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A NITROSAMINE ROUTE TO (±)-MACROSTOMINE

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Summary : In a synthetic approach to macrostomine 1, both side chains of the isoquinoline nucleus are attached by high yield carbon carbon bond formation with lithiated nitrosamines (2b → 3a, 3c → 4a).

Although we have worked out procedures for the safe *in situ* handling of lithiated nitrosamines[1-3], they have found little application[4] in natural product synthesis. We describe here the efficient construction of the carbon skeleton 4 by this method and the aromatization to macrostomine 1, the main alkaloid of *papaver macrostomum Boiss et Huet*[5,6]. Starting material is the 4-hydroxy tetrahydroisoquinoline 2a[7] which is obtained from veratrum aldehyde and α-aminoacetaldehyde acetal by a *Pomeranz-Fritsch* reaction[8] in 63 % overall yield. Quantitative nitrosation of 2a with sodium nitrite/acetic acid (→ 2b), double deprotonation [C(1)H and OH], alkylation with 3.4-methylenedioxybenzylbromide[9] and *in situ* denitrosation[3] furnish a diastereomeric mixture of aminoalcohols 3a (80 % from 2b). After N-benzoylation (→ 3b) and oxidation of the hydroxy function with sodium hypochlorite under phase transfer conditions[10], the high carbonylophilicity of lithiated nitrosamines is used to produce the macrostomine carbon skeleton and functionality pattern: lithio- nitrosopyrrolidine adds to the keto group[11] of 3c to give a mixture of diastereomers 4a in 62 % yield, along with 30 % of unchanged, readily recovered ketone. Denitrosation with *Raney*-nickel[2] gave a compound (4a, R^1 = H instead of NO), the N-methylation and aromatization

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(a) Part of the dissertation of W. Wykypiel, ETH Zürich, 1980

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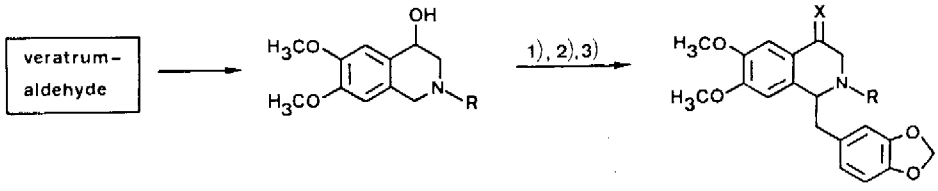
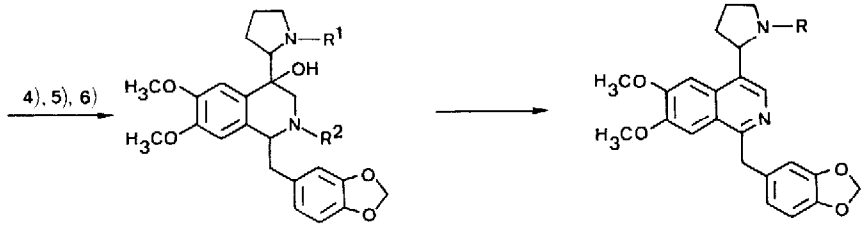


2a : R = H
2b : R = NO

3a : R = H, X = H/OH
3b : R = COC_6H_5, X = H/OH
3c : R = COC_6H_5, X = O



4a : R^1 = NO, R^2 = COC_6H_5
4b : R^1 = H, R^2 = $CH_2C_6H_5$
4c : R^1 = CHO, R^2 = $CH_2C_6H_5$

5 : R = CHO
1 : R = CH_3 (macrostomine)

1) 2b (m.p. 120°C)/2 equiv. LDA/3.4-methylenedioxy-benzylbromide[9]/-78°C, one pot denitrosation[3] 80 % 3a.

2) 3a/C_6H_5COCl/Et_3N/dioxane/40°C, 74 % 3b (m.p. 186°C).

3) 3b/13 % NaOCl/$Bu_4N^{\oplus}HSO_4^{\ominus}$/$CH_2Cl_2$-$CH_3COOEt$[10], 74 % 3c (228°C, dec.)

4) 3c/2-lithio-1-nitroso-pyrrolidine/THF/-78°C[2], 62 % (up to 90 % from unrecovered 3c) 4a (dec. > 91°C).

5) 4a/Raney-Ni/H_2/CH_3OH[2], then LAH/THF, > 90 % 4b (m.p. 146°C).

6) 4b/H_3C-CO-O-CHO/THF/RT, 62 % 4c.

of which we thought would be trivial[12]. It turned out that the pyrrolidine ring had to be rendered less prone to cleavage and dehydrogenation during aromatization of the isoquinoline nucleus. This was accomplished, after reduction of the N(2)-benzoyl to a benzyl group (→ 4b), by formylation to 4c (55 % from 4a). Dehydration and elimination of toluene was then effected by heating with Pd/C (4 h, 180°C, decaline) giving a poor yield[13] of the formamide 5 which was reduced to 1 with lithium aluminium hydride. The (±)-macrostomine thus formed was isolated by HPLC[14] separation and unambiguously identified by TLC, HPLC, UV, and mass spectral comparison with an authentic sample generously provided by *Prof. F. Santavy*[5].

Details about reaction conditions and yield of the single steps are given below the accompanying flow sheet. The results of our current attempts to improve the aromatization conditions will be reported in a forthcoming full paper.

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6. To the best of our knowledge 1 has hitherto not been synthesized. For biogenetic type synthetic attempts see: E. Leete, Tetrahedron Lett. 1979, 4527.
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11. Cf. the cherylline synthesis by A. Brossi, G. Grethe, and S. Teitel, J. Org. Chem. 35, 1100 (1970).

12. However, the OH-group was very resistant to dehydration conditions and both, the 1-benzyl and the 4-(2-pyrrolidinyl) group could be lost under more drastic conditions cf. the mass spectral fragmentation pattern of 1[5]. Furthermore, the N-methyl-pyrrolidine ring in 4, $R^1 = CH_3$, $R^2 = CH_2C_6H_5$, or H highly air sensitive substances, was converted to a pyrrol ring under aromatizing conditions (→ didehydro-macrostomine, MS-M^+ = 402). Interestingly, dehydromacrostomine, a Δ^2-pyrroline derivative, was also isolated from the plant material[5].

13. Simultaneous debenzylation at the 1-position took place.

14. HPLC-conditions: prepacked column, 0.25 m x 46 mm steel, packed with Li-crosorb Si 60, 7 µ, eluent: CH_3OH/Et_2O 1:4, pressure 100 bar, 5 ml/min, UV-detector: 241 nm.

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