Indole Alkaloids. Enantioselective Synthesis of (−)-Alloyohimbane by a Chemoenzymatic Approach

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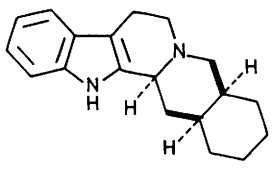
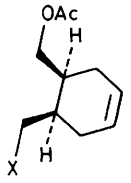
The *pro*-(*R*) enantiotopic specificity of pig liver esterase-catalysed hydrolysis of the *meso*-diacetate (**2**) to give (**3**) enables this chiron to be used in a highly efficient enantioselective synthesis of the natural (−)-alloyohimbane (**1**).

There has been considerable interest in yohimbinoid alkaloids (*e.g.* reserpine, yohimbines) both therapeutically and synthetically, although to date only a few reports deal with the total synthesis of optically active alkaloids embodying this skeletal arrangement.[1] Within this context, Isobe *et al.*[2] have just disclosed the first enantioselective synthesis of (−)-alloyohimbane (**1**), based on a chiron approach utilising carbohydrates as immolative chiral auxiliaries. Here we report an alternative and concise route to (−)-(**1**) involving as the key step a process resulting in dissymmetry (σ- → C_1-symmetry) in the *meso*-diacetate (**2**).

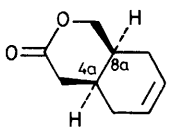
Our synthesis required the hydroxy ester (1*S*,2*R*)-(**3**) as the pivotal intermediate and this can be produced[3] on a preparative scale in good yield (78%) with 96% enantiomeric excess (e.e.) by the *pro*-(*R*) pig liver esterase (PLE)-catalysed hydrolysis[3] of (**2**)† to provide the proper chirality at two of the three stereogenic centres of (**1**). The hydroxy ester (**3**) was then converted into (−)-(4a*R*,8a*S*)-tetrahydroisochroman-3-one (**4**) (64%) {$[\alpha]_D^{20}$ −5.4° (*c* 2, $CHCl_3$); $\nu_{max.}$ 1725 cm^{-1}; δ 4.32 (2H, d, *J* 3.8 Hz) and 5.65 (2H, m, olefinic protons), ≥95% e.e. (determined according to the method of Jakovac and Jones[4])} *via* a straightforward sequence [(i) triflic anhydride, pyridine, CH_2Cl_2, −30 °C; (ii) sodium cyanide, dimethyl sulphoxide (DMSO), 50 °C; (iii) MeOH–20% aq. NaOH (5:1), 36% hydrogen peroxide, 60 °C, then acidic



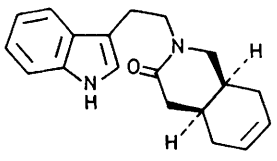
(**1**)



(**2**) X = OAc
(**3**) X = OH



(**4**)



(**5**)

† The presence of the double bond in (**4**) seems to be essential for such a remarkable e.e.

work-up]. Acylation of tryptamine with (**4**) in refluxing xylene, followed by exposure of the resulting hydroxy amide‡ to *N,N*-sulphuryl diimidazole in *N,N*-dimethylformamide (DMF),[5] then adding sodium hydride at −40 °C → 0 °C, led to the crystalline lactam (**5**) {81% yield from (**4**), m.p. 154 °C; $[\alpha]_D^{20}$ −19.4° (*c* 1, $CHCl_3$); δ 2.33 and 2.43 (2H, AB part of ABX pattern, *J* 18.0, 6.0, 5.5 Hz, diastereotopic CH_2CON) and 5.57 (2H, m, olefinic protons)}. This was then sequentially converted into (−)-alloyohimbane (**1**), m.p. 156 °C, $[\alpha]_D^{20}$ −165.9° (*c* 0.5, pyridine) (lit.,[6] −166.5° ± 0.8) as previously reported.[2]

In summary, the overall efficiency for this synthesis compares favourably with that recorded by Isobe *et al.* and demonstrates the great potentiality of chemo-enzymatic methodology for the preparation of optically pure compounds.

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‡ In our hands elaboration of this intermediate according to Isobe's protocol (ref. 2) gave noticeably poorer yields of (**5**).

References

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