NEW AND EFFICIENT SYNTHESIS OF 5,6,7,8-TETRAHYDROINDOLIZIDINES. APPLICATION TO THE SYNTHESIS OF PHARMACOLOGICALLY RELEVANT CHIRAL AMINODERIVATIVES FROM L-ASPARAGINE

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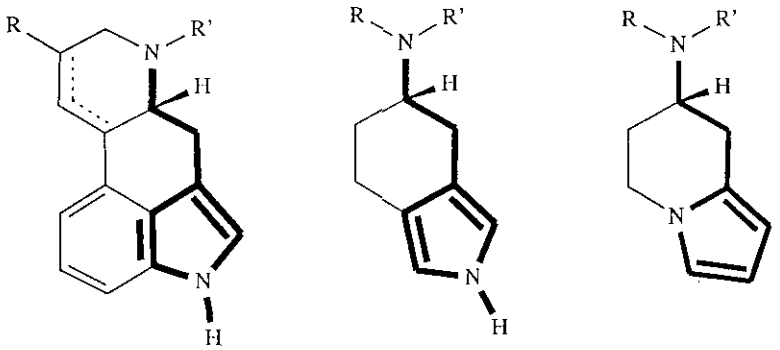
Abstract - A convenient and high yielding cyclization reaction of N-pyrrolylbutyl triflates is shown. The method is applied to afford the potential DA agonists **3**, enantiomerically pure from L-asparagine.

Ergoline (**1**) derivatives attract special interest because of their potent dopaminergic activity.[1] Previously Kornfeld and coworkers have suggested, that the rigid pyrroleethylamine moiety is the portion of **1** (Scheme 1), responsible for interaction with the dopamine (DA) receptor binding sites, demonstrating significant DA agonist properties of the bicyclic structure **2**.[2]

Scheme 1

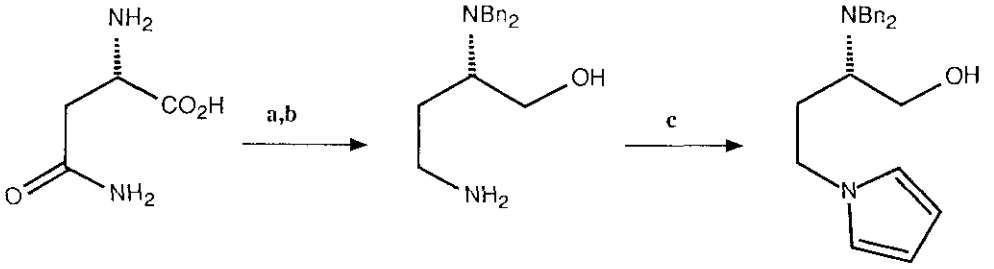


1 **2** **3**

In order to learn, whether the pyrrole NH-group is necessary for binding of ergolines with the DA receptor sites, it was of considerable interest to develop a synthesis for the bicyclic isomer **3**, devoiding the NH feature. Since DA receptor interactions are highly stereospecific,[3] the method was supposed to provide access to both enantiomers.

We planned to approach to the (S) - enantiomer **3** by activation of the alcohol **6** and subsequent cyclization. **6** should be available optically pure from L-asparagine.[4] The dibenzyl group was selected for amine protection, because it was expected to be stable towards hydride reduction and acidic conditions.

Scheme 2

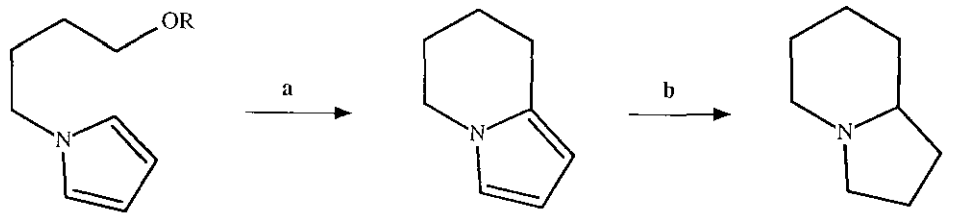


4 **5** **6**

a: PhCHO, Na(BH$_3$)CN, H$_2$O, pH 7, 16 h, RT (83%); b: BH$_3$ x THF, 2 h, reflux (86%); c: 2,5-dimethoxytetrahydrofuran, HOAc / NaOAc, 70°, 30 min (75%).

Reductive coupling of benzaldehyde and L-asparagine (**4**) in water,[5] followed by a borane reduction of both carboxylic functionalities gave the diaminobutanol **5** ([α_D^{20}] +11° (c = 0.5, $CHCl_3$)), which was reacted with 2,5-dimethoxytetrahydrofuran to afford **6** ([α_D^{20}] +67° (c = 1, $CHCl_3$)) in 54 % overall yield (Scheme 2).

