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α-METHYLENE LACTONES.[1] VII. A FACILE ROUTE TO AN OXYGENATED α-METHYLENE-γ-BUTYROLACTONE

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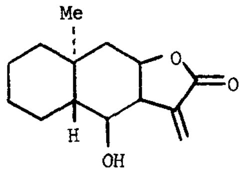
The presence of an α-methylene-γ-butyrolactone is essential for cytotoxic activity[3] among the sesquiterpene lactones. Recently it has been established[3c,4] that the presence of a lipophilic, conjugated ester side chain located homoallylic to the exocyclic double bond of an α-methylene-γ-butyrolactone(e.g. I) contributes to the enhancement of the cytotoxic activity. Such oxygenated α-methylene lactone structural types are commonly found fused to six, seven, and ten membered rings in many naturally occurring sesquiterpene lactones. Synthetic efforts to date[5] have mainly been concerned with the construction of the α-methylene-γ-butyrolactone moiety with little or no attention being devoted to the oxygenated systems[6]. We wish to report a facile route to the homoallylic oxygenated α-methylene-γ-butyrolactone 1 which complements the scheme by Ziegler[6] for the synthesis of the oxygenated α-methylene-γ-lactone 2.



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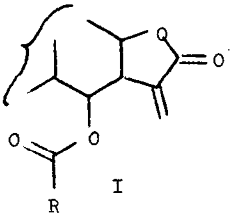

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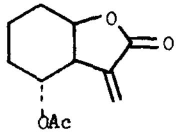

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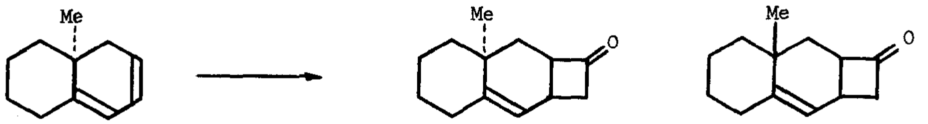
The starting material for the synthetic route was the conjugated diene 3[7]. Treatment of a solution of 3 and dichloroacetyl chloride(excess) in hexane at room temperature with excess triethylamine in hexane resulted in a position-specific, highly stereoselective addition of the elements of dichloroketene.[8] Upon dechlorination of the resultant adduct with excess zinc dust in glacial acetic acid at 60° for ca. 1.5 hr, there was obtained after purification and separation



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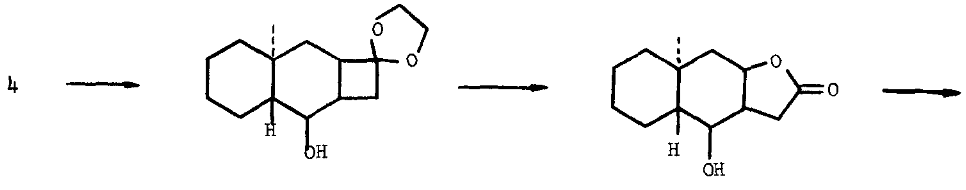

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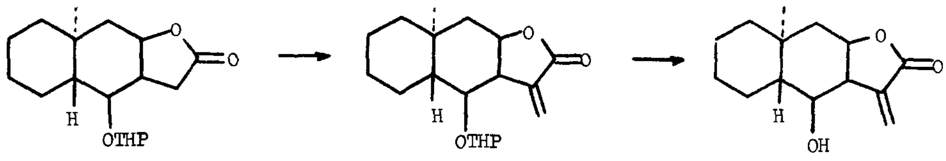

