Tetrahedron Letters No. 21, pp 1769 - 1772, 1976. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF SESQUITERPENE ANTITUMOR LACTONES. V.[1]

A MODEL FOR RINGS B AND C OF VERNOLEPIN

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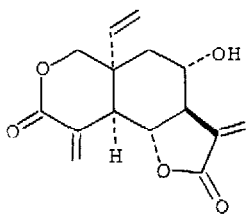
(Received in USA 23 March 1976; received in UK for publication 16 April 1976)

The elemanoid bis-α-methylenelactone vernolepin (1)[2] shows modest *in vitro* cytotoxicity toward cells of human carcinoma of the nasopharynx (KB) and *in vivo* antitumor activity against the Walker intramuscular carcinosarcoma 256.[3] Its congener vernomenin (2) is biologically inactive. Because of their interesting structures, these sesquiterpenoids have elicited considerable synthetic interest.[1,4]



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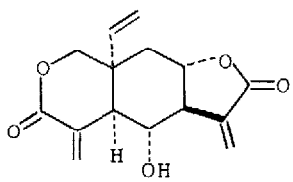

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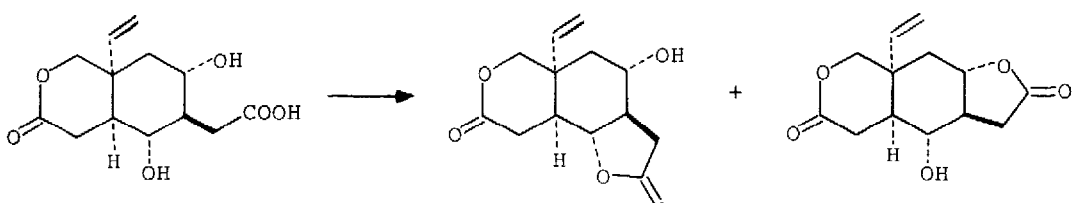
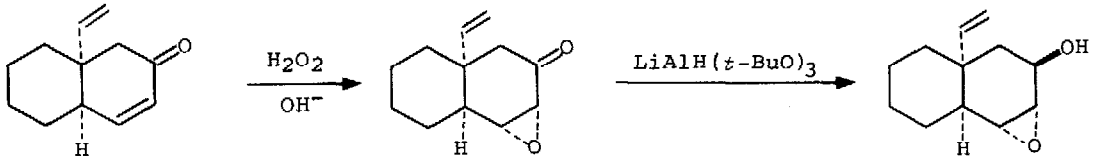
Since only vernolepin shows physiological activity, an attractive goal in any synthetic attempt in this area is the regiospecific production of this isomer. Both the Grieco[4i] and the Danishefsky[4j] total syntheses proceed *via* dihydroxy acid 3, which affords prevernolepin (4) and prevernomenin (5) in a ratio of from 3:1[4i] to 2:1.[4j] Although this fortuitous selectivity does allow the desired isomer to produced in preponderance, and greatly expedites the synthesis by avoiding the necessity of protecting groups, the regiospecific



3 4 5

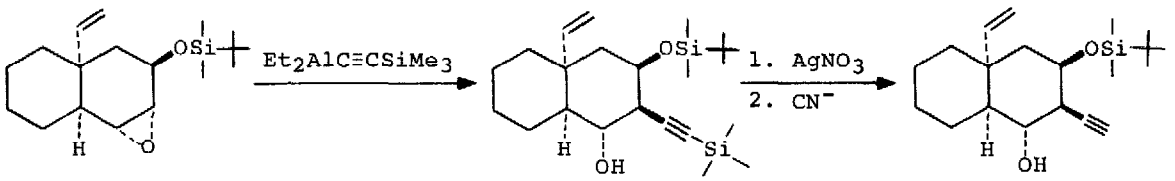
elaboration of the vernolepin lactone must still be considered to be an unsolved problem in this area. In this communication, we report a model study which appears to offer a solution to this problem.

Vinyloctalone 6[5] reacts with alkaline H_2O_2 in CH_3OH at 15-25° to afford epoxy ketone 7 in an isolated yield of 64-68%. Reduction of 7 by $LiAlH(t\text{-}BuO)_3$ in ether gives the nicely crystalline epoxy alcohol 8 in 81-85% yield.



