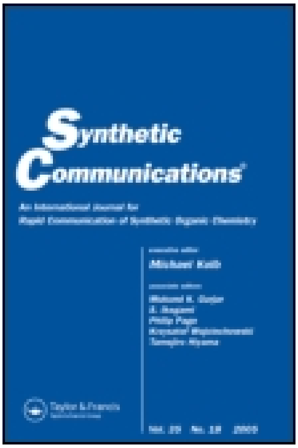

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Chemoselective Formation of 8,9-Epoxy-limonene

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Chemoselective Formation of 8,9-Epoxy-limonene

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Abstract: We present here a synthetic path to produce, exclusively, 8,9-epoxy-limonene in 75% overall yields. We developed a three step synthetic route. First, the 1,2-double bond of limonene was protected by the formation of the bromo-methyl-ether by cohalogenation with NBS in MeOH. Then, this product was oxidized by m-chloro-perbenzoic acid to give the corresponding epoxides. Finally, the 1,2-double bond was restored by a reaction with NH_4Cl/Zn leading to 8,9-epoxy-limonene. The great advantage of this methodology is that the intermediate purification steps are not necessary.

Keywords: Epoxy, limonene, terpene

INTRODUCTION

8,9-Epoxy-limonene is an important synthetic intermediate that can be used to synthesize natural compounds such as uroterpenol,[1] α-bisabolol,[1,2] anymol,[1,2] and 9-hydroxycineoles.[3]

In the literature, we find different methodologies for 8,9-epoxy-limonene preparation from limonene, such as oxidations with porphyrins metallic complexes,[4] titanium complexes,[5] tungsten,[6] ruthenium,[7] hydroperoxide and peroxides formed in situ,[8] photooxidation,[9] and microbiological transformations.[10]

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Until now, the reaction of limonene with nitriles-H_2O_2 has been the most important methodology to prepare 8,9-epoxy-limonene.[11] However, it produces a 1:1 mixture of 1,2-epoxy-limonene and 8,9-epoxy-limonene. The isomers are separated by distillation.

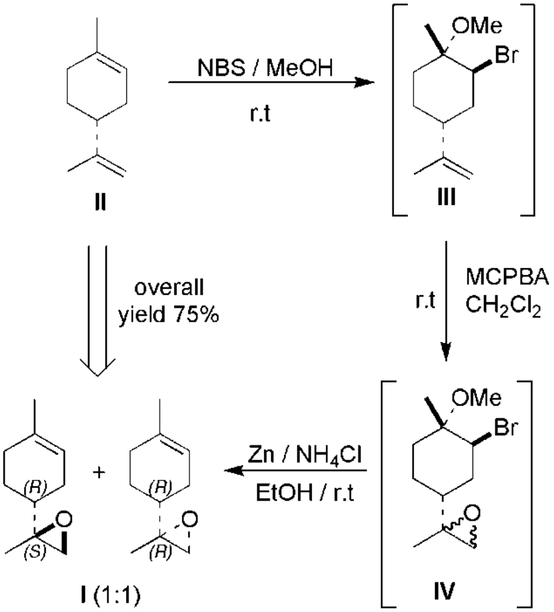
A synthetic method to 8,9-epoxy-limonene at gram scale was described by Carlson in 1971.[11e] This method uses limonene and a mixture of benzonitrile and hydrogen peroxide (35%), and produces a mixture of mono- and di-epoxides (30% being 8,9-epoxy-limonene).

RESULTS

Here we present a specific synthetic route to 8,9-epoxy-limonenes (**I**) in a 75% overall yield.

Recently, de Mattos and Sanseverino[12] published the cohalogenation of limonene (**II**) with $I_2/Cu(OAc)_2 \cdot H_2O$ in aqueous dioxane to produce chemo- and regiospecifically pure iodohydrin.

Based on this result, we developed a three-step synthetic route. First, the 1,2-double bond of limonene was protected by the formation of the bromo-methyl-ether (**III**) by cohalogenation with NBS in MeOH at 0°C (Scheme 1). Then, this product was oxidized by m-chloro-perbenzoic acid (m-CPBA) to give epoxides (**IV**). Finally, the 1,2-double bond was restored



Scheme 1.

by a reaction with NH_4Cl/Zn. The great advantage of this methodology is that the intermediate purification steps are not necessary. In this process, we employed a 10 g scale of limonene to produce 8.4 g of 1:1 mixture of (4R,8R)-8,9-epoxy-limonene and (4R,8S)-8,9-epoxy-limonene (**I**) in 75% overall yield after purification (Scheme 1).

