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An Enantioselective Synthesis of (+)-Pseudohygroline.

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Abstract: The enantioselective synthesis of (+)-pseudohygroline (3), employing a highly diastereoselective ring closure as a key step, has been achieved in seven steps from readily available protected lactaldehyde (6). © 1998 Elsevier Science Ltd. All rights reserved.

We have reported several studies which demonstrate the usefulness of diastereoselective intramolecular oxymercurations of systems such as 1 (X = O).¹⁻³ Critical to the diastereoselectivity of these ring closures is the use of Z-alkenes and a sterically demanding silyloxy group attached to the remote allylic carbon. In this Letter we report the first in a series of studies on the extension of this approach to the synthesis of nitrogen containing heterocycles (ie $X = NR^3$).⁴



The target molecule of this work is the 2-substituted pyrrolidine (+)-pseudohygroline (3). This small molecule occupies a significant place in the history of alkaloid chemistry as it was prepared⁵ as part of the first chemical proof of the absolute stereochemistry of the biosynthetically important (+)-hygroline (4) and (+)-hygrine (5).

 $\begin{array}{c|c} X & Y \\ N & \\ N & \\ H \\ CH_3 \end{array} \begin{array}{c} 3 & X = H, Y = OH \\ 4 & X = OH, Y = H \\ 5 & X = Y = O \end{array} \begin{array}{c} (+) - Pseudohygroline \\ (+) - Hygroline \\ (+) - Hygroline \end{array}$

The Scheme below summarizes the synthetic sequence leading to 3. Wittig coupling¹ of the known protected lactaldehyde 6^6 with the ylid 7^7 derived from 4-bromobutyronitrile, followed by nitrile reduction gave 8 as a single alkene stereoisomer. We had hoped to cyclise this aminoalkene directly, however all attempts failed due to apparent complexation (and resultant precipitation) of the amine with the mercury salt. As it is known⁸ that N-benzyloxycarbonyl ("Z"-) aminoalkenes undergo mercury(II)-promoted cyclisations, the amine was converted into the corresponding carbamate 9.

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(i) Ph3P=CH(CH₂)₂CN (7), THF, 0°C, 64%; (ii) LiAlH₄, Et₂O, reflux, 1h (b) H₂O, 91%; (iii) (a) ClCO₂Bn, toluene, r.t., 1d (b) Aq. NaHCO₃, 87%; (iv) (a) Hg(OAc)₂, CH₂Cl₂, r.t., 3d (b) Aq. NaCl, 84%; (v) Bu₃SnH, AIBN, toluene, 92%; (vi) LiAlH₄, 68%; (vii) NH₄F, MeOH, r.t. 70%. (BPS = tert-butyldiphenylsilyl).

We were pleased to find that treatment of 9 with Hg(OAc)₂ in dichloromethane provided the ring closed product 10 as a single diastereomer in 84% yield after crystallization from diethyl ether⁹ {(m.p. 101-103°C, $[\alpha]_D^{20} + 2.8 \ (c=1.8, CHCl_3))$ }. The reaction was quite slow, typically requiring three to four days for completion. The product was crystalline and a view from its X-ray structure is shown in the Figure. This confirms that the ring closure has produced the same stereochemical outcome as that found in all our earlier work¹⁻³ with oxygen heterocycles. Demercuration¹ of 10 then provided the key intermediate 11 in 92% yield.



Figure. X-ray crystal structure of 10 (some hydrogens omitted for clarity).

Treatment of **11** with lithium aluminium hydride at room temperature,¹⁰ followed by fluorodesilylation using ammonium fluoride in methanol¹¹, gave pure (+)-*pseudohygroline* (**3**) {($[\alpha]_D^{20} + 70.7 (c=2.0, ethanol)$; lit.⁵ $[\alpha]_D^{20} + 84.4 (c=3.4, ethanol)$ }. The success of this approach, especially the excellent diastereoselectivity obtained in the ring closure, lays the foundation for its application to the synthesis of more complex alkaloids. The results of these studies will be reported in due course.

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