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Expedient Syntheses of (+)-*cis*-(2*R*,3*S*)-3-Hydroxyproline and (−)-(1*S*,5*S*)-2-Oxa-6-azabicyclo[3.3.0]octan-3-one (The Geissman–Waiss Lactone): Formal Enantioselective Syntheses of (−)-Retronecine and Related Pyrrolizidine Alkaloids

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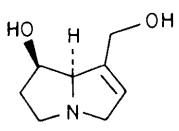
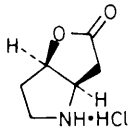
Yeast reduction of the keto-proline (**5**) affords the hydroxyproline derivative (**6**) (diastereoisomeric excess > 99% *cis*; enantiomeric excess, e.e., 80%); subsequent hydrolysis and crystallisation gives (+)-*cis*-(2*R*,3*S*)-3-hydroxyproline (**7**) (93% e.e.) which has been homologated to the bicyclic lactones (**10**) and (**11**), precursors of (−)-retronecine, (+)-platynecine, (−)-croalbinecine and related pyrrolizidines.

Many pyrrolizidine alkaloids are complex dilactones which consist of α,ω-aliphatic dicarboxylic acids esterified by a variety of substituted pyrrolizidines, the so-called necine bases, exemplified by (+)-retronecine (**1**).[1] The necine bases themselves have attracted considerable synthetic interest largely because of the wide variety of biological activity[2] associated with this group of alkaloids. Retronecine (**1**) itself was first synthesised some 25 years ago by Geissman and Waiss[3] who employed the bicyclic lactone [(±)-(**2**)] as a key intermediate; more recently this compound has been prepared in an optically pure state by relatively lengthy sequences starting from *trans*-4-hydroxy-L-proline,[4] D-erythrose,[5] or L-malic acid,[6] and has also been converted into other examples of the necine bases such as (−)-platynecine (**3**) and (+)-croalbinecine (**4**).[7] We reasoned that a somewhat more convenient precursor to lactone (**2**), now often referred to as the Geissman–Waiss lactone, would be *cis*-3-hydroxyproline which should be obtainable in optically active form by asymmetric reduction of the racemic ketoproline (**5**), which is available in quantity by various forms of Dieckmann cyclisation.[8] After a number of trials, we found that yeast reduction (dried Baker's yeast, sucrose, water, 30 °C, 24 h)[9] of the keto-proline (**5**) afforded a 3-hydroxyproline derivative in 75% isolated yield, with $[\alpha]_D$ +18.2° (*c* 1.45, CH_2Cl_2). The product was a single diastereoisomer according to ^1H and ^{13}C n.m.r. spectra and showed a coupling constant of 4 Hz between the 2- and 3-protons, indicating[10] that it was the *cis*-isomer (**6**) or the enantiomer thereof. N.m.r. spectra of a Mosher ester[11] derived from hydroxy-proline (**6**) revealed an enantiomeric enrichment of 80%. The absolute configuration of the major yeast reduction product was found to be (2*R*,3*S*) [*viz.* (**6**)] by complete hydrolysis [20% CF_3CO_2H–CH_2Cl_2, 20 °C, 0.5 h followed by KOH–MeOH–H_2O, 20 °C, 16 h and ion-exchange chromatography (Dowex 50 W)] which gave a sample of 3-hydroxyproline (**7**), m.p. 240—255 °C (decomp.) [lit.[12] m.p. 245—255 °C (decomp.)], $[\alpha]_D$ + 72.44° (*c* 1.0, H_2O) in 77% overall yield. One crystallisation from water gave material with $[\alpha]_D$ +85.2° (*c* 1.25, H_2O); this established the *cis*-(2*S*,3*R*) configuration (**7**) as the enantiomeric *cis*-(2*R*,3*S*)-3-hydroxy-L-proline has $[\alpha]_D$ −91.5 ± 1.6° (*c* 0.61, H_2O)[12] while the corresponding *trans*-(2*S*,3*S*)-3-hydroxy-L-proline is reported[12] to have m.p. 228—235°C (decomp.) and $[\alpha]_D$ −22.8° (*c* 1.0, H_2O). Thus, our crystallised sample of 3-hydroxyproline (**7**) had an enantiomeric enrichment of *ca.* 93%.

