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NEW SYNTHESIS OF LOLIOLIDE, DEHYDROLOLIOLIDE, AND 3-OXOACTINIDOL

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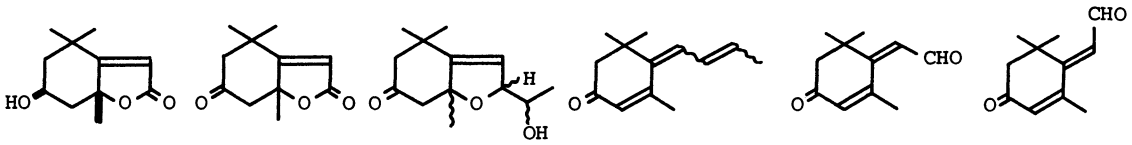
Loliolide, dehydrololiolide, and 3-oxoactinidol were synthesized from megastigma-4,6,8-trien-3-one by regioselective ozonolysis and epoxidation.

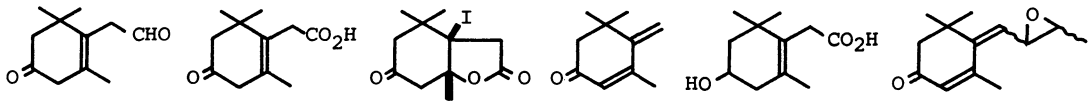
In a preceding paper,[1] we reported an efficient method for the preparation of megastigma-4,6,8-trien-3-one (4), from which the C-3 oxygenated ionone derivatives, such as 3-hydroxy-β-ionone, were selectively synthesized.

In this communication, we wish to report simple and efficient synthesis of loliolide (1),[2,4] dehydrololiolide (2),[3,4] and 3-oxoactinidol (3),[3] starting from the same intermediate 4, by employing regioselective ozonolysis and epoxidation in each key step.

The regioselective ozonolysis of the mixture of four isomers of 4 (6Z/6E = 2/1) in the presence of pyridine in dichloromethane at -78 °C for 0.5 h, followed by the treatment of the resulting ozonide with triphenylphosphine in dichloromethane at room temperature for 1 h, gave a mixture of 2,6,6-trimethyl-4-oxo-2-cyclohexenylidenacetaldehyde, 5a and 5b, (a/b = 2/1) in 71% total yield, both of which also occur in various tobaccos.[5] 2,6,6-Trimethyl-4-oxo-1-cyclohexenylacetaldehyde (6) was obtained by the reaction of the mixture of 5a and 5b with zinc in acetic acid at room temperature for 24 h in 66% yield. [6: IR (neat) 1720, 1665 cm^{-1}; NMR ($CDCl_3$) δ=1.05 (6H, s), 1.68 (3H, s), 2.43 (2H, s), 2.90 (2H, s), 3.28 (2H, s), 9.66 (1H, m)] Furthermore, 6 was also prepared by the treatment of the ozonide with zinc in acetic acid, instead of triphenylphosphine, at room temperature for 1 h in 67% yield. The subsequent oxidation of 6 with CrO_3 and sulfuric acid in water at 5 °C for 1 h gave 2,6,6-trimethyl-4-oxo-1-cyclohexenylacetic acid (7) in 59% yield. [7: IR (KBr) 3600-2400, 1700, 1220, 920 cm^{-1}; NMR ($CDCl_3$) δ=1.07 (6H, s), 1.70 (3H, s), 2.42 (2H, s), 2.91 (2H, s), 3.24 (2H, s), 10.25 (1H, s)]



1 2 3 4 5a 5b



6 7 8 9 10 11

The treatment of 7 with iodine, potassium iodide, and sodium hydrogen carbonate in water at room temperature for 24 h did not afford iodolactone 8, but 3,5,5-trimethyl-4-methylene-2-cyclohexenone (9) in 51% yield, which also occurs in various tobaccos.[5] As an alternative route, the reduction of 7 with lithium aluminum hydride in ether at room temperature for 1 h gave 4-hydroxy-2,6,6-trimethyl-1-cyclohexenylacetic acid (10) in 85% yield. Spectral data of 10 were consistent with those in the literature.[4] Then, according to Demole's method,[4] from 10 loliolide (1) and dehydroloiliolide (2) were synthesized.

On the other hand, the regioselective epoxidation of 4 with m-chloroperbenzoic acid in dichloromethane at 0 °C for 4 h afforded the epoxide 11. The reaction of 11 with trifluoroacetic acid at 0 °C for 0.5 h, followed by the treatment with 10% NaOH in methanol and water (1:1) at room temperature for 4 h gave a mixture of four isomers (3a-3d) of 3-oxoactinidol (3), all of which occur in Burley tobacco,[3] in 34% yield (from 4). The four isomers, 3a-3d, were found in the ratio 28:21:31:20 by means of capillary gas chromatography (PEG 20M). The separation of 3a-3d by means of preparative gas chromatography (PEG 20M) gave three fractions of 3a, a mixture of 3b and 3c, and 3d. All spectral data of three fractions were consistent with those in the literature.[3]

Furthermore, 3 was easily transformed into 2 in 73% yield by the oxidation with pyridinium dichromate in dichloromethane at room temperature for 5 days. Therefor, it turned out that 2 was prepared from 4 in a further short pathway than the above.

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