Reaction of (+)-Maaliol and (-)-Guaiol with Lead Tetraacetate

Shashikumar K. Paknikar[1,2,*] and Joydeep Bhattacharjee[1]

[1]*Department of Chemistry, Goa University, Goa, 403206, India and* [2]*Prof. S.C. Bhattacharyya Organic Synthesis Laboratory, VerGo Pharma, Research, Verna, Goa, 403722, India*

Abstract: Lead tetraacetate oxidation of (+)-maaliol and (-)-guaiol has led to the production of one trinor-4,5-seco eudesmane and two 4,5-secoeudesmane compounds from maaliol and 1,2-dehydroguaioxide from guaiol.

This paper is dedicated to the memory of Dr. Alan F. Thomas whose scientific goodwill and invaluable help in providing spectroscopic data, lively discussions, and supporting our research group in all possible ways.

Keywords: Lead tetraacetate oxidation, (+)-Maaliol, (-)-Guaiol, 4,5-Secoeudesmane, 1,2-Dehydroguaioxide.

1. INTRODUCTION

Among natural products from terrestrial and marine origin, sesquiterpenes occupy a prime position due to a wide range of compounds having diverse carbon frame works and biosynthethetically derived through molecular rearrangements, fragmentation resulting in fission of sigma bonds and olefinic linkages. Whenever a new carbon frame work is derived via ring cleavage it is referred as seco (e.g. 4,5-secoeudesmane) and when the skeletal change is observed by loss of carbon atom the prefix nor is used (e.g. noreudesmane, norguaiane). Biosynthetic pathways, both hypothetical and proven for structure related natural products, can serve as more direct routes for their synthesis from a suitable natural product precursor with established absolute stereochemistry. The simplest representatives of 4,5 secoeudesmane and trinor guaiane are 4,5-diketo-11-hydroxy-eudesmane **1** and trinor-guaidiene **2**. [1-2] respectively (Figure **1**).

Umbellifolide, **3** the extremely bitter diketo -γ-lact-one, represents the first well chracterized 4,5-seco eudesmane sesquiterpene, and was isolated from *Artemisia umbelliformis* Lam in 1983 [3] . Its absolute stereochemistry has been established by x-ray crystall-ography. From the same source Garriboldi and co-workers [3] isolated the hydroperoxy eudesmanolides **4** and **5** and suggested they were precursors for **3**, thus indicating the mode of cleavage of C4-C5 bond of the eudesmane skeleton. Several reports [4-6] have appeared describing new members of this group. Another small and rare group of compounds is formed by cleavage of the C7-C11 bond of the guaiane skeleton resulting in the loss of three carbon atoms and the resultant compounds are grouped under tri-norguaines [2,7-8]. This paper reports the synthesis of 4,5-seco eudesmane and tri-norguaine skeletons using the tertiary hydroxyl group of (+)-maaliol **6** [9] and (-)-guaiol **7** [10] as substrates and the results obtained from lead tetra-acetate oxidation of **6** and **7** (Figure **2**).

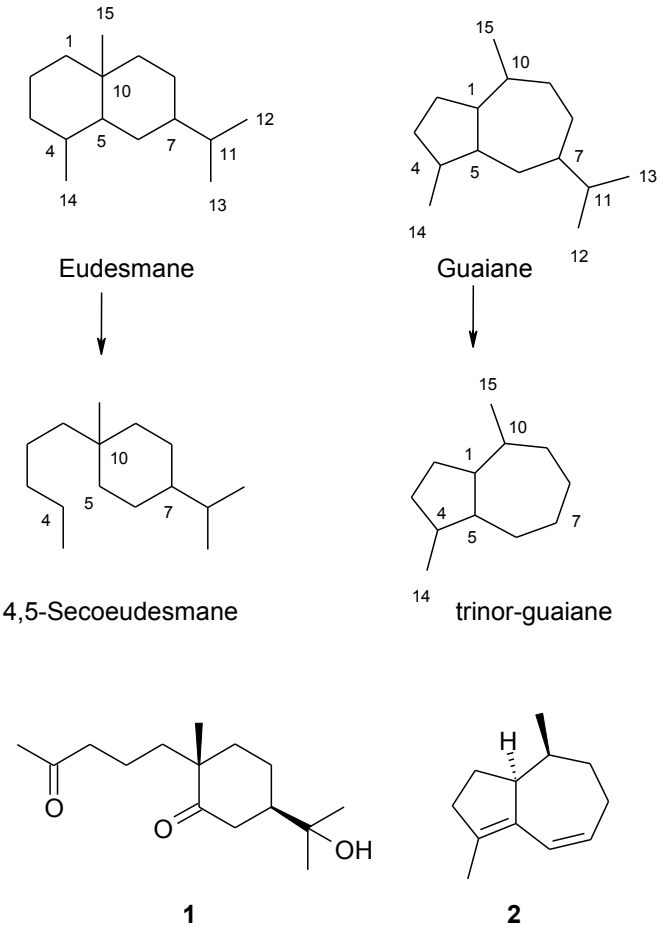


Figure 1:

*Address correspondence to this author at Prof.S.C.Bhattacharyya Organic Synthesis laboratory, Vergo Pharma Research, Verna, Goa, 403 722, India; E-mail: skpakni@yahoo.co.in

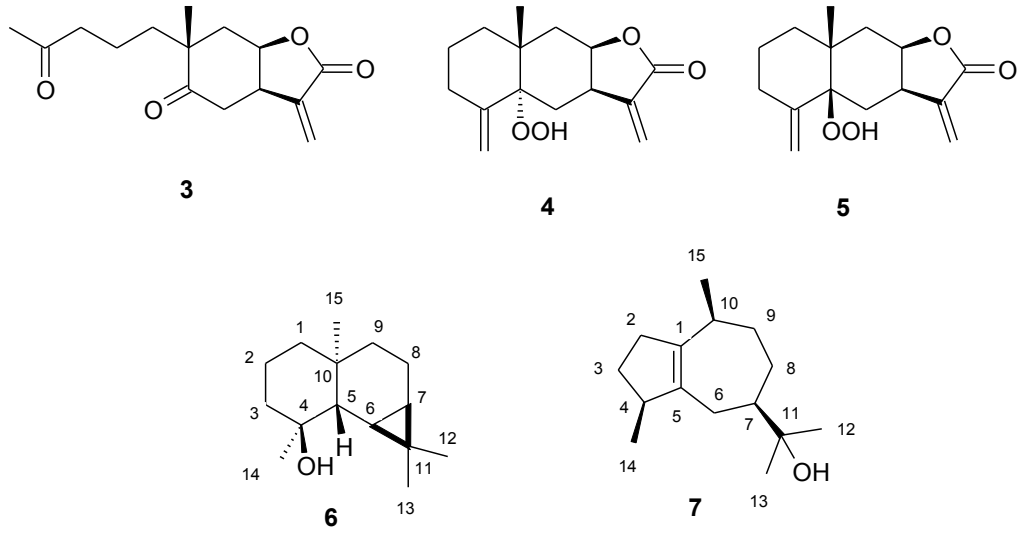


Figure 2:

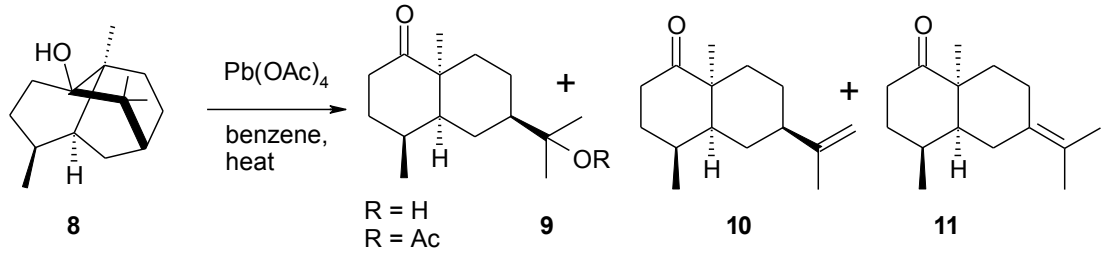


Figure 3:

2. RESULTS AND DISCUSSION

2.1. Oxidation of (+)-Maaliol

Lead tetraacetate is well-known for its ability to oxidize monohydric alcohols and a variety of other functional groups. [11]. Thomas and Ozainne [12] reported regiospecific fragmentation of patchouli alcohol **8** (patchoulol) by lead tetra-acetate in benzene and characterized three oxidation products **9**, **10** and **11** derived via β-cleavage. Based on their findings, it seemed attractive to subject (+)- maaliol **6** to lead tetra acetate oxidation to obtain products based on 4,5-secoeudesmanes in a one pot reaction.

