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EPOXIDES FROM MYRCENE: NEW VERSATILE TOOLS FOR THE SYNTHESIS OF FUNCTIONALIZED ACYCLIC TERPENOIDS

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Abstract: Mono-epoxides prepared from myrcene, were used as synthetic intermediates to obtain citral, linalool, geranylacetone and pseudo-ionone.

Due to its easy availability and good reactivity, myrcene **1** is frequently used to access to high value products[1] (perfumes, cosmetics, vitamins, retinoids,...). Epoxides being versatile synthetic tools[2], we wish to report in this communication new aspects of the utilization of mono-epoxides **2**-**4**, previously obtained[3] from myrcene **1** (Scheme 1).

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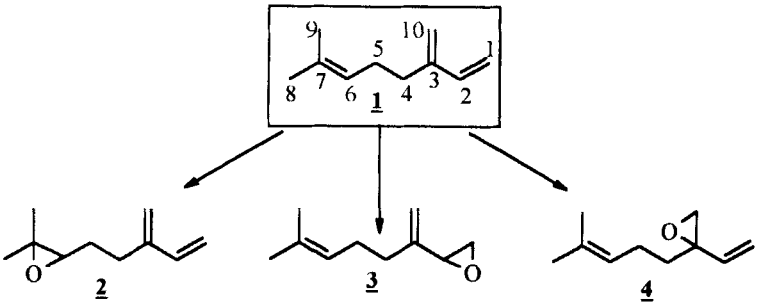
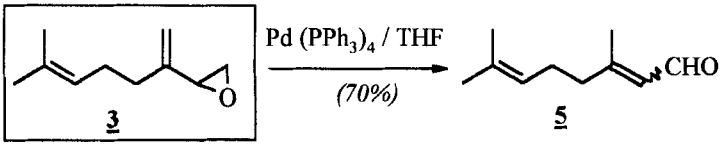


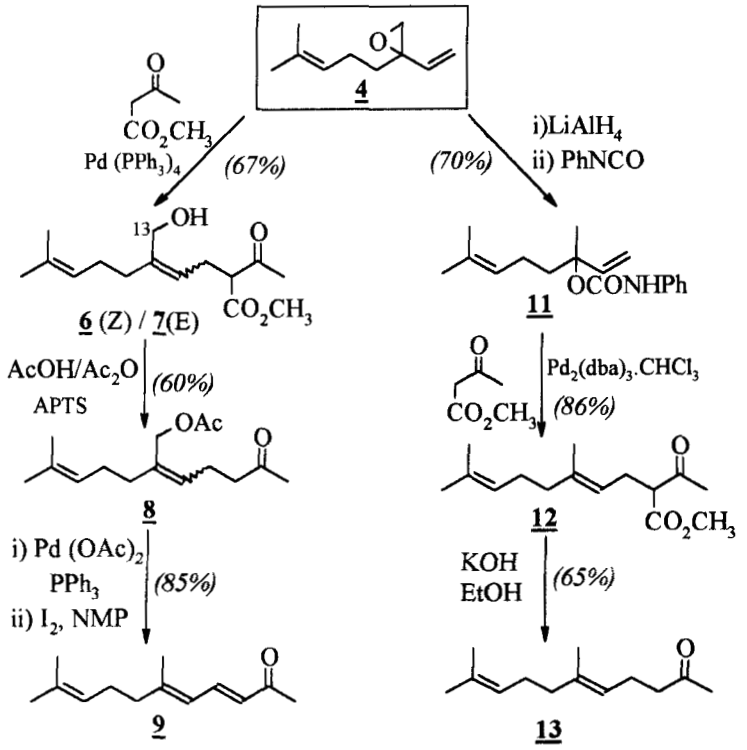
Scheme 1

Under the influence of a catalytic amount of tetrakis (triphenylphosphine)-palladium, myrcene-1,2-epoxide **3** undergoes isomerization[4] to citral **5** in 70% yield (Scheme 2). Citral is a very important compound in perfumery for citrus flavors. It is also industrially used for the large-scale manufacture of vitamin A and carotenoids[5].