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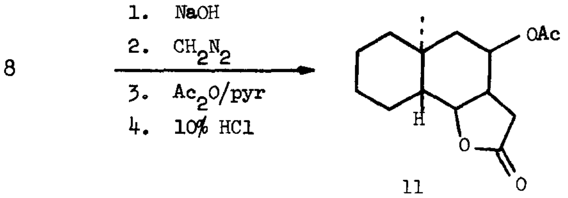
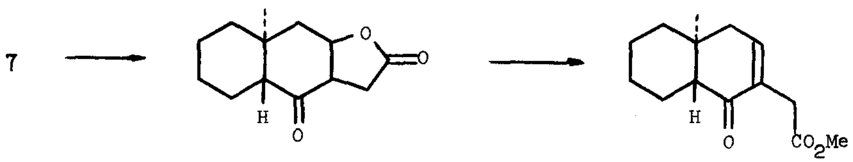
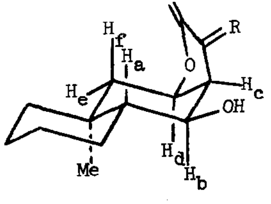




12 13

on silica gel a 70% yield of an 86:14 mixture of the two adducts 4 and 5 respectively from diene 3.[9] Ketalization of 4 followed by hydroboration(BH_3/THF; $NaOH/H_2O_2$) resulted in a greater than 90% yield of ketal alcohol 6. Deketalization(10% HCl/benzene/reflux) followed by Baeyer-Villiger oxidation(HOAc/30% H_2O_2/5°/15hr) produced the crystalline oxygenated butyrolactone 7 [colorless plates, m.p. 155-156°; ir ($CHCl_3$) 3615, 3450, and 1765 cm^{-1}; nmr[10]($CDCl_3$) δ 4.75(1H, dt, J_{df}=11 Hz, $J_{de}=J_{dc}$=6.5 Hz, $-CHO_2C$), 3.72(1H, dd, J_{ba}=11 Hz, J_{bc}=6.3 Hz, $HOC\underline{H}-$), 3.02(1H, m, Hc); m/e 224] in 90% overall yield from 6. Application of the intramolecular nuclear Overhauser effect further substantiated the relative stereochemistry indicated in structure 7. When the α-Me was irradiated, the areas due to H_b and H_d increased by 20-30%, whereas Hc remained unchanged. That the gross structure 7 was correct was corroborated by oxidation(Jones) of 7 to 12[ir ($CHCl_3$) 1770 and 1700 cm^{-1}]. Treatment of 12 with sodium hydroxide followed by esterification with diazomethane produced enone 13[ir ($CHCl_3$) 1725 and 1665 cm^{-1}; nmr ($CDCl_3$ δ 6.65(1H, t), 3.65(3H, s), 3.18(2H, s)]. Tetrahydropyranylation of 7 proceeded in near quantitative yield producing 8 which was readily transformed(80%) into the crystalline acetoxy γ-butyrolactone 11 [colorless needles, m.p. 120°; ir ($CHCl_3$) 1770 and 1730 cm^{-1}].

Finally, conversion of 8 to the oxygenated α-methylene-γ-butyrolactone 1 was accomplished via the α-hydroxymethylation procedure[11] which we developed some years ago. Lactone 8 was converted to its enolate[lithium diisopropylamide, THF, -78°] and treated at -20° with gaseous formaldehyde. The hydroxymethylated lactone obtained was, without purification, converted into its mesylate[$MeSO_2Cl$-pyridine] and then refluxed for 5 hr affording the α-methylene lactone 9[ir ($CHCl_3$) 1755 and 1650 cm^{-1}] in 80% overall yield. Removal of the THP ether[AcOH:H_2O:THF,5:4:1] gave the hydroxylated α-methylene-γ-butyrolactone 1 in 71% yield[ir ($CHCl_3$) 3400, 1756, and 1648 cm^{-1}; nmr[10] ($CDCl_3$) δ 6.36(1H, d, J=3Hz), 6.24(1H, d, J=3Hz), 4.78(1H, dt, J_{df}=11 Hz, $J_{de}=J_{dc}$=6 Hz, $-C\underline{H}CO_2-$), 3.92(1H, dd, J_{ba}=11 Hz, J_{bc}=6 Hz, $HOC\underline{H}-$), 3.53(1H, m, allylic $C\underline{H}$)].



7 R = H,H

1 R = CH_2

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