Synthesis of the *Preininger*-Alkaloid and its Enantioselective Reduction to Macrostomine

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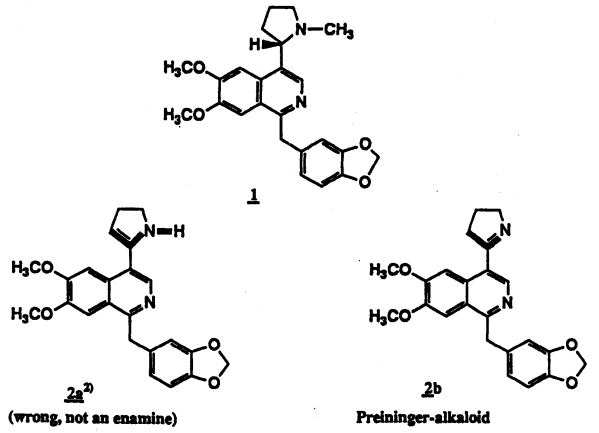
The *Preininger*-alkaloid, dehydro-normacrostomine (**2b**, Scheme 1) was synthesized starting from rac. α-acetyl-3,4-dimethoxybenzylcyanide (**3**) (Scheme 2). The key intermediate 4-acetyl-6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (**11**) is converted via a *Mannich* base to the nitrile **17** (Scheme 7) which in turn is cyclized to the *Preininger*-alkaloid (**2b**) by careful hydrogenation. - Reduction of **2b** with a modified *Iwakuma*-reagent, followed by N-formylation and subsequent $LiAlH_4$-reduction produced (*R*)-(+)-macrostomine (enantiomer of **1**) in 72 % optical purity.

Synthese des *Preininger*-Alkaloids und dessen enantioselektive Reduktion zu Macrostomin

Das *Preininger*-Alkaloid (Dehydro-normacrostomin, **2b**, Scheme 1) wurde ausgehend von rac. α-Acetyl-3,4-dimethoxybenzylcyanid (**3**) über die Schlüsselverbindung 4-Acetyl-6,7-dimethoxy-1-(3,4-methylendioxybenzyl)isochinolin (**11**) synthetisiert. Die Umsetzung von **11** über eine *Mannich*-Base zum Nitril **17** (Scheme 7) und dessen schonende Hydrierung führten zum *Preininger*-Alkaloid (**2b**). - Die Reduktion von **2b** mit einem modifizierten *Iwakuma*-Reagenz, N-Formylierung und Alanat-Reduktion lieferten (*R*)-(+)-Macrostomin (Enantiomer von **1**) in 72 proz. optischer Reinheit.

In 1974 *Šantavý, Preininger* et al. [1] reported upon isolation and structure elucidation of a benzylisoquinoline alkaloid from *papaver macrostomum*, *papaveraceae*, named macrostomine (**1**). For this alkaloid *S*-configuration at C-2 of the pyrrolidine-increment was established by chiroptical comparison with (*S*)-(-)-nicotine and (*S*)-(-)-brevicoline.

Traces of a new alkaloid, dehydro-normacrostomine (**2a**) were isolated from *papaver macrostomum* by the same group in 1976 [2]. In commemoration of the late *V. Preininger* we have named dehydro-normacrostomine "*Preininger-alkaloid*". Here we describe the synthesis of this alkaloid and a marginal correction of its structural formula (**2b** instead of **2a**, see below).



Scheme 1

Rac. α-acetyl-3,4-dimethoxybenzylcyanide [3] (**3**) was converted to **4** which was reduced by B_2H_6 to the β-phenylethylamine **5**. Aminolysis of methyl (3,4-methylenedioxyphenyl)acetate (**6**) with amine **5** afforded the amide **7** which was cylcized to **8** according to *Bischler-Napieralski* [4]. $NaBH_4$ led to the tetrahydroisoquinoline **9a**. We were not bothered about stereoisomers because the centers of chirality at C-1 and C-4 were abolished in the following steps.

This hydrogenation seems to be a detour because a (dehydrogenated) isoquinoline systems was aspired. On account of the sensitivity of 1-benzyl-3,4-dihydroisoquinoline bases, however, which are easily converted to 1-benzoyl-3,4-dihydroisoquinolines by exposure to air [5], we could not remove the dithioketal protecting group successfully. This step, however, would have been mandatory in order to avoid disturbances of the Pd/C-catalyzed dehydrogenation by the sulfur-increment.

Various attempts for cleaving the dithioketal in **9a** failed [6]. *Meerwein's* reagent [7], e.g., led to *N*-ethylation (**9b**) but did not attack the dithioketal.

According to *Fujita* [8] even those S-protecting groups being resistant against $Tl(NO_3)_3$ can be removed by $Hg(ClO_4)_2$. This reagent has smoothly liberated the ketone moiety of the β-aminoketone **10**. Dehydrogenation of **10** led to the 4-acetyl-1-benzylisoquinoline **11** in 82 % yield besides 6.5 % of **11a**.

A rationalization for the formation of the by-product **11a** is given in Scheme 4.

Alternatively the dithioketal moiety in amide **7** was removed by $Hg(ClO_4)_2$ producing compound **12** which was cyclized to the 3,4-dihydroisoquinoline **13**, but direct dehydrogenation of **13** afforded the 4-acetyl-1-benzylisoquinoline **11** in 18 - 22 % yield only.

*) Dedicated to Prof. Dr. *K. Bernauer*, Basel, on the occasion of his 65 th birthday.

