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Enantioselective Synthesis of Some Nicotiana Alkaloids

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A modified approach to myosmine **(6)** via a silyl enol ether of 3-acetylpyridine **(1)** is described. Chiral reduction of **6** with *N*-(benzyloxycarbonyl)-*L*-proline/$NaBH_4$ and formylation leads to (*R*)-*N*-formylnornicotine **(8)** (35 % ee) which in turn is converted to (*R*)-nornicotine **(11)** and (*R*)-nicotine **(10)**.

Enantioselektive Synthese einiger Nicotiana-Alkaloide

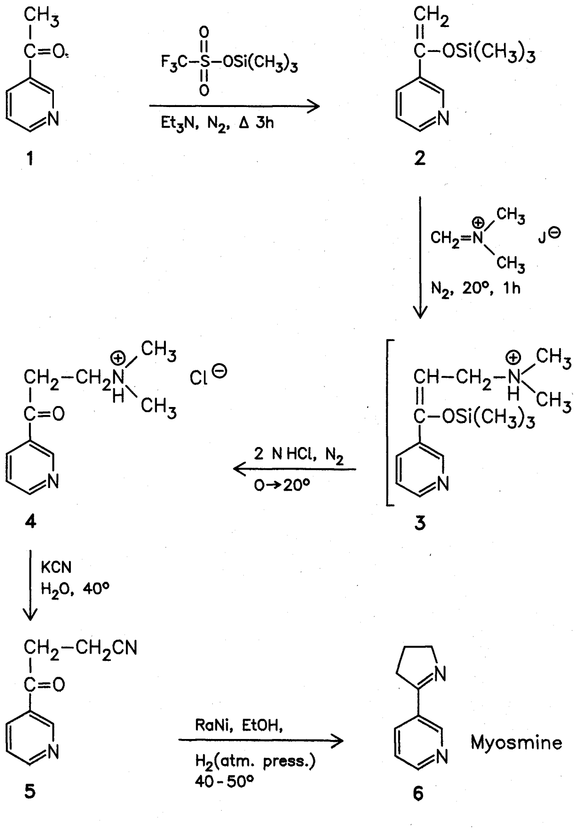
Wir beschreiben eine modifizierte Synthese des Myosmins **(6)** über einen Silylenolether des 3-Acetylpyridins **(1)**. Chirale Reduktion von **6** mit N-Benzyloxycarbonyl-L-Prolin/$NaBH_4$ und N-Formylierung (35 % ee) führen zu (R)-N-Formylnornicotin **(8)**, das in (R)-Nornicotin **(11)** bzw. (R)-Nicotin **(10)** überführt wird.

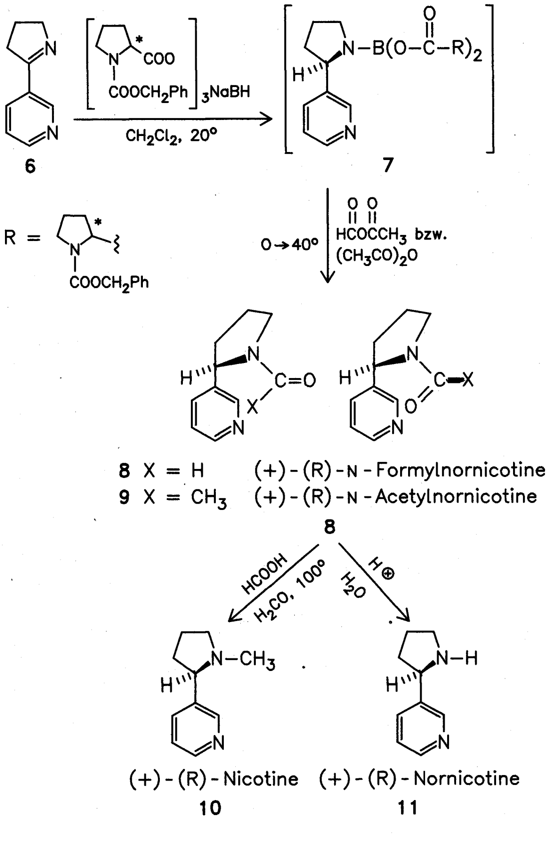
Various methods for the synthesis of nicotiana alkaloids as racemates are reported, inter alia[1-3]. We here describe a modified approach to myosmine **(6)** and strategies for chiral syntheses of nicotine derivatives.

