Organic Process Research & Development **2000**, *4*, 159–161

A Practical and Efficient Synthesis of *p*-Menthane-3,8-diols

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Abstract:

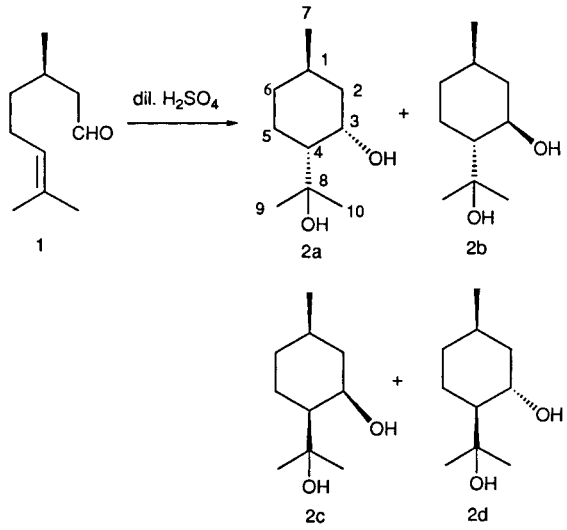
The diastereomeric repellents of *p*-menthane-3,8-diol were produced from citronellal by treatment with 0.25% sulfuric acid at 50 °C for 11 h to give 97.9% conversion and 92.3% selectivity and citronellal acetal by-products with only 2.7%. The crude products were crystallized from *n*-heptane at −50 °C for 20 h to give *p*-menthane-3,8-diols in 80% yield and high purity. The stereochemistry of the citronellal acetal by-products was determined by 2D NMR and NOE.

Introduction

The *p*-menthane-3,8-diols (**2**) are naturally occurring compounds. However, the *cis*- and *trans*-*p*-menthane-3,8-diols in the form of racemic mixtures were obtained from *Eucalyptus citriodora* by Nishimura et al.[1] These compounds are known to exert a repellent effect on insect pests such as mosquitoes and fleas.[2−4] It has been found that the *cis* isomer is more active than the *trans* isomer as an insect repellent.[4] Zimmerman reported the synthesis of the *cis* (**2a**)- and *trans* (**2b**)- *p*-menthane-3,8-diols through acid-catalyzed cyclization of citronellal.[5] Nishimura et al. also synthesized the (±)-*cis* and (±)-*trans* isomers, however, they have not been reported in detail.[1]

In this publication using (+)-citronellal (**1**) as starting material and by treatment of a sulfuric acid aqueous solution (5−9%) for 27 h at room temperature (Scheme 1), the *cis*/*trans* *p*-menthane-3,8-diols were obtained in a ratio of about 2:1−5:2. These compounds were obtained in pure form after chromatographic separation and recrystallization. However, the reported acid-catalyzed cyclization of **1** produced a mixture of 40−45% *cis*- and 60−55% *trans*-*p*-menthane-3,8-diols **2**. Furthermore, Clark et al., have investigated the reaction rate enhancement and stereochemical course of the acid-catalyzed cyclization of **1** to **2a** and **2b**. They identified

Scheme 1. **The cyclization of (+)-citronellal using dilute sulfuric acid.**



two isomeric isopulegols as reaction products.[6] Also, they found a group of by-products with a molecular weight substantially higher than that of **2**. This group includes two main components which are the citronellal acetals of **2**.[7,8] Each of these components comprise a mixture of two diastereomeric compounds that are epimeric at the acetal carbon.

After acid-catalyzed cyclization of **1**, the reaction mixture contains about 15−20% low-boiling materials (including citronellal), about 50−60% *p*-menthane-3,8-diols and 20% acetals. This purity and yield of the *p*-menthane-3,8-diols **2** are not sufficient for large-scale production. For this reason, we investigated the sulfuric acid-catalyzed cyclization of citronellal more closely.[9]

Results and Discussion

We investigated the parameters concentration (H_2SO_4), reaction temperature, and reaction time. The results are shown in Table 1. Conversion of (+)-citronellal, selectivity torwards the *p*-menthane-3,8-diols (*cis*/*trans* mixture) and the production rate of the acetals were measured by gas chromatography (Figure 1). Peaks 6 and 8 could not be

