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SYNTHESIS OF SESQUITERPENE ANTITUMOR LACTONE I
A NEW SYNTHESIS OF THE CIS-FUSED δ-VALEROLACTONE AB RING MODEL IN VERNOLEPIN AND VERNOMENIN

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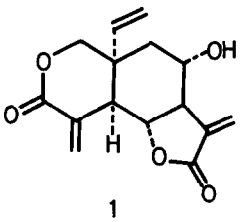
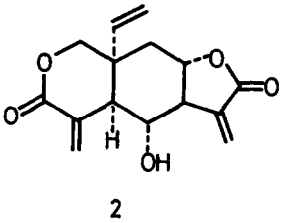
Summary: Reaction of (5) with chloromethyl methyl ether undergoes successively stereo and regioselective alkylation. Compound (6) was subsequently transformed to the cis-fused angular vinyl δ-valerolactone (7).

Vernolepin (1) and vernomenin (2),[1] novel elemanolide bis-α-methylenelactones, are the major constituents of *Vernonia hymenolepis*. Of these two molecules, vernolepin (1) shows significant in vitro cytotoxity toward cells derived from human carcinoma of the nasopharynx(KB) in cell culture and in vivo antitumor activity against the Walker intramuscular carcinosarcoma in rats.[1] In the recent paper published by Grieco,[3e,3f] deoxyvernolepin (3) and dihydrodeoxyvernolepin (4) have been shown to be more active than natural vernolepin (1) by at least one order of magnitude.



1



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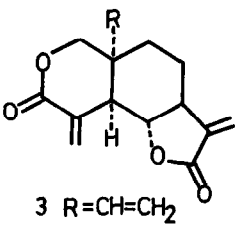
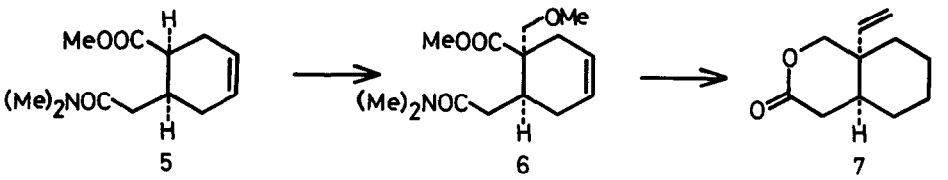


3 R=CH=CH$_2$
4 R=CH$_2$CH$_3$

Several groups have focussed their efforts on the synthesis of a functionalized cis-fused 2-oxa-3-decalone system[2-9] and the total syntheses of these biologically active substances have been achieved independently by Grieco,[3d] Danishefsky,[5d] Schlessinger,[2] and by Isobe and Goto.[7b]

In this paper, we want to report a new synthetic method for preparation of the cis-fused 2-oxa-3-decalone derivative (7) as our initial synthetic objective.

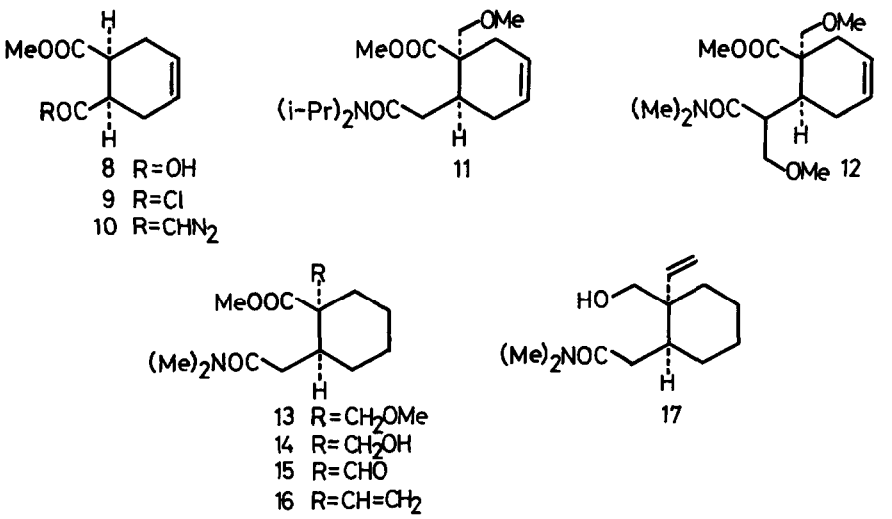
The crucial step of our synthesis involves elaboration of a stereoselective introduction of alkyl group into cyclohexene derivative (5) (Scheme I).



