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A STEREOSPECIFIC SYNTHESIS OF AN ANDROGRAPHOLIDE DERIVATIVE*

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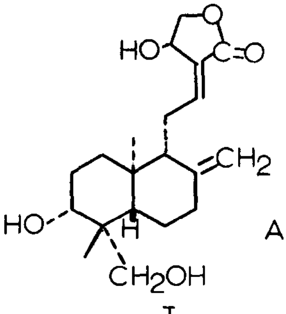
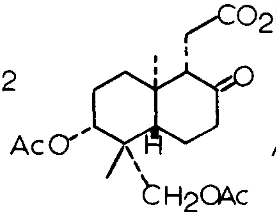
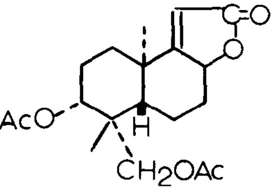
The elegant work of Cava and his collaborators has established the structure[1] and, with the exception of the configuration of the allylic alcohol, the stereochemistry[2] of andrographolide[3] (I). We wish to report the stereoselective synthesis of the racemic α,β-unsaturated lactone (III), which has been obtained previously in the optically active form by ozonolysis of triacetyl andrographolide to the diacetoxyketo acid (II), followed by refluxing with acetyl chloride[2]. This synthesis confirms the structure and stereochemistry of rings A and B of andrographolide.



I



II



III

Condensation of 2-methylcyclohexane-1,3-dione with methyl acrylylacetate[4] in the presence of anhydrous potassium fluoride[5] in dry methanol, gave directly the enone-ester (IV)[6] m.p. 70-71°; λ_{max}^{EtOH} 250 $m\mu$ (10,100); ν_{max} (Nujol) 1733, 1704,

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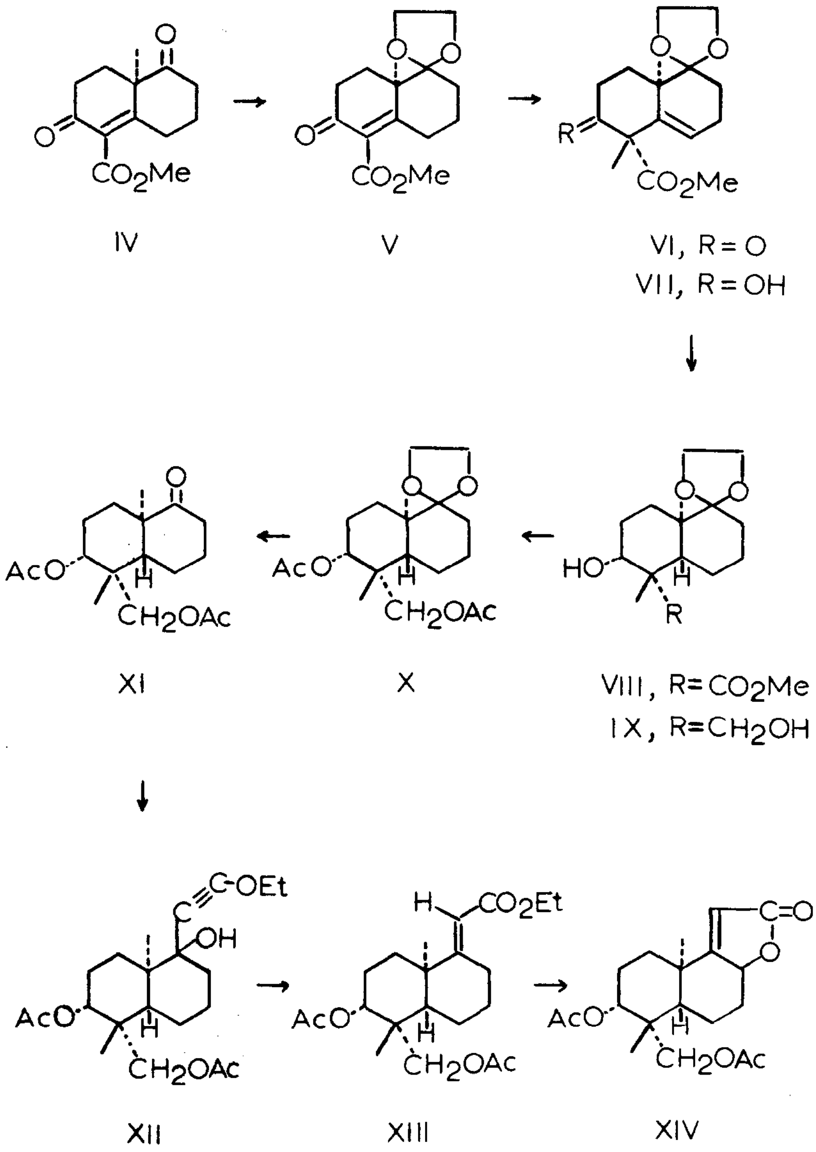
[*] Part II of a thesis by R. L. Chappell submitted to the Graduate School in partial fulfillment of the requirements for the Ph.D. in Chemistry.