It was of interest to determine the path of transformation, if it involved a cyclopropyl-carbinyl cation intermediate (Path a, Scheme **3**) to give the oxidation products or not. Maaliol **6**, on LTA oxidation in benzene followed by the usual workup yielded a brown oil, which on column chromatography over silica gel furnished two fractions. The GC-MS of the first fraction showed the presence of two compounds, one major compound A (92 %) and a minor compound-B (8 %). Compound A was obtained as a colourless oil using preparative GLC. The GC-MS of the second fraction also gave a mixture composed of compound-C (82 %) and unreacted maaliol (18 %). Compound C was also obtained by preparative GLC. The IR spectrum of compound A exhibited absorption bands at ν_{max} 2950, 1716, 1642 (terminal methylene), 1716 (CH_3CO-) and 741 (*cis*-disubstituted double bond) cm^{-1}. The ^{1}HNMR spectrum in $CDCl_3$ showed three methyl singlets at δ_H 0.98 (H-15), 1.75 (H-12) and 2.15 (H-14). The olefinic methylenes were observed at δ_H 4.62 and 4.76 (brs, 1H each, H-13a and H-13b) and *cis*-disubstituted olefinic methines at 5.48 and 5.49 ppm (d, 1-H each, *J* = 10.0 Hz, H-5 and H-6) . The data imply three double bond equivalents Therefore the compound must be monocyclic. The tricyclic skeleton of **6** was converted into a monocyclic skeleton by the cleavage of the C4-C5 and C6-C11 bonds. The ^{1}H NMR data of **12** when compared to those of maaliol **6** [13](^{1}HNMR spectra (300 MHz, $CDCl_3$, δ) 0.51 (1H,dd, J=5.1, 7.2 Hz, H-6), 0.63(1H, dd, J=7.2, 7.2Hz, H-7), 0.87 (3H, s, H-12), 0.94 (3H, s, H-13), 1.05(3H, s, H-15),1.26 (3H, s, H-14) shows the C-10 methyl of maaliol **6** has remained intact and cleavage of C4-C5 and C6-C11 resulted in **12**. Comparable chemical shifts were reported [14] for a structurally similar compound p-mentha-5,8-diene-2-ol for olefinic hydrogens and isopropenyl methyl. Its EI

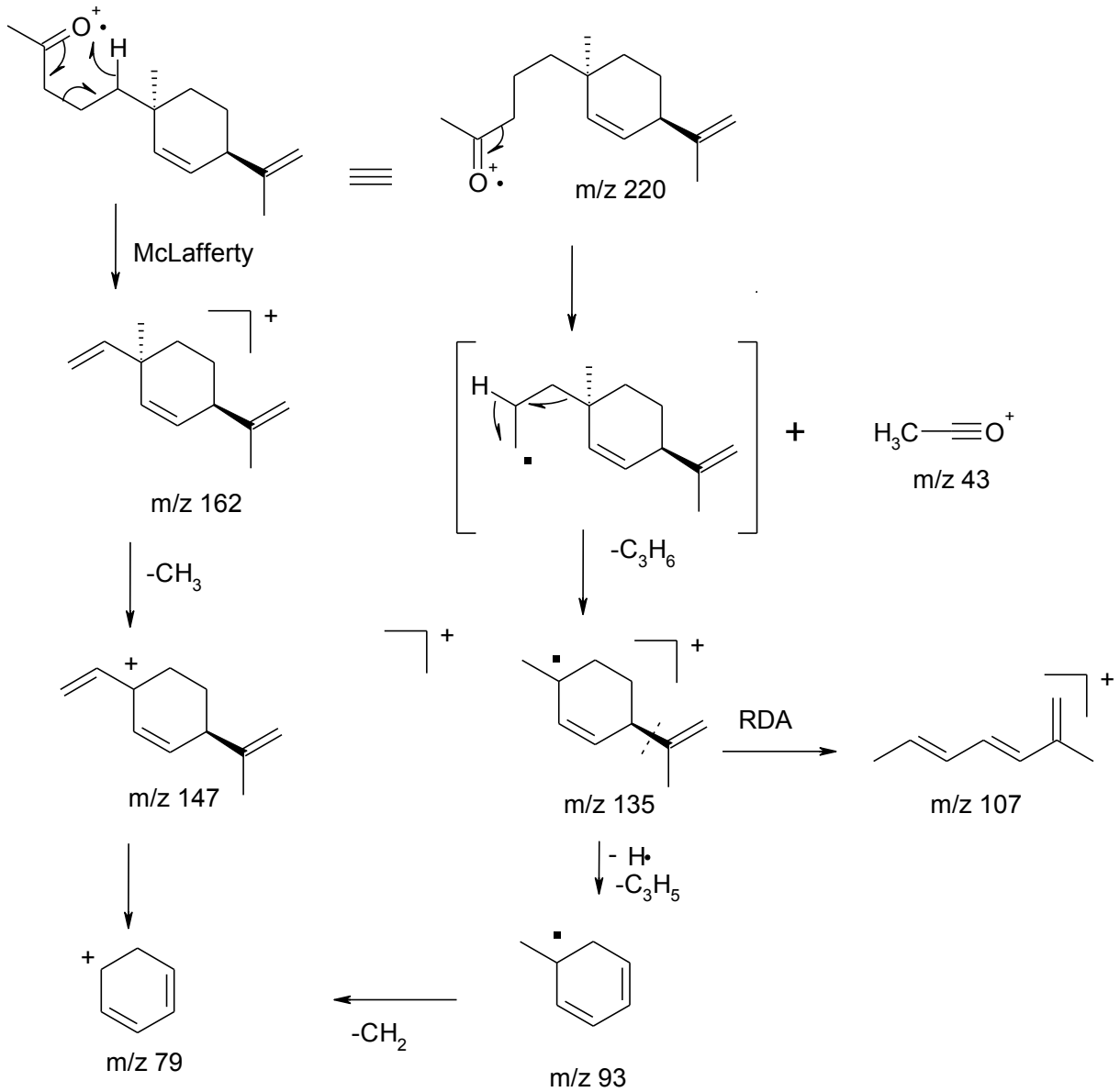
mass spectrum showed the molecular ion at m/z 220 and the significant mass fragments are given in Scheme **1**.