Scheme 3



c → **7a** R = H; **7b** R = SO_2Ph

8 **9**

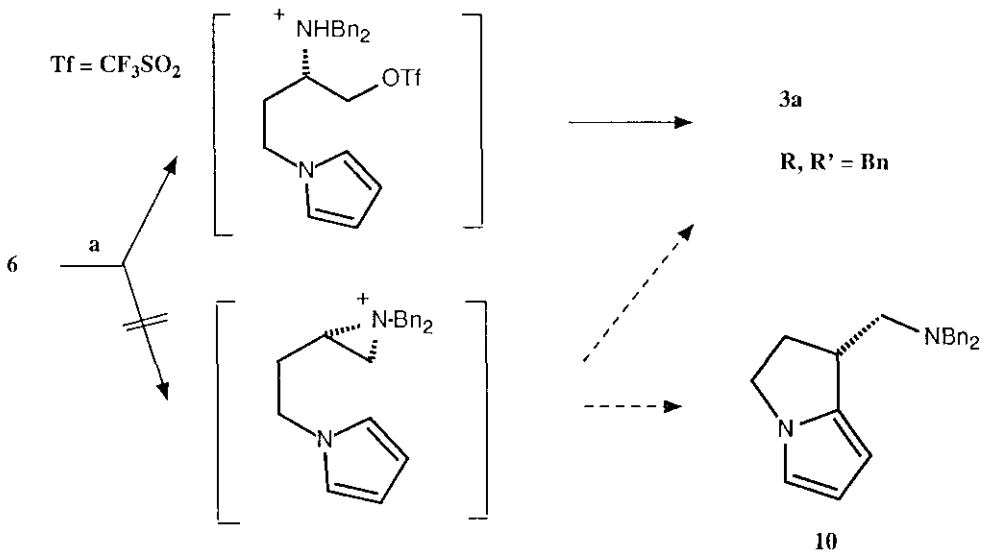
a: 7a, Et$_3$N (100 mol %), Tf$_2$O (100 mol %), CH$_2$Cl$_2$, 3 h, RT, (95%); b: see ref.10; c: PhSO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$, 3 h, RT (85%).

Only a few examples have appeared in the literature for cationic cyclizations in which the terminator is a pyrrole.[6] A method providing 5,6,7,8-tetrahydroindolizidines by an exo-tet typed reaction has not been described yet. This is likely due to the instability of pyrroles towards oxygen, acids and heating. So we decided to elaborate the reaction conditions for the preparation of the unsubstituted heterocycle from the easily available 4-(1-pyrrolyl)butanol (**7a**).[7] **7a** was transformed to the benzenesulfonate **7b**, which failed to cyclize. Several

attempts to activate the pyrrole 2-position of **7b** by lithiation[8] or conversion into an organocuprate didn't afford the desired bicycle **8** either. However treatment of **7a** with Tf_2O/Et_3N yielded **8** quantitatively via a highly reactive triflate intermediate (Scheme 3).

5,6,7,8-Tetrahydroindolizidines are synthetic precursors of octahydroindozidines,[9] including a number of natural products. For example the alkaloid δ-coniceine **9** can be derived from **8** by catalytic hydrogenation.[10]

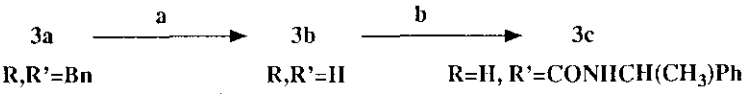
Scheme 4



a: Tf_2O (200 mol %), CH_2CL_2, 16 h, RT (94%).

Treatment of **6** with Tf_2O afforded **3a** ($[\alpha_D^{20}]$ -50° (c = 1, $CHCl_3$)) nearly quantitatively.[11] This reaction was only high yielding when renouncing a proton scavenger as Et_3N or pyridine. Obviously protonation of the triflate protects from side reactions, such as polymerization or formation of isomer **10** (Scheme 4).

Scheme 5



a: $Pd(OH)_2/C$-H_2, n-PrOH (85%); b: (R)-2-phenylethylisocyanate, THF, 0° C.

Hydrogenolysis of **3a** afforded the primary amine **3b** [12] (Scheme 5). The optical integrity of the synthesis was proved by derivatizing **3b** with optically pure 1-phenylethylisocyanate. **3c** turned out to be isomerically pure (de>99%) by high resolution ^{1}H-nmr spectroscopy (400 MHz).

SAR-studies with various derivatives of **3** and its enantiomers, readily available from D-asparagine are in progress.

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11 **3a**: ^{1}H-nmr (400 MHz): δ = 7.37 (d, J= 7.3 Hz, 4H), 7.28 (t, J= 7.3 Hz, 4H), 7.20 (t, J =7.2 Hz, 2H), 6.45 (dd, J= 2.5, 2 Hz, 1H), 6.09 (t, J= 2.5 Hz, 1H), 5.82 (dd, J= 2.5, 2 Hz, 1H), 4.10 (ddd, J= 12.5, 5.8, 2.2 Hz, 1H), 3.77 (dt, J= 12.5, 4.4 Hz,1H), 3.73 (d, J= 14 Hz, 2H), 3.66 (d, J= 14 Hz, 2H), 3.09 (m, 1H), 3.05 (m, 1H), 2.85(dd, J= 15.5, 11.8 Hz, 1H), 2.15 (m, 1H), 2.0 (ddd, J= 24.2, 12.5, 5 Hz, 1H). The formation of the 6 membered ring instead of isomer **10** was assigned by ^{13}C-nmr spectroscopy, indicating a CH_2-group adjacent to the pyrrole 2-position (diagnostic signals only): δ = 104.7 (dddt, J= 168 Hz, 7.0 Hz, 4.5,2.5 Hz) (**C1**); 53.5, dept 135 positive (**C7**); 25.5, dept 135 negative (**C8**).

12 **3b** can be stored conveniently as its dibenzoyl-L-tartaric acid salt, $[\alpha_D^{20}]$ -65° (c = 0.1, DMSO).

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