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A novel reductive aminocyclization for the syntheses of chiral pyrrolidines: stereoselective syntheses of (*S*)-nornicotine and 2-(2′-pyrrolidyl)-pyridines

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Abstract

(*S*)-Nornicotine **2** was synthesized in four steps. A key step in the synthesis involved reductive aminocyclization of a 1,4-ketoaldehyde with 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosylamine **1** in the presence of sodium cyanoborohydride, diastereoselectively affording the corresponding stereoisomer **6** in 45% yield. The aminosugar moiety could be easily removed by acidic hydrolysis to furnish **2**. The aminocyclization was further extended to asymmetric syntheses of novel chiral 2-(2′-pyrrolidyl)-pyridine ligands **12** and **13**. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: chiral template; aminocyclization; diastereoselectivity; reduction; synthesis.

Chiral monosubstituted pyrrolidines are abundant in nature and display a wide range of biological activities. To date, several ingenious methods have been developed towards the stereoselective syntheses of these compounds.[1] However, most of them are rather lengthy with respect to the structural simplicity of these alkaloids. Our approach to these molecules featured diastereoselective reductive aminocyclizations of 1,4-ketoaldehydes with various chiral amines, such as (*R*)-1-phenylethylamine, (*S*)-α-amino acids, (*S*)-methyl-α-amino acid esters and (*S*)-1,2-aminoalcohols (Scheme 1).[2,3] In our study, although the desired cyclization products were obtained in good yields, the chiral templates could not be subsequently cleaved from **6′** or its derivatives by catalytic hydrogenolysis, Curtius rearrangement, or dehydration reactions.[3b] Finally, 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosylamine **1**[4] was found to be a good candidate as the chiral amine source, removable after construction of the pyrrolidine rings. In this paper, we describe the application of the reductive aminocyclization reaction with **1** to the stereoselective synthesis of (*S*)-nornicotine **2**, a minor component of tobacco alkaloids and a biotransformation product of nicotine in the brain (Scheme 1). The cyclization reaction was further extended to asymmetric preparation of novel chiral 2-(2′-pyrrolidyl)-pyridine ligands **12** and **13**.

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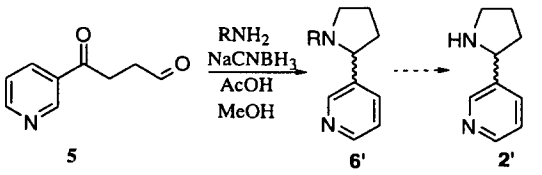
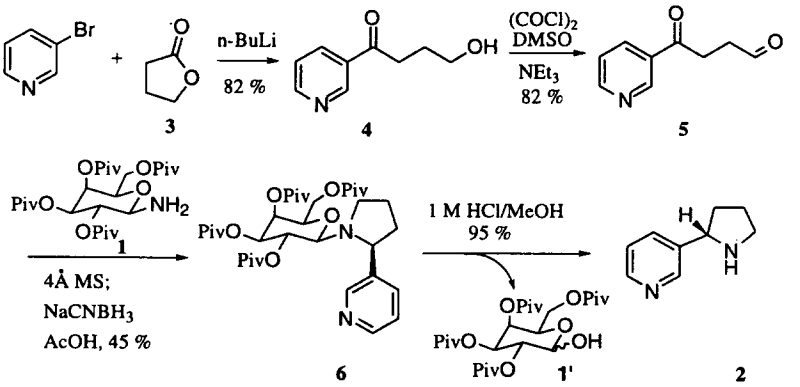


Scheme 1.

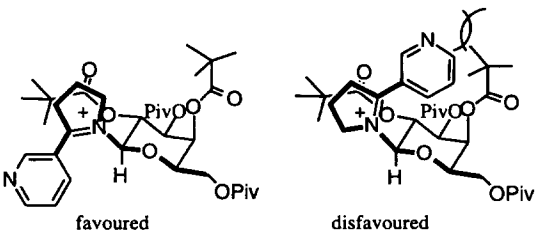
The precursor for the aminocyclization reaction, **5**, was prepared in two steps from a γ-lactone (Scheme 2). Halogen–lithium exchange of 3-bromopyridine with *n*-BuLi followed by treatment with the lactone **3** afforded the hydroxyketone **4** in 82% yield.[2] Subsequent oxidation of **4** to the aldehyde **5** was accomplished with the Swern method in good yield. The reaction conditions for the reductive aminocyclization of **5** and **1** have been explored extensively. Standard Savoia's conditions[3] gave only 16% yield. After much variation in reaction conditions, such as temperature, solvent and amount of reagents, the best result was obtained when the pre-formed imine was treated with 1 equivalent of sodium cyanoborohydride in the presence of 0.5 equivalents of acetic acid. The desired product **6** was obtained as a single diastereomer in 45% isolated yield.† Acidic hydrolysis of **6** afforded optically pure nornicotine **2**. All the spectroscopic data of **2** are in good accord with the reported values.[5a] Compound **6** was determined to be of (*S*)-configuration at its chiral center on the pyrrolidine ring based on the optical rotation of **2** ($[\alpha]_D^{25}$ −35.6 (*c* 1.256, MeOH); Lit. $[\alpha]_D^{20}$ −34.9 (*c* 0.313, MeOH)).[5b] Furthermore, the sugar moiety **1′** can be converted back to **1** by a reported procedure.[4]



Scheme 2.