The minor component of fraction-1, compound B was not isolated in sufficient quantity for spectral characterization but could be identified as **13** by its characteristic mass spectral fragmentation pattern and M^+ = 194 corresponding to $C_{12}H_{18}O_2$. The major fragments are presented in Scheme **2**.

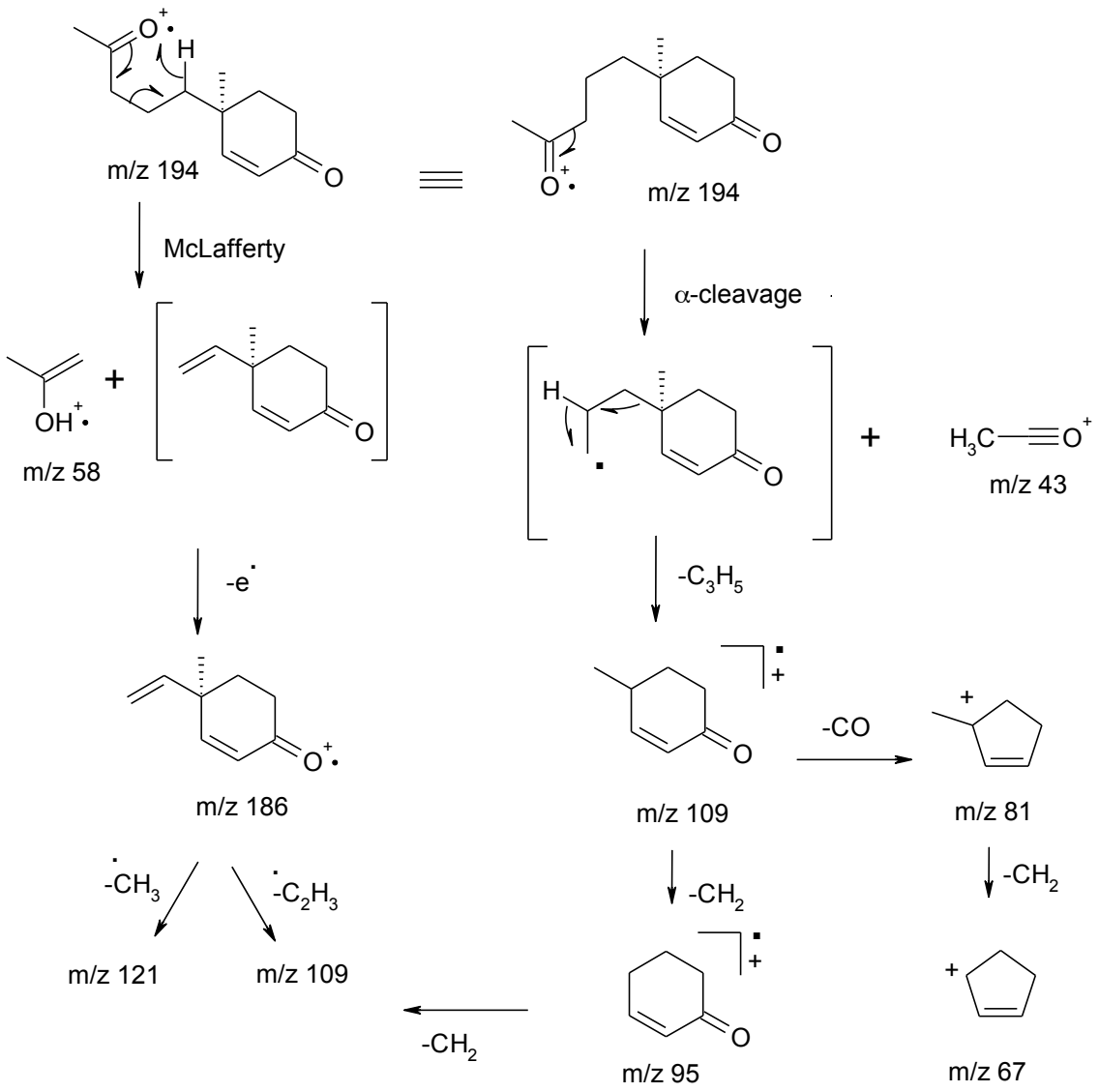
A small amount of **13** was also observed in the proton spectrum of **12** with characteristic chemical shifts at δ_H 1.14, s, 3H, H-15; 2.16, s, 3H, H-14; 5.87, d, 1H, J =10Hz, H-6 and 6.68, (d, 1H, J = 10Hz, H-5) ppm. The reported chemical shifts [15] of the tertiary methyls and olefinic protons of 4,4-dimethylcyclohex-2-ene-1-one were in agreement with those observed for **12**.