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10.1021/op9901036 CCC: $19.00
Published on Web 03/18/2000

Table 1. **Influence of various concentrations of sulfuric acid upon the cyclization of (+)-citronellal[a])**

run	concd H_2SO_4 (%)[b]	temp. (°C)	time (%)	conv. (%)	low boiling compds[c] (%)	select.[d] of **2** (%)	select.[d] of **3** (%)	yield[e] of **2** (%)
1	10	35	4	97.1	5.9	73.8	20.3	63
2	5	35	6	98.9	5.5	72.0	22.5	62
3	3	35	6	98.3	6.3	78.8	14.9	69
4	1	25	16	96.9	20.5	72.0	7.5	61
5	0.5	25	20	95.3	5.7	89.5	4.8	75
6	0.25	50	11	97.9	5.0	92.3	2.7	79
7	0.25	60	7	98.2	5.7	91.5	2.8	80
8	0.25	70	6	99.0	6.3	90.1	3.6	78
9	0.15	60	10	97.8	6.4	91.7	1.9	78
10	0.05	60	20	95.4	7.9	91.0	1.1	76
11	0.05	100	5	98.7	10.3	87.7	2.0	75
12	0.02	100	10	97.4	11.1	87.4	1.5	75
13	0.01	100	20	97.5	16.5	80.8	2.7	70

[a] Conversion and selectivty determined by GC. [b] Concentration of sulfuric acid aqueous solution is in wt %. [c] The low-boiling point compounds are citronellal, neoisopulegol, isopulegol, and an unknown compound. [d] The percentages of **2** and **3** consist of the **2** isomers and **3** isomers, respectively. [e] Isolated yield of **2**.

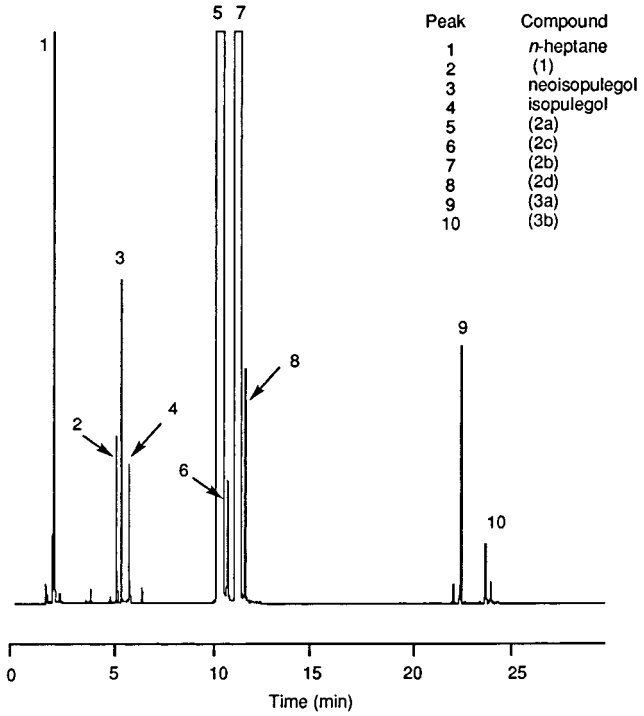

Figure 1. **GC chromatogram of the cyclization products of citronellal using sulfuric acid. Reaction and GC conditions are described in the Experimental Section.**

isolated but were determined to be compounds **2c** and **2d**, respectively (GC/MS). When the *p*-menthane-3,8-diols **2** were produced by treatment of (+)-citronellal with 0.25% sulfuric acid at 50 °C for 11 h to give the citronellal, acetal by-products **3** are as low as 2.7%, whereas conversion and the selectivity to give **2** reach 97.9 and 92.3%(*cis*/*trans* = 63.6:36.4), respectively.

On the other hand, in the experiments of runs 1 and 2, acetals **3** were produced with more than 20%, consequently, the experiments described in the literature[6] are reproducible.

