

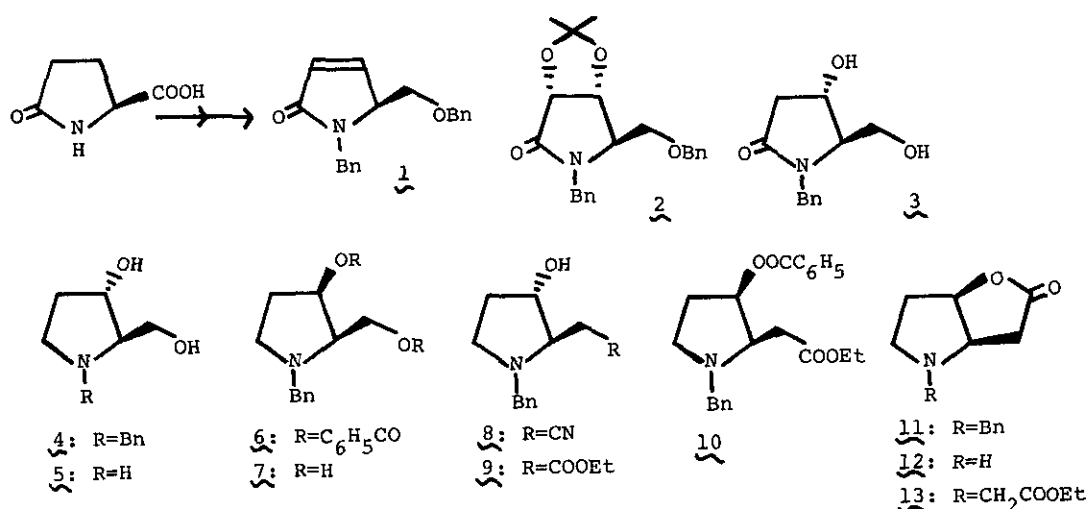
SYNTHESIS OF (2R,3S)-2-HYDROXYMETHYL-3-HYDROXYPYRROLIDINE
AND THE GEISSMAN-WAISS LACTONE FROM (S)-PYROGLUTAMIC ACID

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Abstract—The synthesis of (2R,3S)- and (2R,3R)-2-hydroxymethyl-3-hydroxypyrrrolidine derivatives (5 and 7) and the Geissman-Waiss lactone (12) has been achieved from (S)-pyroglutamic acid.

We have recently communicated¹ the synthesis of (-)-swainsonine and its stereoisomers, in which the trihydroxylated pyrrolidinones such as 2 were the important intermediates. In continuation of our work on the utility of chiral pyroglutamic acid derivatives^{1,2} for the synthesis of indolizidine and pyrrolizidine alkaloids, we now describe the facile synthesis of (2R,3S)- and (2R,3R)-2-hydroxymethyl-3-hydroxypyrrrolidine (5 and 7) and the Geissman-Waiss lactone (12),³ which could be converted efficiently into the pyrrolizidine alkaloids such as (+)-heliotridine and (+)-retronecine. Treatment of 2^{1,4} (mp 70-71°C, $[\alpha]_D^{20} -3.7^\circ$ (c=2, CHCl₃)), obtained by *cis*-dihydroxylation of the unsaturated lactam (1) with OsO₄ followed by *O*-isopropylideneation, with sodium (5 eq) in liquid ammonia followed by work-up with aqueous NH₄Cl yielded a dihydroxy lactam (3) in 67% yield. Successive treatments of 3 with borane-dimethyl sulfide complex in THF and debenylation (H₂-Pd/C-EtOH-HCl) afforded the hydrochloride of (2R,3S)-2-hydroxymethyl-3-hydroxypyrrrolidine (5) in 82% yield, mp 63-65°C, $[\alpha]_D^{20} +46^\circ$ (c=0.3, H₂O) (lit.⁵ mp 108-112°C; $[\alpha]_D^{21} +46.5^\circ$ (H₂O)), which was recently isolated from *Castanospermum australe* and identified. It was identical with the hydrochloride of natural 5 in the ¹H nmr and ¹³C nmr spectra. Conversion of the primary hydroxy group of 4 to nitrile⁶ (Bu₃P/CCl₄/KCN/18-crown-6/CH₃CN) followed by transformation of the cyano function into the ester group (HCl/EtOH) gave the hydroxy ester (9, $[\alpha]_D^{20} -83.3^\circ$ (c=1, CHCl₃)) in 70% yield. On the other hand, *N*-benzyl-(2R,3R)-2-hydroxymethyl-3-hydroxypyrrrolidine (7, $[\alpha]_D^{20} -56.5^\circ$ (c=0.5, CHCl₃)), obtained from 4 in 63% yield by the Mitsunobu



