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-hydroxy pyrrolidine derivatives (5 and 7) and the Geisman-Waiss lactone (12) has been achieved from \((S)\)-pyroglutamic acid.

We have recently communicated 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 for the synthesis of indolizidine and pyrrolizidine alkaloids, we now describe the facile synthesis of \((2R,3S)\)- and \((2R,3R)\)-2-hydroxymethyl-3-hydroxy pyrrolidine (5 and 7) and the Geisman-Waiss lactone (12), which could be converted efficiently into the pyrrolizidine alkaloids such as (+)-heliotridine and (+)-retronecine. Treatment of \((\frac{1}{2})\) (mp 70-71°C, \([\alpha]_D^{20} -3.7^\circ (c=2, \text{CHCl}_3)\), obtained by \(\text{cis}\)-dihydroxylation of the unsaturated lactam (1) with \(\text{OsO}_4\) followed by \(\text{D}-\text{isopropylidenation, with sodium (5 eq) in liquid ammonia followed by work-up with aqueous NH}_4\text{Cl 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-hydroxy pyrrolidine (5) in 82% yield, mp 63-65°C, \([\alpha]_D^{20} -46^\circ (c=0.3, \text{H}_2\text{O})\) (lit. mp 108-112°C; \([\alpha]_D^{21} +46.5^\circ (\text{H}_2\text{O})\)), which was recently isolated from Castanospermum australe and identified. It was identical with the hydrochloride of natural 5 in the \(^1\text{H}\) nmr and \(^13\text{C}\) nmr spectra. Conversion of the primary hydroxy group of 4 to nitrile \((\text{Bu}_3\text{P/\text{CCl}_4/\text{KCN/18-crown-6/CH}_2\text{CN}})\) followed by transformation of the cyano function into the ester group (HCl/EtOH) gave the hydroxy ester (9, \([\alpha]_D^{20} -83.3^\circ (c=1, \text{CHCl}_3)\) in 76% yield. On the other hand, \(\text{N}-\text{benzyl-}\((2R,3R)\)-2-hydroxymethyl-3-hydroxy pyrrolidine (7, \([\alpha]_D^{20} -56.5^\circ (c=0.5, \text{CHCl}_3)\), obtained from 4 in 63% yield by the Mitsunobu
reaction\(^7\) (5 equiv. of diethyl azodicarboxylate, PhCOOH, and Ph\(_3\)P in THF) followed by treatment of \(\mathbf{6}\) with sodium methoxide in methanol, did not give the corresponding nitrile under the conditions as in the synthesis of \(\mathbf{8}\). The Mitsunobu reaction of \(\mathbf{9}\) to invert the stereochemistry of the secondary hydroxy group followed by removal of the benzoyl group and lactonization of \(\mathbf{10}\) in a single step (MeONa/MeOH) gave the \(\text{N-benzyl Geissman-Waiss lactone (11)}\), 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]\(^{20}\)_D +47.5°(c=0.4, MeOH) (lit.\(^3a\) mp 185-186°C; \([\alpha]\)_D +48.5°(c=1.5, MeOH)). The \(\text{N-(ethoxycarbonyl)methyl Geissman-Waiss lactone (13, mp 47-48°C; \([\kappa]\)\(^{20}\)_D -35.9°(c=0.8, CHCl\(_3\)), lit.}\(^3g\) mp 52-53°C; \([\kappa]\)_D \(-35.2°(c=0.56, CHCl\(_3\))\) was also obtained from \(\mathbf{12}\) in 94% yield (BrCH\(_2\)COOEt, K\(_2\)CO\(_3\), EtOH). \(^1\)H Nmr spectrum of \(\mathbf{13}\) 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

4. Satisfactory spectral and/or analytical data were obtained for all new compounds.

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