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A HIGHLY EFFICIENT ONE-STEP SYNTHESIS OF (±) DIHYDROACTINIDIOLIDE

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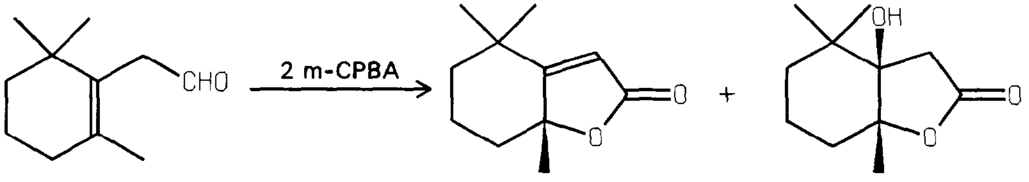
Abstract: An unprecedented reaction of a β,γ-unsaturated aldehyde (1) was discovered and has been used to synthesize (±) dihydroactinidiolide (2) and (±) aeginetolide (3).

A recent report described the isolation of a phytotoxic compound from spikerush (Eleocharis spp.).[1] The principal toxin, dihydroactinidiolide (2),[2] was shown to be a potent inhibitor of seed germination and root length elongation. Our interest in this molecule has led to a new and efficient single-step synthesis of (±) 2 [1-6] via an unprecedented reaction of the commercially available aldehyde 1. Furthermore, a simple procedural modification afforded a convenient route to (±) aeginetolide (3).

It was expected that the action of one equivalent of m-CPBA on 1 would produce a β,γ-epoxy aldehyde or an α,β-unsaturated lactol derived therefrom; instead, a vigorous exotherm was witnessed as well as the need for one additional equivalent of peracid to effect the complete disappearance of 1 by glc. When this experiment was repeated using two equivalents of m-CPBA in CH_2Cl_2 at 20°C for one hour, a good yield of a 23/77 mixture of only 2 and 3 was obtained (Scheme I).

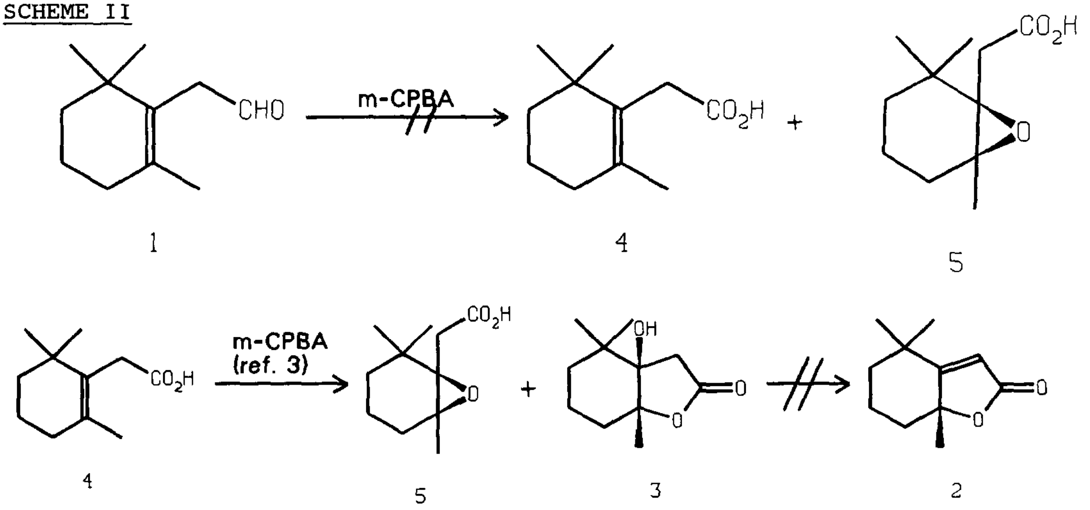
SCHEME I



1 2 3

Examination of the literature failed to find any precedent for this process. Although the mechanism is not understood in complete detail, certain facts help in ruling out some obvious possibilities. First, a literature report[3] that was verified in these laboratories indicated that 1 was not oxidizing to the carboxylic acids 4 or 5. Acid 4 was converted by m-CPBA in CH_2Cl_2 at 25°C into 5 (an isolable intermediate undetected in the reaction of 1 with m-CPBA) which slowly transformed into 3 upon prolonged stirring. (Scheme II)

