Steroeselective Total Synthesis of (±)-Hirsutine and Related *Corynanthé* Alkaloids

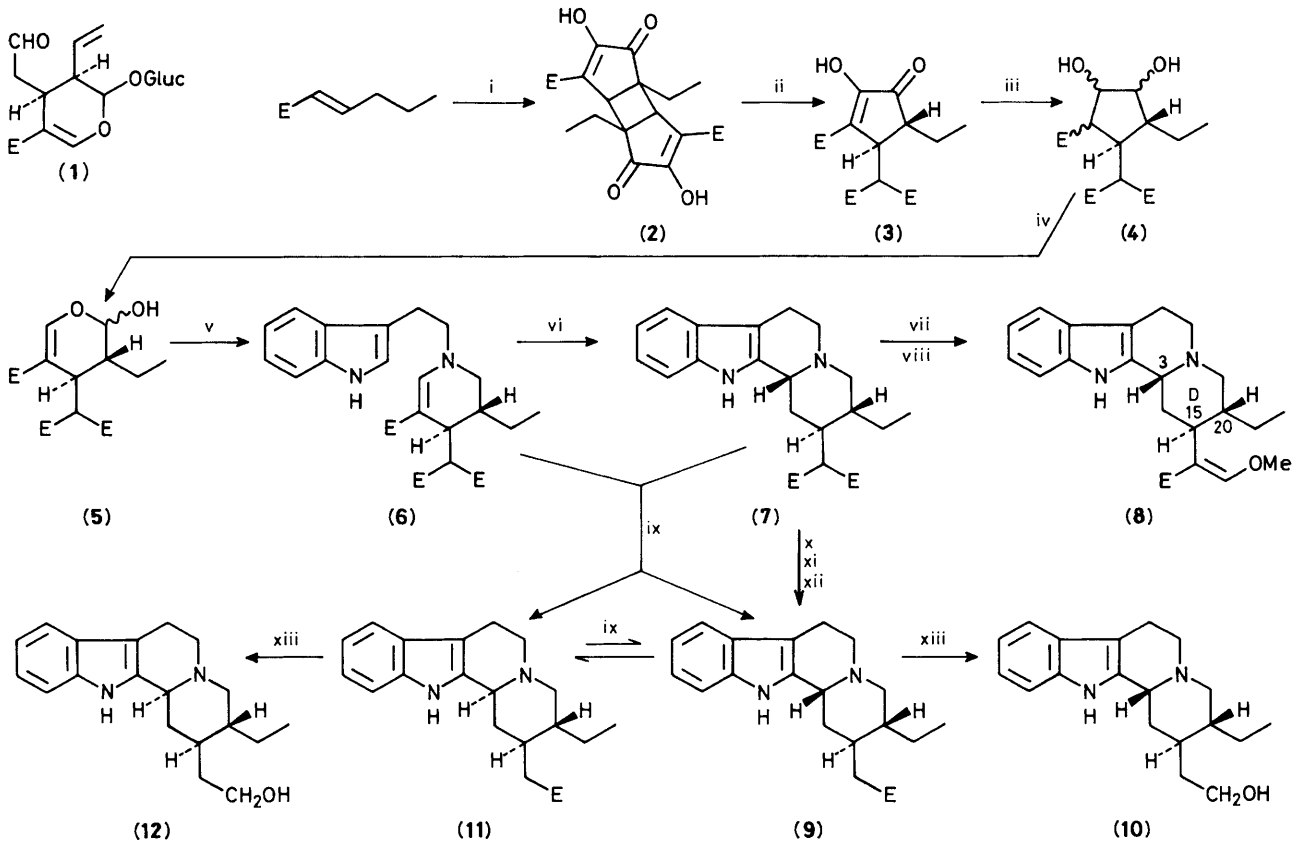
Richard T. Brown,* Martin F. Jones, and Mark Wingfield
Department of Chemistry, The University, Manchester M13 9PL, U.K.

In a completely stereoselective sequence, an analogue of dihydrosecologanin aglucone has been synthesised *via* a novel cyclopentenedione dimer and converted into tetracyclic indole alkaloids.

Indole alkaloids of the *Corynanthé* type, such as dihydrocorynantheol (**12**) and hirsutine (**8**), have been the subjects of several syntheses over the past three decades.[1] Because of the three chiral centres at C-3, -15, and -20, controlling stereochemistry in the production of diastereoisomers has always presented major problems. A common feature of the various synthetic approaches is that the stereochemical centres have almost invariably been introduced by manipulation of functional groups on the six-membered ring of the piperidine derivative which eventually constitutes ring D of the alkaloids, and as a consequence the degree of stereoselectivity has often been less than ideal. We considered that it would be preferable to introduce the relative configuration of the adjacent C-15 and C-20 *via* a five-membered ring intermediate, where potential eclipsing 1,2 interactions would result in essentially complete selectivity for *trans* substituents under equilibrating conditions. Again, since we have converted the natural precursor secologanin (**1**) into several alkaloids by various routes,[2,3] it was evident that stereoselective total syntheses would be feasible *via* synthetic analogues of (**1**). We now report the incorporation of both features into a short synthesis of the dihydrosecologanin aglucone analogue (**5**) and its transformation into (±)-hirsutine (**8**) and other tetracyclic *Corynanthé* alkaloids.