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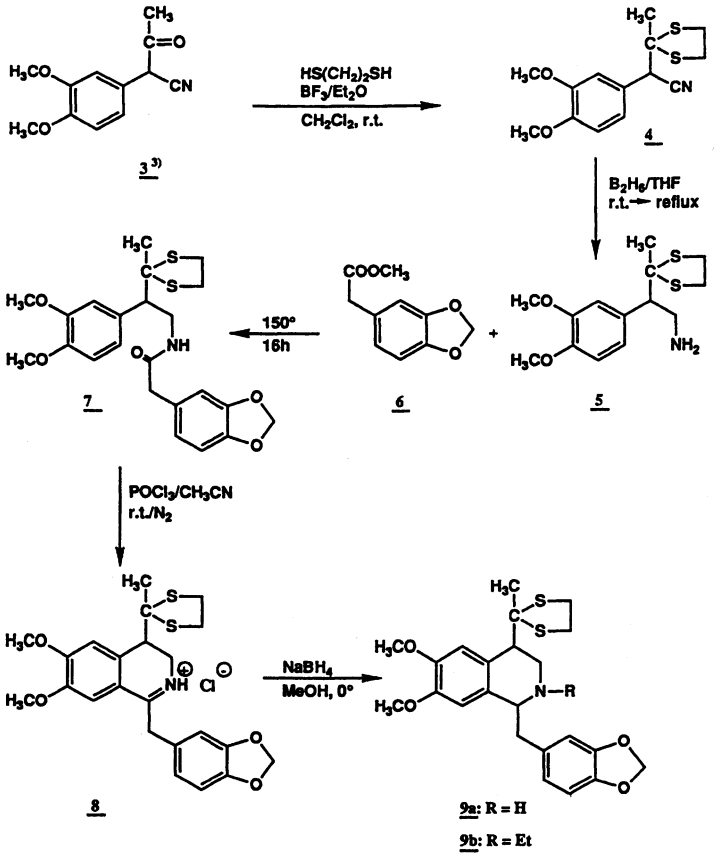
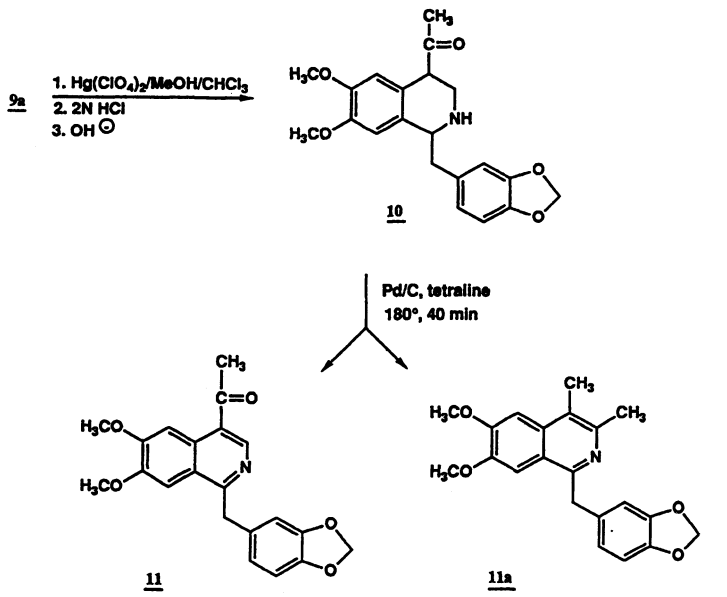


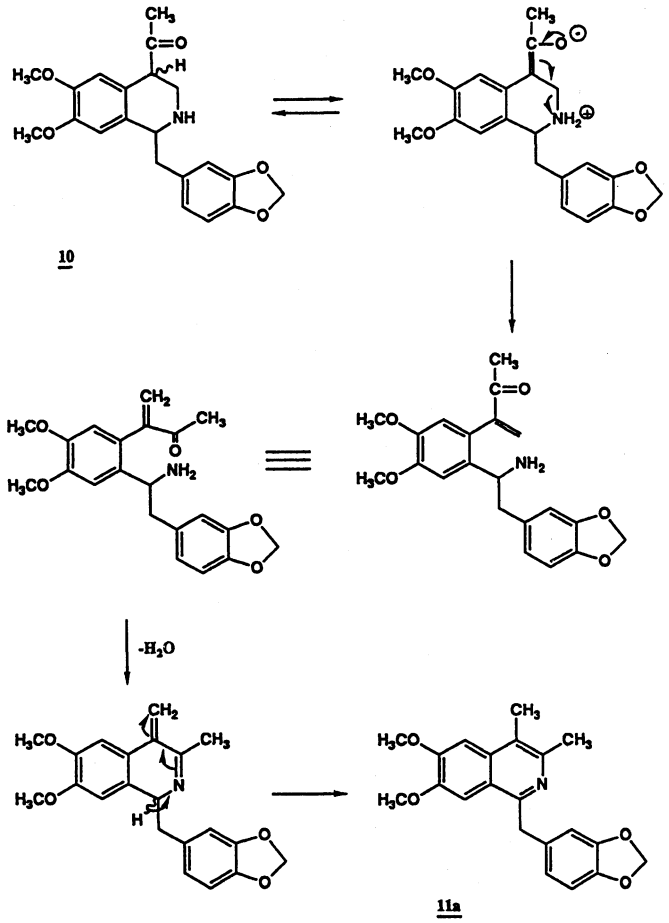
Scheme 2



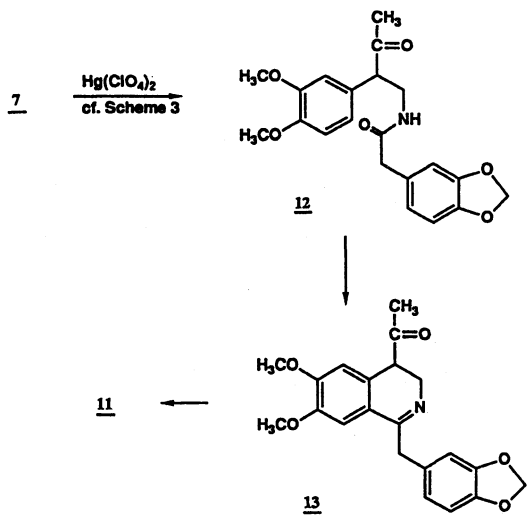
Scheme 3

Our efforts to build up the pyrroline moiety of *Preininger*-alkaloid adopting synthetic routes elaborated by *Leete* [9], *Knott* [10], or *Burckhalter* [11] and nicely working in the preparation of 2-(hetero)aryl-pyrrolines [12] failed: *Böhme* salt (*N,N*-dimethyl-methyleneammonium chloride) [13] or the corresponding acetate [14] did not react with **11** at room temp., whilst at 80°C (chloride form) or 40°C (acetate form) the CH_2-group was attacked leading to the aza-*Mannich* base **14** (Scheme 6).

We had been aware of this possibility but 1-(3,4-methylenedioxybenzyl)-6,7-dimethoxyisoquinoline [15] did not react under these conditions. Probably the 4-acetyl increment in **11** increases the C-H-acidity of the CH_2-

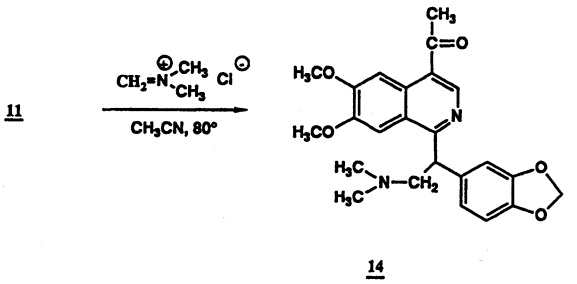


Scheme 4



Scheme 5

group. Therefore, the following steps were performed analogously to those described for our modified synthesis of the nicotiana alkaloid myosmine[16].



Scheme 6

Our key compound **11** was silylated according to *Simchen*[17] affording the enol derivative **15**, which was treated with *N,N*-dimethyl-methyleneammonium iodide (*Eschenmoser* salt) followed by hydrolysis with dil. HCl, producing the *Mannich* base **16**; both steps are analogous to those reported by *Danishefsky* [18]. **16**-HCl is converted by CN^- to the β-cyanoketone **17**. This step does not work with **16**-base, because it decomposes easily by a retro-*Mannich*-reaction. Careful hydrogenation (cf. Scheme 7) led to **2b**, the *Preininger*-alkaloid.

