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STEREOSPECIFIC SYNTHESIS OF *ERYTHRO* CINCHONA ALKALOIDS FROM SECOLOGANIN

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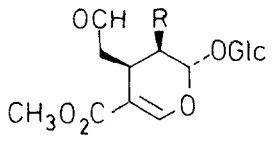
Summary A short, diastereoselective synthesis of (+)-dihydrocinchonine (7) and (-)-dihydrocinchonidine (8) from their biogenetic precursor, secologanin (1a), and lepidine has been achieved in 28% overall yield.

Since the first successful synthesis of quinine by Woodward and Doering[1] in 1945, the pharmacologically important Cinchona alkaloids have been the targets of several synthetic schemes [2,3]. In the main these have led to racemic mixtures, so that an approach from the readily available secologanin (1a), the chiral monoterpenoid precursor in vivo of the Cinchona alkaloids, has the intrinsic advantage of already being in the correct enantiomeric series. We now report a short, diastereoselective synthesis of the erythro pair (+)-dihydrocinchonine (7) and (-)-dihydrocinchonidine (8) from dihydrosecologanin (1b) obtained by catalytic hydrogenation of 1a.

In a 'one-pot' sequence, 4-quinolylacetic acid (2) was prepared by consecutive treatment of lepidine with lithium diisopropylamide, carbon dioxide gas and an equivalent of pyridine hydrochloride and condensed under Knoevenagel conditions with 1b to give in 90% yield the E-vinylquinoline 3† ($J_{8,9}$ = 15 Hz; λ max. 228, 305 nm) exclusively. Subsequent enzymic glucolysis and reductive amination[4], under carefully controlled conditions to minimise addition to the conjugated alkene by hydride or other nucleophiles, afforded the tetrahydronicotinate 4 (λ max. 230, 282, 305 nm) in 55% yield after chromatography. This was hydrolysed and decarboxylated with acid to an imine, reduced in situ to the piperidine 5 (86% yield) by sodium cyanoborohydride rather than the previously used borohydride[4] to avoid reduction of the vinyl group. At this stage the structure of 5 was confirmed by the identity of its acetamide with a sample prepared from dihydrocinchonine by mesylation and LAH reduction[5], followed by ring opening with acetic anhydride.

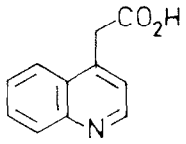
† All new compounds were fully characterised by spectroscopic and analytical data.



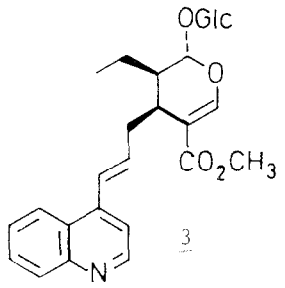
R

1 a $CH{:}CH_2$
b CH_2CH_3
c $CH(OH)CH_3$
d CH_2CH_2OH

1b MeOH/py/piperidine RT 36h

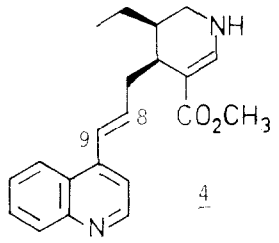


2



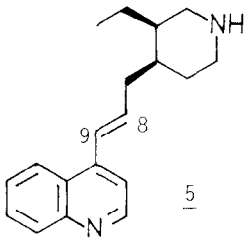
3

β-glucosidase
$NH_4OAc/NaCNBH_3$
pH 6.2 18h



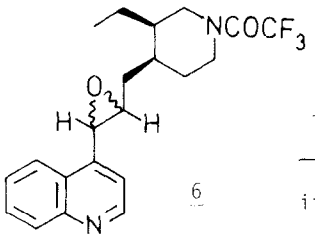
4

i) 3% HCl/aq.MeOH/Δ 40 mins
ii) $NaCNBH_3$



5

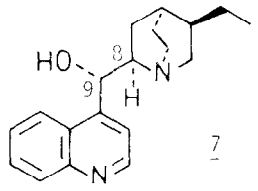
i) $(CF_3CO)_2O$ 0°
ii) CF_3CO_3H/CH_2Cl_2
Na_2HPO_4
RT 12h



6

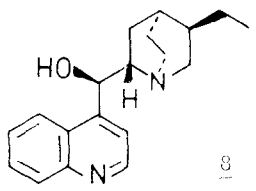
threo

i) K_2CO_3/MeOH/RT 2h
ii) PhMe/EtOH/Δ 24h



7

(+)-Dihydrocinchonine



8

(-)-Dihydrocinchonidine

The next step was crucial, requiring selective epoxidation of the 8,9 alkene in presence of secondary and tertiary amines, and even though the former could be protected as an amide, the latter would still readily form an N-oxide. Furthermore, because of the electron withdrawing quinoline moiety, the alkene is electron-deficient and hence would be expected to react sluggishly with peracids. On the other hand, it was contemplated that the conjugated alkene might undergo nucleophilic epoxidation with alkaline hydrogen peroxide in a manner analogous to an αβ-unsaturated ketone[6], but unfortunately this approach was totally unsuccessful under various conditions.

As expected, treatment of the chloroacetamide of 5 with m-chloroperbenzoic acid rapidly converted it to the quinoline N-oxide (λ max. 352 nm), but we were pleased to observe that this slowly reacted further over three days to give an epoxide (λ max. 330 nm). After removal of the chloroacetyl group with thiourea[7], cyclisation to a quinuclidine was attempted but results were inconclusive due to difficulty with the N-oxide, and even though methods for its reduction are known[8], we decided to explore ways of avoiding N-oxidation.

One possibility is to use an acid strong enough to protect the nitrogen by protonation, although a buffer might be needed to minimise acid catalysed hydrolysis of the epoxide. Experiments on model compounds indicated that selective epoxidation of the alkene in high yield (>90%) was feasible using trifluoroperacetic acid and granular disodium hydrogen phosphate under anhydrous conditions. In the event, a convenient 'one-pot' procedure was evolved whereby 5 was converted to the trifluoroacetamide with excess anhydride, which then gave peracid on addition of 90% hydrogen peroxide. Since 5 was an E-alkene the threo pair of epoxides 6 was obtained exclusively, but despite the presence of two chiral centres, there was no appreciable evidence of any stereofacial selectivity, both isomers being formed to a similar extent. Mild hydrolysis of the trifluoracetyl group and cyclisation of the liberated secondary amine to a quinuclidine by warming in toluene/ethanol[9] then afforded the erythro pair of alkaloids (66% yield from 5) by inversion of configuration at C-8. These were separated by chromatography (silica; $CH_2Cl_2/Et_2O/Et_2NH$ 13:10:2) and shown to be identical with authentic samples of (+)-dihydrocinchonine (7) and (-)-dihydrocinchonidine (8).

We have thus achieved a short, diastereoselective synthesis of erythro Cinchona alkaloids in the reasonable overall yield of 28% from readily available starting materials. Obviously, by the use of substituted lepidines and picolines other analogues can be obtained, but a more interesting project would be the synthesis from secologanin derivatives such as 1 c, d of metabolites[3] of quinine and quinidine as well as the parent alkaloids. An ultimate prospect is chiral epoxidation to differentiate between the erythro alkaloids, but this is more nebulous as no really effective method currently exists for this type of alkene[10].

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