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TOTAL SYNTHESIS OF MONOTERPENOID ISOQUINOLINE ALKALOIDS

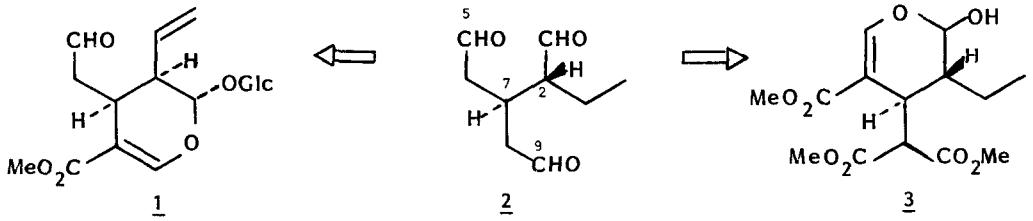
By Richard T. Brown and Martin F. Jones

Department of Chemistry, The University, Manchester. M13 9PL

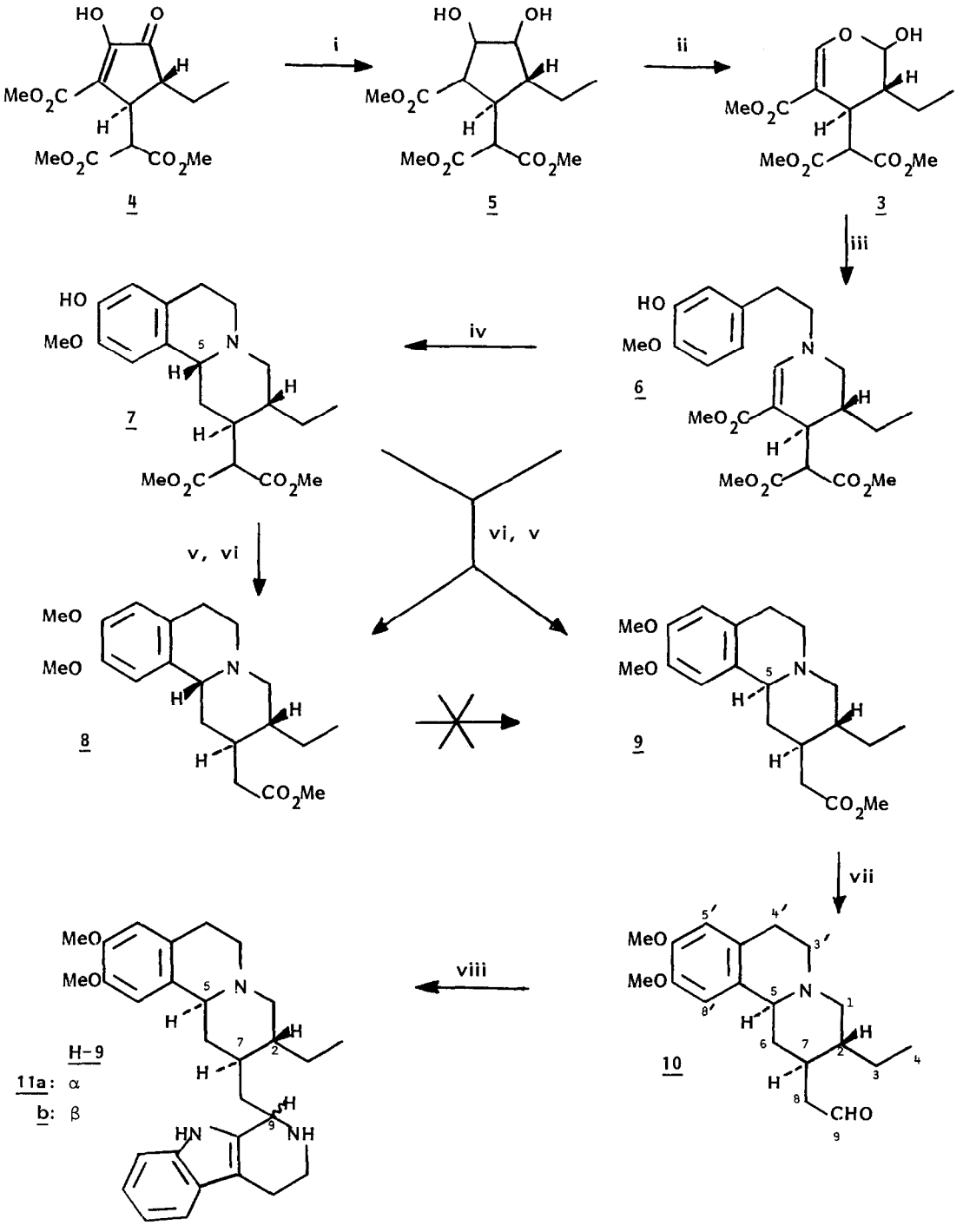
ABSTRACT

A novel analogue (3) of dihydrosecologanin aglucone has been synthesised via a substituted cyclopentenolone and converted into (±)-protoemetine (10) and related Ipecac alkaloids.