If the enol derivative **15** is allowed to react with *Böhme-Eschenmoser* salt (iodide form) for 12 h (instead of 90 min only) and the crude mixture is treated with KCN followed by hydrogenation as described above, the C-9-methylated *Preininger*-alkaloid **18** is obtained.

We assume that also in this case the CH_2-group had reacted with the N,N-dimethyl-methyleneammonium salt to an aza-*Mannich* base. Loss of dimethylamine from the pertinent enamine tautomere to the C-9-methylene increment und subsequent hydrogenation then affords compound **18** (cf. Scheme 8).

As mentioned in the introductory remarks formula **2a** had been attributed to dehydro-normacrostomine [2], whilst on the other side compound **2b** fits all the analytical data cited by *Šantavý, Preininger* et al. [2)*]. These authors have deduced the enamine-structure from H/D-exchange experiments with "deuterioethanol", giving rise of an (M+1)-peak in the mass spectrum and "to a smaller extent" of (M+2). Obviously the quantity available (7 mg [2]) of this alkaloid was too small for ^{1}H-NMR-experiments at that time. - There are no experimental data for that H/D-exchange experiment. We used CD_3OD and found only 10 % exchange. Because a D^+-catalyzed reaction is conceivable (traces of CD_3-COOD in the deuterioethanol ?) we have stirred **2b** with CD_3-COOD at 30°C for 3 h. The result (up to 5 H exchanged) is shown in fig. 1.

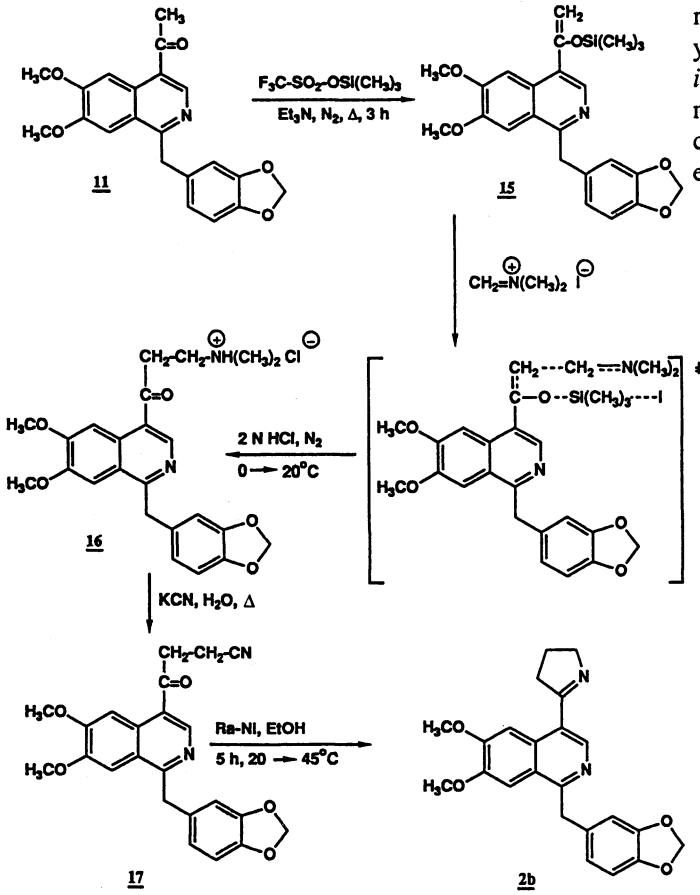
Obviously not only the aza-allyl system but also the benzylic CH_2-group is prone to H/D-exchange. - The ^{1}H-NMR-spectrum of **2b** is shown in fig. 2.

We have reported on the enantioselective hydrosilylation of the *Preininger*-alkaloid (**2b**) affording (*S*)-(-)-macrostomine (**1**) with 33 % ee [19].

Reduction of **2b** with $NaBH_4$/N-benzyloxycarbonyl-L-proline (cf. *Iwakuma* [20]) and subsequent *N*-formylation by CH_3-CO-O-CO-H afforded rotamers of (*R*)-(+)-*N*-formyl-normacrostomine (**19**) which were reduced to (*R*)-(+)-mac-

*) The enamine/imine tautomerism is generally discussed by *O. Cervinka* in: Enamines, 2 nd ed., p. 460, *G.A. Cook*, ed., M. Dekker, Inc., New York ...

rostomine (enantiomer of **1**) by $LiAlH_4$ in 90 % chemical yield and 72 % optical purity (calculated by adopting *Preininger's* $[\alpha]_D^{25}$ = 51° (+/- 3°), c = 0.9, $CHCl_3$, for natural macrostomine (**1**)) [2]. Because the reducing reagent for **2b** can also be prepared with D-proline this method opens an easy access to natural macrostomine (**1**) (Scheme 8).



Scheme 7

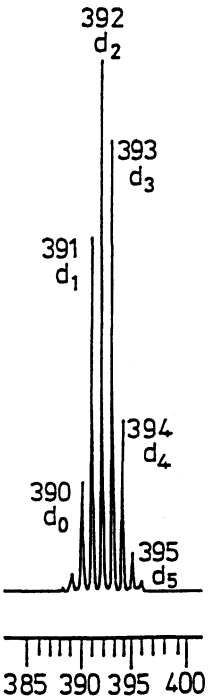


Fig. 1: H/D-exchange; Preininger-alkaloid (**2b**)

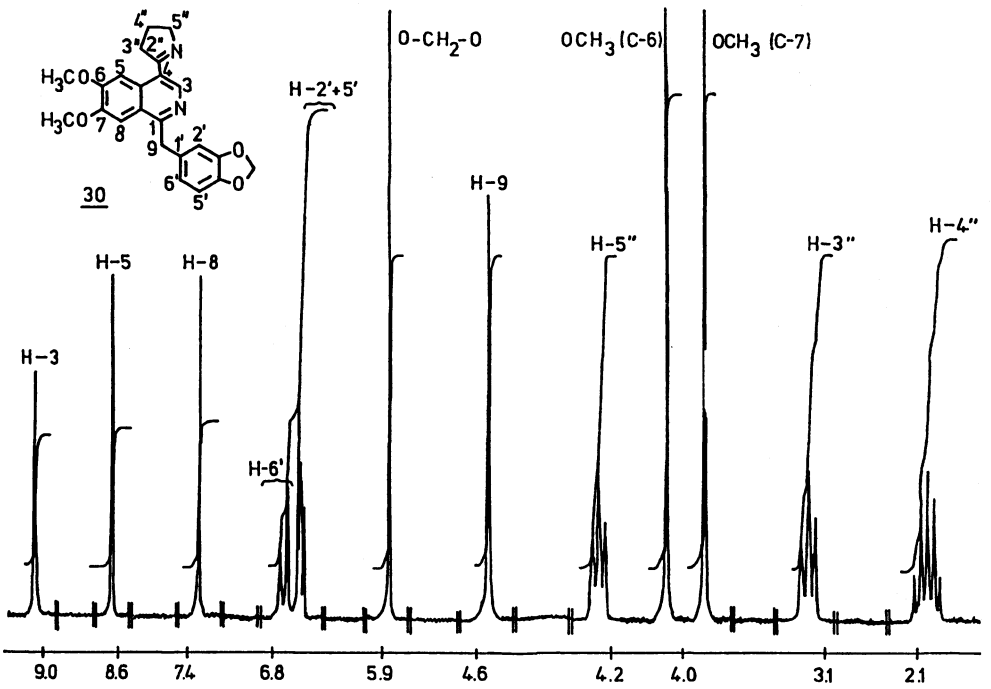
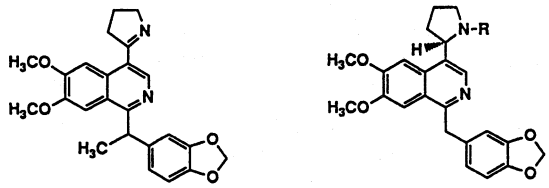


