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A NEW SYNTHESIS OF THE VERNOLEPIN A-RING

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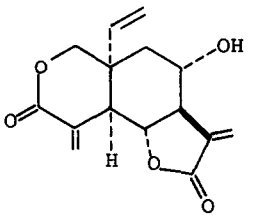
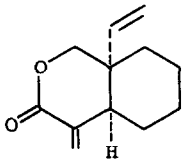
The sesquiterpene bis-lactone vernolepin (1) shows significant cytotoxic and anti-tumor activity.[1] Grieco has recently outlined a rather lengthy synthesis of 2, which constitutes a model for rings A and B of vernolepin.[2] In connection with our own interest in this problem, we have devised a much more efficient synthesis of 2.



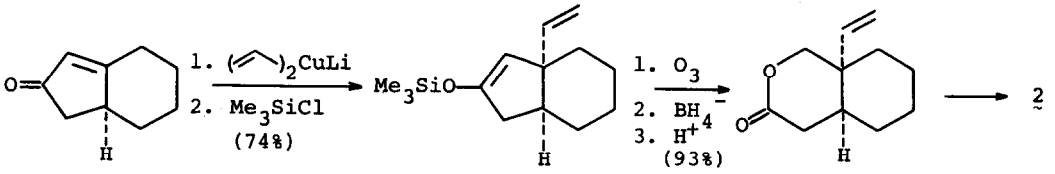
1



2

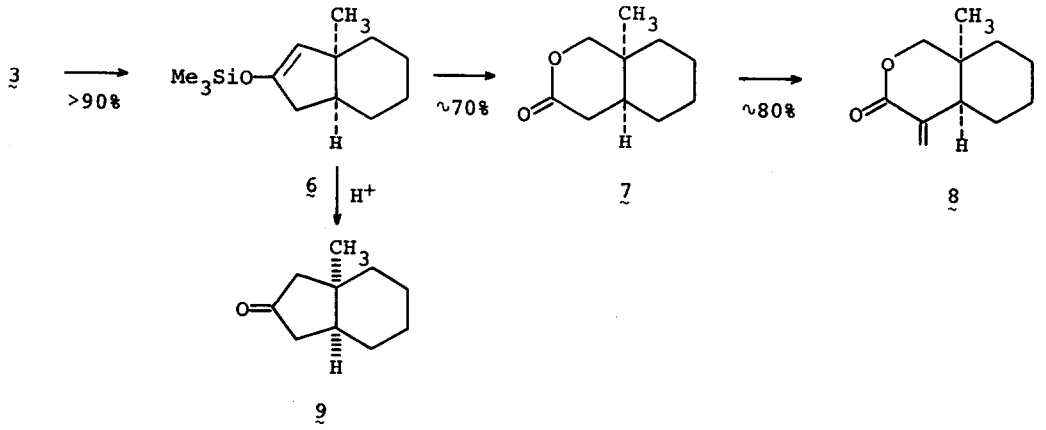
Enone 3[3] (10 mmoles) in 10 ml of ether is added at -75° to a solution of 15 mmoles of lithium divinylcuprate, prepared by the addition of 30 mmoles of a THF solution of vinyllithium to a -75° solution of 17.4 mmoles of cuprous iodide in a mixture of 10 ml ether and 5 ml of dimethyl sulfide.[4,5] After 45 min, the solution is warmed to -40° and treated with HMPA, triethylamine, and trimethylsilyl chloride.[6] After dilution with pentane the solution is poured into 10% HCl. Removal of solvent and distillation affords silyl enol ether 4 in 74% yield.[7] Compound 4 is treated with 1.0 equiv. of ozone in methanol at

-78°. The solution is treated with excess $NaBH_4$ and warmed to room temperature. After evaporation of solvent, the residue is stirred briefly with 10% aqueous HCl and worked up by ether extraction to give lactone 5 in 93% yield. A sample of lactone 5, purified by preparative glpc, melted at 44-46° (lit. 44-45°).[2] Compound 5 was converted into 2 by Grieco's two-stage process.[2,8]



3 4 5

One of the advantages of this process is that vernolepin analogs may be easily prepared in which the angular vinyl group is replaced by other groups. For example, enone 3 has been converted in a similar process into the vernolepin analog 8 by the sequence of reactions outlined below.



The nmr spectra of compounds 7 and 8 are similar to the comparable spectra of compounds 5 and 2. In each case, the complex vinyl absorption in the δ=5-6 ppm region is replaced by a sharp singlet at δ=1.07 ppm. The cis ring juncture in

8 is shown by the fact that compound 6 is hydrolyzed to the known cis-2-hydrindanone, 9.[9]

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