Scheme 2

The myrcene-3,10-epoxide **4** (Scheme 3) with its vinyl-epoxide moiety could be selectively alkylated on carbon atom-1 with methyl acetoacetate, using $Pd(PPh_3)_4$ catalyzed neutral reactions[6]. We obtained in 67% isolated yield a mixture (86/14) of 13-hydroxy-β-keto esters **6**(Z) and **7**(E) which could be separated by liquid chromatography. The stereochemistry of the 5,6-double bond was established[7] by ^{13}C-NMR, comparing chemical shifts of the hydroxylated



Scheme 3

carbon atom (C-13). The (Z)-configuration was assigned to compound **6**, whose C-13 carbon atom (δ=60ppm) is more shielded than its (E)-isomer **7** (δ=66.5ppm).

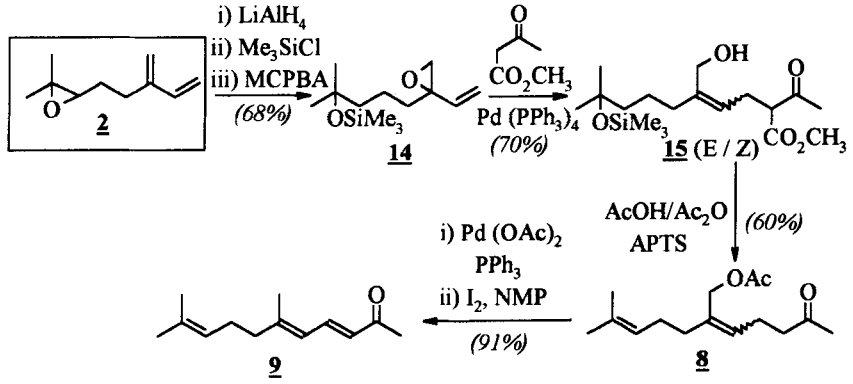
Decarbomethoxylation of the mixture of both isomers **6/7** with the $AcOH/Ac_2O$ system[8] using p-toluenesulfonic acid catalysis resulted in the formation of keto acetate **8** in 60% yield, without loss of configurational purity. Treatment[9] of **8** with $Pd(OAc)_2/PPh_3$ gave a mixture which treated with iodine catalyst in 1-methyl-2-pyrrolidinone (NMP)[10], led to pseudo-ionone **9** in 85% yield. Pseudo-ionone is a precursor of ionones[11], which are components of perfume compositions (violet fragrance) and serve as intermediates in vitamin A synthesis[1d].

The reduction of myrcene-3,10-epoxide **4** by means of lithium aluminium hydride led to linalool **10** in 78% yield. Linalool is used in perfumery (fruity notes) and as an intermediate in the production of vitamin E[1e]. From linalyl phenyl carbamate[12] **11** prepared from linalool **10** (90% yield) we performed palladium-catalyzed homologation reaction[13]. The alkylation with methyl acetoacetate produced in 86% yield β-keto ester **12**[14]. A decarbomethoxylation reaction (KOH/EtOH)[15] led in 65% yield to geranyl acetone **13**. Geranylacetone used in perfumery and in soap perfumes is also an important intermediate in isophytol and vitamin E synthesis[16].

From myrcene-6,7-epoxide **2** we prepared in 68% overall yield the 7-trimethyl-silyloxy-3,10-epoxide **14** (Scheme 4). Treatment of this ene-oxide **14** with methyl acetoacetate in the presence of $Pd(PPh_3)_4$ catalyst gave in 70% yield a mixture (E/Z) of hydroxy β-keto ester **15** in a 3:7 ratio. Decarbomethoxylation ($AcOH/Ac_2O$;APTS) also induced a dealkoxysilylation to give 13-acetoxy geranyl- and nerylacetone **8**. Deacetoxylation in the presence of $Pd(OAc)_2/PPh_3$ and isomerization (I_2, NMP) led to pseudo-ionone **9** in 91% yield.

CONCLUSION

Thus, mono-epoxides **2**-**4**, easily and selectively obtained from myrcene **1**, an industrial raw material, are useful precursors for a new access to citral **5**, linalool **10**, pseudo-ionone **9** and geranyl acetone **13**. These functionalized terpenoids, are key intermediates in the synthesis of perfumes and vitamins.



Scheme 4

EXPERIMENTAL SECTION

Separation and purification of the products were achieved by flash-chromatography (silica gel Merck, 70-230 mesh ASTM). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC 250 (250MHz for ^{1}H and 62.89MHz for ^{13}C) spectrometer using $CDCl_3$ as solvent. Chemical shifts are recorded as δ values in ppm related to internal tetramethylsilane. Mass spectra were obtained with a Micromass VG 7070 F instrument. High-resolution mass spectra (HRMS) data were recorded at an ionizing voltage of 70eV on a VG Micromass 16F. Solvents were freshly distilled from drying agent in a nitrogen atmosphere, before use.