Fig. 2: 400 MHz-^{1}H-NMR-spectrum of Preininger-alkaloid (**2b**)



18

19: R = CHO
20: R = H

Scheme 8

Moreover, **19** can be hydrolyzed to the pertinent normacrostomine **20**.

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Experimental Part

General remarks: lit. [16]; Al_2O_3: activity II-III, Brockmann. - All temp. in °C.

α-(3,4-Dimethoxyphenyl)-α-(2-methyl-1,3-dithiolan-2-yl)acetonitrile (**4**)

54.8 g (0.25 mole) α-acetyl-3,4-dimethoxybenzylcyanide (**3**) [3], dissolved in 400 ml of absol. CH_2Cl_2, 24.54 g (0.26 mole) 1,2-dimercaptoethane and 20 ml BF_3-etherate were stirred at room temp. for 16 h. After addition of water (100 ml) and alkalization with 5 % NaOH the mixture was extracted with CH_2Cl_2. The org. layer was washed with water and dried (Na_2SO_4). After evaporation the light yellow oil was purified by kugelrohr-distillation (210°, 0.05 mm Hg): colourless crystals, m.p. 82 - 83° (MeOH), 70.2 g (95 %). - $C_{14}H_{17}NO_2S_2$ (295.4) Calcd. C 56.4 H 5.70 N 4.7 Found C 56.3 H 5.66 N 4.6. - UV (MeOH): λ max (log ε) = 279 (3.50), 236 nm (3.95). - IR (KBr): 2270 cm^{-1} (CN). - ^{1}H-NMR: δ (ppm) = 1.8 (s; 3H, CH_3), 3.2 - 3.48 (m; 4H, S-CH_2-CH_2-S), 3.89 (s; 3H, OCH_3), 3.91 (s; 3H, OCH_3), 4.2 (s; 1H, CH-CN), 6.85 (d; J_{AB} = 9 Hz, 1H, Ar-H-5), 7.5 (dd; $J_{1/2}$ = 9/1.5 Hz, 2H, Ar-H-6 and H-2).

2-(3,4-Dimethoxyphenyl)-2-(2-methyl-1,3-dithiolan-2-yl)-ethylamine (**5**)

500 ml B_2H_6-tetrahydrofuran complex (1 mole/l) were added drop by drop to 118 g (0.4 mole) of **4** in 350 ml of absol. THF at room temp. under N_2. After 45 min reflux about 750 ml of THF were distilled off and EtOH (130 ml) was added drop by drop at 0°. After alkalization with aqueous NH_3 amine **5** is extracted with $CHCl_3$. After drying (Na_2SO_4) and evaporation the remaining oil is purified by kugelrohr-distillation (190°, 0.01 mm Hg): nearly colourless viscous oil, 116.2 g (97 %). **5**-base was transformed to **5**-HCl by gaseous HCl in Et_2O: colourless crystals, m.p. 233 - 234°. - $C_{14}H_{22}NO_2S_2$·Cl (335.9) Calcd. C 50.1 H 6.55 N 4.2 Found C 50.0 H 6.65 N 4.0. - UV (MeOH): λ max (log ε) = 275 (3.72), 263 nm (3.71). - IR (KBr): 3200 cm^{-1} (N-H^+). - ^{1}H-NMR: δ (ppm) = 1.04 (s; 2H, NH_2, H/D-exchange), 1.66 (s; 3H, CH_3), 2.84 - 3.6 (m; 3H, Ph-CH-CH_2), 3.26 (s; 4H, S-CH_2-CH_2-S), 3.9 (s; 6H, OCH_3), 6.75 - 7.06 (m; 3H, Ar-H).

N-[2-(3,4-Dimethoxyphenyl)-2-(2-methyl-1,3-dithiolan-2-yl)-ethyl]-(3,4-methylenedioxyphenyl)acetamide (**7**)

29.9 g (0.1 mole) amine **5** and 21.3 g (0.11 mole) methyl (3,4-methylenedioxyphenyl)acetate (**6**) are heated together to 150° for 16 h. After cooling **7** is dissolved in ethyl acetate and filtered. After evaporation, amide **7** is purified by cc (Al_2O_3; EtOAc) and kugelrohr-distillation (230 - 240°, 0.01 mm Hg): colourless crystals, m.p. 108 - 109° (CH_3CN), 42.9 (93 %). - $C_{23}H_{27}NO_5S_2$ (461.6) Calcd. C 59.8 H 5.89 N 3.0 Found C 59.7 H 5.73 N 3.1. - IR (KBr): 3310 (N-H); 1660 cm^{-1} (NC=O). - ^{1}H-NMR: δ (ppm) = 1.61 (s; 3H, CH_3) 2.96 - 4.41 (m; 7H, Ph-CH-CH_2 and S-$(CH_2)_2$-S), 3.3 (s; 2H, Ph-CH_2), 3.84 (s; 3H, OCH_3), 3.92 (s; 3H, OCH_3), 5.1 - 5.41 (m; 1H, NH, H/D-exchange), 5.94 (s; 2H, O-CH_2-O); 6.28 - 6.91 (m; 6H, Ar-H).

