

Oxygenated Limonene Analogs. Preparation of Tetramethylated Carvone and Carveols via Regiocontrolled Opening of Tetramethylimonene Oxide.¹

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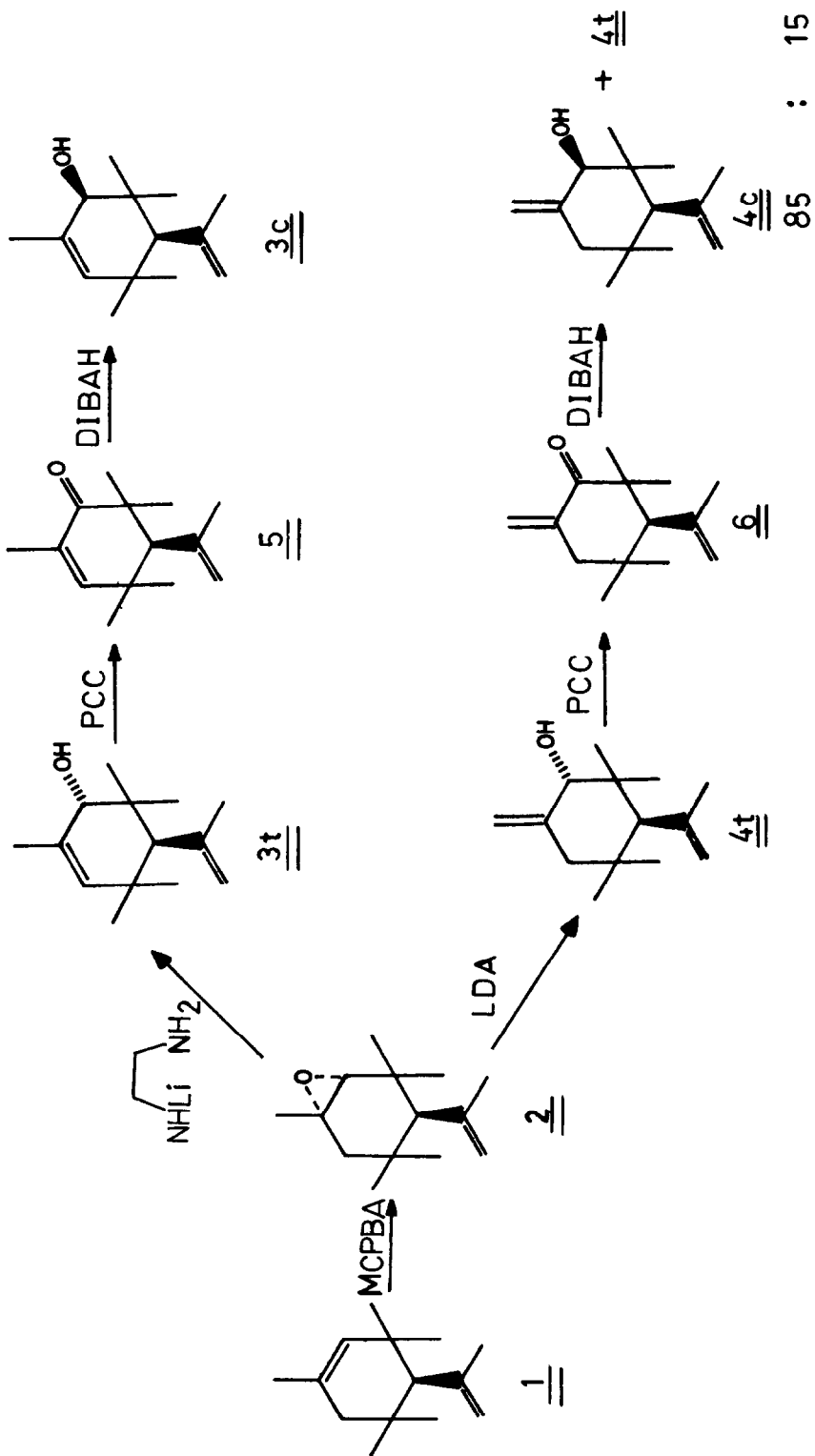
Summary: Regioselective opening of *trans* epoxide 2 gave *endo* and *exo* tetramethylated *trans* carveols 3t and 4t, respectively, which were oxidized to tetramethylcarvone (5) and its unstable exocyclic isomer 6; reduction of 5 with DIBAH gave tetramethylated *cis* carveol 3c exclusively, whilst analogous reduction of 6 produced an epimeric mixture of 4c:4t=85:15.

