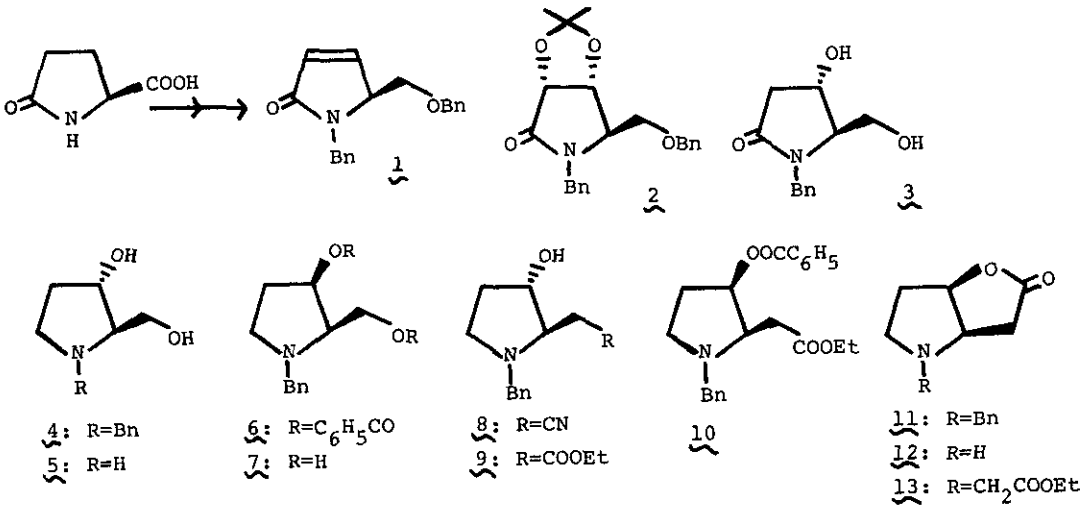
SYNTHESIS OF (2R,3S)-2-HYDROXYMETHYL-3-HYDROXYPYRROLIDINE AND THE GEISSMAN-WAISS LACTONE FROM (S)-PYROGLUTAMIC ACID

Nobuo Ikota* and Akira Hanaki
National Institute of Radiological Sciences, 4-9-1, Anagawa, Chiba 260, Japan

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

We have recently communicated[1] 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-hydroxypyrrolidine (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°(c=2, $CHCl_3$)), obtained by cis-dihydroxylation of the unsaturated lactam (1) with OsO_4 followed by O-isopropylidenation, with sodium (5 eq) in liquid ammonia followed by work-up with aqueous NH_4Cl yielded a dihydroxy lactam (3) in 67% yield. Successive treatments of 3 with borane-dimethyl sulfide complex in THF and debenzylation (H_2-Pd/C-EtOH-HCl) afforded the hydrochloride of (2R,3S)-2-hydroxymethyl-3-hydroxypyrrolidine (5) in 82% yield, mp 63-65°C, $[\alpha]_D^{20}$ +46°(c=0.3, H_2O) (lit.[5] mp 108-112°C; $[\alpha]_D^{21}$ +46.5°(H_2O)), which was recently isolated from Castanospermun australe and identified. It was identical with the hydrochloride of natural 5 in the ^1H nmr and ^{13}C nmr spectra. Conversion of the primary hydroxy group of 4 to nitrile[6] ($Bu_3P/CCl_4/KCN$/18-crown-6/CH_3CN) followed by transformation of the cyano function into the ester group (HCl/EtOH) gave the hydroxy ester (9, $[\alpha]_D^{20}$ -83.3°(c=1, $CHCl_3$) in 70 % yield. On the other hand, N-benzyl-(2R,3R)-2-hydroxymethyl-3-hydroxypyrrolidine (7, $[\alpha]_D^{20}$ -56.5°(c=0.5, $CHCl_3$), obtained from 4 in 63% yield by the Mitsunobu



reaction[7] (5 equiv. of diethyl azodicarboxylate, PhCOOH, and Ph_3P 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 (H_2-10% Pd/C-EtOH-HCl) to provide the Geissman-Waiss lactone (12) in 72% yield, as the crystalline hydrochloride salt, mp 188-189°C, $[\alpha]_D^{20}$ +47.5°(c=0.4, MeOH) (lit.[3a] mp 185-186°C; $[\alpha]_D$ +48.5°(c=1.5, MeOH)). The N-(ethoxycarbonyl)methyl Geissman-Waiss lactone (13, mp 47-48°C; $[\alpha]_D^{20}$ -35.9°(c=0.8, $CHCl_3$), lit.[3g] mp 52-53°C; $[\alpha]_D^{16}$ -35.2°(c=0.56, $CHCl_3$)) was also obtained from 12 in 94% yield ($BrCH_2COOEt$, K_2CO_3, 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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REFERRENCES 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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