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SYNTHESIS OF SESQUITERPENE ANTITUMOR LACTONES I

A FACILE SYNTHESIS OF CIS-FUSED A-RING IN VERNOLEPIN AND VERNOMENIN[1]

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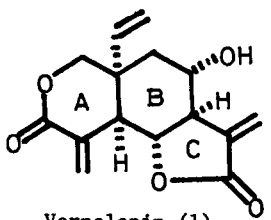
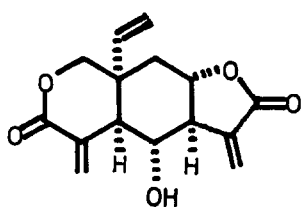
The sesquiterpene antitumor lactone vernolepin (1)[2] and its congener vernomenin (2)[2] have elicited considerable synthetic attention. In the recently reported synthetic studies on these elemane sesquiterpenes, including two total syntheses by Grieco[3d] and by Danishefsky,[4d] most of them involved elaboration of the cis-fused δ-valerolactone system by scission of the C_2-C_3 bond of angularly functionalized trans-bicyclo[4,4,0]decanes.[3,5,6c] Other approaches involved oxidative cleavage of cis-fused precursors synthesized by Diels-Alder strategy[4] or by angular vinylation of bicyclo[4,3,0]non-2-en-1-one with lithium divinyl cuprate.[6] These methods require fairly lengthy steps for construction of the cis-fused lactone ring.

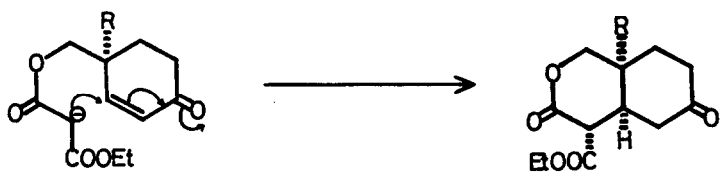


Vernolepin (1)



Vernomenin (2)

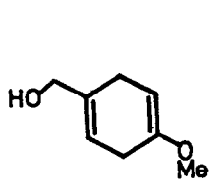
We describe here a facile cis-cyclization which gives a promising precursor for the synthesis of 1 and 2. Our approach to their characteristic cis-fused δ-valerolactone system involves conceptually different process, the crucial step of which is a base-catalyzed intramolecular Michael type cyclization[7] of the enone-malonate (eq. 1).



(eq. 1)

Preparation of the required enone malonate (6) was started from dihydro-p-anisyl alcohol 3.[8] Its ketalization (ethylene glycol, BF_3/THF) and subsequent oxidation (pyridinium chlorochromate,[9] NaOAc/CH_2Cl_2) yielded in ca. 80% unsaturated aldehyde 4 [ν(neat)1700cm^{-1}: δ(ppm:$CDCl_3$) 9.50(1H,s), 6.7(1H,m), 4.00(4H,s), 2.55(2H,m), 2.40(2H,m), 1.75(2H,t,J=6). Treatment of enolate of 4, generated by LDA in THF at -40°, with allyl iodide at 0° for 3 hr gave α-allylated aldehyde 5 [yield 66% after a short path distillation at 10^{-2}mmHg: ν(neat) 1725cm^{-1}: δ(ppm:$CDCl_3$) 9.42(1H,s), 6.0-5.5(1H,brm), 5.7(2H, brs), 5.2-5.0(2H,m), 3.9(4H,s), 2.3(2H,d,J=7)]. Reduction of 5 with $NaBH_4$ in EtOH gave the corresponding alcohol which was esterified with ethyl malonyl chloride in pyridine and then treated with 0.1N HCl in acetone. Overall yield of 6 [ν(neat) 1750sh, 1735, 1680cm^{-1}: δ(ppm:$CDCl_3$) 6.68(1H,d,J=11), 6.00(1H,d,J=11), 6.0-5.5(1H,m), 5.3-5.0 (2H,m), 4.20(2H,q,J=7), 4.12(2H,ABq,J=11), 3.40(2H,s), 2.49(2H,t,J=6), 2.31(2H,d,J=7), 1.96 (2H, t,J=6), 1.28(3H,t,J=7)] from 5 was 75%.

The crucial cyclization was accomplished simply by stirring of 6 with NaH in THF at r.t. for 2 hr to afford quantitatively (89% yield after crystallization from Et_2O) a single product 7 [mp 83-84°: m/e 280(M^+): ν(KBr) 1740sh, 1728, 1720cm^{-1}: δ(ppm:$CDCl_3$) 6.1-5.6(1H,m), 5.35(1H,brs) 5.2(1H,dd,J=7&2), 4.3(2H,q,J=7), 4.12(2H,ABq,J=12), 3.28(1H,d,J=9.5), 2.7-2.2(7H,m), 1.85(2H,t, J=6), 1.30(3H,t,J=7)]. The cis-AB configuration of 7 was proven by interconvertive correlation between 7 and 9. Thus, bromination of 7 with NBS in THF (affording 8[10]) and subsequent enolization with DBU in i-PrOH gave in 68% yield the cyclopropane derivative (9)[11] [mp 66.5-67°: m/e 278(M^+): ν(KBr) 1742, 1735, 1698cm^{-1}: δ(ppm:$CDCl_3$) 2.84(1H,d,J=8), 2.48(1H,d,J=8)], which could be converted back to 7 in 80% yield by treatment with Zn/AcOH. The enolization of cis-fused 7 occurs in the direction same as cis-bicyclo[4,4,0]decan-3-ones predominantly enolize.[12] This was further demonstrated by isolating enol acetate 10 [94% yield: olefinic Hat δ(ppm) 5.38 (brs) couples with ang.H at δ2.80(dd,J=10&3); the latter couples with the active methine H at δ3.36 (d,J=10)] by treatment of 7 with acetic anhydride in the presence of a catalytic amount of perchloric acid.



