCl_3); 4.97 (2H, m, H-9); 4.09 (1H, m, Ha-3); 3.00 (2H, br, OH); 2.09 (1H, td, $J=14.5$ Hz, $J=3$ Hz, Hb-2); 1.99 (2H, m, Hb-6 and Hb-4); 1.78 (4H, m, Hb-5 and H-10); 1.51 (1H, dd, $J=14.5$ Hz, $J=3$ Hz, Ha-2); 1.45 (2H, m, Ha-5 and Ha-6); 1.18 (3H, s, H-7). $^{13}\text{C-NMR}$ (CDCl_3); 147.28 (C-8); 112.07 (C-9); 70.49 (C-1); 68.58 (C-3); 48.48 (C-4); 42.94 (C-2); 39.37 (C-5); 30.94 (C-7); 23.12 (C-10); 20.31 (C-6). IR (KBr); 3479, 3383, 3097, 2969, 2926, 2904, 2858, 2665, 1788, 1648, 1451, 1437, 1420, 1375, 1348, 1330, 1314, 1295, 1253, 1182, 1137, 1109, 1072, 1052, 1030, 1005, 995, 963, 942, 907, 891, 874, 849, 815, 799, 728 cm^{-1} . Anal. calcd $\text{C}_{10}\text{H}_{18}\text{O}_2$: C, 70.55; H, 10.66. Found C, 70.46; H, 10.58.

The (1S,3S,4S) isomer **5** was prepared analogously from (3S)-3-hydroxy citronellal **2b** (80% yield), $[\alpha]_{\text{D}}^{25} = +21.0$ (c 0.43, CHCl_3). hrms (EI): m/z ($\text{M}-\text{H}_2\text{O}$)⁺ calcd for $\text{C}_{10}\text{H}_{16}\text{O}$ 152.12012; Found 152.12110.

(1R,3S,4R)-1-Hydroxy isopulegol **4**

To a stirred solution of (3R)-3-hydroxy citronellal **2a** (60 mg, 0.35 mmol) and under nitrogen was added a catalytic amount of pyridinium para toluene sulfonate (PPTS). The reaction mixture was stirred for 3 days at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (eluent; hexane/EtOAc 7/3) to afford the (1R,3S,4R)-1-hydroxy neoisopulegol **4**; 26 mg (43% yield), $[\alpha]_{\text{D}}^{25} = +1.4$ (c 0.34, CHCl_3). m.p.: 135–137°C; $^1\text{H-NMR}$ (CDCl_3); 4.88 (2H, m, H-9); 3.80 (1H, ddd, $J=10.23$ Hz, $J=4.48$ Hz, $J=4.47$ Hz, Ha-3); 2.05 (1H, ddd, $J=13.15$ Hz, $J=4.46$ Hz, $J=2.6$ Hz, Hb-2); 1.87 (1H, m, Ha-4); 1.73 (4H, m, Hb-5 and H-10); 1.60 (2H, br, Hb-6 and OH); 1.55 (1H, m, Ha-5); 1.42 (1H, m, Ha-6); 1.32 (1H, m, Ha-2); 1.26 (3H, s, H-7). $^{13}\text{C-NMR}$ (CDCl_3); 147.03 (C-8); 113.68 (C-9); 72.03 (C-1); 67.99 (C-3); 54.65 (C-4); 46.80 (C-2); 38.80 (C-6); 32.37 (C-7); 26.01 (C-5); 19.92 (C-10). IR (KBr), 3338, 3076, 2964, 2942, 2926, 2913, 2860, 1648, 1476, 1454, 1439, 1413, 1380, 1334, 1299, 1261, 1241, 1196, 1173, 1137, 1124, 1097, 1062, 1044, 1028, 1001, 987, 944, 929, 914, 884, 832, 803, 702, 609, 552 cm^{-1} . Anal. calcd $\text{C}_{10}\text{H}_{18}\text{O}_2$: C, 70.55; H, 10.66. Found C, 70.30; H, 10.55.

The (1S,3R,4S) isomer **6** was prepared analogously from **2b** (37% yield), $[\alpha]_{\text{D}}^{25} = -2.2$ (c 0.37, CH_3OH). Anal. calcd $\text{C}_{10}\text{H}_{18}\text{O}_2$: C, 70.55; H, 10.66. Found C, 70.47; H, 10.40.

(1S,3R,4S)-1-Hydroxy isomenthol **10**

(1S,3R,4S)-1-Hydroxy isopulegol **6** (25 mg, 0.15 mmol) was dissolved in EtOAc (5 ml) containing 10% palladium-on-carbon (10 mg) and the suspension stirred under 40 bar pressure of hydrogen for 2 h. The catalysis was then filtered and washed several times with EtOAc, the solvent was evaporated to obtain a white solid (25 mg, 98% yield), $[\alpha]_{\text{D}}^{25} = -27.0$ (c 0.36, CH_3OH). m.p.: 152–154°C. $^1\text{H-NMR}$ (CD_3OD); 3.77 (1H, td, $J=10.80$ Hz, $J=4.40$ Hz, H a-3); 2.14 (1H, sept.d, $J=6.95$ Hz, $J=2.70$ Hz, H-8); 1.90 (1H, ddd, $J=12.95$ Hz, $J=4.42$ Hz, $J=2.75$ Hz, Hb-2); 1.55 (1H, m, Hb-6); 1.51 (2H, m, Hb-5); 1.36 (2H, m, Ha-6 and Ha-2); 1.28 (3H, s, H-7); 1.19 (1H, m, H-4); 0.87 (3H, d, $J=7.03$ Hz, H-9 or H-10); 0.77 (3H, d, $J=6.96$ Hz, H-9 or H-10). $^{13}\text{C-NMR}$ (CD_3OD); 72.14 (C-1); 69.22

