

A Practical Synthesis of *d*- α -Terpineol via Markovnikov Addition of *d*-Limonene Using Trifluoroacetic Acid

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Abstract:

d- α -Terpineol (**1**), which is a useful flavor and fragrance compound, has been synthesized from *d*-limonene by Markovnikov addition using trifluoroacetic acid, followed by hydrolysis in 76% yield with 98% purity.

Introduction

d- α -Terpineol (**1**) is a useful flavor and fragrance compound, for which many syntheses have been reported.^{1–2} *d*- α -Pinene is used as a starting material in these methods; however, it is difficult to obtain *d*- α -pinene in high chemical and optical purity. Whereas *d*-limonene (**2**) is a readily available material and some syntheses of *d*- α -terpineol from *d*-limonene have been reported,^{3–4} these reports are not practical methods concerning the conversion, selectivity, and/or yield.

On the other hand, Roberts published a kinetic study of the reaction of limonene with trifluoroacetic acid, and *d*- α -terpinyl trifluoroacetate (**3**) was characterized.⁵ Furthermore, Mattos has revisited this reaction using both enantiomers of limonene.⁶ This compound **3**, which was derived from *d*-limonene by Markovnikov addition using trifluoroacetic acid, can be readily introduced to **1** by hydrolysis. We have re-examined this additional reaction of *d*-limonene with trifluoroacetic acid on a kilogram scale and then the hydrolysis of trifluoroacetate **3**. We now report the practical and effective synthesis of **1** from **2** in order to provide a stable supply of this flavor and fragrance chemical.

Results and Discussion

Initially, we attempted the addition reaction of *d*-limonene **2** with trifluoroacetic acid according to the above-described literature.^{5–6} The comparisons of the selectivity and the isolated yield of **1** in cyclohexane using the literature method⁶

Table 1. Results of solvent effect^{a,b}

	solvent	conv (%)	selectivity (%)	yield of 1 (%)
1	cyclohexane	74	82	62
2	toluene	83	84	76

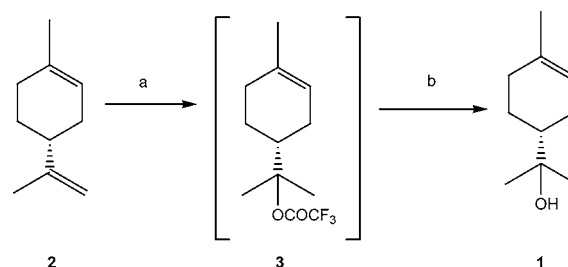
^a 0.5 mol of *d*-limonene and 0.6 mol of CF₃CO₂H were used. ^b The conversion and selectivity were determined by GC.

Table 2. Results of some variable amounts of CF₃CO₂H^{a–c}

	CF ₃ CO ₂ H mol equiv	conv (%)	selectivity (%)	yield of 1 (%)
1	1.0	54	82	45
2	1.2	83	84	76
3	1.5	85	78	65
4	2.0	92	76	62

^a 0.5 mol of *d*-limonene was used. ^b The reaction temperature was room temperature, and toluene was used as the solvent. ^c The conversion and selectivity were determined by GC.

Scheme 1. Synthetic route of *d*- α -terpineol (**1**) from *d*-limonene (**2**)^a



^a Reagents and conditions: (a) CF₃CO₂H, 20–30 °C, 4.5 h. (b) 20% NaOH–H₂O/MeOH, 20–30 °C, 2.5 h.

or toluene as the solvent are shown in Table 1. The solvent could be changed to toluene instead of cyclohexane. Next, the amount of trifluoroacetic acid in toluene as the solvent was investigated (Table 2). 1.2 mol equiv of trifluoroacetic acid for **2** gave the best result (Table 2, run 2). Thus, the 1 kg scale of **2** was treated with 1.2 mol equiv of trifluoroacetic acid in toluene at 20–30 °C for 4.5 h to give trifluoroacetate **3**, which is not stable during column distillation for purification but was stable during the Claisen-type distillation, and then the crude **3** was hydrolyzed by 20% NaOH aq./methanol solution at 20–30 °C for 2.5 h to quantitatively give **1** (Scheme 1). Purification of **1** by column distillation using helipac no. 3 gave **1** with 98% purity in 76% isolated yield. 4-Terpineol and *cis*-/*trans*- β -terpineol as byproducts have been estimated by GC–MS (Figure 1).