In a previous communication we have described the formation of the novel cyclopentenedione dimer (**2**) by vinylogous Claisen condensation of methyl hex-2-enoate and dimethyl oxalate, and its subsequent conversion into the hydroxycyclopentenone (**3**).[4] As anticipated, the steric constraints ensured that the ethyl and malonate groups could only be *trans* in the thermodynamic product of the (reversible) Michael addition. Catalytic hydrogenation of (**3**) over Raney nickel afforded a 2:1 mixture of two isomeric diols (**4**),† of which only the minor product was apparently a *cis*-diol, as indicated by formation of a phenylboronate derivative, m.p. 105—108 °C. However, both were quantitatively cleaved by sodium periodate to yield the desired dihydrosecologanin aglucone analogue (**5**), m.p. 97—98 °C (λ_{max} 234 nm, shifting to 272 nm in alkali). The n.m.r. spectrum showed (**5**) to be a *ca.* 2:1 anomeric mixture in solution in $CDCl_3$.

Following a procedure developed in our laboratory,[5] the lactol was reductively aminated with tryptamine and sodium cyanoborohydride to give the tetrahydropyridine (**6**) (λ_{max} 223, 292 nm) (50%). Subsequent heating with 1% HCl in aqueous methanol under reflux selectively hydrolysed and decarboxylated the β-amino-acrylate ester, and promoted stereoselective Picter–Spengler cyclisation to the 3β tetracyclic base (**7**),[6] m.p. 171—173 °C (HCl salt m.p. 187—



Scheme 1. Gluc = β-D-glucopyranosyl, E = CO_2Me. *Reagents:* i, $(CO_2Me)_2$, KOMe, Et_2O; ii, $CH_2(CO_2Me)_2$, KOMe, MeOH; iii, H_2, Raney Ni, MeOH; iv, $NaIO_4$, MeOH–H_2O; v, tryptamine, $NaCNBH_3$, Pr^iOH; vi, 1% HCl, MeOH–H_2O, heat; vii, Bu^i_2AlH, PhMe, −78 °C; viii, MeOH (1 equiv.), HCl, CH_2Cl_2, −15 °C, 3 days; ix, $EtCO_2H$, heat, 48 h; x, NaOH, H_2O, heat; xi, HCl, heat; xii, $SOCl_2$, MeOH; xiii, $LiAlH_4$, tetrahydrofuran, 0 °C.

189 °C) (35%). Conversion of (**7**) into (±)-hirsutine (**8**) was accomplished in a similar manner to Wenkert *et al.*[6] by partial reduction with Bu^i_2AlH and methylation. Notably, no other stereoisomers were detectable throughout the whole sequence, and the synthesis appears to be completely stereoselective for the crucial C-3, -15, and -20 chiral centres.

Using conventional procedures with alkali and acid, the malonate group of (**7**) was hydrolysed and decarboxylated to an acid which gave (**9**) on re-esterification; subsequent reduction with $LiAlH_4$ furnished 3-epidihydrocorynantheol (**10**) (50%). Standard C-3 epimerisation methods could be used on (**9**) and (**10**) to obtain the corresponding 3-H α isomers. However, we discovered while epimerising (**7**) in refluxing propionic acid that concomitant demethoxycarbonylation of the malonate moiety occurred to give a mixture of the acetate derivatives (**9**) and (**11**) in 97% yield. After chromatographic separation, (**11**) was reduced to (±)-dihydrocorynantheol (**12**)[7] m.p. 181—183 °C. Still further abbreviation of the reaction sequence was achieved when it was found that treatment of the tetrahydropyridine (**6**) itself with propionic acid under reflux afforded a 1 : 3 mixture of (**9**) and (**11**) directly, the isolated yield of 35% being twice that obtained by the stepwise route.

† All compounds were fully characterised by i.r., u.v., n.m.r., and mass spectroscopy and elemental analysis.

Work is in hand with analogues of the versatile intermediate (**2**) to synthesise other alkaloids and cyclopentanoids, and on exploiting the novel dealkoxycarbonylation method for malonate esters and related compounds. Yet a further interesting prospect lies in achieving enantioselection during the Michael reaction of the dimer by the use of chiral substrates or bases.

Two of us (M. W. and M. F. J.) thank the S.E.R.C. for financial support.

Received, 26th March 1984; Com. 409

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