

The Potential Biologically Active Epoxide, Hydroperoxide and Endoperoxide Derivatives Driven from Natural Monoterpene β - Myrcene

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Abstract: β - Myrcene, 7-methyl-3-methylene-1,6-octadiene (1) has been epoxidized using m-chloroperbenzoic acid (mcpba) at room temperature in the presence of florescent lamps or in the dark to give only 2,2-dimethyl-3-(3-methylene-penta-4-enyl)-oxirane (2) as a stereospecific product. Whereas, the photooxygenation reaction of 1 in the presence of tetraphenyl porphin (TPP) as singlet oxygen sensitizer gave a mixture of three hydroperoxide derivatives (3, 4 and 5).

Key words: Photooxygenation, Epoxidation, β -Myrcene, Tetraphenyl porphin, m-Chloroperbenzoic acid.

INTRODUCTION

The natural acyclic-monoterpene, β - myrcene (1), found in bay oil derived from leaves of *Pimenta acris* Kostel (*Myrtaceae*) (M. Pan, *et al* 2007), cardamom oil extracted from fruit of *Elettaria cardamomum* Maton (*Zingiberaceae*) (J. W. Parry, 1969; R.A. Bernhard, *et al.*, 1971), hop oil presented in strobiles of *Humulus lupulus* L (*Moraceae*) (M. Windholz, *et al.*, 1979) and ginger oil extracted from rhizome of *Zingiber officinale* (*Zingiberaceae*) (G. Jagetia, *et al.*, 2004).

A variety of dietary monoterpenes, myrcene (1) like have been shown to act effectively in chemoprevention and chemotherapy fire dragon of different cancers in : animal models, at cellular level and human clinical trials (P.L. Cowell, 1999; J.J. Mills, 1995 and S. Carnesecchi, *et al.*, 2001), also show sensitizing activity of tumor cells to radiation thereapy (M.N. Gould, *et al.*, 2006). It has pestside activities such as : insecticidal activity (M.O. Omolo, *et al.*, 2005), antifungal activity (M. Omidbeygi, *et al.*, 2007) and antimicrobial activity (Beena Joy, *et al.*, 2007).

Plant monoterpenes are subjected to oxidize when exposed to air. Oxidation is enhanced by heat (E. M. Elgendy, 1997), exposure to light (E. M. Elgendy, 1998) or by chemical catalysts (A. Meou, *et al.*, 1999), to give the intermediated epoxides. Furthermore, unsaturated terpenes were trapped the activated oxygen species in vivo to give the intermediated epoxides and hydroperoxide derivatives, which could be alkylated or damage DNA, proteins and other biological species (E. M. Elgendy, 1997; S. Richter, *et al.*, 2003).

Also, the epoxide derivatives can be used exclusively for the formation of the valuable epoxyresins (F. Meng, *et al.*, 2006; C.S. Reddy, *et al.*, 2005).

On the other hand, myrcene (1) is an acyclic pine oleoresin monoterpene that has been linked to the biosyntheses of ipsenol and ipsdienol (S.J. Seybold, *et al.*, 2003). However, the epoxidation reaction of dihydromyrcene using titanium-containing silicates TS-1 and TiAl β with aqueous hydrogen peroxide, tert-butyl hydroperoxide and urea-hydrogen peroxide as oxidants gave epoxide derivative (O.J. Schofield, *et al.*, 2002).

In view of the significant therapeutic value of myrcene (1), it was considered worth while to investigate some oxidation reactions of β myrcene (1) toward epoxidation reactions thermally or photochemically and photooxygenation reaction.

RESULTS AND DISCUSSION

Results:

Photo-epoxidation reaction of β - myrcene (1) was carried out using m-chloroperbenzoic acid (mcpba) in the presence of florescent lamps (UV-A light) in chloroform solution at room temperature to give 2,2-dimethyl-3-(3-methylene-penta-4-enyl)-oxirane (2) as a stereospecific product. Same product was obtained in different yield, when the reaction was repeated in the dark.(cf. experimental section) (Scheme 1).

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The chemical structure of 2 was elucidated by spectral measurements. H,H-NMR cosy spectrum of 2 showed complex pattern at δ 2.75 for the proton at positions 6 which was shifted towards the up field from 5.14 of the starting material 1. ¹³C-NMR spectrum showed beaks at δ 64.07 for carbon at position 6 which was shifted from 124.00 of the starting material 1.

The epoxy resin was obtained when epoxide derivative (2), instead of epichlorohydrin was reacted with 2,2-bis(4-hydroxyphenyl)propane. The resulted epoxy resin showed low molecular weight and sticky character (F. Meng, *et al.*, 2006 and C.S. Reddy, *et al.*, 2005). It showed very good adhesive on metal surface such as copper and iron steel.

