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A PRACTICAL SYNTHESIS OF THE ANTIBIOTIC BOTRYODIPLODIN

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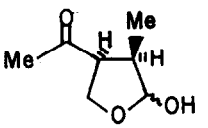
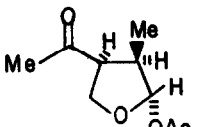
We wish to describe convenient routes for the synthesis of sizable quantities of the antibiotic and anti-leukemic[1] agent Botryodiplodin I,[2] and the corresponding acetate II.[3] The



I



II

synthetic conversions are outlined in Figure 1.

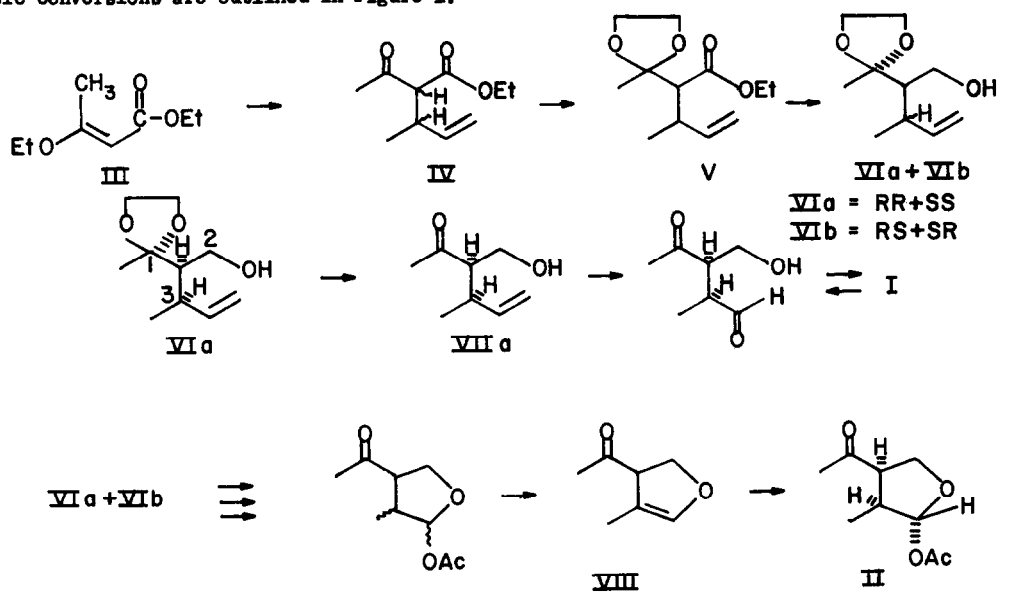
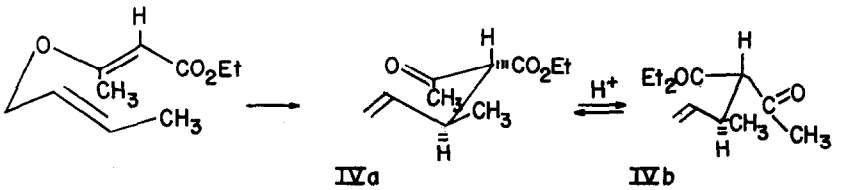


Figure 1

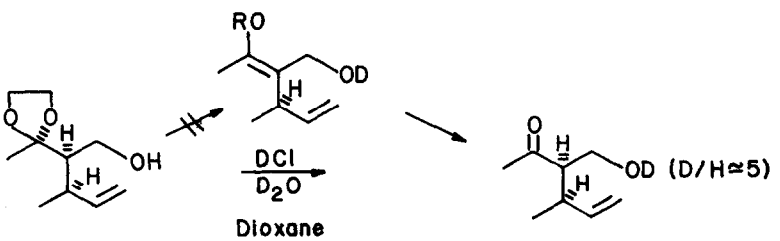
The enol ether of acetoacetic ester (III) when treated with anhydrous trans-crotyl alcohol in hot (130°) xylene in the presence of 4:1, dinitrophenol:potassium bisulfate (2 g/100 g III) underwent smooth trans-etherification and Claisen rearrangement yielding 61% of the alkylated β-keto ester IV. Compound IV (b.p. 74-76° @ 5 mm) was obtained as a 1:1 mixture of diastereomers.

Presumably under these conditions also,[4] the expected diastereomer IVa underwent rapid equilibration, via the enol, to a mixture of IVa and IVb.



Ketalization of IV, using ethylene glycol in the presence of p-toluenesulfonic acid, produced compound V in 80% yield (b.p. 73-82° @ 0.65 mm) also as a 1:1 mixture of diastereomers. Reduction of V with lithium aluminum hydride produced the unsaturated ketal alcohol, VI, in 81% yield (b.p. 68-72° @ 0.1 mm). Separation of VIa and VIb was effected by careful spinning band distillation, diastereomer VIa being the higher boiling of the two (b.p. 50.5° @ 0.025 mm). When VIa was hydrolyzed using 1.0N HCl in aqueous dioxane (1:1) diastereomerically pure VIIa was obtained in 90% yield (b.p. 88-89° @ 4 mm).