6,7-Dimethoxy-4-(2-methyl-1,3-dithiolan-2-yl)-1-(3,4-methylendioxybenzyl)-3,4-dihydroisoquinoline-HCl (**8**)

18.46 g (0.04 mole) amide **7** were dissolved in 50 ml of absol. CH_3CN under N_2. 14 ml $POCl_3$ in 10 ml of absol. CH_3CN were added drop by drop at 0°. The mixture was stirred at room temp. for 4 days, then the crystals were filtered. The filtrate is diluted with acetone (100 ml) and $NaHCO_3$ (10 ml of a saturated solution) was added: the crystals so obtained were combined with the crystals mentioned above and recrystallized from MeOH: colourless crystals, m.p. 241° (decomp.), 17.3 g (90 %). - $C_{23}H_{26}NO_4S_2$·Cl (480.0) Calcd. C 57.5 H 5.45 N 2.9 Found C 57.3 H 5.45 N 3.0. - UV (MeOH): λ max (log ε) = 305 (sh, 3.78), 286 (4.01), 230 nm (4.43). - IR (KBr): 1670 cm^{-1} (C=N). - MS: m/z = 443 (M^+; base, 1 %), 325 (94), 324 (62), 308 (6), 202 (10), 171 (3), 135 (11), 119 (100).

6,7-Dimethoxy-4-(2-methyl-1,3-dithiolan-2-yl)-1-(3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**9a**)

To 14.4 g (0.03 mole) **8**-HCl, dissolved in 130 ml of absol. MeOH, were added under N_2 2.7 g (71.3 mmole) of $NaBH_4$ in portions at 0°. The mixture was stirred for 1 h at 0°. Then excess of $NaBH_4$ was destroyed by 2N HCl, MeOH was distilled off *in vacuo* and the remaining mixture was extracted with CH_2Cl_2. The org. phase is washed with saturated $NaHCO_3$-solution and dried (Na_2SO_4). Evaporation yielded 13 g of an amorphous powder (97 %). **9**- picrate: m.p. 182 - 183° (EtOH). - $C_{23}H_{27}NO_4S_2$ (base) (445.6) Calcd. C 51.7 H 4.45 N 8.30 Found C 51.9 H 4.46 N 8.3. - UV (MeOH): λ max (log ε) = 285 (3.89), 225 nm (4.16). - IR (KBr): 3400 cm^{-1} (broad, N-H). - ^{1}H-NMR: δ (ppm) = 1.85 (s; 3H, CH_3), 1.29 (s; 1H, NH, H/D-exchange), 2.65 - 4.39 (m; 6H, Ph-CH-CH_2 and NH-CH-CH_2), 3.28 (s; 4H, S-$(CH_2)_2$-S), 3.85 (s; 3H, OCH_3), 3.9 (s; 3H, OCH_3), 5.94 (s; 2H, O-CH_2-O), 6.65 - 6.92 (m; 4H, Ar-H), 7.35 (s; 1H, Ar-H). - MS: m/z = 444 ((M - H)$^+$, 1 %), 326 (8), 325 (20), 310 (100), 192 (24), 191 (25), 190 (65), 135 (16), 119 (98).

6,7-Dimethoxy-4-(2-methyl-1,3-dithiolan-2-yl)-N-ethyl-1-(3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**9b**)

200 mg (0.45 mmol) of **9a** were dissolved in 5 ml of absol. CH_2Cl_2 and stirred under N_2 with 170 mg (0.9 mmol) of Et_3O·BF_4 in 2 ml of absol. CH_2Cl_2 at 0° for 1 h, then for 4 h at room temp. After alkalization with 2N NaOH the org. layer was separated, washed with water, and dried (Na_2SO_4). The resulting oil is purified by cc (SiO_2; ethyl acetate): light yellow oil, 175 mg (82 %). - $C_{25}H_{31}NO_4S_2$ (473.7). - ^{1}H-NMR: δ (ppm) = 1.15 (t; J = 7.4 Hz, 3H, CH_2-CH_3), 1.7 (s; 3H, CH_3), 2.37 - 3.83 (m; 12H, S-$(CH_2)_2$-S, Ph-CH-CH_2-N-CH-CH_2, and CH_2-CH_3), 3.57 (s; 3H, OCH_3), 3.86 (s; 3H, OCH_3), 5.9 (s; 2H, O-CH_2-O), 6.07 (s; 1H, Ar-H), 6.5 - 6.8 (m; 3H, Ar-H), 7.47 (s; 1H, Ar-H). - MS: m/z = 471 ((M-H)$^+$, 3 %), 352 (3), 338 (97), 218 (100), 119 (51).

4-Acetyl-6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**10**)

To 7.1 g (16 mmole) dithiolane **9a**, dissolved in 250 ml of $CHCl_3$ and 50 ml of MeOH, were added 5.28 g $Hg(ClO_4)_2$ trihydrate in 180 ml of MeOH. After 1 h stirring at room temp. the precipitate was filtered off and the filtrate was basified by 2N Na_2CO_3. After evaporation of the solvents addition of 30 ml of 2N HCl afforded a Hg-containing crystalline precipitate. The pertinent oily base **10** (5.3 g; 90 %) was liberated by 2N NaOH: **10**-HCl: m.p. 185 - 187° (precipitated from Et_2O). - $C_{21}H_{24}NO_5$·Cl (405.9). Calcd. C 62.1 H 5.96 N 3.5 Found C 62.3 H 5.81 N 3.5. - UV (MeOH): λ max (log ε) = 285 (3.85), 231 nm (4.04). - IR (film): 3335 (sharp, N-H); 1710 cm^{-1} (C=O). - ^{1}H-NMR: δ (ppm) = 1.82 (s; 1H, NH), 2.15 (s; 3H,

CH_3), 2.65 - 4.28 (m; 6H, Ph-CH-CH_2-N-CH-CH_2-Ph), 3.85 (s; 6H, OCH_3), 5.9 (s; 2H, O-CH_2-O), 6.5 - 6.85 (m; 5H, Ar-H).

4-Acetyl-6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (**11**) *and 6,7-dimethoxy-3,4-dimethyl-1-(3,4-methylenedioxybenzyl)isoquinoline* (**11a**)

3 g (8 mmole) of compound **10** were treated with 500 mg Pd/C 10 % in 8 ml of tetraline at 180° for 40 min. After cooling and filtration the solvent was distilled off *in vacuo*, the residue was dissolved in CH_2Cl_2, the solution was dried over Na_2SO_4 and evaporated. The remaining oil was purified by cc (SiO_2, ethyl acetate): 2.7 g of a mixture of **11** and **11a** which was separated at an analytical scale by HPLC (lichroprepsibo, 30 - 40 nm, 20 bar, 22 ml/min; solvent: CH_2Cl_2/CH_3CN 8 + 2). The CH_2Cl_2 used contains 1 % of the following mixture: 134 ml CH_2Cl_2 + 31 g glacial acetic acid + 35.4 g NEt_3. - Retention time for **11**: 2.8 min, for **11a** 6.2 min.

Preparative yields: 2.4 g (82 %) **11** and 0.183 g (6.5 %) **11a**. The isoquinoline **11** was recrystallized from diisopropylether, m.p. 165 - 166°. **11a** was recrystallized from diisopropyl ether/CH_2Cl_2, m.p. 168 - 169°.

