NEW SYNTHESIS OF 
(5R)-2,2,5-TRIMETHYLCYCLOHEPTANE-1,3-DIONE 
FROM R-(+)-PULEGONE 

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Abstract 
Direct treatment of R-(+)-pulegone 1 with H2O2/HCO2H/H2SO4 led to 2,2,5-trimethylcycloheptane-1,3-dione 4. Reaction of epoxypulegone 2 with sulfuric acid gave 4 too, whereas p-toluenesulfonic acid in toluene led to allylic α-ketol 6. 

Keywords: R-(+)-pulegone; 2,2,5-trimethylcycloheptan-1,3-dione; Epoxypulegone; Terpenic sequence; Camphoraceous odor. 

1. Introduction 
R-(+)-Pulegone 1, a monoterpenic ketone, is the major constituent of pennyroyal oil from Mentha pulegium. The oil is used as a fragrance component and flavoring agent. In our continuing interest [1] in the development of strategies for the synthesis of pulegone derivatives, we report herein a novel and convenient method for the synthesis of 2,2,5-trimethylcycloheptane-1,3-dione 4 directly from R-(+)-pulegone. β-diketone 4 is a white crystalline solid, having a terpenic sequence and a camphoraceous odor. 

Two synthetic methods for 4 have been previously reported. Reusch et al. [2] have shown that gas phase pyrolysis of epoxypulegone [3,4] 2 yielded 2,2,5-trimethylcycloheptane-1,3-dione 4 as the major product. In his report [2], the authors have reported a synthesis, in three steps, of β-diketone 4 from pulegone. A key step for this synthesis is the preparation of epoxypulegone 2. Treatment of 2 with boron trifluoride etherate in benzene gave fluorohydrine 3. Heated to 150°C, 3 led a brown tarry residue consisted mainly of β-dikone 4 (scheme 1). 

Tomioka et al. [5] have described a new process for the transformation of enones into β-diketone. This synthesis is carried out in two steps: preparation of lactone then its treatment with an organoaluminium reagents. In their report [5], the authors have indicated that the lactone 5 led to 2,2,5-trimethylcycloheptane-1,3-dione 4 (scheme 2). 

2. Results and discussion 
The methods of synthesis of 2,2,5-trimethylcycloheptane-1,3-dione described previously require the use of high temperatures and several steps from R-(+)-pulegone. We present here a new method for the synthesis of 2,2,5-trimethylcycloheptane-1,3-dione 4, by direct oxidation of
R-(+-)-pulegone with current reagents. Thus, when R-(+-)-pulegone 1 was added to a mixture of hydrogen peroxide and formic acid in sulfuric acid (98%) medium at -10°C, 4 was obtained in 65% yield (scheme 3).

![Scheme 3](image)

The structure of β-diketone 4 is confidently assigned from its spectroscopic data. The mass spectrum shows molecular ion : m/z = 168, and infrared absorption at 1700 cm⁻¹. The 1H NMR spectrum reveals six-protons singlet (δ 1.21ppm), assigned to the gem-dimethyl group; a doublet corresponding to three protons (δ 1.03; J = 6Hz) assigned to the methyl group at C5. In the 13C NMR singlets at 208.2 ppm and 207.1 ppm are recorded to C1 and C3 sp² carbons, and a singlet at 61.6 ppm is assigned to the quarterly carbon atom C2 and a doublet at 35.5 ppm assigned to carbon atom C5. A negative ferric chloride test, and formation of a disemicarbazone derivative suggested a nonenolic diketone. Facile cleavage of 4 to keto-acid mixture has been observed when it was treated with potassium carbonate.

In order to evaluate the rearrangement of pulegone to β-diketone 4, we studied the acid-catalyzed reaction of epoxypulegone 2. Treatment of 2 with sulfuric acid (98%) led β-diketone 4, whereas p-toluenesulfonic acid gave the allylic α-ketol 6 (sheme 4). The identity of 4 obtained by rearrangement of epoxypulegone with the product obtained from treatment of pulegone with H₂O₂/HCO₂H/H₂SO₄ was established by direct comparison of their melting points, infrared and NMR spectra.

![Scheme 4](image)

This result suggests that the pathway to 4 involves the addition of oxygen to double bond of pulegone and a subsequent cleavage of oxirane to effect 1,2 migration of carbonyl group. The formation of 4, directly from pulegone, presumptively to involve in situ acid-catalysed-rearrangement of epoxypulegone (sheme 5).