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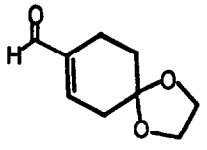

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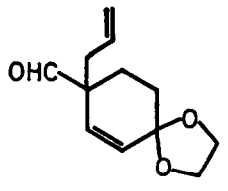

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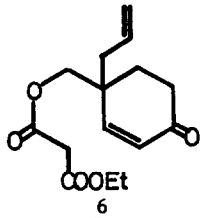

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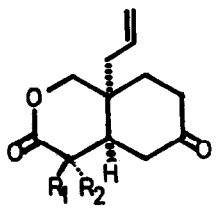
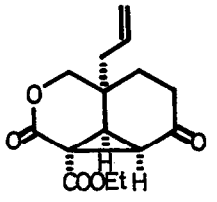


7 (R_1=H; R_2=COOEt)
8 (R_1=COOEt; R_2=Br)



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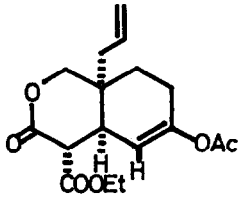

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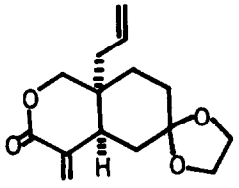
The ester lactone (7), after protecting the ketone group as ethylene ketal, was converted in 57% yield to α-methylene-δ-lactone 11 [mp 88-89°: m/e 264(M^+): δ(ppm:$CDCl_3$) 6.55(1H,s), 5.66 (1H,s), 2.78(1H,dd,J=10&7)] by hydrolysis with aq. NaOH followed by treatment with a mixture of formaldehyde and diethylamine.[13] Thus, construction of A-ring of the title compounds was completed.

The allyl side chain could easily be converted to vinyl group by the following procedure. 12a(R=-$CH_2CH=CH_2$) was ozonized at -78° in CH_2Cl_2. The ozonide, when treated with dimethyl sulfide, gave a complex mixture due to a simultaneous hydrolysis of the ketal group, but the aldehyde 12b(R=-CH_2CHO) [δ(ppm) 9.75(1H,s)] was obtained in almost quantitative yield by decomposing it in the presence of triethylamine. 12b was further treated successively with the following reagents: 1.2eq. $NaBH_4$ at 0° in EtOH (12c, R=-CH_2CH_2OH), MsCl at 0° in pyridine (12d, R=-CH_2CH_2OMs), PhSeNa at r.t. in EtOH (12e, R=-CH_2CH_2SePh), O_3 at -20° and then 50° in $CHCl_3$ (12f, R-CH=CH_2), and aq. trifluoroacetic acid at r.t. affording in ca. 60% overall yield vinyl ketone 13 [olefinic 3H, ABX; δ(ppm) 5.91(dd,J=17&10), 5.30(d,J=10), 5.26(d,J=17)].



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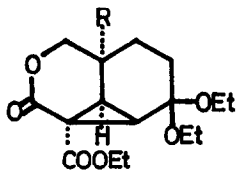

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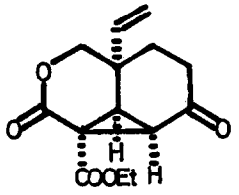

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We have demonstrated that the cis-fused ring formation in eq. 1 can be achieved by a fairly simple manner. Compound 13 is of highly potential utility for the total synthesis of 1 and 2. The rigid tri-cyclic ring of 13 should be conceivably efficient for stereo- and regio-specific reactions to introduce further functional groups. Application of the results discussed here with respect to the sesquiterpene total synthesis is currently being explored.

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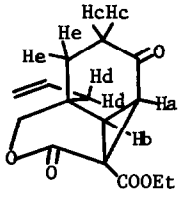
10. The bromide (8) is the major product of ca. 10 : 1 mixture, the minor being its stereoisomer, [R_1=Br, R_2=-COOEt].
11. The preference for Δ^6-enolization in 8 prevented the formation of another plausible ketone 14. The structure of 9 was further confirmed using a NMR shift reagent: δ(ppm, 35% Eu-DPM in $CDCl_3$) 3.50(Ha,d,J=8), 2.94(Hb,d,J=8), 2.72(Hc,m), 2.37(Hd,d,J=7), 2.14(He,m). Treatment of the cage compound 9 with $NaBH_4$ yielded γ-lactone alcohol 15a(R=H) [ν 3500, 1772, 1725cm^{-1}: δ(ppm) 4.95(Ha,m), 3.55(Hb,brs)] whose acetate 15b(R=Ac) showed δ(ppm) 4.90(Ha, m), 4.05(Hb,ABq).



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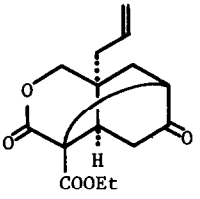

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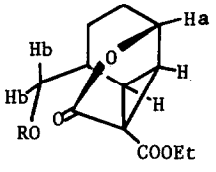

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