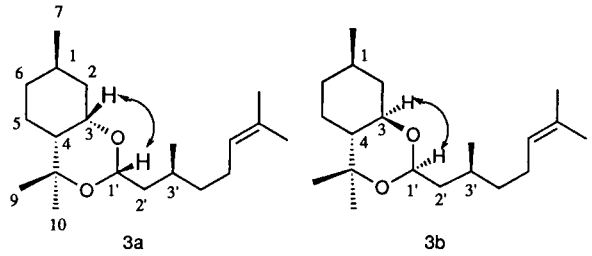

Figure 2. **Important NOEs for 3a and 3b.**

In addition, the cyclization in run 13 was slow and the selectivity lower despite the long reaction time and high temperature (100 °C) due to the very low concentration of sulfuric acid (0.01%).

The best yields of **2** were obtained in the temperature range of 50−60°. The reaction mixture is extracted with an organic solvent and distilled in vacuo directly. However, the acetals **3** cannot be separated from the *p*-menthane-3,8-diol by distillation, therefore, it is difficult to obtain **2** in high purity.

A solution of this problem was crystallization at low temperature. Thus, the reaction mixture was extracted with *n*-heptane, and the organic phase was cooled at −50 °C for 20 h to precipitate **2** as crystals. This was quickly followed by filtration using a centrifuge. The crystals were distilled for complete removal of *n*-heptane to give **2** in 80% isolated yield (purity: 99%). The *cis*/*trans* ratio had changed only slightly (see Experimental Section). Using toluene as a solvent, the crystallization of **2** was difficult. The Experimental Section shows the optimal conditions and results for runs 6 and 7 on a 500 g scale. Moreover, we succeeded in the separation of the two diastereomer acetals **3** by silica gel column chromatography. The structures of **3a** and **3b** were determined by 2D-NMR and nuclear Overhauser effect-(NOE), respectively. Thus, evidence for the *cis* relation between two methine protons in the dioxane ring of **3a** and **3b** were given by enhancement of the H-1′ (acetal) resonance upon irradiation of H-3 (Figure 2). The other diastereomeric acetals were only present in very small amounts and therefore not isolated, but were assumed to be the acetals of **2c** and **2d**. In a pilot plant, we have already produced 100 kg of *p*-menthane-3,8-diol by using the above-described sulfuric acid catalysis and the crystallization method at low temperatures.

In the future, *p*-menthane-3,8-diol **2** will be produced on a a 5-ton scale by our corporation.

Experimental Section

All reagents and solvents were obtained from commercial sources and used without further purification. IR spectra were recorded on a Jasco IR-810, NMR spectra on a Bruker AM-400. ^1H and ^{13}C spectra were determined at 400 and 100 MHz, respectively, and were recorded in $CDCl_3$ with TMS as the internal standard. The chemical shifts were given in δ (ppm).

MS: Hitachi M-80A mass spectrometer at 70 eV.

Optical rotations: Jasco DIP-4 digital polarimeter.

GC: Shimadzu GC-14A with an FID detector. Column: Neutrabond-1 (df = 0.15 μm, 0.25 mm ID × 30m, available

from GL Science Inc., Japan); carrier gas N_2, 0.1 Mpa; oven temperature, 100−250 °C programmed at 10°/min; injection and detector temperatures, 250 °C.

Column chromatography: Merck Kieselgel60, Art.-No.7734.

Melting points: Yanagimoto micro melting apparatus, uncorrected values.

Boiling points: uncorrected values.

