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AN IMPROVED SYNTHESIS OF (±)-DIHYDROACTINIDIOLIDE[1]

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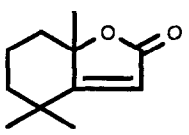
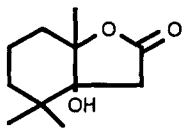
*Summary: An improved synthesis of (±)-aeginetolide (**2**) and (±)-dihydroactinidiolide (**1**) from 2,6,6-trimethyl-1-cyclohexene-1-acetaldehyde (**4**) has been achieved.*

Dihydroactinidiolide (**1**) is a C_{11}-terpenic lactone which is biosynthetically derived from carotenoids. First isolated from the leaves of *Actinidia polygama*[3] and then from black tea,[4] it has also been found in the scent-gland secretion of the red fox[5] and in marine sediments.[6] It is a pheromone component of the red fire ant[7] and a growth inhibitor of seed germination.[8]

Our earlier interest in **1** was due to our discovery[9] of this lactone in tobacco leaves. We have developed renewed interest in **1** and related compounds (e.g., **2** and **3**) in connection with our recent studies on marine products from the Indian Ocean.[10] Loliolide (**3**)[11] and its derivatives[12] have been reported in marine organisms from both the East and West coasts of the Indian peninsula.



(1)



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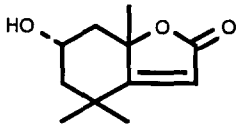
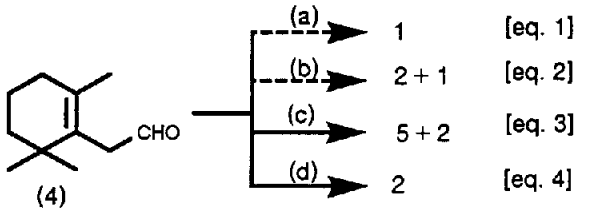


(3)

The synthesis of **1** has been reported by several groups[13,14] including us.[9] During our current studies on dihydroactinidiolide and aeginetolide (**2**), we were interested in an efficient single step synthesis of these lactones from a commercially available aldehyde, **4**, by an "unprecedented reaction" (eq. 1 and 2) as reported by Nickson.[14] But, our attempts to obtain (**1**) or (**2**) under the conditions described[14] have been unsuccessful.[15]

We have observed that when **4** was heated under reflux with 3 equiv. of commercial *m*-chloroperbenzoic acid (*m*-CPBA) of 50-60% purity in $CHCl_3$ for 20 h, an epoxyalcohol (**5**) was obtained as the major product in addition to varying amounts of **2** (eq. 3). No dihydroactinidiolide (**1**) could be isolated from this reaction even with *m*-CPBA of 100% purity.

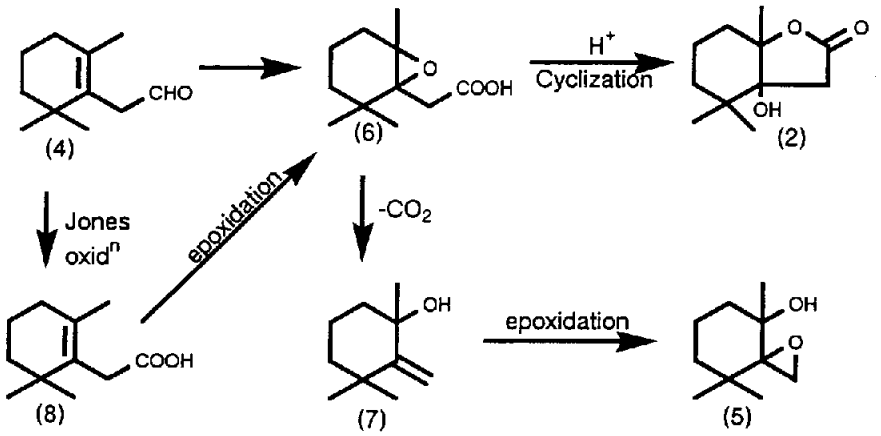


(a) *m*-CPBA (2.2 mol), $CHCl_3$, reflux, 17 h, 83% ; (b) *m*-CPBA (2.2 mol), CCl_4, r.t., 3 h., ca. 85% (c) *m*-CPBA (50-60%, 3.0 mol), $CHCl_3$, reflux, 20 h, ca.70%; (d) *m*-CPBA (50-60% , 2.3 mol), $CHCl_3$, *p*-TSA (100 mg), r.t., 1 h (reflux, 20 min), 70-80%.