We have shown previously that 3,3,5,5-tetramethylimonene (1) can be prepared conveniently in quantities of 25 g per batch by biomimetic acid-catalyzed dehydrative cyclodimerization of 2,4-dimethyl-3-penten-2-ol at room temperature^{1c} and also by acid-catalyzed dimerization of 2,4-dimethyl-1,3-pentadiene under more forcing conditions.² We now describe some oxygenated derivatives of 1, namely the tetramethyl analogs of the carveols and carvone, which are of potential interest in perfumery.

On monoepoxidation with *m*-chloroperbenzoic acid, tetramethylimonene (1) yields predominantly the *trans* epoxide 2, with only ca. 5% *cis* epoxide. In contrast, the parent limonene is known to form a 1:1 *cis/trans* mixture of epoxides under the same conditions.³ Tetramethylimonene oxide (2) is a crystalline, sublimable epoxide, which does not react with 6*N* aqueous potassium hydroxide on refluxing at 130°C for 7 days. The epoxide is also inert to lithium aluminium hydride in toluene or tetrahydrofuran (90°C, 3 days), and, remarkably, even to superhydride⁴ (lithium triethylborohydride) in refluxing tetrahydrofuran. For comparison, superhydride (1*M* in THF) has been reported to react with the epoxide of 1-methylcyclohexene in 5 min at 0°C, giving 1-methylcyclohexanol in 100% yield.⁵

As the S_N2-like opening of epoxide 2 is unusually difficult, presumably because of steric hindrance, we attempted an E2-like opening. Reaction of 2 and aluminium isopropoxide in toluene (110°C, 18 h) gave a 30:70 mixture of olefinic alcohols 3t and 4t in more than 90% yield. However, since the separation of 4t from 3t was not straightforward, we aimed to control the orientation of elimination. The sterically demanding lithium diisopropylamide

REGIOCONTROLLED OPENING OF
TETRAMETHYLLIMONENE OXIDE (2)



gave (3 h at 50°C), after flash chromatography on silica gel, 4t, colorless needles (95% yield), as a single isomer.⁶ In contrast, when N-lithioethylenediamine $H_2NCH_2CH_2NHLi^7$ was allowed to react with 2 at 110°C for 5 h, the tetramethylated trans carveol 3t, mp 38-40°C, was isolated in 90% yield. Thus, the regiochemistry of the E2-like opening of 2 can be controlled by the choice of base.

Independently, the mixture of 3t and 4t (30:70) obtained from the reaction of 2 and aluminium isopropoxide could be equilibrated with N-lithioethylenediamine, which is also a weak protic acid, giving only the olefin of thermodynamic control, i.e. Saytzeff product 3t.

Tetramethylcarvone (5) and its exocyclic isomer 6. The classical procedure, developed in the 19th century, for converting limonene into carvone involves nitrosochlorination, elimination of hydrogen chloride to carvoxime and finally hydrolysis.⁸ Nitrosochlorination of 1 and an independent attempt at preparing tetramethylcarvoxime from 5 and hydroxylamine (pyridine-ethanol, 90°C, 4 h) were not successful. Likewise, an attempt to oxidize the axial alcohol 3t with manganese dioxide failed. However, oxidation with pyridinium chlorochromate⁹ proceeded smoothly, giving tetramethylcarvone 5 as a colorless oil in 85% yield. Similarly, oxidation of 4t with PCC and catalytic amounts of pyridine gave the isomeric enone 6 as a sensitive oil (75% yield) which polymerized upon prolonged standing at room temperature or distillation. However, 6 could be stored up to several weeks in dilute solution at -20°C.