The formation of **13** can be explained by the oxidation of the isopropylidine isomer of 12 (not isolated but expected) either as a result of further oxidation by LTA or by auto oxidation as shown in Scheme **3** and supported by literature reports [16-17].

The IR spectrum of compound C showed absorption bands at ν_{max}1728 (broad) and 1257cm^{-1} due to an acetate group. The absence of an isopropenyl group and the presence of five methyl singlets in its ^{1}HNMR spectrum at δ_H 0.95(H-15), 1.38 (H-12), 1.4 (H-13), 1.97(H-17) and 2.13 (H-14) ppm suggested compound



Scheme 1:

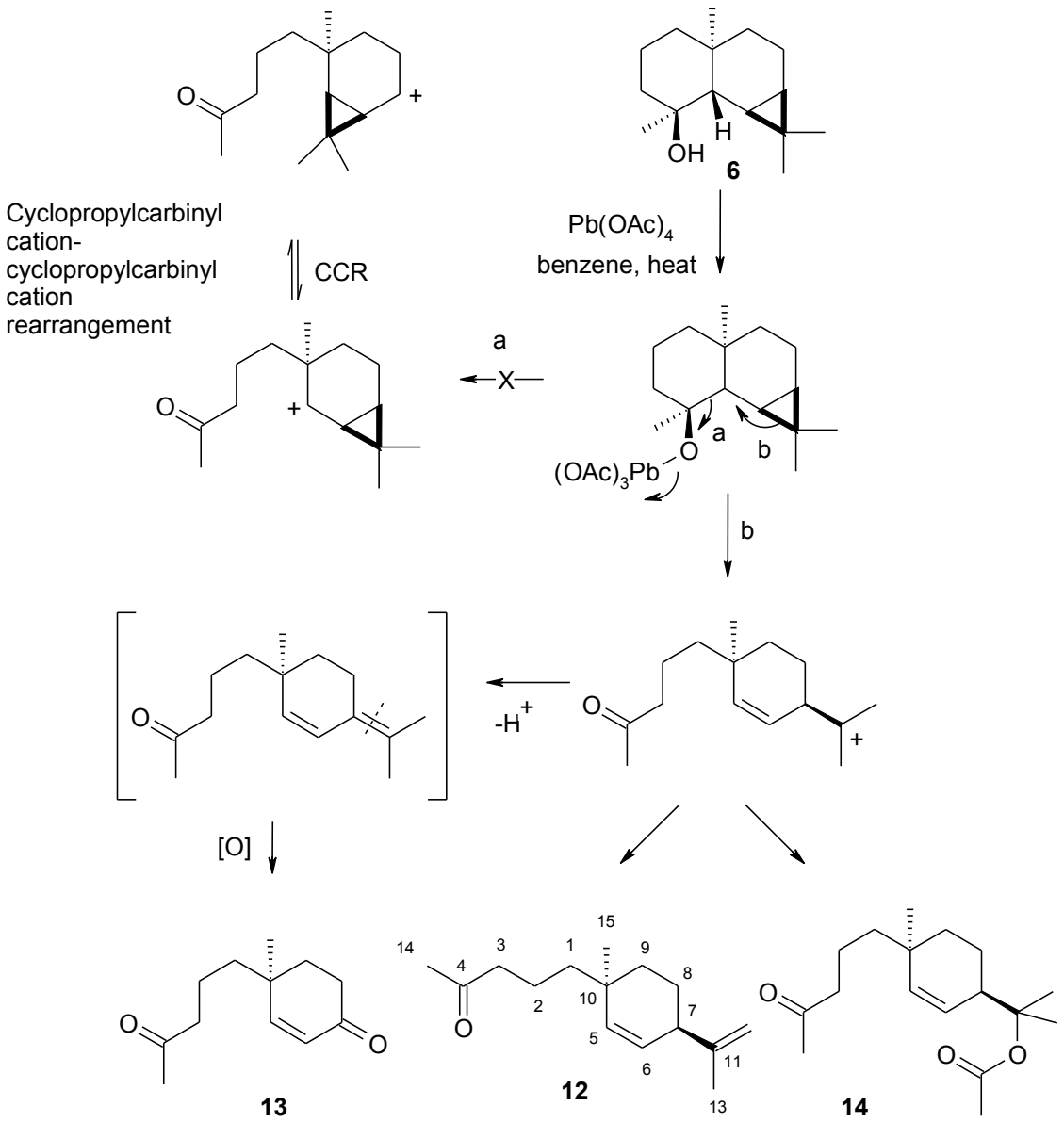


Scheme 2:

C to have a molecular formula $C_{17}H_{28}O_3$. The chemical shifts of the olefinic protons were nearly identical and were observed at δ_H 5.48 (d, J=10 Hz, H-5) and 5.49(d, J=10 Hz, H-6) ppm while the chemical shifts of the methylene protons were observed between 2.35-2.46 (m, H-7 H-3a and H-3b). Its mass spectrum did not show the molecular ion at m/z 280 but the base peak was observed at m/z 220 (M+. -CH_3COOH). The mass spectrum was identical with that of **10** thus confirming structure **14** for compound C. A rational mechanism for the formation of **12**, **13** and **14** from maaliol **6** is presented in Scheme **3**. No product derived via a cyclopropylcarbinyl cation rearrangement (CCR) [18] was detected. The oxidation products **12**, **13** and **14** were formed by a concerted mechanism (path b) without involvement of a cyclopropropyl carbinyl cation intermediate.

2.2. Oxidation of (-)-Guaiol, 7

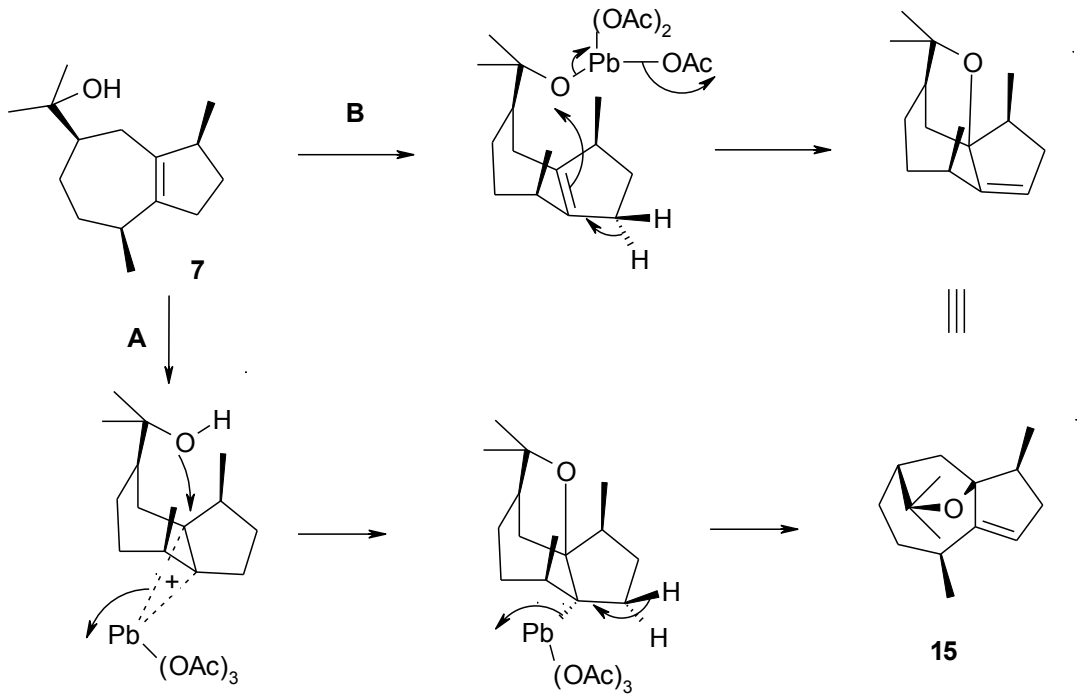
Lead tetraacetate oxidation of (-)- guaiol **7** and the unambiguous characterization of 1,2-dehydroguaioxide **15** was reported by Ourisson and Ehret [19]. Besides the formation of 1,2-dehydroguaioxide there was no mention of the formation of products derived *via* β–cleavage. It was of interest to find out the relative reactivities of the 1,5-tetrasubstituted double bond and the tertiary hydroxyl group at C-11 towards LTA. The aim of this investigation, subjecting guaiol to lead tetraacetate oxidation, was to synthesise a trinorguaiene **13** and related compounds by cleavage of the C7- C11 bond (Scheme **4**) and secondly obtain NMR data for 1,2-dehydroguaioxide **15**. Oxidation of guaiol with lead tetraacetate in benzene was therefore carried out using the experimental conditions as for maaliol **4**.