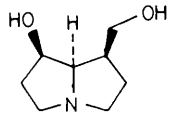
Subsequent homologation of the initial yeast reduction product (**6**) to the Geissman–Waiss lactone [*cf.* (**2**)] proved to be relatively straightforward (Scheme 1). Base hydrolysis provided the corresponding hydroxy-acid (**8a**), m.p. 101—103 °C, $[\alpha]_D$ +55.5° (*c* 1.39, CH_2Cl_2) which was then



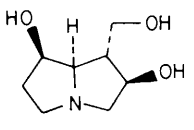
(**1**)



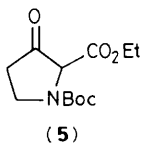
(**2**)



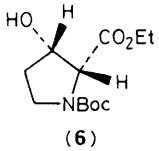
(**3**)



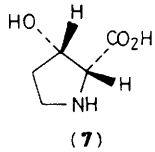
(**4**)



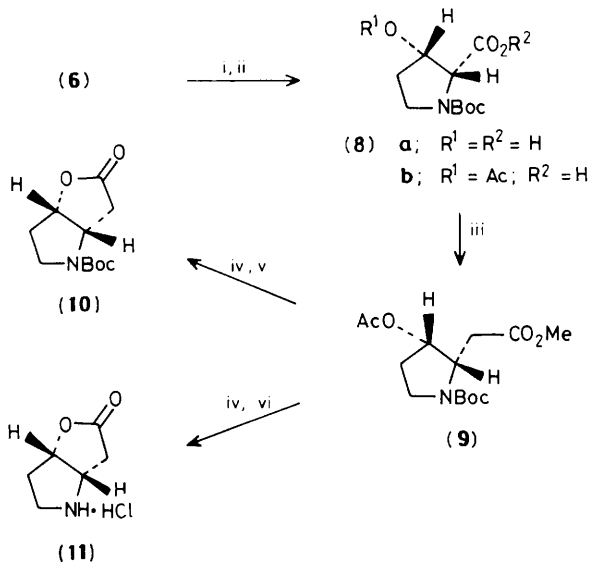
(**5**)



(**6**)



(**7**)



Scheme 1. *Reagents and conditions*: i, KOH, MeOH, H_2O, 20 °C, 16 h (86%); ii, Ac_2O, pyridine, 20 °C, 2 h (85%); iii, (a) $(COCl)_2$, cat. dimethylformamide, pyridine, Et_2O, 0—20 °C, 1 h, (b) CH_2N_2, Et_2O, (c) cat. $PhCO_2Ag$, Et_3N, MeOH, 20 °C, 1 h (66%); iv, K_2CO_3, MeOH, H_2O, 20 °C, 16 h; v, toluene-*p*-sulphonic acid, CH_2Cl_2; vi, 3 M HCl in EtOAc, 20 °C, 2 h.

Boc = t-butoxycarbonyl

protected as the corresponding acetate (**8b**), m.p. 119—121 °C, $[\alpha]_D$ −6.2° (*c* 0.78, CH_2Cl_2). Arndt–Eistert homologation then provided the homologous ester (**9**), $[\alpha]_D$ +27.0° (*c* 1.52, CH_2Cl_2) in 66% isolated yield which upon base hydrolysis followed by brief treatment with acid gave the *N*-protected bicyclic lactone (**10**), m.p. 106—107 °C, $[\alpha]_D$ +96.0° (*c* 0.43, CH_2Cl_2) in 90% yield. Alternatively, final acidification using 3 M HCl led to the hydrochloride (**11**) which showed m.p. 182—184 °C and $[\alpha]_D$ −42.9° (*c* 0.21, MeOH) [lit. m.p. 182—184 °C, $[\alpha]_D$ +45.6° (*c* 0.83, MeOH) for the (1*R*,5*R*) enantiomer (**2**)].[5]

Overall, this route is not only a brief approach to the bicyclic lactones (**10**) and (**11**), it also represents formal total syntheses of the (non-natural) enantiomers (−)-retronecine, (+)-platynecine, and (−)-croalbinecine [*cf.* (**1**), (**3**), and (**4**)];[3,7] furthermore, the yeast reduction step provides probably the simplest route to (2*R*,3*S*)-3-hydroxyproline (**7**) (none of the four enantiomers of this amino-acid are readily available)[12,13] which should therefore be a useful addition to the chiral pool.

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