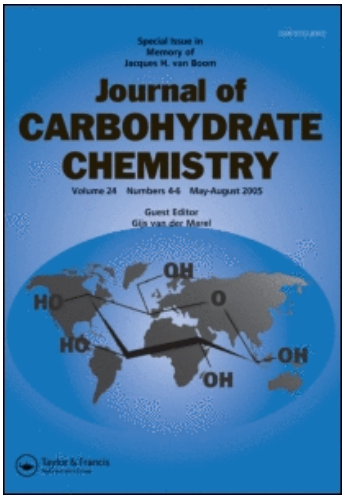

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Duréault, Annie , Greck, Christine and Depezay, Jean-Claude(1990) 'A New Route to Pyrrolidines: One-Step Cyclization of 1,4-Azido Alcohol Synthesis of 1,4-Dideoxy-1,4-Imino-L-Lyxitol', Journal of Carbohydrate Chemistry, 9: 1, 121 — 123
To link to this Article: DOI: 10.1080/07328309008545803
URL: http://dx.doi.org/10.1080/07328309008545803

J. CARBOHYDRATE CHEMISTRY, 9(1), 121-123 (1990)

COMMUNICATIONS

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

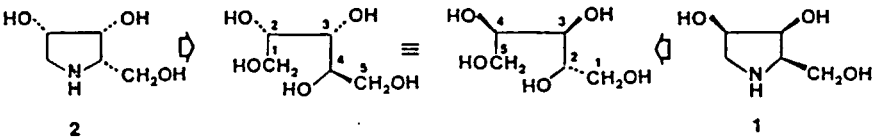
Annie Duréault*, Christine Greck, Jean-Claude Depezay.

Université René Descartes, Laboratoire de Chimie
et Biochimie Pharmacologiques et Toxicologiques
(UA 400 CNRS), 45 rue des Saints-Pères,
75270 Paris Cédex 06, France.

Received May 31, 1989 - Final Form September 19, 1989

Several optically active 3,4-dihydroxy-2-hydroxymethyl pyrrolidines are potent α-glycosidase inhibitors ; for example, 1,4-dideoxy-1,4-imino-D-lyxitol (**1**) is a powerful inhibitor of α-galactosidase.[1] Furthermore, pyrrolidine **1** can be easily converted into the indolizidine alkaloid swainsonine to which it is structurally related.[2] (-) Swainsonine exhibits α-D-mannosidase inhibitory activity and immunoregulatory activity. Certain swainsonine stereoisomers have glycosidase inhibitory activity as well, and therefore have attracted considerable interest.[3] 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.

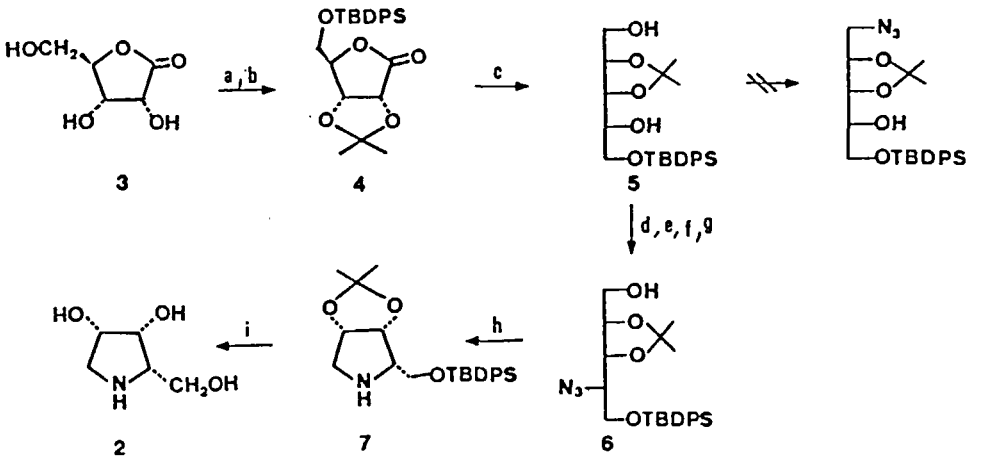
The synthesis of the L-enantiomer **2** required the formation of a D-ribitol derivative in which only the hydroxyl groups of C-1 and C-4 of D-ribonolactone were unprotected. Compound **1** may also be synthesized from the same chiral precursor through a D-ribitol derivative in which only the hydroxyl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



2 1

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.[4] Recent one-step cyclization attempts of a 1,5-azido alcohol have been mentioned, but the piperidine ring could not be obtained.[5] To our knowledge, we describe here the first example of a one-step 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, $CHCl_3$), which was then reduced to the diol **5**, $[\alpha]_D^{20}$ +16°5 (c 2.2, $CHCl_3$), in 80% yield. Since introduction of an azido group at C-1 was not possible (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, a selective 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° (c 1.3, CH_2Cl_2). 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, CH_2Cl_2). 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° (c 0.6), H_2O). The physical characteristics of the hydrochloride correlate well with previously published data for the D-enantiomer ; lit.[1] mp 157-159 °C; $[\alpha]_D^{20}$ +18.8° (c 0.16, H_2O).



Reagents and conditions : (a), t-$BuPh_2SiCl$; imidazole, $HCON(Me)_2$, room temp. ; (b) Me_2CO, $Me_2C(OMe)_2$, p-Me-C_6H_4-SO_3H, room temp. ; (c), $LiAlH_4$, tetrahydrofuran, Et_2O, -30 °C then $NaBH_4$, EtOH, room temp. ; (d), PhCOCl, pyridine, room temp.; (e), $MeSO_2Cl$, pyridine, room temp. ; (f) n-Bu_4NN_3 , $PhCH_3$, 110 °C ; (g), K_2CO_3, MeOH, room temp. ; (h), Ph_3P, $PhCH_3$, 100 °C ; (i), CF_3CO_2H-H_2O (8:2).

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6. All new compounds gave satisfactory analytical and spectral data.