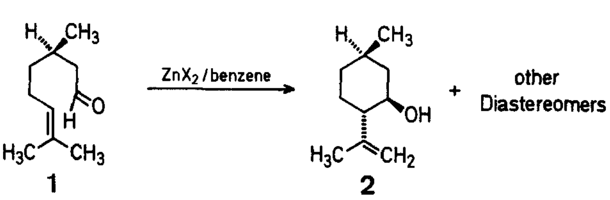
A Highly Stereoselective Preparation of *l*-Isopulegol

Yôichi Nakatani*, Kaoru Kawashima

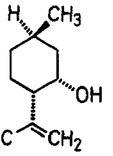
Laboratory of Food Chemistry, Ochanomizu University, Bunkyo-ku, Tokyo, Japan

l-Isopulegol (**2**) is an important intermediate for the manufacture of *l*-menthol[1]. Earlier preparations utilized the cyclization of *d*-citronellal (**1**) with reagents such as active carbon[2], silica gel[3,4], diatomaceous earth[5], sulfuric acid[6], boric acid[4] with or without aluminum oxide, acetic anhydride[6,7], and catalysts[8,9] for hydrogenation such as Cu—Cr, Raney Ni—Fe, etc., or by a simple thermal process[10]. However, these procedures result in mixtures, where extensive purification[1] is needed to isolate pure *l*-isopulegol (**2**).

We report here a highly stereoselective preparation of *l*-isopulegol (**2**) from *d*-citronellal (**1**) using Lewis acids ($ZnCl_2$, $ZnBr_2$, ZnJ_2) for cyclization. The Table summarizes the results.



Under optimum reaction conditions (equimolar amount of $ZnBr_2$ in benzene, 5–10°), the cyclization product is obtained in 70% yield and has a 94% content of *l*-isopulegol (**2**). Of the other three possible diastereomers, *d*-neoisopulegol (**3**) is the main component; the other two diastereomers are only present in trace amounts.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In order to find out if this by-product can possibly be isomerized to isopulegol (**2**) under the reaction conditions used for cyclization

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Table. Cyclization of *d*-Citronellal (**1**) to *l*-Isopulegol (**2**) with Lewis acids in Benzene (5–10°, 15 min)

d-Citronellal [mmol]	Lewis Acid [mmol]	Yield [%]	Ratio of *l*-isopulegol to other diastereomers
20	$ZnCl_2$ (20)	53	88/12
39	$ZnBr_2$ (39)	70	94/6
20	ZnJ_2 (20)	50	95/5
20	ZnF_2 (20)	0	—
20	$Zn(OAc)_2$ (20)	0	—
20	$Zn(NO_3)_2$ (20)	0	—
20	$ZnSO_4$ (20)	0	—
20	$Zn_3(PO_4)_2$ (20)	0	—
20	$FeCl_3$ (2)	20	76/24
20	BF_3 (2)	30	74/26
20	$AlCl_3$ (2)	30	71/29
20	$SbCl_3$ (2)	25	71/29
20	$SbCl_5$ (2)	22	43/57
20	$SnCl_3(OCH_3) \cdot CH_3OH$ (2)	50	71/29
20	$SnCl_3(OC_2H_5) \cdot C_2H_5OH$ (2)	57	69/31
20	$SnCl_4$ (2)	81	69/31
20	$Ti(i\text{-}C_3H_7O)_4 + TiCl_4$ (1.1)	47	63/37
20	$Ti(i\text{-}C_4H_9O)_4 + TiCl_4$ (1.1)	50	58/42
20	$Ti(n\text{-}C_{18}H_{37}O)_4 + TiCl_4$ (1.1)	57	57/43
20	$TiCl_4$ (2)	60	50/50
20	$Ti(OR)_4$[a] (2)	0	—

[a] R = $i\text{-}C_3H_7$, $i\text{-}C_4H_9$, $n\text{-}C_{18}H_{37}$.

of **1**, we prepared a mixture of the diastereomers **2** (64%) and **3** (36%) according to Ref.[7] and subjected this mixture to our reaction conditions. The product mixture thus obtained consisted of 62% **2** and 38% **3** (after distillation). This result indicates that no stereoisomerization takes place under our cyclization conditions.

_l_-Isopulegol (2) from _d_-Citronellal (1) by Cyclization:

To an ice-cooled and stirred solution of *d*-citronellal (**1**; 6.0 g, ~39 mmol; $[\alpha]_D$: +12.1°) in anhydrous benzene (20 ml), powdered zinc bromide (8.8 g, 39 mmol) is added carefully (in portions of ~0.8 g each), while the reaction temperature is kept at 5–10°. After the addition is complete (~10 min), stirring is continued for 10 min at 5–10°. The precipitated zinc bromide is filtered off and the filtrate is steam-distilled for 1 h. The distillate is extracted with ether (3 × 150 ml), washed with saturated sodium chloride solution (3 × 20 ml), and dried with magnesium sulfate. The solvent is removed in vacuo and the residue distilled in vacuo to give a product which consists of 94% *l*-isopulegol (**2**) (by G.L.C. analysis on two columns of different polarity)[11]; yield: 4.2 g (70%); b.p. 58–59°; $[\alpha]_D$: −17.5° (Ref.[10], $[\alpha]_D$: −22°).

$C_{10}H_{18}O$ (154.3)

M.S.: $m/e = 154$ (M^+), 139, 136, 121, 95, 93, 84, 81, 71, 69, 55, 43, 41.

I.R. ($CHCl_3$): $\nu_{max} = 3560; 3450; 3070; 1640; 1050; 1020; 900\ cm^{-1}$.
^1H-N.M.R. ($CDCl_3$): $\delta = 0.95$ (d, 3H, $J = 5.5$ Hz); 1.72 (d, 3H, $J = 0.5$ Hz); 3.47 (t × d, 1H, $J_t = 10$ Hz, $J_d = 4.5$ Hz); 4.86 ppm (m, 2H).

These data are consistent with those of an authentic sample.

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* Author to whom correspondence should be addressed.

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[11] The following columns were used for G.L.C. analysis: (1) 25% SE 30 on Chromosorb AW, 3 mm (i. d.) × 3 m Stainless Steel Column, temperature 130° (isothermal), detector TCD: *l*-isopulegol 6.3 min; (2) 1% OV 101 on Gaschrom Q, 2 mm (i. d.) × 2.1 m glass column, temperature 80→120° (2°/min), detector FID: *l*-isopulegol 7.8 min, acetate 13.2 min. The products were identified by coinjection with authentic samples.