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SYNTHETIC STUDIES IN THE TETRANORDITERPENE LACTONE SERIES. I.
THE TOTAL SYNTHESIS OF DIHYDRO-8-EPI-ACROSTALIDIC ACID[1].

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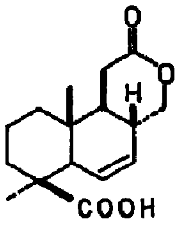
Abstract. The total synthesis of dihydro-8-epi-acrostalidic acid (8b) and other related tetranorditerpene lactones are described.

Acrostalidic Acid (1), a tricyclic δ-lactone possessing the tetranorlabdane skeleton was isolated in 1974 by Sato and Kakisawa[2] from an *Acrostalagmus* mutant known as NRRL-3481, and shown[3] to inhibit celular growth in *Avena* coleoptile. Its structure closely resembles those of the related inumakilactones[4], nagilactones[5], and podolactones[5,6], all of which are well known plant growth inhibitors[7]. Furthermore, the related metabolite LL-Z 127α also shows fungicidal properties[8].

The structural similarities and interesting physiological properties characteristic of such compounds prompted us to study the synthesis of lactone 1 as a possible general entry into the more complex norditerpenebislactones, and for this purpose acrostalic acid 19-methyl ester (3a) was initially prepared from the readily available methyl podocarpate (2)[9] essentially as described by Bell and coworkers[10].



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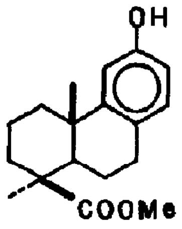

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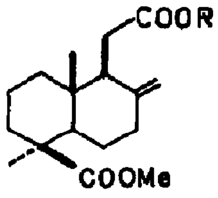
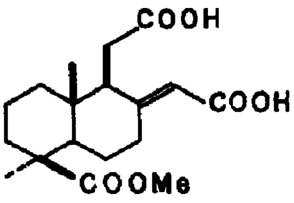


3 a R=H
b R=Me

The main modifications introduced into the reported sequence[10] require: (a) that the copper chromite utilized for the decarboxylation of intermediate 4[11] be prepared according to method of Lazier and Arnold[12], and (b) that the crude decarboxylation mixture be esterified (Me_2SO_4/K_2CO_3) prior to purification, thus allowing the isolation of dimethyl acrostalate (3b), mp 109-110°, in an overall 30% yield from 2. Mild alkaline hydrolysis of 3b furnished acid 3a, mp 153-155° (lit.[13]



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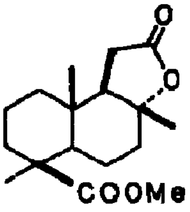

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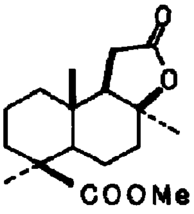

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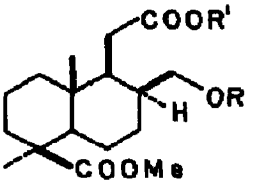
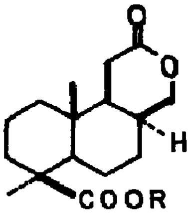


7

a R=H, R'=Me

b R= Ac, R'=Me

c R=R'=H



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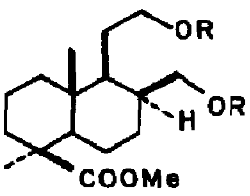
a R= Me

b R= H



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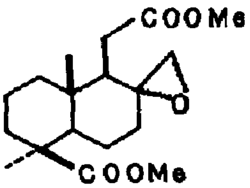
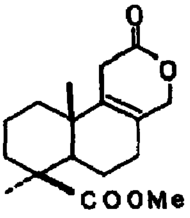
a R=H

b R=Ac



10 α- epoxide

11 β- epoxide



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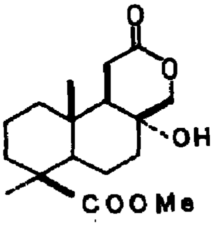

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mp 153-155°) in quantitative yield.

As expected, brief acid treatment (HCl/THF) of 3a gave the known[2] *trans*-γ-lactone 5, mp 196-198° (lit.[2] mp 195-197°), which is known to slowly convert, in unspecified yield, into the more stable *cis*-lactone 6, methyl dihydroacrostalidate. However, in our hands, diester 3b furnished directly an 84% yield the γ-lactone 6, mp 140-141.5°, (lit.[2] mp not given), upon heating with 98% formic acid.

Whereas careful hydroboration of 3b produced a 3:1 mixture of the oily primary alcohol 7a[14] and the *cis*-δ-lactone 8a, mp 108-110°, in 52% yield, use of excess diborane caused concomitant reduction of the C-12 methoxycarbonyl grouping to give a 3:1:1.66 mixture of 7a:8a:9a. Diol 9a, mp 179-180°, afforded the oily diacetate 9b under the usual conditions. Base treatment of either 7a or 7b produced acid 7c, which smoothly cyclized (Ac_2O) to lactone 8a, thus demonstrating that attack by borane took place in all cases from the less hindered α-side of the molecule to produce a β-oriented hydroxymethyl functionality.

Since lactone 8a is in fact methyl dihydro-8-epi-acrostalidate, we proceeded next to hydrolyze the remaining C-19 ester moiety by treatment with BBr_3[15] to produce dihydro-8-epi-acrostalidic acid 8b[2b], mp 240-240.5°, in 66% yield. By performing the hydrolysis and cyclization steps directly on the crude hydroboration mixture (*vide supra*), lactone 8a can be obtained in an overall 40% yield from the unsaturated diester 3b.

Moreover, epoxidation of 3b produced a 95% yield of an 8:1 mixture of the α- and β-epoxides 10 and 11, mp 104-105.5° and 85-87.5°, respectively. If extreme care to avoid incoming moisture is not observed, varying amounts of the $\Delta^{8,9}$-lactone 12, mp 140-142°, are also obtained. The attempted BF_3-catalyzed rearrangement[16] of the α-epoxide resulted instead in the formation of hydroxy-δ-lactone 13, mp 125-126°, arising from a competing intramolecular attack of the C-9 acetic ester side chain at the less substituted carbon of the Lewis acid-complexed oxirane system, necessarily through an intermediate boat conformation.

Finally, whilst the direct dehydration of lactone 13 gave exclusively the unsaturated analog 12, treatment with 98% formic acid at room temperature furnished the 17-formate of methyl-17-hydroxy-dihydro-8-epi-isoacrostalidate 14, mp 145.5-147°.

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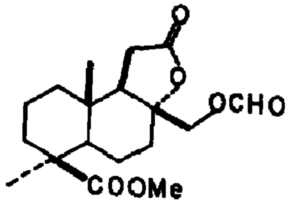

14

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