5 6 7

Scheme I

Reaction of the readily available cis-4-cyclohexene-1,2-dicarboxylic acid mono ester (8)[10] with thionyl chloride in refluxing benzene afforded the acid chloride (9). The crude acid chloride (9) was treated with diazomethane in ether containing triethylamine[11] as base to produce in 76% yield the diazoketone (10) [ir max(film) 3090,3025,2940,2905,2840,2220,1728,1630 cm^{-1}; nmr($CDCl_3$)δ 5.69(bs, 2H),5.46(s,1H),3.67(s,3H),2.80-3.18(m,2H),2.31-2.56(m,4H)]. The Wolff rearrangement of (10) with silver benzoate in a solution of dioxane and dimethylamine gave in 91% yield the required amide (5)[bp 72°C/0.01mmHg; ir max(film) 1723,1639 cm^{-1}; nmr($CDCl_3$)δ 5.65(bs,2H),3.66(s,3H),2.99(s,3H),2.93(s,3H); MS m/e 225(M^+)]. Alkylation of (5) was carried out by chloromethyl methyl ether using lithium diisopropylamide as base in THF-HMPA(4:1) at room temperature for 14h to give the methoxymethyl derivative (6)[ir max(film) 1726,1640 cm^{-1}; nmr($CDCl_3$)δ 5.63(bs,2H),3.70(s,3H),3.51(s,2H),3.28(s,3H),2.98(s,3H),2.94(s,3H); MS m/e 269(M^+) in 54% yield after chromatography on silica gel.



8 R=OH
9 R=Cl
10 R=CHN_2

11

12

13 R=CH_2OMe
14 R=CH_2OH
15 R=CHO
16 R=$CH=CH_2$

17

GLC analysis of the crude products obtained in this way showed three peaks of alkylation products, (6), (11), and (12) in a ratio of 87:6:7. None of the stereoisomers other than these compounds were observed among the reaction products. Thus, perfectly stereo and highly regioselective alkylation took place under these conditions. Since stereochemical assignment of (6) could not be fully confirmed by spectral data, the following chemical transformations were made to give the known 2-oxa-3-decalone derivative (7).[3a-c,4a,6a]

Compound (6) was hydrogenated with platinum in ethyl acetate to afford the cyclohexane derivative (13)[bp 59°C/0.004mmHg; ir max(film) 1725,1640 cm^{-1}; nmr ($CDCl_3$)δ 3.69(s,3H),3.47(s,2H),3.25(s,3H),3.01(s,3H),2.95(s,3H),2.70-1.25(m,11H); MS m/e 271(M^+)] in 92% yield. Treatment of (13) with boron tribromide in methylene chloride at -78°C gave the alcohol (14)[ir max(film) 3350,1722,1620 cm^{-1}; nmr ($CDCl_3$)δ 4.65-4.30(m,1H),3.65(s,3H),3.61-3.48(bs,2H),3.04(s,3H),2.96(s,3H),2.90-2.75(m,1H); MS m/e 257(M^+)] in 64% isolated yield. Subsequent oxidation of (14) with pyridinium chlorochromate[12] in methylene chloride at room temperature for 4h provided in 71% yield the aldehyde (15)[ir max(film) 1733,1712,1639 cm^{-1}; nmr ($CDCl_3$)δ 9.56(s,1H),3.77(s,3H),3.01(s,3H),2.93(s,3H),2.55(m,2H),2.16(m,1H); MS m/e 255(M^+)]. The aldehyde (15) was converted in 45% yield to the vinylcyclohexane derivative (16)[bp 56°C/0.003mmHg; ir max(film) 1721,1639 cm^{-1}; nmr($CDCl_3$)δ 5.85 (d-d,1H,J=10.5 and 17Hz),5.14(d-d,1H,J=1 and 10.5Hz),5.01(d-d,1H,J=1 and 17Hz), 3.72(s,3H),3.02(s,3H),2.94(s,3H); MS m/e 253(M^+)] by treatment with methylene-triphenylphosphorane in benzene at -20°C for 1h. Selective reduction of (16) with lithium aluminum hydride in ether at -45°C for 20min gave in 56% yield the alcohol amide (17)[ir max(film) 3380,1612 cm^{-1}, nmr($CDCl_3$)δ 5.90(d-d,1H,J=11 and 17Hz), 5.29(d-d,1H,J=2 and 11Hz),5.19(d-d,1H,J=2 and 17Hz),3.52(m,2H),3.05(s,3H),2.98 (s,3H); MS m/e 225(M^+)]. Lactonization of (17) with 10% hydrochloric acid in THF at room temperature for 16h provided in 95% yield the cis-fused angular vinyl lactone (7), colorless prisms mp 44.5-46°C[ir max($CHCl_3$) 1721,1634,926 cm^{-1}; nmr (CCl_4)δ 2.17,2.65(AB portion of an ABX,2H,J=5,7,and 18Hz),4.15(Δν=18Hz,2H,J=12Hz), 5.22(d,1H,J=18Hz),5.26(d,1H,J=9Hz),5.78(d-d,1H,J=9 and 18Hz); MS m/e 180(M^+)], whose spectral properties were identical with those reported previously.[3a,6c]

In conclusion we have achieved on model study the formation of cis-fused 2-oxa-3-decalone system in ten steps(total yield, ca.4%). The methoxymethyl derivative of (6) may be useful for the stereo and regioselective introduction of the other functional groups into B ring. The total synthesis of vernolepin and its analogs employing the results described in this paper is now progress.

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