![Scheme 5](image)

3. Conclusion

β-diketone 4 resulted from the 1,2-migration of carbonyl group to an adjacent developing positive center in pulegone. This 1,2-migration was largely studied and it is generally carried out in three steps from α,β-enones [6-9] : preparation of enone oxides followed by lewis acid treatment (generally boron trifluoride etherate), and then the resulting fluorohydrine was heated at high temperatures . Direct 1,2-migration that we observed with
mixture H₂O₂ /HCO₂H/H₂SO₄ in one step via the intermediate epoxypulegone will be extended to others carbonyl compounds α,β-insatureds (Ketones, esters, thioesters …).

4. Experimental section

Infrared (IR) spectra were recorded on Schimatzu IR-470. ¹H NMR spectra were recorded on a varian XL 200 (200 MHz) spectrometer. ¹³C NMR spectra of CDCl₃ solution were recorded on varian XL 200 (50.309 MHz) with Me₄Si as the internal standard. Mass spectra was obtained on varian MAT311 mass spectrometer. Melting points are uncorrected and were obtained on a capillary apparatus.

Synthesis of 2,2,5-trimethylcycloheptane-1,3-dione 4

A mixture of 30% hydrogen peroxide (11ml) and 88% formic acid (13ml) was cooled to –10°C, and concentrated 98% sulfuric acid (10ml) was added dropwise with stirring. 4 g of pulegone was added, drop by drop. The reaction mixture was stirred and allowed to warm to room temperature in 6 h. After elimination of formic acid under reduced pressure, 20 ml of water was added. The mixture was extracted with three 30 ml portions of ether, the combined ether layers were washed with saturated solution of NaHCO₃. The ethereal solution was then dried (MgSO₄), the solvent was removed and the crude oil was purified by chromatography on silica gel (methylene chloride). Yield 65%, mp. 55°C. IR(CCl₄) : 3400 (harmonic of the 1700 band cm⁻¹), 1700, 1540, 1380 cm⁻¹. ¹H NMR (CDCl₃) : 2,76 (2H, m), 2,26 (2H, m), 2,03 (2H, m), 1,52 (6H, s), 1,03 (6H, d, J = 6 Hz). ¹³C NMR (CDCl₃) : 208,1 (s), 207,1 (s), 61,6 (s), 48,5 (t), 35,1 (d), 39,8 (t), 35,9 (t), 23,02 (q), 20,6 (q); mass spectrum : m/z = 168 (29%), (mass calculated for C₁₀H₁₆O₂ : 168,1150; mass found: 168,1146), 140 (38), 125 (100), 124 (7), 123 (48), 97 (23), 83 (41), 70 (47),55 (31),28 (63).

Preparation of epoxypulegone 2

To a stirred sulfuric acid 98% (2ml) was added, by smalls portions, 1g of epoxypulegone at –10°C. After 2h of stirring at –10°C, water is gently added until complete deposition of β-diketone 4. The solid was filtered and washed with saturated solution of NaHCO₃. Recrystallization (pentane) gave white solid identified as β-diketone 4. Yield 35%.

Action of p-toluenesulfonic acid on epoxypulegone: obtention of allyl α-ketol 6

The mixture of the two diastereoisomers of Allyl α-ketol 6 was obtained according to the procedure of Reusch et al. [2], except that benzene was replaced by toluene. The solvent was removed after dried (MgSO₄), by distillation at reduced pressure, and the residue oil was chromatographed directly on silica gel (hexane/ether : 80/20). Yield 89%. IR(film) : 3540, 3070, 1741, 1640, 1090 cm⁻¹; ¹H NMR (CDCl₃) : 5,02 and 4,80 (2H, m), 3,65 (1H, S), 1,72 (3H, s), 1,15-1,09 (6H, m); ¹³C NMR (CDCl₃) : 210,2 (s) and 210,0 (s), 144,0 (t) and 143,9 (t), 80,3 (s), 80,0 (s), 48,3 (t) and 46,7 (t), 36,9 (t) and 33,2 (t), 36,0 (d) and 32,3 (d), 31,5 (t) and 28,7 (t), 22,1 (q), 18,5 (q) and 18,4 (q).

References