A SYNTHESIS OF (+)-2-OXA-6-AZABICYCLO[3.3.0]OCTAN-3-ONE (THE GEISSMAN-WAISS LACTONE): A SYNTHON FOR SOME NECINES

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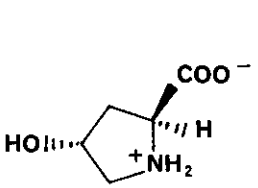
Abstract — The lactone (1), an intermediate in the Geissman-Waiss synthesis of retronecine and a potential synthon for other necines, was synthesised from 4-hydroxy-L-proline.

We report the synthesis of (+)-2-oxa-6-azabicyclo[3.3.0]octan-3-one (1). This lactone was prepared, in racemic form, by Geissman and Waiss[1] from β-alanine, and used by them in the first synthesis of retronecine (2). In principle it also provides access to some other naturally occurring pyrrolizidines, i.e. 1 is a potentially versatile synthon.



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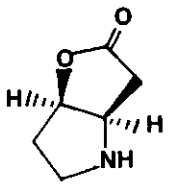

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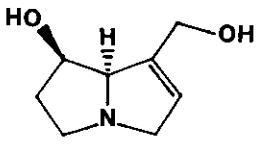

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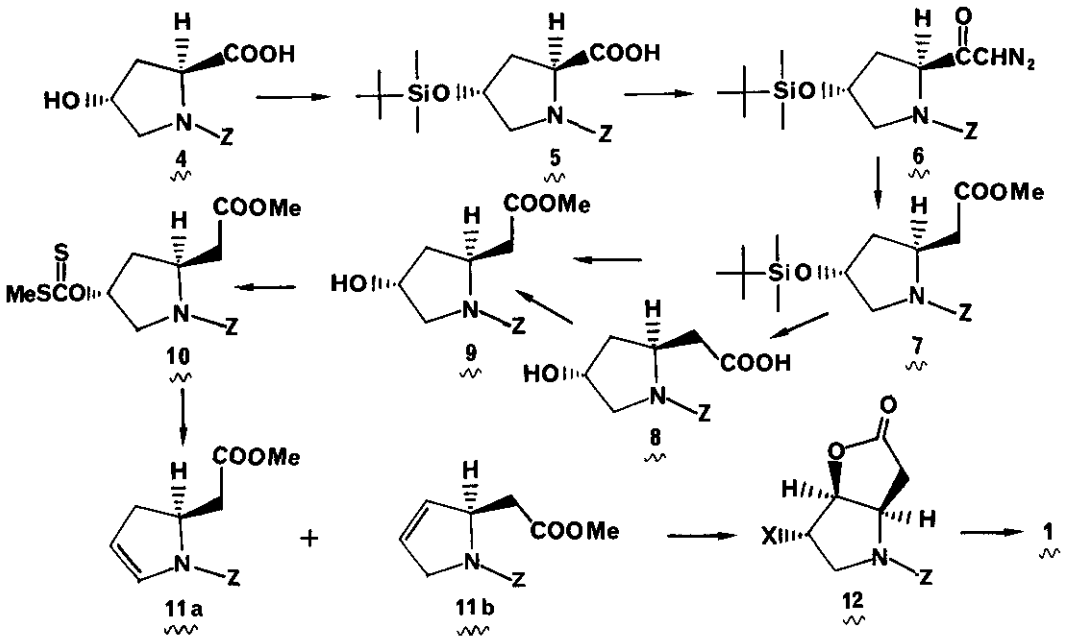
Our approach starts from 4-hydroxy-L-proline (3), in which the stereochemistry at C-2 corresponds to that required at C-8 in the natural (+)-retronecine. Transformation of 3 to 1 requires homologation of the acid, and transposition of the hydroxyl functionality from C-4 to C-3, with inversion of stereochemistry. Our strategy for these conversions is shown in the Scheme.

Commercially available N-carbobenzoxy-4-hydroxy-L-proline (4) was O-protected as the t-butyldimethylsilyl derivative (5)[2], and then homologated. This extension was achieved by means of Wolff rearrangement (methanol, Ag_2O) of the diazoketone (6) itself obtained *via* sequential treatment of 5 with isobutyl chloroformate-triethylamine (mixed anhydride formation), and then diazomethane.

Purification of 7 was achieved by column chromatography on silicic acid. Alternatively, to be sure that diastereomeric impurities were removed, it may be deprotected (n-Bu_4NF/THF, then aq. NaOH) to afford the crystalline acid 8, m.p. 99-100°, $[\alpha]_D$-62.4° (c 3, MeOH): remethylation (CH_2N_2) of which yielded 9. This hydroxy ester, which proved to be identical in all respects with material prepared by deprotection (nBu_4NF/THF) of column chromatographically purified 7, was then converted



to the xanthate (10), and pyrolysed, as described by Dormoy et al.[3] for 4-hydroxy-L-proline. The product, formed in nearly quantitative yield, was a mixture of the two isomeric alkenes 11a and 11b, in which the desired compound 11b predominated (ca. 6:1), and could be readily separated by flash-chromatography on silicic acid. Saponification of 11b ($MeOH-H_2O-Na_2CO_3$) followed by acidification yielded the corresponding acid, and this was subjected to electrophilic lactonisation either with I_2-KI-$NaHCO_3$ to yield the idolactone (12a, X = I) (m.p. 121-121.5°), or benzeneselenenyl chloride[4] to give the phenylselenolactone (12b, X = PhSe) (m.p. 113-114°). Reductive removal of I or PhSe from these products was achieved with tri-n-butyl- or triphenyltinhydride[5], followed by hydrogenolysis (5% Pd/C-EtOH-HCl) to yield 1, as the nicely crystalline hydrochloride salt. As thus obtained 1 had m.p. 185-186° (Lit.[1], for the (±)-1, m.p. 175-177°), and $[\alpha]_D$ + 48.5° (c 1.5, MeOH). A test for enantiomeric purity using the Mosher procedure[6] indicated that this product was at least 99% optically pure.

Formally, (+)-1 can be converted to (+)-retronecine by the Geissman-Waiss route. We are exploring this and other possibilities.

REFERENCES AND NOTES.

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