Methyl-arylketones react with *Böhme-Eschenmoser*-salt[4] to the pertinent *Mannich* bases (type **4**) which in turn are converted to the 3-oxo-3-arylbutyronitriles (type **5**)[3]. Partial hydrogenation with concomittant ring closure leads to 2-aryl-1-pyrrolines (type **6**). This method gives very low yields with methyl-arylketones having low C–H–acidity of the methyl group as we recognized in our synthesis of *Preininger*'s alkaloid[5]. So we adapted *Danishefsky*'s idea of activating the methyl group[6] via its pertinent silyl enol ether[6]: 3-acetylpyridine[7] **(1)** was silylated in 95 % yield with $F_3C-SO_2-O-Si(CH_3)_3$[8] to **2**; **2** reacted with dimethyl-methylen-immonium iodide to give **3**, which was hydrolyzed to the *Mannich* base **4**. **4–HCl** was treated with CN^- to afford the nitrile **5**, the overall yield **2** to **5** is 72–75 %. Partial hydrogenation of **5** with Raney-Ni in $EtOH/NH_3$ led to myosmine **(6)**. An exceeding hydrogenation to racem. nornicotine[3] is prevented by our conditions (cf. Experim. Part) (Scheme 1).

Chiral reduction generates a centre of chirality at C-1 of the former pyrroline group.

Chiral reductions of imines being part of indol and isoquinoline alkaloids with *Iwakuma*'s reagent[9] are known. In our hands usual cleavage of the N-borane adduct **7** as described[9] does not give any defined product. Therefore, we used our work-up procedure with simultaneous N-acylation[4, 10], leading to the rotamers of (+)-(R)-N-formylnornicotine **(8)** in 35 % ee and 90 % chemical yield. Routine procedures[1] (Scheme 2) give rise to (+)-(R)-nicotine **(10)** and (+)-(R)-nornicotine **(11)** of equal optical purity (Scheme 2).





Use of acetic anhydride instead of the mixed anhydride H-CO-O-CO-CH_3 during work-up after chiral reduction affords the racemate of N-acetyl-nornicotine **(9)**[11] with the enantiomer **R-9** being enriched.

Experimental part

General remarks: lit[10]. – Kugelrohr distillations were performed in a Büchi apparatus with at least 5 bulbs and twofold cooling with dry ice. The external temp. is cited.

1-Trimethylsilyloxy-1-(3-pyridyl)-ethene (2)

To 6.05 (0.05 mol) 3-acetylpyridine **(1)**[7] in 80 ml absol. benzene and 6 g Et_3N were added drop by drop 23.05 g $F_3C-SO_2-O-Si(CH_3)_3$[8] then the mixture was refluxed for 3 h. The upper phase (benzene) was evaporated *i. vac.* and the residue sublimated under the condition of Kugelrohr distillation (50–60 °C, 0.05 mm Hg): White crystals (9.18 g, 95 %), m. p. 52–53 °C. – ^{1}H-NMR: δ (ppm) = 0.35 (s; 9H, 3 × CH_3), 4.78 (d; J = 3.3 Hz, 1H, $C{=}CH_2$), 5.24 (d; J = 3.3 Hz, 1H, $C{=}CH_2$), 7.90–8.13 (m; 1H, aromat.), 8.53–8.71 (m; 1H, aromat.), 8.80–9.16 (m; 2H, aromat.).

3-Cyano-1-(3-pyridyl)-propan-1-one (5)

7.73 g (0.04 mol) **2** were dissolved in 20 ml absol. CH_2Cl_2 under purified N_2. Then 8.14 g (10 % excess) dimethyl-methylenimmonium iodide[4] were added at 0 °C in one portion under purified N_2. After addition cooling is removed and after 1 h CH_2Cl_2 is evaporated *i. vac.* under N_2. The residue (colourless oil **3**; the structure of **3** is deduced from *Danishefsky*'s publication[6]) was dissolved at 0 °C in 2N HCl, excess HCl was evaporated *i. vac.* leaving a colourless oil **4**. In the hood dry KCN (3.90 g, 50 % excess) was added in one portion under N_2 followed by 400 ml water of 40 °C. After stirring under N_2 at this temp. until **4** had disappeared (tlc control; Al_2O_3/ethyl acetate or SiO_2/ethyl acetate) the mixture was cooled to room temp. and extracted with CH_2Cl_2. Column chromatography (CC) (Al_2O_3/ethyl acetate) afforded 4.60 g (72 %) **5**; m. p. 66 °C (Et_2O, lit.[3]: 66–67 °C). – IR (KBr): 2264 (C≡N), 1700 cm^{-1} (C=O). – ^{1}H-NMR: ($CDCl_3$): δ (ppm) = 2.60–2.95 (m; J = 6 Hz, 2H, CH_2), 3.30–3.55 (m; J = 6 Hz, 2H, CH_2), 7.38–7.60 (m; 1H, aromat.), 8.15–8.38 (m; 1H, aromat.) 8.80–8.98 (m; 1H, aromat.), 9.16–9.30 (m; 1H, aromat.).