Scheme 3:

The crude oxidation product was obtained as a brown oil and was purified by careful chromatography over silica gel. The only product isolated in 20% yield was identified as 1,2-dehydroguaioxide **15**. No product having trinor-guaiane skeleton was isolated. This clearly confirmed that a five membered oxide intermediate is the preferred pathway. In another report formation of α-agarofuran **17** was observed on LTA oxidation of 10-epi-γ-eudesmol **16** in anhydrous benzene [20]. Trinor-eudesmane compounds resulting by β-cleavage were not found. This clearly shows that besides the solvent, the conformations play a very important role in the products formed. Both guaiol and 10-epi-γ-eudesmol have a common part structure, a tetra substituted γ-δ olefinic linkage with respect to hydroxy-isopropyl group.

The rigid conformations of guaiol shows the proximity of the hydroxy isopropyl group and γ–δ double bond. Two mechanisms can account for the formation of 1,2-dehydroguaioxide **15** from guaiol **7**. The preferred mechanism (path A, Scheme **4**) involves the initial attack of LTA with the 1,5 olefinic linkage of guaiol **7** followed by five member oxide ring formation and elimination of the lead intermediate to 1,2-dehydroguaioxide **15** . In the suggested mechanistic path B, (Scheme **4**) the initially formed lead ester gets converted to guaioxide where fragmentation is totally suppressed which explains the absence of trinor-guaianes. The same sequence of steps may have led to the formation of α-agarofuran **17** from 10-epi-γ-eudesmol **16**.



Scheme 4:

3. EXPERIMENTAL

Isolation of (+)-maaliol: (+)-maaliol was isolated from Indian valerian root oil [21].The oil was fractionated into three parts and the fraction ,b.p. 45-96 /5mm was dissolved in ether and separated into acidic and neutral fractions. The neutral fraction on standing in deep freeze deposited a crystalline solid which on further purification by sublimation under vacuum gave (+) -maaliol ,m.p.104, $[\alpha]_D$ + 21.7°(ethanol,c,5.0), It was identified by mixed m.p with an authentic sample (courtsey Dr. V.K. Sood) and comparison of spectral data given in literature [13]IR, v_{max}, (cm^{-1}): 3496,2915, 2855, 1457, 1383,1100.

Oxidation of (+)-maaliol with lead tetra-acetate: maaliol (2.22 g, 0.01 moles) was added to a mixture of lead tetraacetate (1.5 g) in benzene (25 mL) and the mixture refluxed for 2h. Excess of LTA was decomposed by careful addition of ethylene glycol. The mixture was cooledand the benzene layer was separated and washed with $NaHCO_3$, water and brine. The red brown oil obtained by removal of benzene was chromatographed on 60-80 mesh silica gel. The column was eluted with petroleum ether and polarity was increased using ethyl acetate. The separation was monitored by TLC and visualization of spots by alcoholic solution of phosphomolybdic acid. The GC of fraction1 showed it to be a mixture of two compounds **12** (92 %) and **13** (7 %). The major one **12** was purified by preparative GC on carbowax and obtained as a colourless oil. The mass spectrum for fraction 1 was taken by GC-MS coupling from a Supelcowax column. GC of fraction -2 showed it to be mixture of two substances, **14** (82%) and unreacted maaliol (14 %). Compound **14** was isolated by preparative GC on carbowax.

Compound 12

IR v_{max}, neat (cm^{-1}) : 2950, 1716, 1642, 1452, 1369, 1222, 1165, 891, 741.