Using the now accessible isomeric enones 5 and 6, we were able to produce, by selective reduction, the epimeric carveols 3c and 4c: Treatment of enone 6 with diisobutyl aluminium hydride in toluene (1 h, 0°C)¹⁰ gave the cis alcohol 4c and also some trans epimer 4t (4c:4t = 85:15), whereas reduction of tetramethylcarvone 5 produced tetramethylated cis carveol 3c exclusively. Thus, the cis and trans carveols 3c and 3t, free from their respective epimers, are readily accessible. The 3,3,5,5-tetramethyl structural pattern of our mono-terpenoids also simplifies other reactions and interpretation of ¹H NMR spectra.^{11,12}

References and Notes

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11. ¹H NMR (90 MHz, CDCl₃) and IR (CCl₄, cm⁻¹) spectral data for compounds 3 - 6:
 - 3t: 0.98 (s, 6H, 2CH₃), 1.03 (s, 6H, 2CH₃), 1.43 (br s, 1H, OH), 1.80 (m*, 3H, isopropenyl-CH₃), 1.87 (m*, 3H, cyclohexenyl-CH₃), 2.25 (s, 1H), 3.30 (br s, 1H); olefinic-H's: 4.80 (m, 1H), 5.02 (m, 1H), 5.23 (m, 1H); IR: 3620 (m, sharp OH), 3580 (w, br, OH), 1000 (s, C-O)
 - 3c: 0.92 (s, 3H, CH₃), 0.98 (s, 3H, CH₃), 1.02 (s, 6H, 2CH₃), 1.40 (br s, 1H, OH), 1.72 (m*, 3H, isopropenyl-CH₃), 1.86 (m*, 3H, cyclohexenyl-CH₃), 1.94 (s, 1H), 3.87 (br s, 1H); olefinic-H's: 4.77 (m, 1H), 5.01 (m, 1H), 5.17 (m, 1H); IR: 3640, 3610 (m, sharp, OH), 1060 (m, C-O).
 - 4t: 0.93 (s, 3H, CH₃), 0.95 (s, 3H, CH₃), 0.98 (s, 6H, 2CH₃), 1.53 (d, J = 5 Hz, 1H, OH), 1.85 (m*, 3H, isopropenyl-CH₃), 1.77 (d, J = 13 Hz, 1H), 2.25 (s, 1H), 2.45 (d, J = 13 Hz, 1H), 3.70 (br s, 1H); olefinic-H's: 4.77 (m, 1H), 4.83 (m, 1H), 4.90 (m, 1H), 5.00 (m, 1H); IR: 3620 (m, sharp, OH), 3490 (w, br, OH), 1040 (m, C-O).
 - 4c: inter al.: 0.90 (s, 6H, 2CH₃), 0.97 (s, 3H, CH₃), 1.02 (s, 3H, CH₃), 1.60 (d, J = 6 Hz, 1H, OH), 1.55-1.95 (m, 2H), 1.83 (m*, 3H, isopropenyl-CH₃), 2.02 (s, 1H), 3.97 (d, J = 6 Hz, 1H); olefinic-H's: 4.80 (m, 2H), 5.00 (m, 2H); IR: 3620 (w, sharp, OH), 905 (s).
 - 5: 1.14 (s, 6H, 2CH₃), 1.21 (s, 6H, 2CH₃), 1.67 (s, 3H, cyclohexenyl-CH₃), 1.77 (m*, 3H, isopropenyl-CH₃), 2.36 (s, 1H); olefinic-H's: 4.75 (m, 1H), 4.92 (m, 1H), 6.04 (m*, 1H, enone-H); IR: 1675 (vs, C=O).
 - 6: 1.03 (s, 3H, CH₃), 1.09 (s, 3H, CH₃), 1.14 (s, 3H, CH₃), 1.20 (s, 3H, CH₃), 1.83 (m*, 3H, isopropenyl-CH₃), 1.55-2.27 (m, 2H), 2.44 (s, 1H); olefinic-H's: 4.75 (m, 1H), 5.00 (m, 1H), 5.15 (m, 1H), 5.86 (m, 1H); IR: 1690 (vs, C=O).
- * allylic W-coupling (J = 1 Hz).
12. This work has been presented in part at the International Symposium on the Chemistry of Carbocations in Bangor, North Wales, Sept. 7-11, 1981. — We thank Prof. W.Kreiser for drawing our attention to ref. 7a, Dr. F.J.Hammerschmidt of Dragoco for GC-MS measurements and the Deutsche Forschungsgemeinschaft as well as the Fonds der Chemie for financial support.

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