In order to show that this deketalization did not involve stereoselective protonation of the tetrasubstituted enol (or enol-ether), the reaction was repeated using 1N DCl in D_2O, dioxane (1:1).



Although the β-hydroxyketone obtained in 85% yield contained ~ 85% R-OD, we could detect no deuterium incorporation via nmr (i.e., within the limits of integration accuracy), in either the methyl or methine α position to the carbonyl moiety.

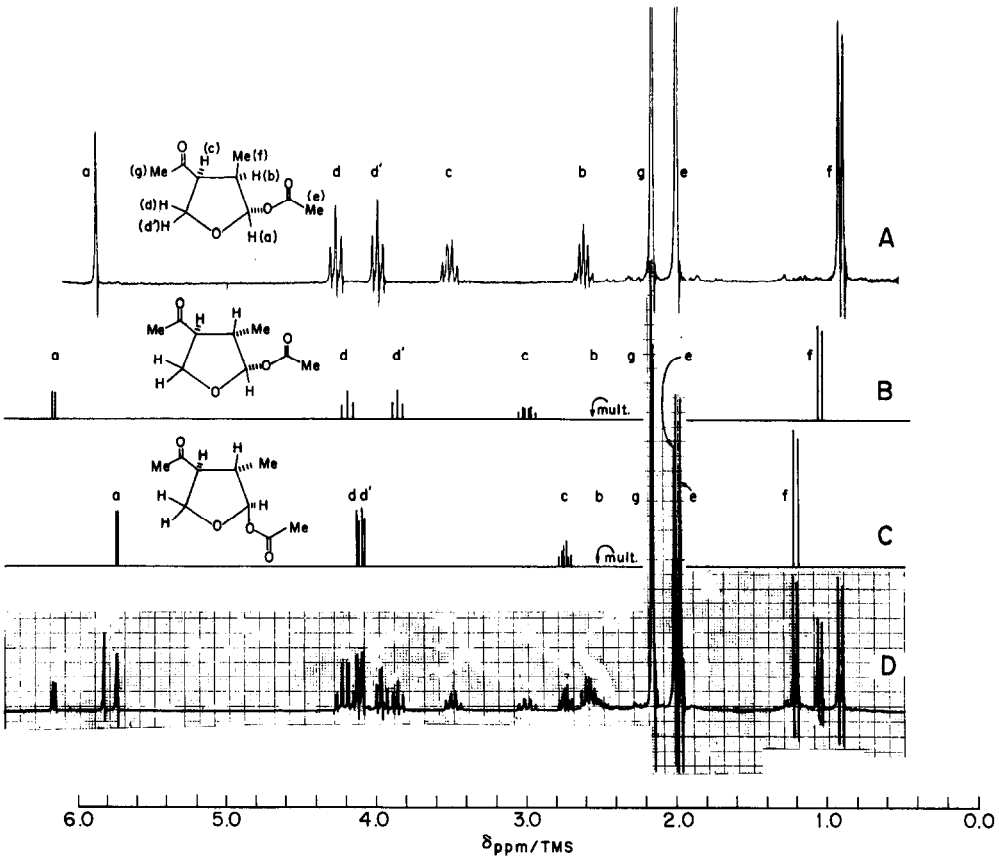


Figure 2. Nmr (250 MHz) spectra: A, synthetic botryodiplodin acetate; D, synthetic mixture of acetates; B and C line assignments for isomers of botryodiplodin acetate.

Ozonolysis of VIIa in CH_2Cl_2 at -78°, followed by reduction (Zn/HOAc) yielded diastereomerically pure material, which was identical with natural botryodiplodin.[5] Synthetic I was obtained in 70% yield (b.p. 111-113° @ 4 mm) as a low melting solid. Acetylation of I (Ac_2O/pyridine) produced the acetate II in 68% yield (b.p. 115-117° @ 4 mm; m.p. (pentane) 53-55°).

Alternatively, the diastereomeric mixture of VIa and VIb was submitted to the above sequence and yielded a mixture of three acetates (see Figure 2 for 250 MHz nmr assignments of each) which, on pyrolysis (420° @ 8 mm) produced a single compound, the enol-ether VIII. When this enol-ether was reacted with one equivalent of anhydrous acetic acid in CCl_4 for 24 hours, only botryodiplodin acetate was detected.

We have therefore shown two relatively short routes (five and eight steps, respectively) for the preparation of stereochemically pure 2-hydroxytetrahydrofuran derivatives. The ozonolysis of related unsaturated alcohols will allow the preparation of analogues of I, and we hope thereby to determine what structural factors relate to anti-cancer activity.

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5. We thank Professor Arsenault for a sample of botryodiplodin.