Isomerization of myrcene-1,2-epoxide 3.

To a solution of tetrakis(triphenylphosphine)palladium (23mg, 0.02mmol) and triphenylphosphine (10mg, 0.04mmol) in THF (2mL) was added myrcene-1,2-epoxide **3** (305mg, 2mmol). The reaction mixture was refluxed for 22 hours. After filtration, the crude mixture was purified by flash-chromatography; elution with petroleum ether-ether (6:4) gave citral **5** (213mg, 70% yield).

Alkylation of myrcene-3,10-epoxide 4.

To a solution of tetrakis(triphenylphosphine)palladium (298mg, 0.24mmol) in THF (100mL), was added myrcene-3,10-epoxide **4** (786mg, 5.17mmol). The mixture was stirred for 5min, then methyl acetoacetate (0.75mL, 6.02mmol) was added. After stirring at room temperature for 24 hours, brine was added. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was separated by flash-chromatography.

Elution with petroleum ether-ether (5:5) gave (Z)-isomer **6** (800mg): ^{1}H-NMR (δ): 1.52 (s, 3H), 1.60 (s, 3H), 2.18 (s, 3H, H-1), 3.48 (t, 1H, H-3), 3.66 (s, 3H, -$CO_2C\underline{H}_3$), 4.05 (m, 2H, -$C\underline{H}_2OH$), 4.99 (m, 1H, H-9), 5.09 (t, 1H, H-5). ^{13}C-NMR (δ): 17.6 (C-12), 25.5 (C-11), 26.3 (C-8), 26.6 (C-4), 29.3 (C-1), 35.4 (C-7), 52.4 (-$CO_2\underline{C}H_3$), 59.3 (C-3), 60.0 (C-13), 123.1 (C-5), 123.7 (C-9), 131.6 (C-10), 141.8 (C-6), 169.9 (-$\underline{C}O_2CH_3$), 202.7 (C-2). SM, m/z (relative intensity): 250 (M^+-H_2O, 2%), 69 (100%). Anal. calcd. for $C_{15}H_{24}O_4$: C, 67.16; H, 8.96. Found: C, 67.42; H, 9.07

Elution with petroleum ether-ether (4:6) gave (E)-isomer **7** (130mg): ^{1}H-NMR (δ): 1.53 (s, 3H), 1.60 (s, 3H), 2.16 (s, 3H, H-1), 3.42 (t, 1H, H-3), 3.66 (s, 3H, -$CO_2C\underline{H}_3$), 3.93 (m, 2H, -$C\underline{H}_2OH$), 4.98 (m, 1H, H-9), 5.24 (t, 1H, H-5). ^{13}C-NMR (δ): 17.7 (C-12), 25.7 (C-11), 26.5 (C-8), 26.8 (C-4), 28.2 (C-7), 29.5 (C-1), 52.7 (-$CO_2\underline{C}H_3$), 59.6 (C-3), 66.5 (C-13), 121.2 (C-5), 124.0 (C-9), 132.3 (C-10), 142.1 (C-6), 170.2 (-$\underline{C}O_2CH_3$), 203.1 (C-2). SM, m/z (relative intensity): 250 (M^+-H_2O, 1.5%), 69 (100%). Anal. calcd. for $C_{15}H_{24}O_4$: C, 67.16; H, 8.96. Found: C, 68.02; H, 9.13

Decarbomethoxylation of hydroxy-β-keto ester 6/7.

