

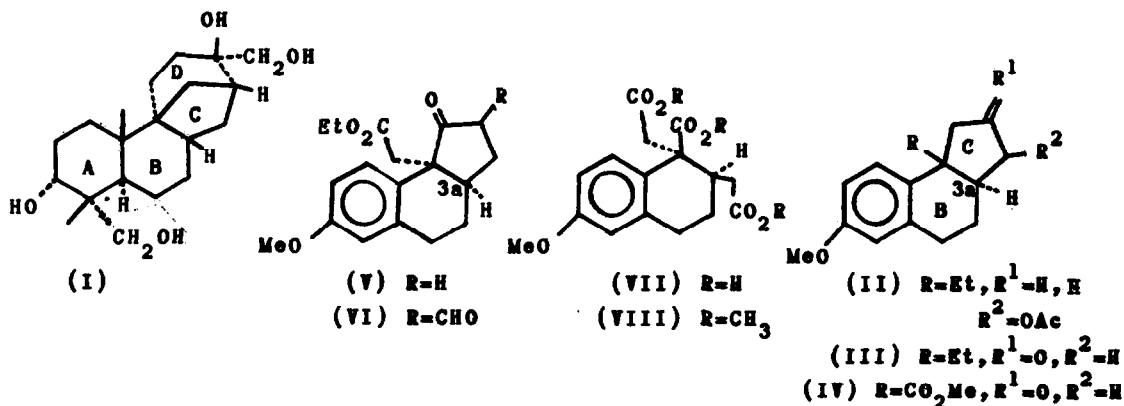
STEREOSPECIFIC SYNTHESIS OF 9b β -CARBOMETHOXY-7-METHOXY-2,3,3a α ,4,5,9b α -HEXAHYDRO-1H-BENZ[e]INDEN-2-ONE; AN INTERMEDIATE TOWARDS PHYSIOLOGICALLY ACTIVE COMPOUNDS

Prebir Kumar Ghosal and Samir Chatterjee*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Calcutta 700032, India

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The recently isolated diterpene antibiotic aphidicelin (I)¹ incorporates a novel tetracyclic skeleton in which the rings B and C are trans-locked. The compounds (II) and (III) have been reported² to show antiandrogenic and anti-metabolic properties. The perhydrobenz[e]indene nuclei present in these also incorporate the rings B and C as trans-locked. In any projected synthesis of skeleta (I), (II) and (III), stereospecific control of B/C ring stereochemistry which is trans may be looked upon as the cardinal aspect since from free energy considerations, the favoured stereochemistry at B/C ring junction may be expected^{3,4} to be cis. We report here a stereospecific synthesis of the title compound (IV) incorporating the requisite ring B/C trans geometry which will serve as an advanced relay towards synthesis of aphidicelin framework. Furthermore, suitable harnessing of existing functionalities in (IV) will lead to formation of (II) and (III).



7-Methoxy-2,3,3a α ,4,5,9b α -hexahydro-1H-benz[e]inden-1-one⁴ was alkylated with ethyl bromoacetate in DME in presence of dry potassium tert-pentoxide yielding the ketoester (V)⁵ in 60% yield; b.p. 160-62°/0.05 mm; ν_{\max} 1740,

1730, 1600 cm^{-1} ; $\delta(\text{CCl}_4)$ 7.36 (1H, d, $J=10$ Hz), 6.7-6.46 (2H, m), 4.0 (2H, q, $J=8$ Hz), 3.7 (3H, s), 1.2 (3H, t, $J=8$ Hz). On well appreciated analogy⁶, alkylation might be considered to have taken place from the direction which should lead to cis relationship with the 3a hydrogen. The ketoester (V) was formylated with excess of ethyl formate in presence of NaH to afford the formyl derivative (VI). Treatment of (VI) in aqueous NaOH solution with 30% H_2O_2 at 25° smoothly cleaved ring C with simultaneous hydrolysis of the side chain ester functionality resulting in the formation of (VII) in 46% yield; m.p. 190°; ν_{max} 1700, 1600 cm^{-1} . This was esterified with ethereal CH_2N_2 solution to afford the triester (VIII) in almost quantitative yield; m.p. 195°; ν_{max} 1730, 1600 cm^{-1} ; $\delta(\text{CDCl}_3)$ 7.1 (1H, d, $J=10$ Hz), 6.78-6.62 (2H, m), 3.8 (3H, s), 3.72 (3H, s), 3.66 (3H, s), 3.5 (3H, s). The triester (VIII) was subjected to Dieckmann cyclization⁷ in presence of dry potassium tert-butoxide in benzene. The resulting β -ketoester (FeCl₃ colouration) was decarboxymethylated⁸ by refluxing with a mixture of moist DMSO and NaCl to afford (IV) as a crystalline solid in 40% yield; m.p. 140°; ν_{max} 1740, 1600 cm^{-1} ; $\delta(\text{CDCl}_3)$ 6.98 (1H, d, $J=10$ Hz), 6.8-6.6 (2H, m), 3.8 (3H, s), 3.64 (3H, s).

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