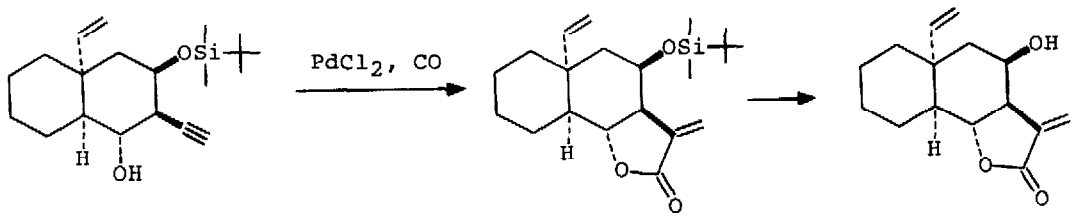
6 7 8

After protecting the hydroxy group as its *t*-butyldimethylsilyl ether[7] (9), the epoxide ring is opened in a *completely regioselective* manner by treatment with diethyl(trimethylsilylethynyl)alane[8] in toluene at 85-100° for 16 hrs, affording 10 in 70% yield. After removal of the trimethylsilyl group by Arens' procedure,[10] ethynyl alcohol 11 is obtained as a low-melting solid in 80% yield.



9 10 11

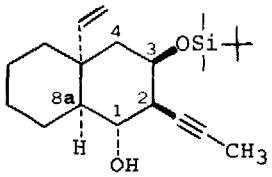
Application of Norton's cyclocarbonylation conditions ($PdCl_2$, thiourea, 50 psi CO in acetone at 50-80° for 16 hrs)[11] affords a reaction product containing up to 50% of the α-methylenebutyrolactone 12 as judged by pmr analysis. Crystalline 12 (mp 183°) may be isolated in yields of up to 21% by chromatographic purification. The *t*-butyldimethylsilyl protecting group is conveniently removed by treatment with tetra-*n*-butylammonium fluoride to obtain alcohol 13.



11 12 13

Although the yield in the cyclocarbonylation reaction leaves something to be desired, we have not yet optimized the reaction conditions for this polyfunctional acetylenic alcohol. It is likely that the yield can be improved, since *trans*-2-ethynylcyclohexanol undergoes the reaction in 94% yield.[11] However, even at the current level, this method of elaborating the α-methylenebutyrolactone is attractive, since the bis-methylenation of 4 affords 1 in only 12% yield.[4i]

The stereochemistry of the epoxidation (6 → 7) and reduction (7 → 8) steps, as well as the regiochemistry of the oxirane opening (9 → 10) is clearly indicated by the high-resolution pmr spectra of 10 and the related alkyne 14. The 360 MHz pmr spectrum of 14 is particularly instructive. All six ring B protons



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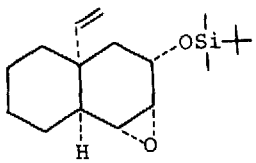
are clearly resolved and reveal the following coupling constants: $J_{4,4'} = 14.7$, $J_{4,3} = 3.0$, $J_{4',3} = 3.1$, $J_{2,3} = 3.0$, $J_{1,2} = 10.4$, $J_{1,8a} = 10.4$ Hz. Although the relative chirality imparted to the secondary hydroxy group in this approach is opposite to that present in vernolepin, this fact is of crucial importance. The isomeric epoxy ether 15[12] is recovered unchanged after being treated with 2.2 equivalents of diethyl(trimethylsilylethynyl)alane in refluxing toluene for 16 hrs. A similar unreactivity has been noticed by Danishefsky in the attempted reaction of tetrahydropyranyl ether 16 with lithium α-lithioacetate.[4] We are currently exploring ways to invert the secondary hydroxy in 13 and plan to apply this approach to a synthesis of vernolepin *via* unsaturated ketone 17, which we have recently prepared.[13]



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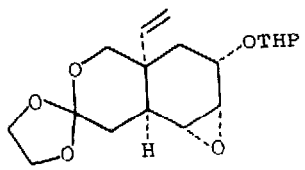

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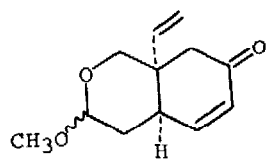

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Acknowledgement. This work was supported by a grant from the National Institutes of Health (no. CA-12617).

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