1672, 1618 cm.$^{-1}$; τ (CCl$_4$) 8.53, 3H singlet, τ 6.25, 3H singlet, in yields varying from 35-50%. Selective ketalization[7] of the saturated carbonyl group by treatment with ethylene glycol-anhydrous p-toluenesulfonic acid gave a 50% yield of the monoketal (V), m.p. 119-120^0; λ_{max}^{EtOH} 247 mμ (10,200); νmax (Nujol) 1739, 1672, 1618 cm.$^{-1}$; τ (CDCl$_3$) 8.59, 3H singlet, τ 6.15, 3H singlet, τ 5.98, 4H singlet. Treatment of V with methyl iodide and potassium tertiary butoxide in benzene introduced the methyl group stereospecifically[4b] to yield the ketoester VI, m.p. 121.5-122.5^0; ν max (Nujol) 1745, 1709, 848 cm.$^{-1}$; τ 8.82 (CCl$_4$), 3H singlet, τ 8.58, 3H singlet, τ 6.35, 3H singlet, τ 6.08, 4H singlet, τ 4.53, 1H triplet.

Since the ketoester (VI) remained unaffected on exposure to hydrogen in the presence of palladium on charcoal, it was reduced first with sodium borohydride to the alcohol (VII), m.p. 90-91^0; νmax (CCl$_4$) 3534, 1710, cm.$^{-1}$; τ (CDCl$_3$) 8.93, 3H singlet, τ 8.45, 3H singlet, τ 6.34, 3H singlet, τ 6.04, 4H singlet, τ 4.17, 1H triplet. Catalytic hydrogenation (Pd/C) at room temperature saturated the Δ^5 bond to give the decalol (VIII); m.p. 132-134^0; νmax (Nujol) 3620, 1710 cm.$^{-1}$; τ 9.17 (CCl$_4$), 3H singlet, τ 8.66, 3H singlet, τ 6.36, 3H singlet, τ 6.13, 4H singlet. Lithium aluminum hydride reduction in ether - THF mixture (1 : 1) gave the diol (IX): m.p. 136.5-137^0; νmax (Nujol) 3330 cm.$^{-1}$; τ 8.98 (CDCl$_3$), 3H singlet, τ 8.75, 3H singlet, τ 6.08, 4H singlet, which was converted with acetic anhydride-pyridine to the diacetate (X): 117-118^0; νmax (CCl$_4$) 1740, 1250, 1235 cm.$^{-1}$; τ (CCl$_4$) 9.03, 3H singlet, τ 8.93, 3H singlet, τ 8.03, 6H singlet, τ 6.10, 4H intensity. When a solution of the ketal diacetate and p-toluenesulfonic acid was allowed to stand at room temperature in aqueous acetone for 48 hours, smooth deketalization occurred to furnish the ketodiacetate (XI) in 68% yield: m.p. 113-114^0; νmax (CCl$_4$) 1745, 1235, (OAc) 1715 (ketone) cm.$^{-1}$; τ 8.98, 3H singlet, τ 8.82, 3H singlet, τ 7.98, 3H singlet, τ 7.95, 3H singlet, τ 5.65, (C$\underline{\text{H}}_2$OAc). Reaction with lithium ethoxyacetylide[8] at -30^0 gave the acetylenic carbinol (XII): νmax (CCl$_4$) 3570, 2273, 1745 cm.$^{-1}$, which without purification was converted to the desired a,β-unsaturated ester (XIII) by treatment with ethanolic 5% sulfuric acid: νmax (CHCl$_3$) 1745, 1235, 1720, 1635 cm.$^{-1}$; τ (CCl$_4$) 4.7, 1H singlet (vinyl proton). Oxidation with selenium dioxide in glacial acetic acid[8] gave the a,β-unsaturated lactone (XIV):[6] m.p. 139-140^0; νmax (KBr)


CO2Me
IV
V
R
VI, R=O
VII, R=OH
AcO
H
CH2OAc
XI
X
HO
VIII, R=CO2Me
IX, R=CH2OH
C-OEt
OH
XII
H
CO2Et
XIII
C=O
XIV

1760, 1740, 1640, 1240, 1260 cm.$^{-1}$; λ_{max}^{MeOH} 210.5 mμ (17,600). The infrared (CCl_4) and mass spectrum of the synthetic lactone were identical in all respects with those of the naturally derived sample as was also their behavior on thin layer alumina chromatoplates in the systems ethyl acetate-ether (1 : 4) and methyl alcohol-benzene (1 : 24), using iodine vapour as the developing agent.

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