Myosmine (6)

Contrary to *Leete*[3] we hydrogenated **5** at atmospheric pressure and 40–50 °C. – To 2.92 (20 mmol) **5** in 100 ml absol. EtOH were added 3 ml of absol. EtOH which was saturated with NH_3 at 0 °C, and 1.5 g Raney-Ni. – The reaction was controled by tlc (Al_2O_3/ethyl acetate or Al_2O_3/Et_2O) in order to prevent further reduction of the C=N double bond. When **5** had been converted completely, the mixture was filtered and evaporated and the residue was purified (short column; Al_2O_3/ethyl acetate) and distilled (Kugelrohr, 60 °C, 0.05 mm Hg): 2.26 g (85 %) white crystals, m. p. 43–43.5 °C (lit.[12]: 40.5–42 °C), picrate: m. p. 183.5–185 °C (lit.[3]: 183–185 °C). – ^{1}H-NMR of **6** (base): δ (ppm) = 1.85–2.26 (m; 2H, pyrroline), 2.80–3.13 (m; 2H, pyrroline), 3.95–4.26 (m; 2H, pyrroline), 7.25–7.5 (m; 1H, aromat.), 8.10–8.34 (m; 1H, aromat.), 8.54–8.8 (m; 1H, aromat.), 8.96–9.13 (m; 1H, aromat.).

(+)-(R)-N-Formylnornicotine (8) *and (+)-(R)-N-Acetylnornicotine* (9)

Modifying *Iwakuma*'s procedure his reagent was prepared as follows: 1.98 g (7.98 mmol) N-benzyloxycarbonyl-L-proline were added in portions to a suspension of 79.44 mg (2.1 mmol) $NaBH_4$ in 13 ml absol. THF at 5 °C under N_2 and stirring. Stirring at this temp. was continued until development of H_2 had ceased. After 3 h at room temp. THF was evaporated at 10 °C under N_2, the residue was dried at 20 °C, 0.05 mmg Hg, and dissolved in 4 ml absol. CH_2Cl_2 at 0 °C under N_2. – To this solution 219.3 mg (1.5 mmol) **6** in 4 ml absol. CH_2Cl_2 were added at 0 °C under N_2. After 10 h at 0 °C and stirring for 3 d at room temp. the solution was divided into two fractions (about 1.5 and 6.5 ml, respectively). Both solutions were evaporated separately (faint yellow oils). The major part was reacted at 0 °C with 6 ml acetic formic anhydride, previously cooled to 0 °C. The mixture was stirred for 30 min at room temp. then 30 min at 40–50 °C, followed by evaporation of the excess of anhydride. To the residue was added $HClO_4$ (70 %) at 0 °C. After 30 min at 0 °C and 30 min at room temp. the mixture was neutralized with N NaOH at 0 °C and rapidly extracted with CH_2Cl_2. After drying and CC (Al_2O_3; CH_2Cl_2/H_3CCN 9:1) **8** was purified by Kugelrohr distillation (95–100 °C; 0.05 mm Hg): 195.4 mg (91 %) colourless oil. – IR (film): 1665 cm^{-1} (CO). – ^{1}H-NMR: δ (ppm) = 1.75–2.15 (m; 3H, pyrrolidine), 2.25–2.60 (m; 1H, pyrrolidine); 3.47–3.97 (m; 2H, pyrrolidine), 4.85–5.20 (m; 1H, pyrrolidine), 7.27–7.54 (m; 2H, aromat.), 8.39 (s; 0.35 H, N–CH=O), 8.15 (s; 0.65 H, N–CH=O), 8.67–8.40 (m; 2H, aromat.). Because **8** was not separated on Chirasil[4, 10] the ee was determined at the stage of N-acetyl-nornicotine **(9)**.

The minor fraction was processed analogously but instead of the mixed anhydride mentioned above 3 ml acetic anhydride were used. Neutralization at -5 °C; CC with $CHCl_3$; Kugelrohr distillation at 95 °C/0.05 mm Hg: 49.75 mg (93 %) colourless oil.