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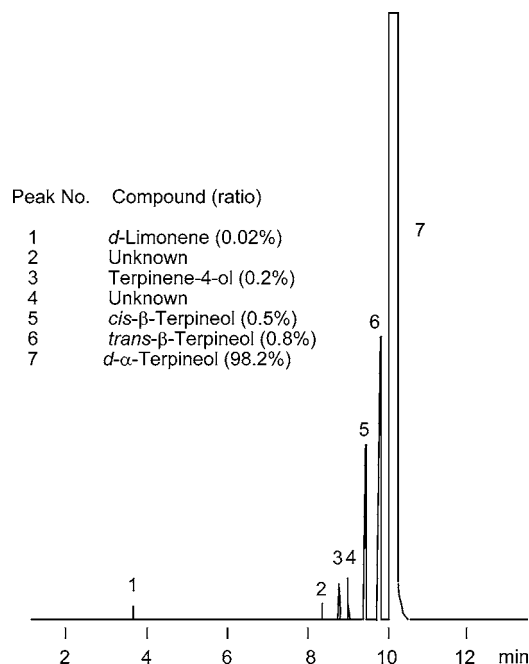


Figure 1. GC chromatogram of distillate *d*- α -terpineol (**1**). GC conditions are described in the Experimental Section.

Experimental Section

All reagents and solvents were obtained from commercial sources, except for *d*-limonene (Takasago), and used without further purification. The boiling points are uncorrected values. The NMR instrument was a Bruker DRX-500. The GC was done using a Shimadzu GC-18A with an FID detector (Column 1, Neutrabond-1 produced by GL Sciences, Inc., Japan, $df = 0.15 \mu\text{m}$, 0.25 mm ID; carrier gas N_2 , 0.1 MPa, oven temperature, 100–230 °C programmed at 5 °C

/min; injection temperature, 230 °C, detector temperature, 250 °C. **2** t_{R} , 5.3 min; **1** t_{R} , 8.0 min; **3** t_{R} , 8.1 min. Column 2, BC-Wax produced by GL Sciences, Inc., Japan, $df = 0.15 \mu\text{m}$, 0.25 mm ID; carrier gas N_2 , 0.1 MPa, oven temperature, 100–230 °C programmed at 5 °C /min; injection temperature, 230 °C, detector temperature, 250 °C. **2** t_{R} , 3.2 min; **3** t_{R} , 6.1 min; **1** t_{R} , 10.2 min (see Figure 1).

Scale-up Procedure of *d*- α -Terpineol (1**).** In a 10-L glass vessel, toluene (2 L) and *d*-limonene [1068 g, 7.34 mol, 96.7% purity, $[\alpha]_{\text{D}}^{23} = +99.9^\circ$ (neat), lit.⁶ $[\alpha]_{\text{D}}^{20} = +118.7^\circ$ (neat)] were added, and then trifluoroacetic acid (1,004 g, 8.81 mol) was dropwise added over 4 h at 20–30 °C. The reaction mixture was stirred for 30 min, and water (4 L) was added. The organic layer was separated and washed with 5% NaHCO_3 solution (4 L) and then 5% NaCl solution (4 L). After the solvent was recovered under reduced pressure (30 Torr, 50 °C), an oily residue (2,025 g) appeared. The residue was dissolved in MeOH (2 L), and 20% NaOH solution (1600 g) was dropwise added for 1.5 h at 20–30 °C and then the mixture was stirred for 1 h. A conc. HCl solution (360 g) and *n*-heptane (1.5 L) were added. The organic layer was separated and washed with water (4 L \times 4). Solvent was recovered under reduced pressure (30 Torr, 50 °C) to give the crude product (1137 g) as a viscous oil, and then the crude product was purified using a ten theoretical plate column distillation with helipac no. 3 to give **1** (861.5 g, 76%, 98.2% purity). Bp 72 °C/4 Torr, 43 °C/0.1 Torr (lit.⁷ 104 °C/15 Torr). $[\alpha]_{\text{D}}^{23} = +81.7^\circ$ (neat) [lit.⁷ $[\alpha]_{\text{D}}^{20} = +100.5^\circ$ (neat)]. The NMR data of the products are identical with those in the literature.

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