reaction⁷ (5 equiv. of diethyl azodicarboxylate, PhCOOH, and Ph₃P in THF) followed by treatment of 6 with sodium methoxide in methanol, did not give the corresponding nitrile under the conditions as in the synthesis of 8. The Mitsunobu reaction of 9 to invert the stereochemistry of the secondary hydroxy group followed by removal of the benzoyl group and lactonization of 10 in a single step (MeONa/MeOH) gave the *N*-benzyl Geissman-Waiss lactone (11), which was catalytically debenzylated (H₂-10% Pd/C-EtOH-HCl) to provide the Geissman-Waiss lactone (12) in 72% yield, as the crystalline hydrochloride salt, mp 188-189°C, [α]_D²⁰ +47.5° (c=0.4, MeOH) (lit.^{3a} mp 185-186°C; [α]_D +48.5° (c=1.5, MeOH)). The *N*-(ethoxycarbonyl)methyl Geissman-Waiss lactone (13, mp 47-48°C; [α]_D²⁰ -35.9° (c=0.8, CHCl₃), lit.^{3g} mp 52-53°C; [α]_D¹⁶ -35.2° (c=0.56, CHCl₃)) was also obtained from 12 in 94% yield (BrCH₂COOEt, K₂CO₃, EtOH). ¹H Nmr spectrum of 13 was identical with that reported.^{3g}

Further synthetic studies on utilizing the hydroxylated pyrrolidinone derivatives are under investigation.

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REFERENCES AND NOTES

1. N. Ikota and A. Hanaki, Chem. Pharm. Bull., 1987, 35, 2140; idem, Heterocycles, 1987, 26, 2369.
2. N. Ikota and A. Hanaki, Heterocycles, 1984, 22, 2227.
3. Synthesis of the (+)-Geissman-Waiss lactone and related compounds; from trans-4-hydroxy-(S)-proline, a) H. Rueger and M. Benn, Heterocycles, 1982, 19, 23; from D-erythrose, b) J. G. Buchanan, G. Singh, and R. H. Wightmann, J. Chem. Soc., Chem. Commun., 1984, 1299; from (S)-malic acid, c) K. Shishido, Y. Sukegawa, K. Fukumoto, and T. Kametani, Heterocycles, 1985, 23, 1629; 1986, 24, 641; idem, J. Chem. Soc., Perkin Trans. 1, 1987, 993, d) A. R. Chamberlin and J. Y. L. Chung, J. Org. Chem., 1985, 50, 4425; e) J-K. Choi and D. J. Hart, Tetrahedron, 1985, 41, 3959; f) T. Kametani, H. Yukawa, and T. Honda, J. Chem. Soc., Chem. Commun., 1988, 685; from (R)-malic acid, g) H. Niwa, O. Okamoto, Y. Miyachi, Y. Uosaki, and K. Yamada, Tetrahedron Lett., 1986, 27, 4605; idem, J. Org. Chem., 1987, 52, 2941; by chemicoenzymatic asymmetric induction for the (-)-Geissman-Waiss lactone; h) J. Cooper, P. T. Gallagher, and D. W. Knight, J. Chem. Soc., Chem. Commun., 1988, 509.
4. Satisfactory spectral and/or analytical data were obtained for all new compounds.
5. R. J. Nash, E. A. Bell, G. W. J. Fleet, R. H. Jones, and J. M. Williams, J. Chem. Soc., Chem. Commun., 1985, 738.
6. A. Mizuno, Y. Hamada, and T. Shioiri, Synthesis, 1980, 1007.
7. O. Mitsunobu and M. Eguchi, Bull. Chem. Soc. Japan, 1971, 44, 3427.

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