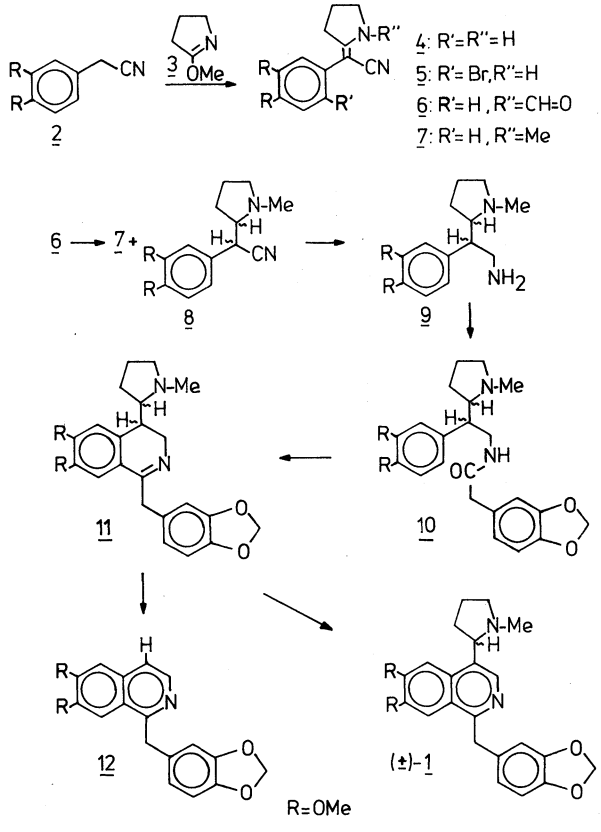
Synthesis of (±)-Macrostomine *

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_3N,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): $M^{+\cdot}$ = $C_{15}H_{16}N_2O_3$) and partial reduction ($LiAlH_4$, THF, 0°, 5–8 min) led to the nitrile **7** and its dihydroderivative **8** (1:2) which were separated by HPLC (Si 100 5 μ; 90% CH_2Cl_2, 10% CH_3CN). 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): $M^{+\cdot}$ = $C_{24}H_{30}N_2O_5$) were cyclized ($POCl_3$, benzene, reflux 1.5 h) to the dihydroisoquinoline **11** (MS (HR): $M^{+\cdot}$ = $C_{24}H_{28}N_2O_4$) (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 (±)-**1** (main product): (±)-**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:

1 *V.A.Mnatsakanyan, V.Preininger, V.Simanek, A.Klasek, L. Dolejs* and *F.Santavy:* Tetrahedron Letters *1974*, 851.
2 *W.Wykypiel* and *D.Seebach:* Tetrahedron Letters *1980*, 1927.
3 *T.Kametani, K.Takahashi, M.Thara* and *K.Fukumoto:* J.C.S. Perkin I, (1976) 389.
4 *W.Wiegrebe:* Arch. Pharm. (Weinheim) *300*, (1967) 708.

Separatdruck aus *Chimia 35* (1981) Nr. 8 (August), Seite 288
Fachzeitschrift für Forschung, Technik und Wirtschaft
im Bereich der Chemie
Monatszeitschrift des Schweizerischen Chemiker-Verbandes
BAG Brunner Verlag AG, Postfach, CH-8036 Zürich