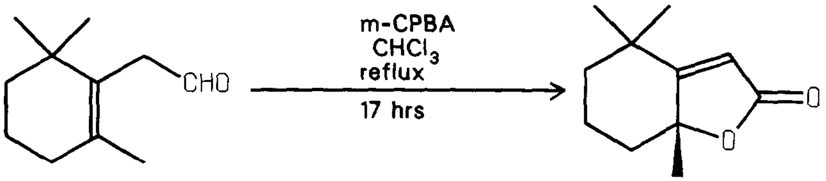
SCHEME II



Second, it appeared that 3 was not the precursor to 2 when the experiments were run at room temperature. As shown above (Scheme II), dehydration of 3 was not a facile process but required more forcing conditions (i.e., $CHCl_3$/m-CBA/17hrs/reflux). Last, the possibility was considered that a mixture of cis and trans hydroxy-lactone 3 formed and that the trans product rapidly dehydrated. However, the formation of a trans-lactone from a planar (i.e., carbenium ion) or epoxide intermediate is highly disfavored based on geometric considerations[5].

We can routinely obtain an 83% yield of (±) dihydroactinidiolide (2)[7] by gradually adding two equivalents of m-CPBA to 1 refluxing in $CHCl_3$ and heating for 17 hrs. Alternatively, a 14:86 ratio of 2 to 3 is obtained by slowly adding two equivalents of m-CPBA to a CCl_4 solution of 1 at 0°C and stirring for 3 hrs. Chromatography of this mixture on silica gel (25% EtOAc in cyclohexane) gives pure (±) aeginetolide ($\underline{3}$)[8] in 73% yield.

To the best of our knowledge, this reaction of mCPBA with a β,γ-unsaturated aldehyde is unknown. We hope to further elucidate the mechanism of this process and explore its generality and utility in preparing various lactone derivatives.



1

2

PROCEDURE

A solution of $\underline{1}$ (1.82g, 10 mmoles) in $CHCl_3$ (10mL) was refluxed as m-CPBA (5.5g, 22 mmoles) was added as a solution in $CHCl_3$ (40mL) over a 0.5 hr period. The final brown solution was heated for 17 hrs at reflux at which time it was cooled to RT and diluted with pet-ether (35°-75°, 150mL). Filtration recovered the m-CBA and the organic was washed with 10% $NaHSO_3$ (1X50mL) and 10% NaOH (1X50mL). Concentration followed by flash chromatography on silica gel eluting with 20% ethyl acetate in cyclohexane gave $\underline{2}$ (1.5g, 83%)[7].

A solution of $\underline{1}$ (3.6g, 20 mmole) in CCl_4 (40mL) was cooled to 0°C and treated with m-CPBA (8.8g, 44 mmoles) in ten portions over 3 minute periods. The reaction was then brought to RT and allowed to stir for 3 hrs. At this point the reaction, a thick mass, was filtered and the cake washed with a 1:2 mixture of CH_2Cl_2 : pet. ethers (100mL). The final organic layer was washed with 10% NaOH (1X 50mL), dried ($MgSO_4$) filtered and concentrated to give a 14:86 mixture of $\underline{2}$:$\underline{3}$. This mixture would crystallize on standing but it was more expedient to chromatograph the crude product on silica gel (25% ethyl acetate in cyclohexane) to give 2.9g of pure $\underline{3}$[8].

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7) (±) Dihydroactinidiolide (**1**) mp 36-38° (lit^3 42°); IR (CCl_4) 1737 cm-^{1}, 1621 cm-^{1}; ^{1}H-nmr (400 MHz, $CDCl_3$) δ 1.16 (S,3H), 1.21 (S,3H), 1.22 (td, J=12.5, 4.0 Hz, 1H), 1.40 (td., J=12.3, 4.9 Hz, 1H), 1.50 (S,3H), 1.66 (complex, 3H), 2.18 (ddd, J=15.5, 4.9, 3.3 Hz, 1H), 5.58 (S,1H); MS (CI) 181 (M+1, 100%). Analysis calculated for $C_{11}H_{16}O_2$: C,73.33, H, 8.89. Found: C, 73.04; H, 9.04.

8) (±) Aeginetolide (**2**) mp 172-173° (lit^3 167); IR (CCl_4) 3580 cm-^{1}, 1755 cm-^{1}; ^{1}H-nmr (300 MHz, $CDCl_3$) δ 0.99 (S,3H), 1.04 (S,3H), 1.38-1.64 (complex, 5H), 2.09 (complex, 1H), 2.16 (brS,1H), 2.36 and 2.93 (AB quartet, J=17.2 Hz, 2H); MS (CI), 199 (M+1, 100%). Analysis calculate for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09. Found: C, 66.69; H, 9.20.

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