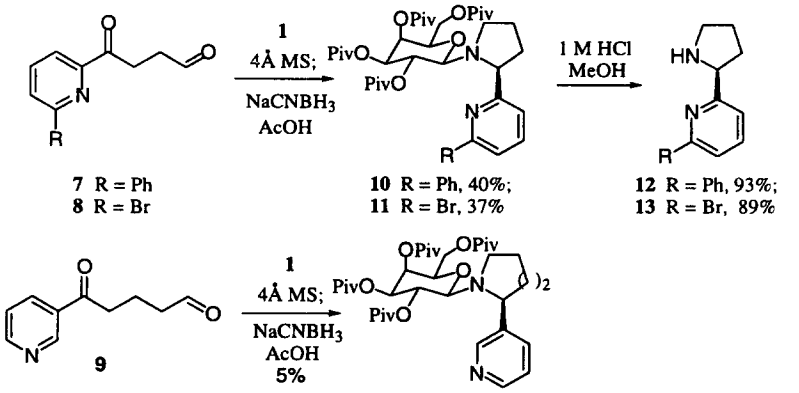
† A typical procedure is as follows. A suspension of activated molecular sieve 4Å (0.3 g), 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine **1** (0.5 mmol, 258 mg) and (pyridin-3′-yl)-4-oxobutanone **5** (0.5 mmol, 82 mg) in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 16 h. The suspension was filtered in a nitrogen atmosphere and the filtrate was concentrated under vacuum. The concentrate was cooled to 0°C, to which was then slowly added a solution of glacial acetic acid (0.25 mmol, 14 μL) and sodium cyanoborohydride (0.5 mmol, 31 mg) in 10 mL of dry methanol. The resulting solution was stirred at 0°C for 2 h and then at room temperature for another 14 h. A saturated sodium carbonate solution (3 mL) was added to quench the reaction. The crude product was extracted with EtOAc (10 mmol×3). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, concentrated in vacuo, and purified by flash column chromatography (hexane:ethyl acetate, 4:1) to afford the product **6** as a colourless oil in 45% yield (0.045 mmol, 27.8 mg). ^{1}H NMR of **6** (300 MHz, $CDCl_3$) δ: 8.52–8.50 (m, 2H), 7.62 (dt, *J*=2.0, 7.8 Hz, 1H), 7.23 (dd, *J*=4.8, 7.9 Hz, 1H), 5.41 (t, *J*=9.8 Hz, 1H), 5.33 (d, *J*=2.5 Hz, 1H), 4.96 (dd, *J*=3.1, 10.1 Hz, 1H), 4.19–4.10 (m, 2H), 4.01–3.94 (m, 2H), 3.77 (t, *J*=6.8 Hz, 1H), 3.22 (t, *J*=7.0 Hz, 2H), 2.25–2.13 (m, 1H), 1.92–1.83 (m, 2H), 1.74–1.65 (m, 1H), 1.27 (s, 9H), 1.20 (s, 9H), 1.17 (s, 9H), 1.09 (s, 9H).

The (*S*)-configuration observed for **6** may be explained by steric considerations (Scheme 3). The reaction involves two subsequent reductive amination steps, first with the aldehyde group and then intramolecularly with the ketone group. Hydride transfer to the iminium intermediate determines the chirality on the pyrrolidine ring. The aromatic group is preferentially pointing downward to avoid close contact with the axial pivaloyl group. Since the bulky pivaloyl group on the galactopyranosyl ring shields the back *Si* face of the iminium group, the hydride is preferentially transferred from the front *Re* face to afford (*S*)-nornicotine **2**.



Scheme 3.

Next, the aminocyclization reactions with other 1,4-ketoaldehydes **7** and **8** were tested using our procedure. Similarly, the desired products **10** and **11** were obtained as single isomers in moderate yields (Scheme 4). Acidic hydrolyses of **10** and **11** furnished optically pure 2-(2′-pyrrolidyl)-pyridine ligands **12** and **13** in excellent yields. The stereochemistries of **12** and **13** were assigned by analogy with **2**. However, the 1,5-ketoaldehyde **9** only gave rise to a trace amount of the piperidine product. This particular difficulty in piperidine formation might be due to difficulty in the formation of the six-membered-ring iminium intermediate.



Scheme 4.

In summary, pure (*S*)-nornicotine **2** was synthesized from commercially available starting materials in four steps. Its stereochemistry was set by using an aminosugar as the chiral template. To our knowledge this is the first highly stereoselective synthesis of the natural product ever reported[5,6] and it is complementary to Kunz's synthesis for (*S*)-anabasine.[4e] (*S*)-Nornicotine could be *N*-alkylated by further reductive aminations with various aldehydes, affording (*S*)-nicotine and its analogues. Additionally, its (*R*)-isomer may be obtained from 2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamine.[4d] Furthermore, two novel 2-(2′-pyrrolidyl)-pyridine ligands **12** and **13** were also synthesized in optically pure forms.

Acknowledgements

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