

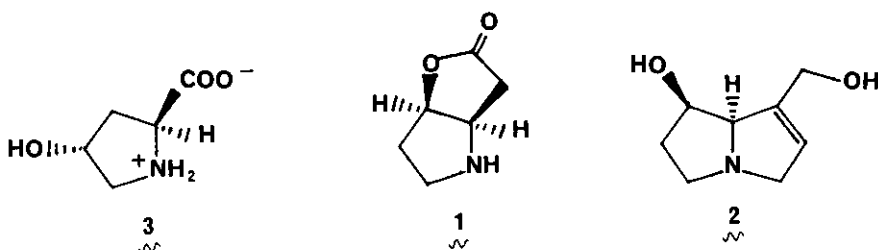
A SYNTHESIS OF (+)-2-OXA-6-AZABICYCLO[3.3.0]OCTAN-3-ONE (THE GEISSMAN-WAISS LACTONE): A SYNTHON FOR SOME NECINES

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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.

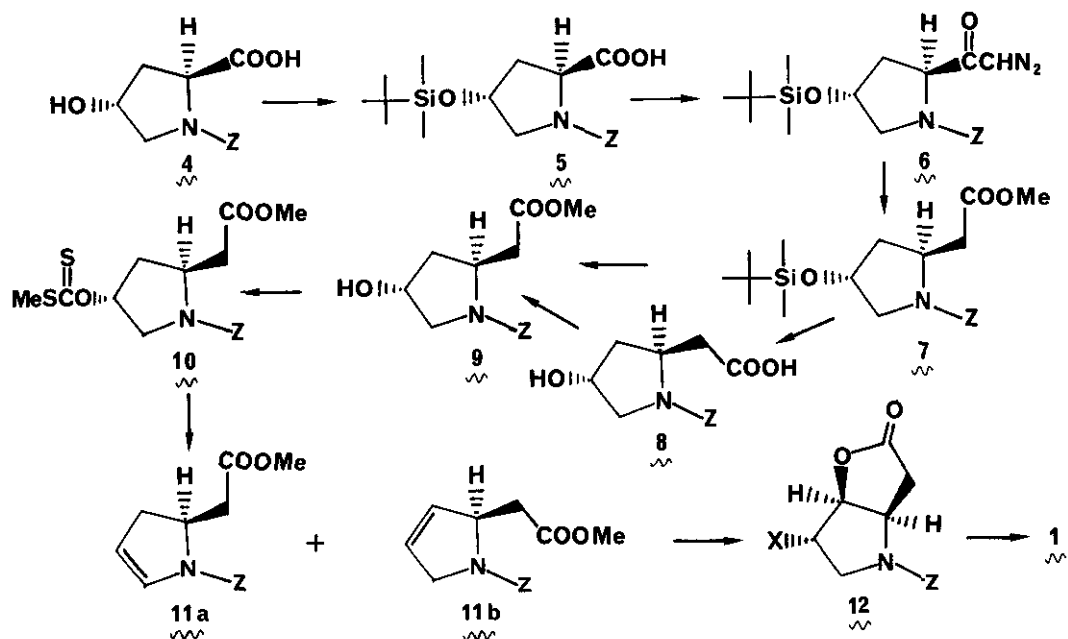
We report the synthesis of (+)-2-oxa-6-azabicyclo[3.3.0]octan-3-one (**1**). This lactone was prepared, in racemic form, by Geissman and Waiss<sup>1</sup> from  $\beta$ -alanine, and used by them in the first synthesis of retronecine (**2**). In principle it also provides access to some other naturally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



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-butyl-dimethylsilyl derivative (**5**)<sup>2</sup>, and then homologated. This extension was achieved by means of Wolff rearrangement (methanol, Ag<sub>2</sub>O) 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<sub>4</sub>NF/THF, then aq. NaOH) to afford the crystalline acid **8**, m.p. 99-100°, [ $\alpha$ ]<sub>D</sub>-62.4° (c 3, MeOH): remethylation (CH<sub>2</sub>N<sub>2</sub>) of which yielded **9**. This hydroxy ester, which proved to be identical in all respects with material prepared by deprotection (nBu<sub>4</sub>NF/THF) of column chromatographically purified **7**, was then converted



to the xanthate (10), and pyrolysed, as described by Dormoy *et al.*<sup>3</sup> 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<sub>2</sub>O-Na<sub>2</sub>CO<sub>3</sub>) followed by acidification yielded the corresponding acid, and this was subjected to electrophilic lactonisation either with I<sub>2</sub>-KI-NaHCO<sub>3</sub> to yield the idiolactone (12a, X = I) (m.p. 121-121.5°), or benzeneselenenyl chloride<sup>4</sup> 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<sup>5</sup>, 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.<sup>1</sup>, for the (±)-1, m.p. 175-177°), and [α]<sub>D</sub> + 48.5° (c 1.5, MeOH). A test for enantiomeric purity using the Mosher procedure<sup>6</sup> 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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