To a solution of crude hydroxy-β-keto esters (**6**/**7**)(531mg, 1.98mmol) in acetic acid (10mL) and acetic anhydride (0.2mL) was added APTS (45mg, 0.26mmol). The reaction mixture was heated at 70°C for one hour, and then hydrolyzed with water (20mL). After extraction with Et_2O, the organic layers were washed with a NaCl saturated solution and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash-chromatography. Elution (7:3 petroleum ether-ether) gave 13-acetoxy geranyl-and nerylacetone[17] **8** (300mg, 60% yield). To a solution of **8** (300mg, 1.19mmol) in dioxane (3mL) was added $Pd(OAc)_2$ (3mg) and triphenylphosphine (37mg, 0.15mmol). The reaction mixture was stirred for one hour at 80°C. The solvent was evaporated under reduced pressure and the residue was heated at 160°C for one hour with 1-methyl-2-pyrrolidinone (1.16g) and iodine (2mg). The reaction mixture was diluted with Et_2O (100mL), washed with 10% $Na_2S_2O_3$ solution (100mL),10% HCl solution (100mL), brine and dried. After elimination of solvent the residue was purified by flash-chromatography. Elution with petroleum ether-ether (9:1) gave pseudo-ionone[18] **9** (194mg, 85%): ^{1}H-NMR (δ): 1.59 (s, 3H), 1.66 (s, 3H), 1.88 (s, 3H), 2.25 (s, 3H), 5.07 (m, 1H), 5.96-6.09 (m, 2H), 7.33-7.47 (m, 1H). ^{13}C-NMR (δ): 17.5 (C-13), 17.7 (C-12), 25.7 (C-11), 26.3 (C-8), 27.5 (C-1), 40.5 (C-7), 123.2 (C-9), 123.7 (C-5), 128.2 (C-3), 132.3 (C-10), 139.5 (C-4), 151.2 (C-6), 198.2 (C-2). SM, m/z (relative intensity): 192 (M^+, 9%), 69 (100%).

Alkylation of linalool 10.

To a suspension of $LiAlH_4$ (152mg, 4mmol) in Et_2O (2mL) was added at

0°C myrcene-3,10-epoxide **4** (152mg, 1mmol). The reaction mixture was stirred for 16 hours at room temperature. After hydrolysis with H_2O (5mL) and then 5% HCl (2mL), extraction with Et_2O, the solvent was evaporated to give linalool **10** (120mg, 78% yield).

To tris(dibenzylideneacetone)dipalladium-chloroform adduct (103mg, 0.10mmol) and triphenylphosphine (104mg, 0.4mmol) in THF (6mL) were added linalyl phenylcarbamate **11**[12](1.1g; 4.02mmol) in THF (4mL) and methyl acetoacetate (233mg, 2.01mmol). The reaction mixture was stirred for 12 hours at 40°C. After elimination of solvent under reduced pressure, the residue was treated with Et_2O (10mL). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash-chromatography; elution with 9:1 petroleum ether-ether gave **12**(E) (437mg, 86% yield): ^{1}H-NMR (δ): 1.57 (s, 3H), 1.59 (s, 3H), 1.61 (s, 3H), 2.21 (s, 3H, H-1), 3.39 (t, 1H, H-3), 3.71 (s, 3H, -CO_2CH_3), 4.96 (m, 2H, H-5, H-9). ^{13}C-NMR (δ): 17.7 (C-13), 17.8 (C-12), 25.8 (C-11), 26.5 (C-4), 27.1 (C-8), 29.3 (C-1), 39.8 (C-7), 52.4 (-CO_2CH_3), 59.9 (C-3), 119.7 (C-5), 124.0 (C-9), 131.6 (C-10), 138.6 (C-6), 170.1 (-CO_2CH_3), 203.2 (C-2). SM, m/z (relative intensity): 252 (M^+, 2%), 69 (100%). HRMS : calcd. for $C_{15}H_{24}O_3$: 252.1725; found : 252.1726.

Obtention of geranylacetone 13(E).

To EtOH (0.58mL) was added a solution of KOH (174mg) in H_2O (0.29mL) and β-keto-ester **12** (368mg, 1.48mmol). The reaction mixture was stirred at room temperature for 4 hours, acidified with HCl and heated to reflux for 2 hours. After addition of water, the mixture was extracted with Et_2O. The organic

layers were washed with a NaCl saturated solution and dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash-chromatography (9:1 petroleum ether-ether) to give geranylacetone **13**(E) (184mg, 65% yield): ^{1}H-NMR (δ): 1.52 (s, 3H), 1.54 (s, 3H), 1.61 (s, 3H), 2.07 (s, 3H, H-1), 5.00 (m, 2H, H-5, H-9). ^{13}C-NMR (δ): 16.0 (C-13), 17.7 (C-12), 22.3 (C-4), 25.7 (C-11), 26.6 (C-8), 30.0 (C-1), 39.6 (C-7), 44.0 (C-3), 122.5 (C-9), 124.2 (C-5), 131.4 (C-10), 136.4 (C-6), 207.8 (C-2).

Obtention of 3,10-epoxy-7-trimethylsilyloxy myrcene 14.

