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STEREOSELECTIVE SYNTHESIS OF THE BASIC SKELETON OF APHIDICOLAN DITERPENES SYNTHETIC APPROACH TO APHIDICOLIN

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Summary The basic skeleton of aphidicolan-type diterpenes was stereoselectively synthesized via thermolysis of a benzocyclobutene

Aphidicolin (1), isolated from a culture of Cephalosporium aphidicola Petch by Hesp[1], has a unique carbon-framework and has been shown to display antiviral activity Two elegant total syntheses of 1 have recently been published by Trost[2] and McMurry[3] Ireland[4] has also reported an interesting synthetic approach to 1 We here wish to report a stereoselective synthesis of the basic aphidicolan skeleton by an alternative approach which involves thermolysis of a benzocyclobutene as the key reaction

The banzocyclobutene (2)[5] was alkylated with the ethylene acetal (3) to give the acetal (4) in 73 % yield After deprotection of the carbonyl with acid, the aldehyde (5) was treated with 3-butenyl-1-magnesium bromide to afford the alcohol (6) which was converted to the corresponding ketone (7) in 71 % yield using pyridinium chlorochromate[6] Spectral data [ν_{max} ($CHCl_3$) 2235 (C≡N) and 1715 (C=O) cm^{-1}, δ ($CDCl_3$) 2 22 (3H, s, Ar-CH_3), 3 17 (1H, d, J=14 Hz, Ar-$\underset{H}{\overset{H}{C}}$-), 3 67 (1H, d, J=14Hz, Ar-$\underset{H}{\overset{H}{C}}$-), 3 83 (3H, s, OCH_3), 5 00 - 5 30 (2H, m, -CH=CH_2), 5 68 - 6.28 (1H, m, -CH=CH_2), 6 85 (1H, br s, arom) and 6 91 (1H, br s, arom), m/e 283 (M^+)] is consisted with structure 7 Thermolysis of the benzocyclobutene (7) was carried out in refluxing o-dichlorobenzene for 6 h to furnish the cyclized product (8) in 55 % yield, [ν_{max} ($CHCl_3$) 2225 (C≡N) and 1705 (C=O) cm^{-1}, δ ($CDCl_3$) 2 40 (3H, s, Ar-CH_3), 3 82 (3H, s, OCH_3), 6 80 (1H, br s, arom) and 6 95 (1H, d, J=2Hz, arom), m/e 283 (M^+) Base treatment of the compound (8), followed by acid hydrolysis, gave the tetracyclic compound (9), m/e 284 (M^+) The i r spectrum of 9 showed two carbonyl absorptions (at 1735 and 1710 cm^{-1}) and no nitrile absorption The stereochemical assignment was made on the basis of the n m r spectrum [δ ($CDCl_3$) 2 20 (3H, s, Ar-CH_3), 3 87 (3H, s, OCH_3), 6.70 (1H, d, J=2Hz, arom) and 7 63 (1H, d, J=2Hz, arom) which showed one low field aromatic proton From an examination of molecular models it is seen that the aphidicolan-type stereoisomer (9) can be depicted as in (A) or (B) of Fig 1 In formula A, one aromatic proton is cleary deshieled by a carbonyl group As this effect was observed in the n m r spectrum of the above product the stereochemistry is assigned as in formula 9 The same effect has been observed with the A-ring aromatic iso-drimenin ring system[7] The conversion of 9 to aphidicolin (1) is now under progress in this laboratory

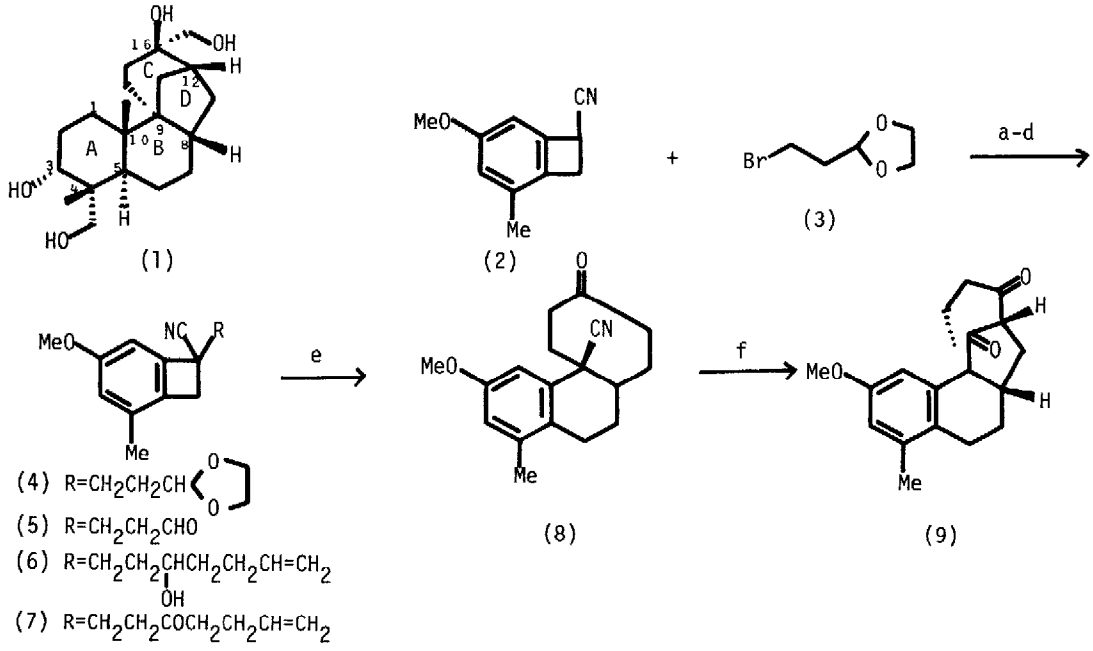
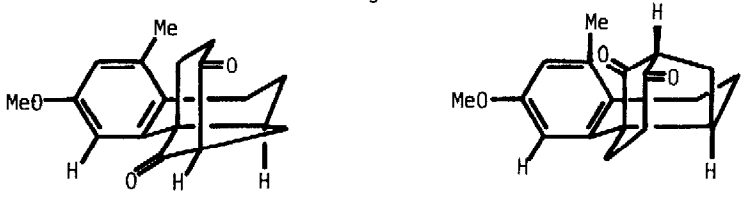


Fig 1



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