In a recent letter[1] we described the stereoselective synthesis of a series of novel cyclopentenolones from cyclopentenedione dimers produced by double vinylogous Claisen condensation of γ-substituted crotonate esters and dimethyl oxalate. We now report the use of such a cyclopentenolone (4) to prepare lactol 3 as a synthetic equivalent to the hypothetical synthon 2 constituting the monoterpenoid moiety of the alkaloids protoemetine (10), deoxytubulosine (11a) and related bases. *In vivo*, of course, 2 is derived from the iridoid glucoside, secologanin (1)[2], and, indeed, we have previously carried out the transformation of 1 into Ipecac alkaloids[5]. One advantage of the present approach is that the *trans* stereochemistry at C-2 and C-7 required for the alkaloids is generated exclusively during the Michael addition forming the cyclopentenolone, and in turn these centres can be used to achieve a measure of control over the C-5 configuration.

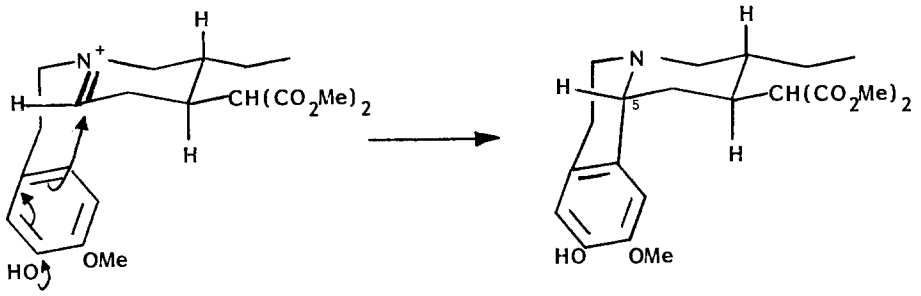


Catalytic hydrogenation of 4 over Raney nickel gave a pair of diastereomeric alcohols[3] (5), both of which were cleaved with sodium periodate to a dialdehyde isolated as the crystalline



Reagents: i, H_2-Ni; ii, $NaIO_4$; iii, $NaCNBH_3$, 3-hydroxy-4-methoxyphenethylamine; iv, H_3O^+, MeOH, Δ; v, CH_2N_2; vi, $EtCO_2H$, Δ; vii, i-Bu_2AlH; viii, H_3O^+, tryptamine.

lactol (3), m.p. 97-8°C. This lactol is essentially an analogue of 3,4-dihydrosecologanin aglucone, and following a procedure developed in this laboratory with the latter[4], 3 was reductively aminated with 2-3'-hydroxy-4'-methoxyphenethylamine to afford the tetrahydronicotinate derivative 6 (40% isolated yield from 4). Selective hydrolysis and decarboxylation of 6 with 1% HCl in refluxing aq. methanol, and concomitant Picter-Spengler condensation gave the tricyclic base 7 . We had previously observed that an analogous 3,4-dimethoxyphenethylamine derivative did *not* cyclise under these conditions, a *para* phenolic hydroxyl group being essential to activate the aromatic ring sufficiently for condensation to occur[5]. Another notable feature of this reaction was the complete selectivity for 5β stereochemistry , which can be rationalised by postulating a requirement for axial attack by the phenol at C-5 in the immonium intermediate where equatorial ethyl and malonyl substituents determine the half-chair conformation:



After methylation of the phenolic group in 7, inversion of C-5 to the thermodynamically preferred 5α epimer was attempted by treatment with refluxing propionic acid for 36 hours - a standard method for tetrahydro-β-carboline alkaloids - but proved ineffectual. However, complete conversion to a new compound 8 had occurred *via* a slow but smooth monodecarbomethoxylation of the malonate moiety (92% isolated yield). This novel process enabled us to shorten the projected route by avoiding the tedious and inelegant conversion of malonate to acetate by conventional procedures. In the event, it was found that the unmethylated precursor (7)

did equilibrate C-5 in refluxing propionic acid to give majorly the H-5α epimer in addition to decarbomethoxylation. Subsequent methylation afforded the required product 9 together with 8 in a ratio of 1.7:1 (72% yield). Yet further abbreviation of the route proved possible by heating the tetrahydronicotinate 6 directly in propionic acid when both decarbomethoxylations, Picter-Spengler cyclisation and H-5 epimerisation were all achieved in one pot (overall yield 40%).

After chromatographic separation, 9 was reduced with Dibal-H (90% yield) to (±)-protoemetine (10)[6]. The rather unstable product was identified by full n.m.r. analysis[7], and by condensation with tryptamine to form (±)-deoxytubulosine (11a), m.p. 137-140°, and its C-9 epimer (11b) identical by comparison of t.l.c. and spectroscopic data with authentic samples of the natural products[5]. Since protoemetine has previously[6] been converted into cephaeline and emetine, our sequence also constitutes a formal total synthesis of these alkaloids.

In addition to the above products with naturally occurring stereochemistry this synthetic approach can afford the other diastereoisomers. Not only is the 5β epimer of protoemetine readily available from 8, but appropriate strategies with the lactol may be envisaged (*cf.* ref. 5) to effectively exchange the rôles of C-5 and C-9 in synthon 2 and hence afford 2,7 *cis* isomers. An even more interesting prospect would be to achieve enantioselection in the Michael addition leading to the cyclopentenolone 4 and hence chiral total syntheses.

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