Synthesis of *p*-Menthane-3,8-diols (2). In a 3-L round-bottomed flask 636 g (16.3 mmol; 0.5 mol %) of a 0.25 wt % sulfuric acid aqueous solution was charged and heated at 55 °C with stirring. (+)-Citronellal **1** (500 g, 3.24 mol) (produced by Takasago Int. Corp., 98.6% and 96% ee) was added dropwise over 1 h. The reaction mixture was maintained at 55 °C for 10 h. Conversion of **1** and selectivity of **2** were 99.0 and 92.3% (**2a**/**2c**/**2b**/**2d** = 61.2/1.2/35.0/2.6) by GC, respectively. Acetals **3 (**2.1%) were detected as well. Then 8 g (50 mmol) of an aqueous 25 wt % sodium hydroxide solution were added, followed by addition of 1200 mL of *n*-heptane. The organic layer was washed with 500 mL of water, separated, and refluxed to separate the water azeotropically. The organic solution was cooled to −50 °C and stirred for 20 h at this temperature. The colorless crystalline **2** was filtered using a centrifuge. The crystalline **2** was distilled to yield 447 g (80%) of the *p*-menthane-3,8-diols **2**. (The boiling point of the mixture **2** was 100−130 °C/0.8 Torr.) The distilled oily product crystallizes at 30 °C again. The purity of the diastereomeric mixture **2** was 99.5% (**2a**/**2c**/**2b**/**2d** = 64.7/0.2/ 34.0/1.1); only 0.15% of the acetals **3** were detected (GC). Other impurities: 0.1% of citronellal and 0.25% of neoisopulegol and isopulegol; 25 g of the *p*-menthane-3,8-diols **2** obtained by the above-mentioned method were purified by column chromatography (silica gel 300 g, eluent: ethyl acetate/*n*-hexane = 1: 5) to give 5.2 g of the *cis* form **2a** and 3.5 g of the *trans* form **2b**.

Spectral data of *cis*-*p*-menthane-3,8-diol (2a): mp 67 °C, $[\alpha]^{20}_D = +15.4°$ (c = 0.5, $CHCl_3$). IR(KBr) ν = 3260 cm^{-1}. ^1H NMR 0.86−0.96 (m, 1H), 0.87 (d, J = 6 Hz, 3H, CH_3), 1.05 (t, 9 Hz, 1H,), 1.13−1.18 (m, 1H), 1.22 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.64−1.86 (m, 5H), 2.97 (s, 1H), 3.25 (d, J = 2 Hz, 1H,), 4.40 (brs, 1H). ^{13}C NMR 20.3 (CH_2), 22.2 (CH_3), 25.6 (CH), 28.7 (CH_3), 28.9 (CH_3), 34.9 (CH_2), 42.5 (CH_2), 48.3 (CH), 67.9 (CH), 73.2 (C). EI-MS (*m*/*e*, relative intensity) 157 (M^+-15, 4), 154 (M^+-18, 5), 139 (11), 121 (9), 111 (7), 96 (53), 81 (100), 67 (18), 59 (62), 54 (23), 43 (34). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.65, H, 11.79.

Spectral data of *trans*-*p*-menthane-3,8-diol (2b): mp. 73 °C, $[\alpha]_D^{20} = -14.4°$, (c = 0.5, $CHCl_3$). IR(KBr) ν = 3260 cm^{-1}. ^1H NMR 0.84−0.98 (m, 2H), 0.92 (d, J = 6.5 Hz, 3H, CH_3), 1.04 (q, J = 11, 24 Hz, 1H), 1.22 (s, 6H, CH_3), 1.35−1.49 (m, 2H), 1.63−1.73 (m, 2H), 1.92−1.97 (m, 1H), 3.71 (m, 1H), 3.95 (s, 1H), 4.21 (d, J = 3 Hz, 1H). ^{13}C NMR 21.9 (CH_3), 23.5 (CH_3), 26.9 (CH_2), 29.7 (CH_3), 31.2 (CH), 34.5 (CH_2), 44.4 (CH_2), 53.0 (CH), 72.6 (CH), 74.8 (C). EI-MS (*m*/*e*, relative intensity) 157(M^+ − 15, 4), 154 (2), 139 (9),121 (6), 111 (4), 96 (49), 81 (100), 67 (18), 59 (79), 54 (25), 43 (16). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.62, H, 11.80.

The mother liquor of recrystallized **2** was concentrated in vacuo and purified by column chromatography (silica gel, eluent: ethyl acetate/*n*-hexane = 1:20) to give the *cis* form and the *trans* form of the *p*-menthane-3,8-diol citronellal acetals **3** separately.