Interesting is the photooxygenation reaction of 1, in the presence of tetraphenyl porphin (TPP) as singlet oxygen sensitizer to give a mixture of the regioisomers 6-hydroperoxy-7-methyl-3-methylene-1,7-octadiene (3), 7-hydroperoxy-7-methyl-3-methylene-1,5-octadiene (4) and 5-(3',6'-dihydro-[1',2']-dioxin-4'-yl)-2-methyl-penta-3-ene-2-yl-hydroperoxide (5) in the yields of 25 %, 20 % and 11 % respectively. Which were successfully separated in pure form. (Scheme 1, Table 1).

The structures of 3-5 were supported by spectral studies. The H,H-NMR cosy spectrum of 3 showed complex pattern at δ 4.20, for proton in position 6, doublet at 4.9 for methylene protons in position 8 and singlet at 8.00 for OOH group. The spectrum showed also disappearance of one of CH₃ group. Whereas, The H,H-NMR cosy spectrum of 4 showed complex pattern at δ 4.22 for the proton in position 5, (which was shifted from 2.23 of the starting material 1), doublet at 5.65 for methenyl proton in position 6 and singlet at 8.00 for OOH. Similarly, the ¹H-NMR spectrum of 5 showed two doublets at δ 3.90 and 4.0 for two protons in position 3' and complex pattern for two protons in position 6', doublet at 5.27 for proton in position 5', doublet at 5.37 for proton in position 3, double triplets at 5.60 for methenyl proton in position 4 and singlet at 9.57 for OOH proton. Their MS spectra showed molecular ion m/z 200.

Discussions:

It was interesting to investigate the epoxidation reaction photochemically of the β - myrecene (1), which has three active side. Therefore, under carefully controlled, the epoxidation reaction of β - myrecene (1) using m-chloroperbenzoic acid (mcpba) in presence of florescent lamps (UV-A light) gave the stereoselective 2,2-dimethyl-3-(3-methylene-penta-4-enyl)-oxirane (2) as a sole epoxide product. Same result was obtained when the reaction was carried out in the dark. The epoxidation was happened only at the double bond at position 6, whereas, the other two double bonds at positions 1 and 3 still inert, even the reaction time was prolonged. The result was in a good agreement with the previous work (E.M. Elgendy and S.A. Khayyat, *inpress*). In addition, (O.J. Schofield, *et al.*, 2002) reported that the epoxidation reaction of dihydromyrecene in presence of hydrogen peroxide gave 2,2-methyl-3-(3-methylene-pentyl)-oxirane.

The probable mechanism for production of epoxide derivative of 1 is believed to be through the formation of the oxirane intermediates (A) via elimination of m-chlorobenzoic acid. (Scheme 2).

On the other hand, it has been interested to focus on the photooxygenation reaction of β - myrecene (1) using tetraphenyl porphin (TPP) as a singlet oxygen sensitizers, which gave a regioisomers 6-hydroperoxy-7-methyl-3-methylene-1,7-octadiene (3), 7-hydroperoxy-7-methyl-3-methylene-1,5-octadiene (4) and 5-(3',6'-dihydro-[1',2']-dioxin-4'-yl)-2-methyl-penta-3-ene-2-yl-hydroperoxide (5).

Frontier orbital analysis show that singlet oxygen ¹O₂ in lowest unoccupied molecular orbital (LUMO) (excited transition state) was combined with the double bond in the myrecene (1) in highest occupied molecular orbital (HOMO) (ground electronic state) as peroxirane intermediate (B) followed by hydrogen transfer from α position (cis form) (K. H. Schulte-Elte, and V. Rautenstrouch, 1980) via two probable pathways to obtain the hydroperoxide derivatives (3 & 4). (Scheme 3).

Again the hydroperoxide 4 was reacted with other mole of singlet oxygen through [2 + 4] cycloaddition reaction (Diels-Alder type) to give endoperoxy-hydroperoxide derivative (5). (Scheme 3).

Experimental:

β - Myrecene (1) was supplied from Merck Co. IR spectra were performed on a Perkin-Elmer 16 FPC FT-IR spectrophotometer as thin films. ¹H-NMR spectra were obtained in CDCl₃ solution with a Bruker AVANCE D.P.X. 400 MHz apparatus. GCMS were determined by Joel JMS 600H, GC Hewlett Packard, HP 6890 Series, with capillary column (30m x 0.32 mm x 0.25 μ m) HP-5 cross linked 5% dimethyl polysiloxane. A mercury lamp (HRI-T250W) was used for photo-irradiation reactions. Thin layer chromatography (TLC) and preparative layer chromatography (PLC): Polygram SIL G/W 254, Mecherey-Nagel. A rotatory evaporator (at 20°C/15 torr) was used to remove the solvents.