An examination of the product profile during the course of this oxidation reaction by ^{1}H-NMR spectroscopy was undertaken. It was observed that the epoxy acid (**6**), which is formed rapidly, is slowly decarboxylated to an allylic alcohol (**7**) that is epoxidized to **5**. The epoxy acid (**6**) undergoes fast cyclization to **2** in presence of strong acids (e.g., *p*-toluenesulphonic acid).[16]

Jones oxidation of **4** to **8**[16] followed by its epoxidation with one equiv. of *m*-CPBA led to the epoxy acid, **6**. When **6** was oxidized further with *m*-CPBA, the same products were obtained as in the oxidation of **4** (Scheme 1). This confirms the role of **6** as an intermediate in the oxidative pathway from **4** to **2**.

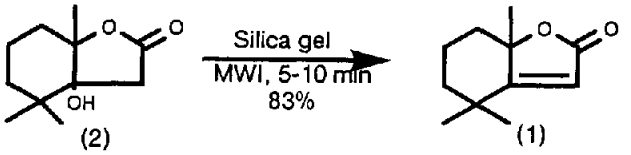
Scheme 1



Based on the foregoing, we have devised a single step synthesis of aeginetolide (**2**). This was accomplished by the reaction of **4** with *m*-CPBA (50-60% pure, 2.3 equiv.) in $CHCl_3$ in presence of a catalytic amount of P-TSA (or, triflic acid) at room temperature for 1 h or at reflux for 20 min in 70-80% yield (eq. 4). The use of conc. HCl, however, reduced the

yield of the product.

The dehydration of **2** to the target compound **1** has been achieved earlier by heating **2** with aqueous NaOH, at 60°C for 24 h or with $SOCl_2$ and pyridine at room temperature for 5 h.[17] Recently several laboratories including our own have reported the acceleration of organic reactions under microwave irradiation either in homogeneous solutions[18] or in the solid state.[19] We have observed expeditious and convenient dehydration under microwave irradiation (MWI) of **2** supported on silica gel. Thus irradiation of **2** for 5-10 min in a commercial microwave oven at high power level (1.0 Kw) produced **1** in about 80% yield (eq. 5).



[eq. 5]

Procedure:

Epoxyalcohol (5) : To a solution of **4** (85% pure, 5g, ca. 25mmol) in $CHCl_3$ (20 mL) under reflux was added dropwise a solution of *m*-CPBA (50-60% pure, 25g, 73 mmol) in $CHCl_3$ (150 mL). The reaction mixture was heated under reflux for 20 h and cooled to rt. The precipitated solid was filtered and the organic layer was washed successively with 10% $NaHSO_3$, 10% NaOH and water. The residue obtained after removal of $CHCl_3$ was dissolved in hexanes and refrigerated; aeginetolide (**2**, 170mg) precipitated. Concentration of the mother liquor followed by chromatography over silica gel gave **5** (2.8g).[20]

(±)-Aeginetolide (2): To a solution of **4** (85% pure,0.85g, 4.3 mmol) in $CHCl_3$ (25 mL) was added *m*-CPBA (50-60% pure, 3.5 g, 10 mmol) at room temperature; an exothermic reaction was observed. *p*-Toluenesulphonic acid (100 mg) was introduced and the reactants were stirred at rt for 1 h. The precipated solid was dissolved in 50 mL of $CHCl_3$ and the solution washed with 10% NaOH followed by water. Evaporation of the solvent gave **2** (700 mg, 81%) with spectral data comparable to those reported for aeginetolide.[14]

(±)-Dihydroactinidiolide (1): Aeginetolide **2** (400 mg) adsorbed on silica gel (230-400 mesh, 10g) was placed in a beaker covered with a petri dish and heated in a microwave oven (GE, 1KW) at high power level for 5-10 min. The product, **1** (300 mg, 83%), was obtained by eluting with $CHCl_3$ and evaporating the solvent. The spectral data on **1** matched those recorded for dihydroactinidiolide.[14]

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20. Colorless liquid, i.r. (neat) 3503 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.87 (3H,s), 1.09(3H,s), 1.32(3H,s), 1.40 -1.90(6H,m) 2.43(1H,bs), 2.73(1H,d,J=4.5Hz), 2.88(1H,d,J=4.5Hz); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 19.6, 25.9, 26.0, 34.4, 39,5, 40.4, 46.0, 66.4 and 69.5; MS (CI, CH_4 + NH_4Cl, 120°C) m/z: 188 $(M + NH_4)^+$, 171 $(M + H)^+$, 153 $(M + H - H_2O)^+$; HRMS m/z: 170.1330 (obsd.), 170.1307 (Calcd. for $C_{10}H_{18}O_2$).

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