Spectral data of *cis*-*p*-menthane-3,8-diol citronellal acetal (3a): bp 123−127 °C/ 0.2 Torr., $[\alpha]_D^{23} = -8.33°$ (c = 1.08, $CHCl_3$). IR (neat) ν = 2950, 1455, 1380 cm^{-1}. ^1H NMR 0.82−0.95 (m, 1H), 0.84 (d, J = 6.4 Hz, 3H, CH_3), 0.89 (d, J = 6.6 Hz, 3H, CH_3), 0.98−1.06 (m, 1H), 1.13−1.19 (m, 1H), 1.12 and 1.32 (each s, 3H, ring $C(CH_3)_2$), 1.32−1.40 (m, 3H), 1.54−1.62 (m, 1H), 1.66−1.75 (m, 4H), 1.59 and 1.68 (each s, 3H, $=C(CH_3)_2$), 1.87−2.03 (m, 3H), 4.09 (brs, 1H, −CH−O), 4.87 (t, J = 4.3 Hz, 1H, O−CH−O), 5.08−5.12 (m,1H, $-CH=C(Me)_2$). ^{13}C NMR 17.6 (CH_3), 19.6 (CH_3), 22.1 (CH_2), 22.3 (CH_3), 23.5 (CH_3), 25.3 (CH_2), 25.7 (CH_3), 25.9 (CH), 27.7 (CH_3), 28.3 (CH), 34.4 (CH_2), 37.5 (CH_2), 40.6 (CH_2), 41.5 (CH), 42.3 (CH_2), 71.0 (CH), 73.5 (C), 94.4 (CH), 125.0 (CH), 130.9 (C). EI-MS (*m*/*e*, relative intensity) 308 (M^+, 2), 307 (M^+ − 1, 5), 290 (6), 250 (6), 223 (8), 205 (11), 183 (28), 154 (93), 137 (100), 121 (32), 112 (42), 95 (32), 81 (89), 69 (9). HRMS calcd for $C_{20}H_{36}O_2$: 308.5032; found: 308.5031.

Spectral data of *trans*-*p*-menthane-3,8-diol citronellal acetal (3b): bp 125−128 °C/0.2Torr., $[\alpha]_D^{23} = +19.81°$ (c = 1.06, $CHCl_3$). IR (neat) ν = 2930, 1455, 1380 cm^{-1}. ^1H NMR 0.86−0.89 (m, 3H), 0.90 (d, J = 6.7 Hz, 3H, CH_3), 0.93 (d, J = 6.6 Hz, 3H, CH_3), 1.14−1.16 (m, 3H), 1.19 and 1.21 (each s, 3H, ring $C(CH_3)_2$), 1.32−1.40 (m, 3H,), 1.40−1.53 (m, 1H), 1.56−1.61 (m, 1H), 1.66−1.70 (m, 1H), 1.59 and 1.67 (each s, 3H, $=C(CH_3)_2$), 1.90−2.04 (m, 3H), 3.43 (dq, J = 8.2, 4.1 Hz, 1H, −CH−O), 4.87 (t, J = 5.5 Hz, 1H, O−CH−O), 5.08−5.13 (m, 1H, $-CH=C(Me)_2$). ^{13}C NMR 18.3 (CH_3), 19.4 (CH_3), 20.4 (CH_3), 22.9 (CH_3), 25.9 (CH_2X2), 26.0 (CH_3), 29.1 (CH), 29.7 (CH_3), 31.9 (CH), 35.4 (CH_2), 37.9 (CH_2), 41.6 (CH_2), 43.1 (CH_2), 50.5 (CH), 75. 2(C), 75.7 (CH), 94.8 (CH), 125.6 (CH), 131.7 (C). EI-MS (*m*/*e*, relative intensity) 308 (M^+, 1), 307 (M^+ − 1, 3), 306 (6), 289 (4), 249 (6), 222 (12), 182 (40), 154 (84), 137 (100), 121 (27), 111 (34), 95 (47), 81 (94), 69 (33), 59 (26), 43 (67). HRMS calcd for $C_{20}H_{36}O_2$: 308.5032; found: 308.5033.

Acknowledgment

We are grateful to Mr. Hiroyuki Kenmoch and Mr. Teruyoshi Akiyama for their skillful technical assistance.

Received for review November 29, 1999.

OP9901036