Epoxidation reaction of β - Myrecene (1): Method A :

A solution of 1 (1.36 g, 10 mmol) in CHCl_3 (25 ml) was irradiated using florescent lamps, m-chloroperbenzoic acid (15 mmol, 80 %) was added in small portions wise to the reaction mixture at 0°C ., then stirred at room temperature. The reaction mixture was washed with a saturated aqueous solution of NaHCO_3 (3 X 10 ml), then with distilled water (3 X 10 ml). The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure at room temperature to give 1.52 gm of 2,2-dimethyl-3-(3-methylene-penta-4-enyl)-oxirane (2) as the quantitative yield.

Method B:

A solution of 1 was repeated in the same condition as in the cas of method A in the dark to give 1.2 gm of the epoxide 2 as 80 % yield.

Preparation of epoxy-resin:

The preparation of the new epoxy-resin was carried out as in the case of epoxy-resin from the epichlorohydrin (W. R. Sorenson and T. W. Campblell, 1962).

General Photooxygenation of β - myrecene (1):

A solution of compound (1) (1.36 g, 10 mmol) in CHCl_3 solution according to the type of sensitizers was irradiated externally by means of sodium lamp at -5°C . During the irradiation a continuous stream of dry oxygen gas was allowed to pass through the reaction mixture at a slow rate to avoid evaporation of solvent. The solvent was evaporated at $20^\circ\text{C}/15$ Torr. The crude products were purified by preparative layer chromatography (PLC). Eluting with a mixture of petroleum ether 60 – 80 $^\circ\text{C}$ and ethyl acetate (8 : 2) to give 6-hydroperoxy-7-methyl-3-methylene- 1,7-octadiene (3), 7-hydroperoxy-7-methyl-3-methylene- 1,5-octadiene (4) and 5-(3',6'-dihydro-[1',2']-dioxin-4'-yl)-2-methyl-penta-3-ene-2-yl-hydroperoxide (5). The results are given in table 1.

Table 1:

Comp.	Start Wt. gm	Solvent	Sensitizer.	Reaction time	Photo Products: Isolated gm Yield %
1	1.36	CHCl_3	TPP	17	3 : (0.42) 25 %; 4 : (0.34) 20 %, 5 : (0.22) 11 %

2,2-dimethyl-3-(3-methylene-penta-4-enyl)-oxirane (2):

IR (thin film), ν , cm^{-1} : 2920, 1640, 1595, 1376, 1106. H,H-NMR cosy (CDCl_3) : δ , 1.26 (s, 3H, C^8H_3), 1.31 (s, 3H, C^9H_3), 1.72 (comp. pat., 2H, H-5), 2.33 (comp. pat., 1H, H-4), 2.44 (comp. pat., 1H, H-4), 2.75 (comp. pat., 1H, H-6), 5.05 (dd, 2H, J= 6,13 Hz, H-10), 5.08 (d, 1H, J= 10 Hz, H-1), 5.24 (dd, 1H, J= 6, 17 Hz, H-1), 6.38 (dd, 1H, J= 10, 17 Hz, H-2) ppm. ^{13}C -NMR (CDCl_3) : δ : 18.60 (CH_3^8), 25.00 (CH_3^9), 27.41 (C-5), 27.67 (C-4), 58.32 (C-7), 64.07 (C-6), 113.43 (C-10), 116.49 (C-1), 138.58 (C-2), 146.00 (C-3) ppm. GCMS, R.T. : 13.95 min., m/z 152 (M^+ , $\text{C}_{10}\text{H}_{16}\text{O}$) (4 %), 136 (M^+-O) (38 %), 125 ($\text{M}^+-\text{C}_2\text{H}_3$) (2 %), 99 ($\text{C}_6\text{H}_{11}\text{O}$) (4 %), 83 (C_6H_{11}) (78 %), 68 (C_5H_8) (100 %), 55 (C_4H_7) (18 %).

