Hydrolysis and Selective Reduction with Yeast: Enantiospecific Synthesis of Antirhine from Secologanin

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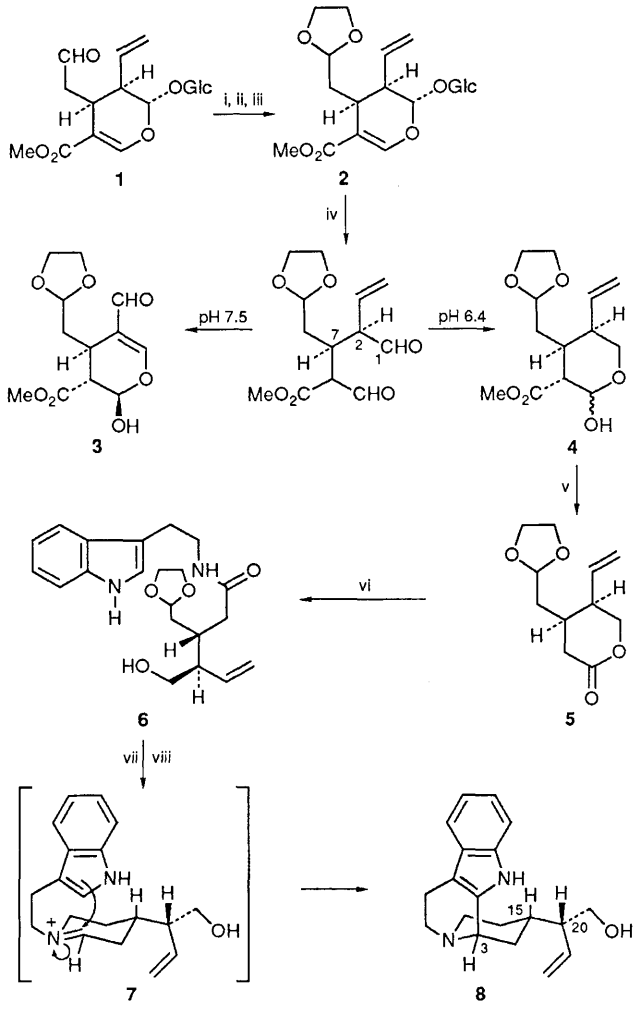
Glucoside hydrolysis and chemoselective reduction of secologanin ethylene acetal **2** with baker's yeast affords a C-1 reduced aglucone **4** from which (+)-antirhine **8** is obtained in a four-step sequence.

Enzymes of the whole cells of baker's yeast, *Saccharomyces cerevisiae*, have been used both for asymmetric carbonyl reduction and for hydrolysis of glycosides[1] as exemplified for millenia by the transformation of maltose to ethanol in the brewing process. We have previously cleaved the sugar from derivatives of secologanin **1** with β-glucosidase, where we found that the product is dependent upon the pH of the medium; at pH 5 the aglucone rearranged to a dihydropyran predominantly, whereas at pH 7 a carbocyclic compound was obtained, and both compounds were used for enantiospecific synthesis of heteroyohimbine and yohimbine alkaloids.[2] We decided to try baker's yeast as a cheap replacement for β-glucosidase, and, in the event, treatment of secologanin ethylene acetal **2** with yeast at pH 7.5 afforded the carbocyclic aglucone **3** in 45–55% yield.[3] However, at pH 6.4 a combination of hydrolysis *and* selective reduction was achieved wherein the C-1 reduced aglucone **4** became the major product, notably with conservation of the labile chiral centre at C-2. Thus, simple control of the pH ensures that either product can be obtained.

It was evident to us that **4** could be used as a synthetic precursor for antirhine **8**.[4] The major difficulties faced in previous syntheses of antirhine or its derivatives[5] have involved the control of chiral centres, in particular at C-20, a problem which is resolved by using **4**. We now report a completely stereoselective and enantiospecific synthesis of antirhine from secologanin.

Secologanin was converted to its ethylene acetal tetraacet-



Scheme 1 *Reagents and conditions*: i, Ac_2O, py, 12 h; ii, $(CH_2OH)_2$, tetrahydrofuran (THF), trifluoroacetic acid, heat, 1 h; iii, NaOMe, MeOH, 2 h; iv, yeast, 25 °C, 7 days; v, 4 mol dm^{-3} NaOH, heat, 2 h, then HCl; vi, tryptamine (1.2 equiv.), EtOH, heat, 5 days; vii, $LiAlH_4$, THF, heat, 24 h; viii, 3 mol dm^{-3} HCl, aq. acetone, heat, 3 h

ate, m.p. 122–125 °C, which was deacetylated to give **2**. Hydrolysis of the glucoside and concomitant reduction, using whole cells of *S. cerevisiae* at pH 6.4 for seven days at 25 °C, afforded in 60 to 80% yield the C-1 reduced aglucone epimers **4** in a ratio of 9:1 as indicated by NMR spectroscopy. Saponification and deformylation of **4** by heating with sodium hydroxide (4 mol dm^{-3}) under reflux for 2 h gave on acidification a 76% yield of the lactone **5** $[\alpha]_D^{20}$ +39° ($CHCl_3$), which was then reacted with tryptamine for five days in refluxing ethanol to form the amide **6**. Subsequent reduction to an amine with lithium aluminium hydride, followed by acid-catalysed hydrolysis of the acetal and concomitant Pictet–Spengler condensation, afforded antirhine **8**, m.p. 106–108 °C, $[\alpha]_D^{20}$ +3° (MeOH), as the only stereoisomer in 69% yield from **5**. Such high stereoselectivity in the cyclisation is attributed to a chair-like transition state **7** with an equatorial C_4 substituent at C-15 which generates the C-3 chiral centre by axial attack of the indole, leading directly to a *cis*-quinolizidine conformation. The ^1H NMR in $CDCl_3$ of antirhine showed H-3 as a broadened singlet at δ 4.2, as expected for a *cis* C/D junction.[6]

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