To a suspension of $LiAlH_4$ (811mg, 21.3mmol) in Et_2O (10mL) was added at 0°C, myrcene-6,7-epoxide **2** (2.163g, 14.2mmol) in Et_2O (15mL). The solution was stirred for 4 hours at room temperature, hydrolyzed with a 5% H_2SO_4 solution (50mL) and extracted with Et_2O. The organic layers were washed with a NaCl saturated solution, dried ($MgSO_4$) and evaporated under reduced pressure to give myrcenol (1.76g, 80%yield). To this crude product was added at 0°C, CH_2Cl_2 (40mL), triethylamine (5mL), 4-dimethylaminopyridine (209mg, 1.7mmol) and trimethylchlorosilane (2.88mL, 22.8mmol). The stirring was kept for 24hours at room temperature. The reaction mixture was washed with brine, the organic layers were dried ($MgSO_4$) and concentrated to give 7-trimethylsilyloxy myrcene (2.27g, 88% yield). From 7-trimethylsilyloxy myrcene (815mg, 3.6mmol), the epoxidation with m-chloroperbenzoic acid, according to usual work-up, gave after purification by flash-chromatography (98:2 petroleum ether-ether) 3,10-epoxy-7-trimethylsilyloxy myrcene **14** (840mg, 96% yield): ^{1}H-NMR (δ): 0.03 (s,9H, $(CH_3)_3Si$), 1.14 (s, 6H), 2.64 (m, 2H, H-10), 5.20 (m, 2H, H-1), 5.71 (m, 1H, H-

2). ^{13}C-NMR (δ): 2.5 (($\underline{C}H_3)_3Si$), 19.8 (C-5), 29.6 (C-8), 29.7 (C-9), 33.8 (C-4), 44.2 (C-6), 54.7 (C-10), 58.5 (C-3), 73.6 (C-7), 116.0 (C-1), 137.4 (C-2). SM, m/z (relative intensity): 227 (M^+-CH_3^-, 1%), 131 (100%).

Alkylation of 3,10-epoxy-7-trimethylsilyloxy myrcene 14.

From 3,10-epoxy-7-trimethylsilyloxy myrcene **14** (1.210mg, 5mmol), tetrakis-(triphenylphosphine)palladium (289mg, 0.25mmol) and methyl acetoacetate (1.16g, 10mmol) in THF solution (80mL), according to the previously described procedure, we obtained 10-trimethylsilyloxy-β-keto ester **15** (E/Z 3:7) (125 mg, 70% yield):

15 (E):^{1}H-NMR (δ): 0.00 (s, 9H), 1.10 (s, 3H), 2.12 (s, 3H, H-1), 3.27 (m, 1H, H-3), 3.72 (s, 3H, -$CO_2C\underline{H}_3$), 3.91 (m, 2H, H-13), 5.23 (t, 1H, H-5). ^{13}C-NMR (δ): 2.6 (($\underline{C}H_3)_3Si$), 23.0 (C-8), 26.0 (C-4), 28.3 (C-7), 29.8 (C-1), 29.9 (C-11, C-12), 44.6 (C-9), 52.9 (-$CO_2\underline{C}H_3$), 60.6 (C-3), 66.1 (C-13), 73.8 (C-10), 121.2 (C-5), 141.9 (C-6), 168.7 (-$\underline{C}O_2CH_3$), 203.1 (C-2). **15** (Z): ^{1}H-NMR (δ): 0.00 (s, 9H), 1.10 (s, 6H), 2.14 (s, 3H, H-1), 3.36 (m, 1H, H-3), 3.70 (s, 3H, -$CO_2C\underline{H}_3$), 4.02 (m, 2H, H-13), 5.07 (t, 1H, H-1). ^{13}C-NMR (δ): 2.6 (($\underline{C}H_3)_3Si$), 22.7 (C-8), 26.3 (C-4), 29.8 (C-1), 29.9 (C-11, C-12), 35.8 (C-7), 44.3 (C-9), 53.0 (-$CO_2\underline{C}H_3$), 59.8 (C-13), 60.6 (C-3), 73.9 (C-10), 123.3 (C-5), 141.9 (C-6), 168.8 (-$\underline{C}O_2CH_3$), 203.2 (C-2).

Obtention of pseudo-ionone 9.

From 7-trimethylsilyloxy-β-keto ester **15** (531mg, 1.33mmol), according to the previously described protocols (decarbomethoxylation and deacetoxylation), we obtained pseudo-ionone **9** (279mg, 54% overall yield).

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