

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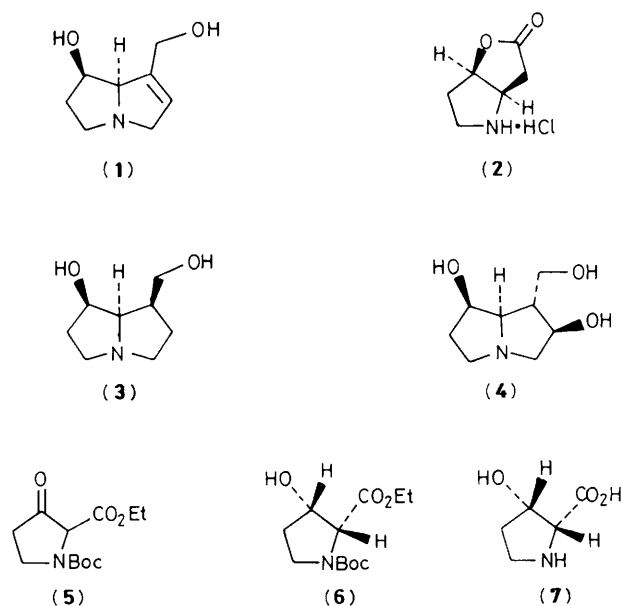
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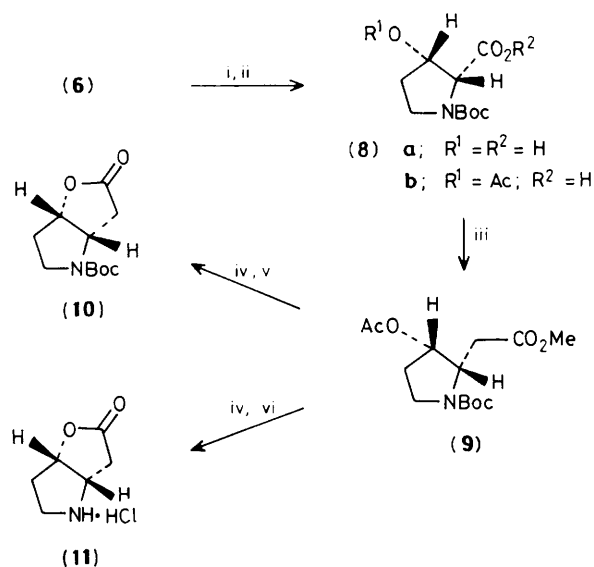
Yeast reduction of the keto-proline (**5**) affords the hydroxyproline derivative (**6**) (diastereoisomeric excess > 99% *cis*; enantiomeric excess, e.e., 80%); subsequent hydrolysis and crystallisation gives (+)-*cis*-(2*R*,3*S*)-3-hydroxyproline (**7**) (93% e.e.) which has been homologated to the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

Many pyrrolizidine alkaloids are complex dilactones which consist of  $\alpha,\omega$ -aliphatic dicarboxylic acids esterified by a variety of substituted pyrrolizidines, the so-called necine bases, exemplified by (+)-retronecine (**1**).<sup>1</sup> The necine bases themselves have attracted considerable synthetic interest largely because of the wide variety of biological activity<sup>2</sup> associated with this group of alkaloids. Retronecine (**1**) itself was first synthesised some 25 years ago by Geissman and Waiss<sup>3</sup> 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,<sup>4</sup> D-erythrose,<sup>5</sup> or L-malic acid,<sup>6</sup> and has also been converted into other examples of the necine bases such as (–)-platynecine (**3**) and (+)-croalbinecine (**4**).<sup>7</sup> 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.<sup>8</sup> After a number of trials, we found that yeast reduction (dried Baker's yeast, sucrose, water, 30 °C, 24 h)<sup>9</sup> of the keto-proline (**5**) afforded a 3-hydroxyproline derivative in 75% isolated yield, with  $[\alpha]_D +18.2^\circ$  (*c* 1.45, CH<sub>2</sub>Cl<sub>2</sub>). The product was a single diastereoisomer according to <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra and showed a coupling constant of 4 Hz between the 2- and 3-protons, indicating<sup>10</sup> that it was the *cis*-isomer (**6**) or the enantiomer thereof. N.m.r. spectra of a Mosher ester<sup>11</sup> 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<sub>3</sub>CO<sub>2</sub>H–CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 0.5 h followed by KOH–MeOH–H<sub>2</sub>O, 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.<sup>12</sup> m.p. 245–255 °C (decomp.)],  $[\alpha]_D +72.44^\circ$  (*c* 1.0, H<sub>2</sub>O) in 77% overall yield. One crystallisation from water

gave material with  $[\alpha]_D +85.2^\circ$  (*c* 1.25, H<sub>2</sub>O); this established the *cis*-(2*S*,3*R*) configuration (**7**) as the enantiomeric *cis*-(2*R*,3*S*)-3-hydroxy-L-proline has  $[\alpha]_D -91.5 \pm 1.6^\circ$  (*c* 0.61, H<sub>2</sub>O)<sup>12</sup> while the corresponding *trans*-(2*S*,3*S*)-3-hydroxy-L-proline is reported<sup>12</sup> to have m.p. 228–235 °C (decomp.) and  $[\alpha]_D -22.8^\circ$  (*c* 1.0, H<sub>2</sub>O). 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,  $[\alpha]_D +55.5^\circ$  (*c* 1.39, CH<sub>2</sub>Cl<sub>2</sub>) which was then





**Scheme 1.** Reagents and conditions: i, KOH, MeOH, H<sub>2</sub>O, 20 °C, 16 h (86%); ii, Ac<sub>2</sub>O, pyridine, 20 °C, 2 h (85%); iii, (a) (COCl)<sub>2</sub>, cat. dimethylformamide, pyridine, Et<sub>2</sub>O, 0–20 °C, 1 h, (b) CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O, (c) cat. PhCO<sub>2</sub>Ag, Et<sub>3</sub>N, MeOH, 20 °C, 1 h (66%); iv, K<sub>2</sub>CO<sub>3</sub>, MeOH, H<sub>2</sub>O, 20 °C, 16 h; v, toluene-*p*-sulphonic acid, CH<sub>2</sub>Cl<sub>2</sub>; vi, 3 M HCl in EtOAc, 20 °C, 2 h.

Boc = *t*-butoxycarbonyl

protected as the corresponding acetate (**8b**), m.p. 119–121 °C,  $[\alpha]_D -6.2^\circ$  (*c* 0.78, CH<sub>2</sub>Cl<sub>2</sub>). Arndt–Eistert homologation then provided the homologous ester (**9**),  $[\alpha]_D +27.0^\circ$  (*c* 1.52, CH<sub>2</sub>Cl<sub>2</sub>) 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,  $[\alpha]_D +96.0^\circ$  (*c* 0.43, CH<sub>2</sub>Cl<sub>2</sub>) in 90% yield. Alternatively, final acidification using 3 M HCl led to the hydrochloride (**11**) which showed m.p. 182–184 °C and  $[\alpha]_D -42.9^\circ$  (*c* 0.21, MeOH) [lit. m.p. 182–184 °C,  $[\alpha]_D +45.6^\circ$  (*c* 0.83, MeOH) for the (1*R*,5*R*) enantiomer (**2**).<sup>5</sup>

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**)];<sup>3,7</sup> 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)<sup>12,13</sup> which should therefore be a useful addition to the chiral pool.

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