Compound **11**: $C_{21}H_{19}NO_5$ (365.4) Calcd. C 69.0 H 5.20 N 3.8 Found C 69.1 H 5.37 N 3.6. - UV (MeOH): λ max (log ε) = 335 (3.68), 322 (3.62), 286 (3.89), 240 (sh, 3.96), 226 (sh, 4.70), 214 (4.76). - IR (KBr): 1680 cm^{-1} (C=O). - ^{1}H-NMR: δ (ppm) = 2.75 (s; 3H, CH_3), 3.9 (s; 3H, OCH_3), 4.04 (s; 3H, OCH_3), 4.57 (s; 2H, Ph-CH_2), 5.89 (s; 2H, O-CH_2-O), 6.72 (broad s; 3H, Ar-H), 7.39 (s; 1H, H-5), 8.54 (s; 1H, H-8), 9.0 (s; 1H, H-3). - MS: m/z = 365 ($M^{+\cdot}$, 76 %), 364 (100), 350 (40), 334 (26), 322 (11), 307 (9), 306 (16), 135 (16).

11a: $C_{21}H_{21}NO_4$ (351.4) Calcd. C 71.7 H 6.02 N 3.98 Found C 72.3 H 6.18 N 4.18 - ^{1}H-NMR: δ (ppm) = 2.48 (s; 3H, C-3-CH_3), 2.68 (s; 3H, C-4-CH_3), 3.83 (s; 3H, OCH_3), 3.89 (s; 3H, OCH_3), 4.45 (s; 2H, Ph-CH_2), 5.83 (s; 2H, O-CH_2-O), 6.7 (broad s; 3H, Ar-H), 7.1 (s; 1H, H-5), 7.25 (s; 1H, H-8). - MS: m/z = 351 ($M^{+\cdot}$, 58 %), 336 (100), 320 (21), 308 (10), 305 (9), 292 (20), 276 (11), 248 (8), 235 (7), 160 (9).

N-[2-Acetyl-2-(3,4-dimethoxyphenyl)ethyl]-(3,4-methylenedioxyphenyl)-acetamide (**12**)

To 2.3 g (5 mmole) **7**, dissolved in 100 ml of MeOH and 50 ml of Et_2O, were added drop by drop 2.1 g (5.93 mmole) $Hg(ClO_4)_2$ trihydrate in 50 ml of MeOH. The suspension was stirred for 1 h at room temp. The precipitate was filtered off, washed with CH_2Cl_2 and discarded. The combined org. phases were washed with 30 ml of 2N NaOH and with saturated NaCl-solution. After drying (Na_2SO_4) and evaporation, compound **12** was purified by cc (Al_2O_3; CH_2Cl_2/CH_3N 9 + 1) and kugelrohr-distillation (200°, 0.05 mm Hg): colourless crystals, mp. 117 - 118°, 1.8 g (93 %). - $C_{21}H_{23}NO_6$ (385.4) Calcd. C 65.4 H 6.01 N 3.6 Found C 65.2 H 6.18 N 3.7. - UV (MeOH): λ max (log ε) = 283 (3.81), 235 nm (4.00). - IR (KBr): 3330 (sharp, N-H); 1720 (C=O); 1655 cm^{-1} (NC=O). - ^{1}H-NMR: δ (ppm) = 2.02 (s; 3H, CH_3), 3.3 - 4.3 (m; 3H, Ph-CH-CH_2-N), 3.39 (s; 2H, NCO-CH_2-Ph), 3.81 (s; 3H, OCH_3), 3.84 (s; 3H, OCH_3), 5.7 - 6.03 (m; 1H, NH), 5.92 (s; 2H, O-CH_2-O), 6.49-6.92 (m; 6H, Ar-H).

4-Acetyl-6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)-3,4-dihydroisoquinoline (**13**) *and its dehydrogenation to* **11**

1.3 g (3.4 mmole) **12** were heated under reflux for 4 h with 3 ml of $POCl_3$ in 30 ml of absol. CH_3CN under N_2. The solvent was evaporated, the residue was dissolved in ice/water and basified with Na_2CO_3 under N_2. Extraction with Et_2O, drying of the org. phase (Na_2SO_4) and evaporation *in vacuo* afforded the dihydroisoquinoline **13**, which was dissolved in 10 ml of tetraline and dehydrogenated by heating this solution to 190 - 200° with 300 mg Pd/C 10 % for 3 h. Then the solvent was distilled off, the residue was suspended in CH_2Cl_2 and the catalyst war removed by filtration. The org. phase was dried (Na_2SO_4) and evaporated. The oily residue was purified by cc (SiO_2; ethyl acetate). - Yield (both steps): 250 mg (20 %) **11**.

4-Acetyl-6,7-dimethoxy-9-(N,N-dimethylaminomethyl)-1-(3,4-methylenedioxybenzyl)isoquinoline (**14**)

28 mg (0.3 mmole) N,N-dimethyl-methyleneammoniumchloride and 100 mg (0.27 mmole) **11** in 3 ml of absol. CH_3CN were heated to 80° for 3 h. After evaporation of the solvent *in vacuo* the residue was treated with 2N Na_2CO_3-solution and extracted with CH_2Cl_2. Drying (Na_2SO_4) and evaporation *in vacuo* afforded an oil which was purified by cc (SiO_2; MeOH): light yellow crystals, m.p. 138 - 141° (Et_2O/hexane), yield 90 mg (71 %). - $C_{24}H_{26}N_2O_5$ (422.5). - UV (MeOH): λ max (log ε) = 333 (3.87), 2.91 (3.81), 251 (sh, 4.46), 2.35 nm (4.51). - IR (KBr): 1690 cm^{-1} (C=O). - ^{1}H-NMR (400 MHz): δ (ppm) = 2.35 (s; 6H, $N(CH_3)_2$), 2.76 (s; 3H, $COCH_3$); 3.03 - 3.08 (AA'B, dd, $J_{1/2}$ = 12.4/6.95 Hz, 1H, Ph-CH-C$\underline{H}_2$), 3.64 - 3.77 (AA'B, dd, $J_{1/2}$ = 12.4/6.95 Hz, 1H, Ph-CH-C$\underline{H}_2$), 3.98 (s; 3H, OCH_3), 4.02 (s; 3H, OCH_3), 5.0 - 5.15 (m; 1H, Ph-C$\underline{H}$-CH_2), 5.85 (d, J = 1.4 Hz, 1H, O-CH_2-O), 5.88 (d; J = 1.4 Hz, 1H, O-CH_2-O), 6.69 - 6.90 (m; 3H, Ar-H), 7.51 (s; 1H, Ar-H), 8.50 (s; 1H, Ar-H), 9.04 (s; 1H, H-3). - MS: m/z = 422 ($M^{+\cdot}$, 6 %), 389 (25), 307 (100), 292 (98).

