Synthesis of (±)-Macrostomine *

Wolfgang Wiegrebe**, Siavosh Mahboobi, Gerd Dannhardt, Klaus K. Mayer and Ernst Eibler
Faculty of Chemistry and Pharmacy, University of Regensburg, P.O. Box 397, D-8400 Regensburg 2, Germany

In 1974 Preininger, Santavy et al. [1] have published the isolation and structure elucidation of macrostomine (S-1); the racemate (±)-1 has been synthesized via a lithiated nitrosamine by Wykypiel and Seebach [2].

Our synthesis of (±)-1 is shown in the scheme. The benzylcyanide 2 was condensed with 3 (Et$_3$N, N$_2$, 120°, 4 d) to the enamine 4, previously obtained by Kametani et al. [3] by debromination of 5. Formylation (CH$_3$-CO-O-CH=O, 50°, 5 min) of 4 to 6 (MS (HR): M$^+ = C_{15}H_{16}N_2O_3$) and partial reduction (LiAlH$_4$, THF, 0°, 5-8 min) led to the nitrile 7 and its dihydro-derivative 8 (1:2) which were separated by HPLC (Si 100 5μ, 90% CH$_2$Cl$_2$, 10% CH$_3$CN). Reduction under more vigorous conditions (LiAlH$_4$, ether 0°, 15 min, then r.t. 30 min) generates the diastereomers 9, which were used without separation because the centre of chirality at the benzylic C disappears in the aromatization step (see below). The amides 10 (MS (HR): M$^+ = C_{24}H_{30}N_2O_5$) were cyclized (POCl$_3$, benzene, reflux 1.5 h) to the dihydroisoquinoline 11 (MS (HR): M$^+ = C_{24}H_{30}N_2O_4$) (di-HCl m.p. 176-178°), which

* Received July 7, 1981. Preliminary communication.

** Prof. Dr. W. Wiegrebe to whom correspondence may be addressed.
was dehydrogenated (Pd/C 5%, large excess, tetraline, 205–210°, 20–25 min) to \(12\) [4] and \((\pm)-1\) (main product): \((\pm)-1\) and \(S\)-1, kindly provided by Prof. Santavy and Prof. Preininger, Olomouc, CSSR, give identical UV- and mass spectra and behave identically in various tlc-systems.

**Literature:**