6-hydroperoxy-7-methyl-3-methylene-1,7-octadiene (3):

IR (thin film), ν , cm^{-1} : 3421, 2926, 1600, 1378,1279, 1100. H,H-NMR cosy (CDCl_3) : δ , 1.70 (s, 3H, CH_3), 1.75 (comp. pat.,2H, H-5), 2.22 (comp. pat., 2H, H-4), 3. 91 (d, 1H, J= 15 Hz, H-10), 4.20 (comp. pat., 1H, H-6), 4.23 (d, 1H, J= 14 Hz, H-10), 4.9 (d, 2H, J= 20 Hz, H-8), 5.20 (dd, 1H, J= 10, 21 Hz, H-1), 5.40 (dd, 1H, J= 17, 21 Hz, H-1), 5.96 (dd, 1H, J = 10, 17 Hz, H-2), 8.00 (s, 1H, OOH) ppm. ^{13}C -NMR (CDCl_3) : δ : 14.12 (CH_3^9), 25.41 (C-5), 31.01 (C-4), 85.32 (C-6), 112.47 (C-8), 114.60 (C-10), 128.86 (C-1), 132.46 (C-7), 142.33 (C-2), 144.88 (C-3) ppm. GCMS, R.T. : 18.97 min., m/z 168 (M^+ , $\text{C}_{10}\text{H}_{16}\text{O}_2$) (1 %), 150 ($\text{M}^+-\text{H}_2\text{O}$) (5 %), 123 ($\text{M}^+-\text{C}_2\text{H}_5\text{O}$) (2 %), 109 ($\text{C}_7\text{H}_9\text{O}$) (4 %), 97 ($\text{C}_6\text{H}_9\text{O}$) (4 %), 81 (C_6H_9) (5 %), 69 (C_5H_9) (100 %), 56 (C_4H_8) (40 %).

7-hydroperoxy-7-methyl-3-methylene-1,5-octadiene (4):

IR (thin film), ν , cm^{-1} : 3427, 2929, 1600, 1378, 1261, 1100. H,H-NMR cosy (CDCl_3) : δ : 1.35 (s, 6H, 2CH_3), 1.73 (d, 2H, J= 18 Hz, H-4), 4.22 (comp. pat., 1H, H-5), 4.75 (d, 1H, J= 19 Hz, H-10), 4.80 (br.s, 1H, H-10), 5.05 (dd, 1H, J= 11, 22 Hz, H-1), 5.25 (dd, 1H, J= 6, 22 Hz, H-1), 5.65 (d, 1H, J= 15, Hz, H-6), 6.40 (dd, 1H, J= 6, 11 Hz, H-2), 8.00 (s, 1H, OOH) ppm. ^{13}C -NMR (CDCl_3) : δ 23.00 (CH_3^8), 24.00 (CH_3^9), 39.00

(C-4), 59.00 (C-7), 120.30 (C-1), 124.40 (C-5), 129.00 (C-6), 131.00 (C-2), 132.60 (C-3) ppm. GCMS, R.T. : 19.18 min., m/z 168 (M^+ , $C_{10}H_{16}O_2$) (10 %), 152 (M^+-O) (3 %), 134 ($M^+-H_2O_2$) (2 %), 125 ($M^+-C_2H_3O$) (2 %), 107 (C_8H_{11}) (3 %), 99 ($C_6H_{11}O$) (4 %), 81 (C_6H_9) (20 %), 67 (C_5H_7) (100 %).

5-(3',6'-dihydro- [1',2']-dioxin-4'-yl)-2-methyl-penta-3-ene-2-ylhydroperoxide (5):

IR (thin film), ν , cm^{-1} : 3434, 2928, 1599, 1378, 1275, 1124. 1H -NMR ($CDCl_3$) : δ , 1.30 (s, 3H, C^1H_3), 1.40 (s, 3H, C^6H_3), 2.1 (comp. pat., 2H, H-5), 3.90 (d, 1H, J= 13 Hz, H-3'), 4.00 (d, 1H, J= 13 Hz, H-3''), 4.20 (comp. Pat., 2H, H-6'), 5.27 (dd, 1H, J= 11, 19 Hz, H-5'), 5.37 (d, 1H, J= 9 Hz, H-3), 5.60 (dt, 1H, J= 6, 18 Hz, H-4), 9.57 (s, 1H, OOH) ppm. ^{13}C NMR ($CDCl_3$) : δ 23.04 (CH_3^1), 23.78 (CH_3^6), 38.76 (C-5), 69.27 (C-6'), 84.24 (C-3'), 85.31 (C-2), 114.58 (C-4), 130.96 (C-5'), 132.48 (C-3), 142.53 (C-4') ppm. GCMS, R.T. : 19.87 min., m/z 200 (M^+ , $C_{10}H_{16}O_4$) (20 %), 183 (M^+-HO) (8 %), 125 ($C_7H_9O_2$) (2 %), 115 ($C_6H_{11}O_2$) (25 %), 99 ($C_6H_{11}O$) (4 %), 85 (C_3H_6O) (26 %), 68 (C_5H_8) (100 %).

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