Biomimetic Synthesis of Indole Alkaloids: Dihydromancunine

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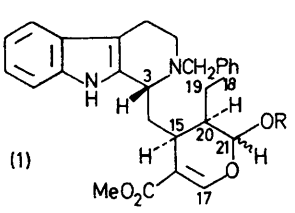
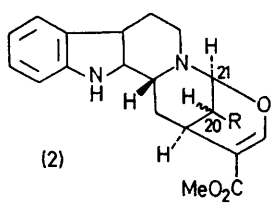
Summary Dihydromancunine (**2a**), a model for a proposed biosynthetic intermediate, has been synthesised from vincoside and converted into *Corynanthé* indole alkaloids in a biomimetic sequence; hirsutine (**6b**) and dihydrocorynantheine (**6c**) have also been synthesised.

IN a recent communication[1] we suggested that a pentacyclic amino-acetal (**2c**) would be a plausible biosynthetic intermediate on the route from vincoside to *Corynanthé* indole alkaloids. Evidence supporting this suggestion has now been provided by the synthesis of a dihydro-derivative (**2a**) of the hypothetical intermediate, mancunine, and more importantly, its subsequent ready conversion into a standard *Corynanthé* structure. Condensation of dihydrosecologanin with N^b-benzyltryptamine afforded N^4-benzyl-18,19-dihydrovincoside (**1a**) $[\alpha]_D^{26}$ $-108°$ (MeOH), further characterised as the crystalline tetra-acetate, m.p. 203—205°, $[\alpha]_D^{25}$ $-97°$ ($CHCl_3$), and identified by correlation with the known vincoside lactam.[2] Removal of the sugar with β-glucosidase yielded a mixture of two readily interconvertible aglycones (**1b**) and (**1c**) which on hydrogenolysis with Pd–C in methanolic acetic acid gave 20α-dihydromancunine (**2a**), m.p. 174—176°, $[\alpha]_D^{25}$ + 266° ($CHCl_3$), together with a trace of 3β-dihydrovallesiachotamine (**7**).



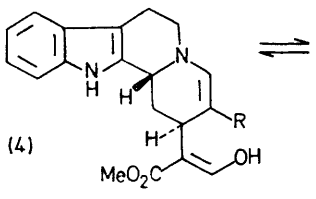
(1)

	H-21	R
a;	β	Gluc.
b,	β	H
c,	α	H



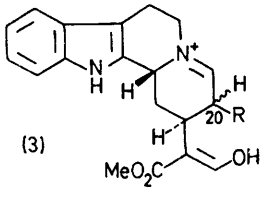
(2)

	H-20	R
a;	α	Et
b;	β	Et
c;	β	$CH=CH_2$



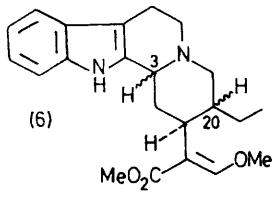
(4)

	R
a;	Et
b;	$CH=CH_2$



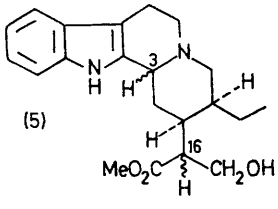
(3)

	H-20	R
a;	α	Et
b;	β	Et
c;	β	$CH=CH_2$



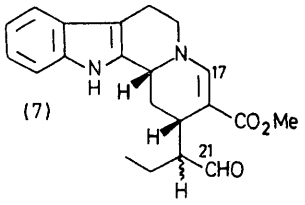
(6)

	H-3	H-20
a;	α	α
b;	β	β
c;	α	β



(5)

	H-3
a;	α
b;	β



(7)

The structure of dihydromancunine was elucidated by i.r., u.v., c.d., ^1H and ^{13}C n.m.r., and mass spectra, and finally established by the chemical correlation with corynantheidine (**6a**) below.

In agreement with an amino-acetal function the u.v. spectrum of (**2a**) did not show an immediate shift on addition of alkali, but an ionised β-hydroxyacrylate chromophore slowly developed over a period of hours. This indicated that gradual ring-opening to the enamine (**4a**) was occurring, which eventually resulted in conversion into the vallesiachotamine derivative (**7**). Accordingly prolonged treatment of (**2a**) with $NaBH_4$ in MeOH intercepted the intermediate (**3**) and afforded a compound with the *Corynanthé* structure (**5b**), $[\alpha]_D^{25}$ +15° (MeOH). Subsequent epimerisation of 3-H by treatment with $Pb(OAc)_4$ followed by $NaBH_4$ yielded dihydroisositsirikine (**5a**), identical with that obtained from corynantheidine (**6a**) by acid-catalysed cleavage of the enol ether and borohydride reduction. In addition to establishing the structure this sequence showed that 20-H had been inverted from β to α in the conversion of (**1a**). Reduction of dihydromancunine (**2a**) in CH_3OD incorporated only one deuterium (at C-16) into the product, proving that no epimerisation occurred at this stage and dihydromancunine was already 20α.

The configuration of the aglycones (**1**) at C-20 was almost certainly β, since methylation of both with diazomethane gave the same enol ether, which on catalytic hydrogenation afforded only hirsutine (**6b**), m.p. 105—107°, $[\alpha]_D^{25}$ +66° ($CHCl_3$).[1,3,4] Final proof of the C-20 stereochemistry was obtained by 3-H epimerisation of hirsutine as above to dihydrocorynantheine (**6c**), m.p. 109—111°, $[\alpha]_D^{25}$ +23·5° (MeOH)[4] and comparison of both with authentic samples.

Hence the inversion at C-20 is probably occurring when N-4 cyclises to C-21. The initially formed 20β-dihydromancunine (**2b**) has an axial ethyl group which can, however, be changed to a more stable equatorial orientation by epimerisation *via* the enamine (**4a**) to the 20α-isomer (**2a**). *In vivo* mancunine would presumably undergo an analogous opening of the ether bridge to give a 3β-dehydrogeissoschizine (**4b**), which could then be transformed into the different *Corynanthé* alkaloids by various combinations of reduction, methylation, cyclisation, and 3-H epimerisation.

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