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MODEL STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF VERNOLEPIN: CONSTRUCTION OF THE α-METHYLENE-δ-LACTONE PORTION OF VERNOLEPIN.

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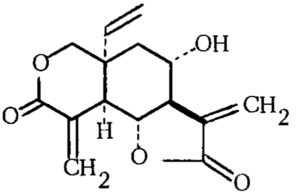
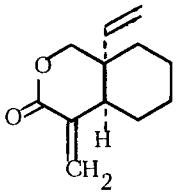
Vernolepin(I)[1] is a novel elemanolide dilactone tumor inhibitor which has been isolated during the course of searching for antitumor agents from plant sources.[2] No substantial progress toward partial synthesis of I has been reported. Our studies, aimed at total synthesis, have concentrated on the synthesis of the cis-fused angular vinyl AB-α-methylene-δ-lactone II which constitutes the left hand portion of the vernolepin molecule. The synthesis of II serves to demonstrate a) the formation of the cis-fused arrangement of rings A and B, b) introduction of the angular vinyl group, and c) construction of the α-methylene-δ-lactone system. We now describe the synthetic steps leading to II.



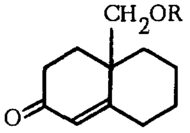
I



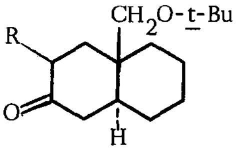
II

The hydroxymethyl octalone III[3] was converted(isobutylene/conc H_2SO_4/methylene chloride/r.t./16 hr) to the t-butyl ether IV[4][ir max(film) 6.05, 6.19 μ; nmr δ(CCl_4) 1.20(s, 9H), 3.40(s, 2H), 5.64(s, 1H)] in 80% yield after chromatography on silica gel. Reduction of enone IV(Li/Liq. NH_3/t-BuOH/THF) to the desired trans-decalone V[ir max(film) 5.85 μ; nmr δ(CCl_4) 1.20(s, 9H), 3.52(s, 2H), no olefinic protons; semicarbazone[4], colorless needles mp 204-205°] was achieved in 75% yield after purification. Cleavage of the C-2, C-3 bond in V(steroid numbering) in such a way as to allow formation of an angular vinyl group and a potential carboxylic acid function at C-3 would provide an approach to II. Such a fragmentation has been realized *via* the second order Beckmann fragmentation[5] of oxime VII.

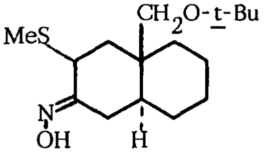
Formylation of V followed by treatment with methyl thiotosylate[6] (potassium acetate/ethanol/reflux) resulted in a 90% crude yield of the desired α-methylthioketone VI[4], mp 62-63° [ir max($CHCl_3$) 5.85 μ; nmr $\delta(CCl_4)$ 1.18(s, 9H), 2.00(s, 3H), 3.43(q, 1H)]. Oximation of VI produced oxime VII which underwent the desired fragmentation upon treatment with methanesulfonyl chloride in refluxing pyridine. The structure of the enol thioether nitrile VIII[4] was in complete agreement with the observed spectral data: ir max(film) 4.48, 6.17, 10.68(*trans*-substituted enol thioether) μ; nmr $\delta(CCl_4)$ 1.20(s, 9H), 2.20(s, 3H), 3.30(AB quartet, 2H), 5.62(AB quartet, J=16Hz, 2H)]. The overall yield of VIII from VI after purification by



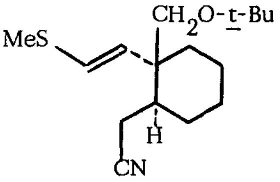
III R=H
IV R=*t*-Bu



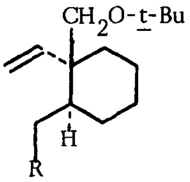
V R=H
VI R=SMe



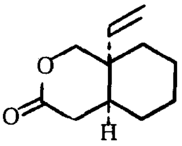
VII



VIII



IX R=CN
X R=COOH



XI

chromatography on silica gel was 45%. VIII was cleanly desulfurized(W-2 Raney Ni/refluxing ethanol/ 4 hr) in ca. 90% yield to IX[4] [ir max(film) 3.24, 4.48, 6.12, 10.95 μ; nmr δ(CCl_4) 1.20(s, 9H), 3.30(AB quartet, J=8Hz, 2H), 4.80-5.95(complex ABC system, 3H)]. Hydrolysis of the nitrile IX (KOH/H_2O/diethylene glycol/reflux) afforded a 70% (purified) yield of the carboxylic acid X[ir max(film) 2.74-4.10, 5.86 μ]. Treatment of X with p-toluenesulfonic acid in refluxing benzene produced in 80-85% yield the cis-fused angular vinyl lactone XI[4], colorless prisms mp 44-45°[ir max($CHCl_3$) 5.79, 6.12, 10.90 μ; nmr[7] δ(CCl_4) 5.16-5.68(8 line ABC pattern, J_{AB}=18Hz, J_{AC}=10Hz, J_{BC}=0Hz, 3H, -CH=CH_2), 4.14(AB quartet, J_{AB}=11Hz, 2H, -O-$\underline{C}\underline{H}_2$-C), 2.17-2.61(AB portion of an ABX system, J_{AB}=17Hz, J_{AX}=7Hz, J_{BX}=5Hz, 2H, -CO-$\underline{C}\underline{H}_2$-C$\underline{H}$)].

Introduction of the α-methylene unit found in II was achieved via direct α-hydroxymethylation[8] of lactone XI. To a solution of lithium di-isopropylamide in anhydrous THF at -78° was added a solution of lactone XI in THF. After 30 minutes, the reaction mixture was warmed to -20° and gaseous formaldehyde(generated by heating paraformaldehyde at 200°) in a stream of nitrogen was passed into the reaction vessel containing the α-lithiated lactone. After an additional 30 minutes, the reaction was quenched by the addition of 10% hydrochloric acid. The crude α-hydroxymethyl lactone was converted into it's corresponding mesylate and thence(refluxing pyridine) to II[4][ir max($CHCl_3$) 5.84, 6.10, 6.17 μ; nmr[7] δ(CCl_4) 6.34(s, 1H), 5.44(s, 1H), 5.00-5.80(complex ABC pattern, 3H, -CH=CH_2), 4.12(AB quartet, J=11Hz, 2H), 2.52(s, broad, 1H)] in 50% overall yield from XI. The method described represents a simple, efficient and potentially general technique for constructing the α-methylene-δ-lactone structural unit.

Studies involving a functionalized ring B for the eventual construction of the α-methylene-γ-butyrolactone unit are now in progress.

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