3-Cyano-1-[6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)isoquinolin-4-yl]-propan-1-one (**17**)

3.65 g (10 mmole) **11** were dissolved in 70 ml of absol. benzene under N_2 and stirred with 1.2 g Et_3N and 2.16 ml of F_3C-SO_2-O-Si$(CH_3)_3$ at 0° for 30 min and for 3 h at reflux temp. After cooling the benzene phase was separated and evaporated; viscous orange oil of **15** (4.4 g) which was not purified but directly dissolved in 30 ml of absol. CH_2Cl_2 under N_2 at 0° and stirred with 2 g of N,N-dimethyl-methyleneammonium iodide first at 0° for 1 h than for 3 h at room temp.. After evaporation of CH_2Cl_2 the colourless oil was dissolved in 12 ml of 2N HCl at 0° under N_2, then the solution was stirred for 2 h at room temp. After evaporation the *Mannich* base **16**-HCl was obtained (colourless oil). - This oil and 0.7 g KCN were dissolved in 80 ml of water of 90° and refluxed for 2 h under N_2. After cooling extraction with CH_2Cl_2, drying (Na_2SO_4), and evaporation led to the nitrile **17** which was purified by cc (Al_2O_3; $CHCl_3$): colourless crystals from EtOH, m.p. 172 - 173°, total yield (4 steps): 2.06 g (51 %). - $C_{23}H_{20}N_2O_5$ (404.4) Calcd. C 68.3 H 4.98 N 6.6 Found C 68.2 H 4.98 N 6.6 - UV (MeOH): λ max (log ε) = 333 (3.88), 291 (3.81), 246 (sh, 4.47), 231 nm (4.54). - IR (KBr): 2260 (C≡N); 1675 cm^{-1} (C=O). - ^{1}H-NMR: δ (ppm) = 2.87 (t; J = 7.5 Hz, 2H, CH_2-C$\underline{H}_2$CN), 3.56 (t; J = 7.5 Hz, 2H, C$\underline{H}_2$-CH_2-CN), 3.94 (s; 3H, OCH_3), 4.08 (s; 3H, OCH_3), 4.58 (s; 2H, Ar-CH_2-Ph), 5.9 (s; 2H, O-CH_2-O), 6.69 - 6.8 (m; 3H, Ar-H), 7.4 (s; 1H, Ar-H-5), 8.54 (s; 1H, Ar-H-8), 9.0 (s; 2H, Ar-H-3). - MS: m/z = 404 ($M^{+\cdot}$, 80 %), 403 (100), 389 (35), 373 (23).

6,7-Dimethoxy-1-(3,4-methylenedioxybenzyl)-4-(1-pyrrolin-2-yl)-isoquinoline (**2b**), *Preininger-alkaloid*

600 mg (1.5 mmole) **17**, dissolved in 100 ml of absol. EtOH, were heated to 40 - 45° for 5 h with 2 g Raney-Ni in 6 ml of absol. EtOH, previously saturated with NH_3 at 0°. Efficient cooling in order to prevent escaping of NH_3 is mandatory. In addition the reflux condenser has to be closed by a stopper plug. After cooling the catalyst was filtered off and the solvent was evaporated *in vacuo*. **2b** is purified by cc (Al_2O_3; $CHCl_3$): colourless crystals from acetone, m.p. 192 - 193° (lit.: 193° - 195° [2]), 540 mg (92 %). - UV (EtOH): λ max (log ε) = 332 (sh, 3.45), 317 (3.47), 293 (3.52), 247 nm (4.26). - UV (EtOH + HCl): λ max (log ε) = 340 (3.95), 262 (4.49), 235 nm (4.44). - IR (KBr): 1620 cm^{-1} (C=N). - ^{1}H-NMR: δ (ppm) = 2.02 - 2.10 (m; 2H, pyrr.-H-4''), 3.12 - 3.16 (m; 2H, pyrr.-H-3''), 3.92 (s; 3H, OCH_3 (C-7)), 4.03 (s; 3H, OCH_3 (C-6)), 4.21 - 4.25 (m; 2H, pyrr.-5''-H), 4.56 (s; 2H, Ph-CH_2), 5.88 (s; 2H, O-CH_2-O), 6.7 - 6.72 (m; 2H, H-2' and H-5'), 6.77 (dd; J_o = 7 Hz, J_m = 1 Hz, H-6'), 7.37 (s; 1H, H-8), 8.61 (s; 1H, H-5), 9.02 (s; 1H, H-3). - MS: m/z = 390 ($M^{+\cdot}$, 99 %), 389 (100), 375 (49), 359 (19), 135 (24).

6,7-Dimethoxy-9-methyl-1-(3,4-methylenedioxybenzyl)-4-(1-pyrrolin-2-yl)-isoquinoline (**18**)

Compound **18** is formed, if the silylated enol derivative **15** reacts for 12 h with N,N-dimethyl-methyleneammonium iodide. For the following steps, leading to nitril **17**, the mixture was not separated. Compound **18** is easily separated from *Preininger*-alkaloid (**2b**) by cc (SiO_2; CH_2Cl_2/CH_3CN 8 + 2) and recrystallization from EtOH: colourless crystals m.p. 142.5 - 143°, 7 - 9 % yield. - $C_{24}H_{24}N_2O_4$ (404.5) Calcd. C 71.3 H 5.98 N 6.9 Found C 71.4 H 6.11 N 6.8. - UV (EtOH): λ max (log ε) = 328 (sh, 3.87), 314 (3.89), 292 (3.94), 246 nm (4.52). - IR (KBr): 1625 cm^{-1} (C=N). - ^{1}H-NMR: δ (ppm) = 1.84 (d; J = 6 Hz, 3H, Ph-CH-C<u>H</u>$_3$), 1.85 - 2.25 (m; 2H, pyrr.-H-4), 2.98 - 3.31 (m; 2H, pyrr.-H-3), 3.90 (s; 3H, OCH_3), 4.1 (s; 3H, OCH_3), 4.1 - 4.37 (m; 2H, pyrr.-H-5), 4.89 (q; J = 6 Hz, 1H, Ph-C<u>H</u>-CH$_3$), 5.84 (s; 2H, O-CH_2-O), 6.63 - 6.93 (m; 3H, Ar-H), 7.44 (s; 1H, Ar-H), 8.75 (s; 1H, Ar-H), 9.16 (s; 1H, H-3). - MS: m/z = 404 (M^+ ·, 100 %), 403 (86), 389 (35), 373 (8), 149 (8), 135 (12).