The ee was determined as described[4, 10]: 35.4 % (+)-(R)-**9**. – IR (film): 1660 cm^{-1} (CO). – ^{1}H-NMR: δ (ppm) = 1.70–2.70 (m; 4H, pyrrolidine), 1.82 (s; 3H, CO-CH_3), 3.48–3.85 (m; 2H, pyrrolidine), 4.83–5.28 (m; 1H, pyrrolidine), 7.40–7.58 (m; 2H, aromat.), 8.35–8.85 (m; 2H, aromat). – The ms revealed the fragment ions described[11] in similar rel. int.

(+)-(R)-Nicotine (10)

88 mg (0.5 mmol) **8** were stirred in an autoklave with 2 ml HCOOH (98 %) and 2 ml H_2CO (37 %) at 100 °C for 18 h. After cooling to 0 °C the excess of the reagent was evaporated at 28 °C, the residue (oil) was triturated at 0 °C with pre-cooled 2N NaOH, the mixture was saturated with NaCl and extracted with CH_2Cl_2 repeatedly. After drying (Na_2SO_4) and Kugelrohr distillation with *intensive cooling* (35–40 °C; 0.01 mm Hg, Lit.[13]: 109 °C, 8 mm Hg) we obtained **10** as a colourless oil (81 mg, 91 %). – IR (film): 2793 cm^{-1} (N–CH_3). – ^{1}H-NMR: δ (ppm) = 1.50–2.52 (m; 5H, pyrrolidine), 2.11 (s; 3H, N–CH_3), 2.92–3.44 (m; 2H, pyrrolidine), 7.12–7.37 (m; 1H, aromat.), 7.59–7.80 (m; 1H, aromat.), 8.38–8.63 (m; 2H, aromat.). – $[\alpha]^{24}_{D} = +\ 28.07°$ (aqueous 1 % KOH[13], c = 0.9): 36.1 % ee (lit:[13] $[\alpha]^{24}_{D} = +\ 77.78°$).

(+)-(R)-nornicotine (11)

52.86 mg (0.3 mmol) **8** were refluxed with 10 ml 3N HCl for 2 h, then cooled to 0 °C and made alcaline with $NaHCO_3$. After saturation with NaCl and extraction with CH_2Cl_2 the org. layer was dried (Na_2SO_4) and *carefully* evaporated (20 °C, 20 mm Hg) in order to prevent evaporation of **11**: colourless pure residue (NMR). *Careful* Kugelrohr distillation at 25–30 °C, 0.2 mg Hg (118–119 °C, 3 mm Hg[14]) afforded 40 mg (90 %) **11** as an colourless oil. – IR (film): 3300 cm^{-1} (br., NH). – ^{1}H-NMR: δ (ppm) = 1.50–2.40 (m; 4H, pyrrolidine), 1.98 (s; 1H, NH, D_2O exchange), 2.83–3.42 (m; 2H, pyrrolidine), 4.04–4.35 (m; 1H, pyrrolidine), 7.13–7.40 (m; 1H, aromat.), 7.60–7.81 (m; 1H, aromat.), 8.40–8.68 (m; 2H, aromat.).

References

1 M. Nakane and C. R. Hutchinson, J. org. Chem. *43*, 3922 (1978).
2 G. F. Alberici, J. Andrieux, G. Adam, and M. M. Plat, Tetrahedron Lett. *1983*, 1937.
3 E. Leete, M. R. Chedekel, and G. B. Bodem, J. Org. Chem. *37*, 4465 (1972).

4 H. Brunner, R. Becker, S. Mahboobi, and W. Wiegrebe, Angew. Chem. *97*, 969 (1985) and lit. cited there.
5 S. Mahboobi and W. Wiegrebe, Sci. Pharm. *54*, 217 (1986).
6 S. Danishefski, T. Kitahara, R. McKee, and P. F. Schuda, J. Am. Chem. Soc. *98*, 6715 (1976).
7 3-Acetylpyridine from EGA-Chemie, D-7900 Steinheim.
8 G. Simchen and W. Kober, Synthesis *1976*, 259.
9 K. Yamada, M. Takeda, and T. Iwakuma, J. Chem. Soc. Perkin Trans. I *1983*, 265.
10 H. Brunner, A. Kürzinger, S. Mahboobi, and W. Wiegrebe, Arch. Pharm. (Weinheim) *321*, 73 (1988).
11 A. H. Warfield, W. D. Galloway, and A. G. Kallianos, Phytochemistry *11*, 3371 (1972).
12 D. Spitzner, Synthesis *1977*, 242.
13 E. Späth, C. S. Hicks, and E. Zajic, Ber. Dtsch. Chem. Ges. *68*, 1388 (1935).
14 T. Kisaki and E. Tamaki, Arch. Biochem. Biophys. *92*, 351 (1961).

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