^{1}HNMR spectra (300 MHz, $CDCl_3$, δ) 0.98 (3H, s, H-15,), 1.75 (3H, s, H-12,), 2.15 (3H, s, H-14), 1.2 -1.38 (m, 4H, H-1a, H-1b, H-9a, H-9 b),1.5 -1.62 (m, 3H, H-2 a, H-2 b, H-8b), 2.35-2.46 (m, 3H, H-8 a, H-3a and H-3b), 2.62 (t, 1H, H-7), 4.62 and 4.76 (bs, 1H each, H-13 a and H-13b), 5.48 and 5.49 (d, 1-H each, J= 10.0 Hz).

EIMS, m/z(rel.Int.): 220(M+,)(2), 162(30), 147(12), 135(97), 107(85), 93(95), 85(25), 79(75), 67(15), 55(25), 43(100).

Compound 13

EIMS, m/z (rel. Int.): 194(M+) (5), 179(8), 136(20), 123(30), 109(52), 95(40), 79(50), 67(38), 53(20), 43(100).

Compound 14

IR, v_{max}, neat (cm^{-1}): 2950, 1728, 1462, 1367, 1257, 1137, 1019, 941, 737.

^{1}HNMR spectra (300 MHz, $CDCl_3$, δ ppm) 0.90(s, 3H, H-14), 1.38 (s, 3H, H-12), 1.40 (s, 3H, H-13), 1.97(s, 3H, H-17) and 2.13 (s, 3H, H-15),1.28-1.36 (m, 4H), 1.5 -1.62 (m, 4H), 2.35-2.46 (m, 3H, H-7, H-3a and H-3b), 5.48 (d, *J* = 10 Hz, H-5) and 5.49(d, *J* = 10 Hz, H-6).EIMS, m/z (rel. Int.): 220 (M^+ -CH_3COOH) (8), 162 (28), 135 (97), 119 (18), 107 (50), 93 (15), 85 (15), 79 (50), 43 (100).

Isolation of (-)-guaiol: (-)-guaiol was isolated from Guaic wood oil, Paraguay (courtsey Merck, India). The oil was stirred in hexane and left in the deep freeze for few days. The solid obtained was crystallised from hexane, fine needles, 91-92 degree C, $[\alpha]_D$ -28^o (ethanol, c.5.0). It was identified by physical properties and comparison of spectral data given in literature [22]. IR, v_{max}, KBr(cm^{-1}): 3400, 1460, 1385,1365,1150,920,881, 821. ^{1}HNMR spectra (300 MHz, $CDCl_3$, δ) 0.95 (3H,d,J=7.0),0.98 (3H,d, J=7.0),1.17(3H,s),1.19 (3H,s).

Oxidation of (-)-guaiol: Guaiol (2.24 g, 0.01 mol) was added to a mixture of lead tetra acetate (1.5 g) and benzene (25 mL) and mixture was refluxed fo 2 h. Excess of LTA was decomposed by careful addition of ethylene glycol. The mixture was cooled, benzene layer was separated and washed with $NaHCO_3$, water and brine. Concentration afforded an oil which was purified by column chromatography over silica gel using combination of petroleum ether and ethyl acetate as eluent. Colorless oil (0.43 g, 20 %) of 1,2-dehydroguaioxide**15**.

^{1}HNMR (300 MHz ,$CDCl_3$,δ ppm): 1.12 d, 3H, J= 7 Hz, H-14), 1.17 (d, 3H, J= 7Hz, H-15), 1.20 (s, 3H, H-12), 1.35 (s, 3H, H-13), 1.50 (m, 1H, H-8a), 1.50 (m, 1H, H-6a), 1.79(m, 1H, H-6b), 1.81(m, 1H, H-9a), 1.90 (m, 1H, H-8b), 1.98(m, 1H, H-4), 2.00(m, 1H, H-7), 2.00(m, 1H, H-9b), 2.15(m, 1H, H-3a), 2.18(m,1H, H-3b), 2.30(m, 1H, H-10), 5.45(s, 1H, H-2).

^{13}CMR (75 MHz, $CDCl_3$, δ ppm): 13.2 (q, C-15), 20.5 (q, C-14) , 23.6(q, C-12), 31.1(q, C-13), 31.4 (t, C-8), 33.3(d, C-10), 33.8 (t, C-6), 38.1(t, C-3), 38.4 (t, C-9), 42.5 (d, C-7), 45.1(d, C-4), 81.8(s, C-11), 93.5(s, C-5), 123.8 (d, C-2), 153.6(s, C-1).

Mass m/z (rel. int.): 220 (M^+) (80), 205 (100), 187 (25), 177 (15), 159 (32), 147 (62), 131 (25), 119 (45), 105 (45), 91 (65), 79 (38), 69 (35), 55 (65), 43 (85).

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