(R)-(+)-N-Formylnormacrostomine (**19**)

The reducing reagent was prepared by adding 750 mg of L-Z-proline to 35 mg of $NaBH_4$ in 5 ml absol. THF. This mixture was stirred for 1 h at 0° and 3 h at room temp.. After evaporation of THF the reducing complex is used as such. - 70 mg (0.18 mmole) **2b**, dissolved in 4 ml of absol. CH_2Cl_2, were added to the proline-complex mentioned above; the mixture was stirred for 2 h at 0° and 60 h at room temp.. After evaporation the residue was dissolved in 2 ml of H-CO-O-CO-CH_3 at 0° and stirred for 15 min at 0° and 15 min at room temp.. After 40 min heating at 70° excessive anhydride was distilled off *in vacuo*. The residue was dissolved in CH_2Cl_2, the solution was dried (Na_2SO_4) and evaporated, the remaining oil was purified by cc (Al_2O_3, $CHCl_3$): colourless crystals, m.p. 140°. - IR- and mass-spectrum are identical with those reported for the (S)-(-)-enantiomer [10]. - Optical rotation: (+), qual.

(R)-(+)-normacrostomine (**20**)

17 mg (0.04 mmole) **19** were heated to reflux in 2.5 ml of 3N HCl for 2.5 h. After cooling and neutralization with $NaHCO_3$ **20** was extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated: 13 mg (84 %) light yellow amorphous powder. - $C_{23}H_{24}N_2O_4$ (392.5). - UV (MeOH, qual.): λ max = 329; 315; 284; 245 (sh); 240 nm. - IR (KBr): 3400 cm^{-1} (N-H, broad). - ^{1}H-NMR (250 MHz): δ (ppm) = 1.85 - 4.71 (m; 8H, CH-$(CH_2)_3$-NH: pyrr.-H), 3.89 (s; 3H, OCH_3), 4.02 (s; 3H, OCH_3), 4.46 (s; 2H, Ph-CH_2), 5.86 (s; 2H, O-CH_2-O), 6.68 - 6.76 (m; 3H, Ar-H), 7.31 (s; 1H, Ar-H), 7.46 (s; 1H, Ar-H), 8.46 (s; 1H, Ar-H-3). - MS (12 eV): m/z = 392 (M^+ ·, 100 %). - Optical rotation: (+), qual.

(R)-(+)-macrostomine ((+)-**1**)

50 mg (0.12 mmole) **19**, dissolved in 4 ml of absol. THF, were added drop by drop under N_2 to 70 mg $LiAlH_4$ in 5 ml of absol. THF at 0°C. This mixture was stirred for 15 min at 0°, 15 min at room temp. and 40 min under reflux. After cooling to 0°, excessive $LiAlH_4$ was destroyed by as little as possible water and the mixture was extracted with Et_2O (3 x 10 ml) and 10 ml of CH_2Cl_2. The combined org. phases were dried (Na_2SO_4) and evaporated. (+)-**1** was purified by cc (Al_2O_3; CH_2Cl_2/CH_3CN 9 + 1): light yellow powder, 44 mg (90 %). - m.p. 95 - 100°C (lit. [2]: 107 - 110° for optically pure (-)-**1**). - $[\alpha]_D^{25}$ = 37° (c = 0.9, $CHCl_3$; lit. [2]: 51°); optical purity = 72 %. - ^{1}H-NMR (400 MHz): δ (ppm) = 1.9 - 2.08 (m; 3H, H-3'', H-4'', H-5''), 2.25 (s; 3H, N-CH_3), 2.29 - 2.37 (m; 2H, H-3'', H-4''), 3.28 - 3.33 (m; 1H, H-5''), 3.5 - 3.56 (m; 1H, H-2''), 3.89 (s; 3H, OCH_3), 3.99 (s; 3H, OCH_3), 4.49 (s; 2H, Ph-CH_2), 5.87 (s; 2H, O-CH_2-O), 6.7 - 6.72 (m; 1H, H-6'), 6.77 - 6.79 (m; 2H, H-2' and H-5'), 7.32 (s; 1H, H-8), 7.79 (s; 1H, H-5), 8.40 (s; 1H, H-3).

References

1 V.A. Mnatsakanyan, V. Preininger, V. Šimánek, A. Klásek, L. Dolejš, and F. Šantavý, Tetrahedron Lett. *1974*, 851.

2 V.A. Mnatsakanyan, V. Preininger, V. Šimánek, J. Jurina, A. Klásek, L. Dolejs, and F. Šantavý, Collect. Czech. Chem. Commun. *42*, 1421 (1977).

3 E. Wenkert and R.D. Haugwitz, Can. J. Chem. *46*, 1160 (1968); G.A. Stein, H.A. Bronner, and K. Pfister, J. Am. Chem. Soc. *77*, 700 (1955).

4 J. March, Advanced Organic Chemistry, 3rd ed., p. 495, J. Wiley & Sons, New York ... 1985.

5 J.S. Buck, R.D. Haworth, and W.H. Perkin, jun., J. Chem. Soc. (London) *125*, 2176 (1924). - W. Wiegrebe, Arch. Pharm. (Weinheim) *297*, 362 (1964).
N.H. Martin, S.L. Champion, and Ph.B. Belt, Tetrahedron Lett. *21*, 2613 (1980) got best results with $^1O_2$, whilst A. Jossang, M. Leboeuf, and A. Cavé, Heterocycles *26*, 2193 (1987), describe a radical reaction with $^3O_2$, explaining their rusults in the field of noraporphines.

6 S. Mahboobi, Thesis, p. 67, Regensburg 1988.

7 T. Oishi, K. Kamemoto, and Y. Ban, Tetrahedron Lett. *1972*, 1085.

8 E. Fujita, Y. Nagao, and K. Kaneko, Chem. Pharm. Bull. *26*, 3743 (1978).

9 E. Leete, M.R. Chedekel, and G.B. Bodem, J. Org. Chem. *37*, 4465 (1972).

10 E.B. Knott, J. Chem. Soc. *1948*, 186.

11 J.H. Burckhalter and J.H. Short, J. Org. Chem. *23*, 1281 (1958).

12 R. Becker, H. Brunner, S. Mahboobi, and W. Wiegrebe, Angew. Chem. *97*, 969 (1985).

13 J. March, Advanced Organic Chemistry, 3rd ed., p. 802, J. Wiley & Sons, New York ... 1985.

14 A. Ahond, A. Cavé, C. Kan-Fan, and P. Potier, Bull. Soc. Chim. Fr. *1970*, 2707.

15 C. Mannich and O. Walther, Arch. Pharm. *265*, 1 (1927). - W. Wiegrebe, Arch. Pharm. (Weinheim) *300*, 708 (1967).

16 S. Mahboobi and W. Wiegrebe, Arch. Pharm. (Weinheim) *321*, 175 (1988).

17 G. Simchen and W. Kober, Synthesis *1976*, 259.

18 S. Danishefsky, T. Kitahara, R. McKee, and P.F. Schuda, J. Am. Chem. Soc. *98*, 6715 (1976).

19 H. Brunner, A. Kürzinger, S. Mahboobi, and W. Wiegrebe, Arch. Pharm (Weinheim) *321*, 73 (1988).

20 K. Yamada, M. Takeda, and T. Iwakuma, J. Chem. Soc. Perkin Trans. I *1983*, 265.

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