The analysis of the reaction was performed by high-resolution gaseous chromatography (HRGC), and the product was characterized by spectroscopic methods[13] and co-injection with the standard sample.

This synthetic route is a simple and efficient one for preparing a 1:1 mixture of (4R,8R)-8,9-epoxy-limonene and (4R,8S)-8,9-epoxy-limonene in good yields and in >99% purity without any trace of 1,2-epoxide-limonenes.

EXPERIMENTAL

10 g (73.5 mmol) of limonene, 60 mL of methanol, and 13 g (73.5 mmol) of N-bromo-succinimide (added slowly) were added to a 250-mL flask in an ice bath. The solution was stirred for 24 h and filtered, and the solvent was evaporated to obtain an oil. The oil was dissolved in 15 mL of CH_2Cl_2, the solution was cooled in an ice bath, and 13 g of m-chloroperbenzoic acid in 50 mL of CH_2Cl_2 was added dropwise for 20 min. The reaction was stirred for 72 h. Then, a solution of an aqueous 20% KI was added, producing a violet solution. A saturated solution of sodium thiosulfate was added until the violet color vanished completely. The phases were separated and the organic phase was washed with an aqueous 20% $NaHCO_3$ solution. The organic combined extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated. The oil was dissolved in 25 mL of EtOH, and 3 g of Zn and 3 g of NH_4Cl were added. The suspension was stirred vigorously for 24 h at rt, filtered through celite, and fractionated by chromatography on a silica column (hexano/ethyl acetate 9:1), producing 8.4 g (55.3 mmol) of 1:1 mixture of (4R,8R)-8,9-epoxy-limonene and (4R,8S)-8,9-epoxy-limonene (75% yield and >99% purity by HRGC).

Lit. data:[12] ^{1}H NMR, δ: 1.26 (3H, s), 1.64 (3H, bs), 1.75–2.05 (5H, m), 2.57, 2.64 (Abq 1H, $J = 5$ Hz, 2H), 5.36 (1H, bs); ^{13}C NMR, δ: 18.16 (CH_3), 23.42 (CH_3), 25.05 (CH_2), 27.57 (CH_2), 30.14 (CH_2), 40.21 (CH), 53.33 (CH_2), 59.18 (C), 119.92 (CH), 134.12 (C); m/z (rel. int.%) 152 ($M + \bullet$ 2), 121 (23), 119 (11), 105 (16), 95 (17), 94 (100), 93 (38), 91 (33), 79 (89), 77 (24), 67 (34), 55 (27), 53 (30), 43 (38), 41 (55).

(4R,8R)-8,9-epoxy-limonene and (4R,8S)-8,9-epoxy-limonene (**I**): ^{1}H NMR (TMS, $CDCl_3$), δ: 1.26 (3H, s), 1.50 (2H, m), 1.64 (3H, bs), 1.75–2.05 (5H, m), 2.57 (1H, dd, $J = 4.5$ Hz), 2.64 (1H, dd, $J = 4.5$ Hz), 5.37 (1H, bs); ^{13}C NMR (TMS, $CDCl_3$), δ: 18.51 (CH_3), 23.37 (CH_3), 24.95 (CH_2), 27.51 (CH_2), 30.05 (CH_2), 40.12 (CH), 53.44 (CH_2), 59.47 (C), 120.04 (CH), 134.12 (C); EIMS m/z (rel. int.%) 152 ($M + \bullet$ 3), 137 (19), 121 (90), 119 (25), 109 (13), 105 (39), 93 (72), 91 (65), 84 (28), 79 (100), 77 (42), 67 (48), 55 (25), 53 (30), 43 (48), 41 (40), and 39 (44). Lit. data:[11e] ^{1}H NMR, δ: 1.20 (3 H, s), 1.3–2.2 (10 H, m), 1.63 (3 H, s), 2.35–2.60 (2 H, dd), 5.37 (1 H, bs).

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