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COMMUNICATIONS

## A NEW ROUTE TO PYRROLIDINES : ONE-STEP CYCLIZATION OF 1,4-AZIDO ALCOHOL SYNTHESIS OF 1,4-DIDEOXY-1,4-IMINO-L-LYXITOL

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Several optically active 3,4-dihydroxy-2-hydroxymethyl pyrrolidines are potent  $\alpha$ -glycosidase inhibitors ; for example, 1,4-dideoxy-1,4-imino-D-lyxitol (1) is a powerful inhibitor of  $\alpha$ -galactosidase.<sup>1</sup> Furthermore, pyrrolidine 1 can be easily converted into the indolizidine alkaloid swainsonine to which it is structurally related.<sup>2</sup> (-) Swainsonine exhibits  $\alpha$ -D-mannosidase inhibitory activity and immunoregulatory activity. Certain swainsonine stereoisomers have glycosidase inhibitory activity as well, and therefore have attracted considerable interest.<sup>3</sup> 1,4-Dideoxy-1,4-imino-L-lyxitol (2) (enantiomer of 1) could be of biological interest. This communication describes the first synthesis of 2, starting from D-ribonolactone.

The synthesis of the <u>L</u>-enantiomer 2 required the formation of a <u>D</u>-ribitol derivative in which only the hydroxyl groups of C-1 and C-4 of <u>D</u>-ribonolactone were unprotected. Compound 1 may also be synthesized from the same chiral precursor through a <u>D</u>-ribitol derivative in which only the hydroxyl groups of C-2 and C-5 of <u>D</u>-ribonolactone are unprotected.

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The synthesis of 2 required the introduction of nitrogen and the linking of C-1 and C-4 by nitrogen with inversion of configuration at C-4. In our strategy the pyrrolidine ring formation resulted from a one-step reductive cyclization of a 1,4-azido alcohol by triphenylphosphine. Such a reaction is well known in aziridine synthesis.<sup>4</sup> Recent one-step cyclization attempts of a 1,5-azido alcohol have been mentioned, but the piperidine ring could not be obtained.<sup>5</sup> To our knowledge, we describe here the first example of a onestep cyclization of 1-4 azido alcohol into a pyrrolidine ring.

D-Ribonolactone (3) was converted in 87% yield into the protected derivative 4,6 mp 98 °C;  $[\alpha]_D^{20}$  -13° (c 1.0, CHCl<sub>3</sub>), which was then reduced to the diol 5,  $[\alpha]_D^{20}$  +16°5 (c 2.2, CHCl3), in 80% yield. Since introduction of an azido group at C-1possible was not (cyclization into trihydroxytetrahydrofuran occurred during tosylation at C-1), diol 5 was converted into the 4-azido alcohol 6. After benzoylation at C-1 followed by mesylation at C-4 and nucleophilic displacement by azide ion, selective а deprotection of the hydroxyl group at C-1 led to the required azido alcohol 6 of lyxo configuration (37% yield from 5)  $[\alpha]_D^{20}$  +14° (<u>c</u>1.3, CH<sub>2</sub>Cl<sub>2</sub>). By reaction with triphenyl phosphine, 6 underwent intramolecular cyclization to give the protected 1,4-imino-L-lyxitol (7) in 75% yield,  $[\alpha]_D^{20}$  +34.5° (c 0.9, CH2Cl2). Complete acidic removal of the protective groups and purification by ion exchange chromatography gave the free base (90% yield), which was crystallized as the hydrochloride, mp 155-157 °C;  $[\alpha]_D^{20}$  -18.3° (<u>c</u> 0.6), H<sub>2</sub>O). The physical characteristics of the hydrochloride correlate well with previously published data for the <u>D</u>-enantiomer ; lit.<sup>1</sup> mp 157-159 °C;  $[\alpha]_D^{20}$  +18.8° (g 0.16, H<sub>2</sub>O).



Reagents and conditions : (a), t-BuPh2SiCl ; imidazole, HCON(Me)2, room temp. ; (b) Me2CO, Me2C(OMe)2, p-Me-C6H4-SO3H, room temp. ; (c), LiAlH4, tetrahydrofuran, Et2O, -30 °C then NaBH4, EtOH, room temp. ; (d), PhCOCl, pyridine, room temp.; (e), MeSO2Cl, pyridine, room temp. ; (f) n-Bu4NN3, PhCH3, 110 °C ; (g), K2CO3, MeOH, room temp. ; (h), Ph3P, PhCH3, 100 °C ; (i), CF3CO2H-H2O (8:2).

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