(C-3); 51.54 (C-4); 49.25 (C-2); 39.42 (C-6); 31.88 (C-7); 27.08 (C-8); 21.84 (C-9 or C-10); 20.28 (C-5); 16.73 (C-9 or C-10). Anal. calcd $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found C, 69.50; H, 11.74.

The (1*R*,3*S*,4*R*) isomer **9** was prepared analogously from (1*R*,3*S*,4*R*)-1-hydroxy isopulegol (90% yield), and showed identical properties, $[\alpha]_D^{25}=+23.2$ (c 0.45, CH_3OH). Anal. calcd $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found C, 69.67; H, 11.62.

(1*R*,3*R*,4*R*)-1-Hydroxy neoisomenthol **7**

The (1*R*,3*R*,4*R*)-1-hydroxy neoisomenthol **7** was prepared analogously to the isomer **10** from (1*R*,3*R*,4*R*)-1-hydroxy neoisopulegol **3** (95% yield), $[\alpha]_D^{25}=-19.2$ (c 0.17, CH_3OH). 1H -NMR ($CDCl_3$); 4.11 (1H, dd, $J=2.83$ Hz, $J=2.69$ Hz, H-3); 3.26 (2H, br, OH); 1.93 (1H, td, $J=14.42$ Hz, $J=3.13$ Hz, Hb-2); 1.71 (1H, ddd, $J=13.50$ Hz, $J=3.15$ Hz, H-4); 1.58 (3H, m, Hb-5 and H-8); 1.41 (1H, dd, $J=14.42$ Hz, $J=2.84$ Hz, Ha-2); 1.34 (1H, m, Ha-5); 1.15 (3H, s, H-7); 0.92 (3H, d, $J=2.76$ Hz, H-9 or H-10); 0.90 (3H, d $J=2.75$ Hz, H-9 or H-10). ^{13}C -NMR ($CDCl_3$); 71.44 (C-1); 69.14 (C-3); 48.52 (C-6); 44.03 (C-2); 39.74 (C-5); 31.49 (C-7); 29.60 (C-8); 21.69 (C-9 or C-10); 21.35 (C-9 or C-10); 20.67 (C-6). hrms (EI): m/z ($M-H_2O$)⁺ calcd for $C_{10}H_{18}O$ 154.13577; Found 154.13510.

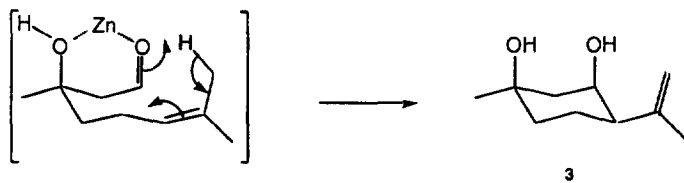
The (1*S*,3*S*,4*S*)-1-hydroxy neoisomenthol **8** was prepared analogously from (1*S*,3*S*,4*S*)-1-hydroxy neoisopulegol **5** (78% yield), and showed identical properties, $[\alpha]_D^{25}=+17.1$ (c 1.09, CH_3OH). hrms (EI): m/z ($M-H_2O$)⁺ calcd for $C_{10}H_{18}O$ 154.13577; Found 154.13510.

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8. Crystallographic data for compound (**3**). $C_{10}H_{18}O_2$, orthorhombic, space group P 21 21 21, $a=9.052(1)$, $b=10.381(1)$, $c=10.664(1)$, $V=1002.1(2)$ Å³, $Z=4$, 1043 independent reflections, 3129 observed reflections [$I>2\sigma(I)$], final $R1=0.0322$, $Rw2=0.0724$, Goodness of fit 1.056, residual density: max./min. 0.125/–0.116 e Å^{–3}. Absorption coefficient $\mu=0.076$ mm^{–1}, no correction for absorption was applied. Suitable crystals of **3** were grown from EtOAc/hexane as white plates. Intensity data were collected at 213 K on a Stoe AED2 4-circle diffractometer using MoK α graphite monochromated radiation ($\lambda=0.71073$ Å) with $\omega/2\theta$ scans in the 2θ range 4–45°C. The structure was solved by direct methods using the programme SHELXS-86 (Ref. 10) which was also used for refinement and all further calculations. Hydrogen atoms were located from difference maps and refined isotropically. The hydroxyl H-atoms were located in a difference map and refined isotropically. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2 . The bond lengths and angles are normal within experimental error. Full tables of atomic parameters and bond lengths and angles may be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ (UK) on quoting the full journal citation.
9. The stereochemistry of C-3 is the opposite of that described in Ref. 7 for the cyclization of citronellal in the same condition. In this case, the asymmetric induction is totally controlled by the C-3 chiral center of the substrate by the chelation of the metal with the hydroxy group.



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