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# A Short Diastereoselective Synthesis of the Natural (2*R*, 3*R*, 4*R*)-2-Hydroxymethyl-3,4-Dihydroxypyrrolidine

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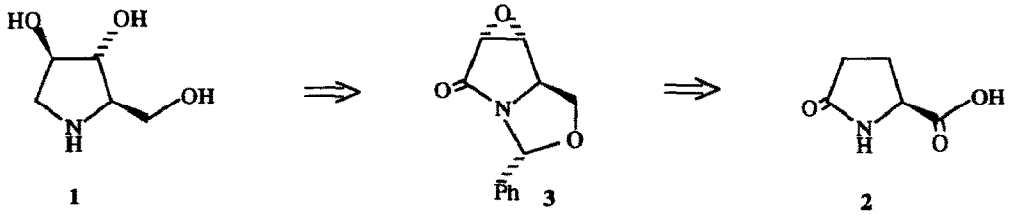
**Abstract** : *1,4-Dideoxy-1,4-imino-D-arabinitol 1, a glycosidase inhibitor constituent of Arachniodes standishii[1] and Angylocalyx boutiqueanus[2] was synthesized from (S)-pyroglutamic acid through regioselective ring opening of the epoxide 3.*

Naturally occuring polyhydroxylated pyrrolidines have received much attention due to their ability to inhibit glycosidases.[3-5] Among them, 1,4-dideoxy-1,4-imino-D-arabinitol **1**, isolated from *Arachniodes standishii* [1] and *Angylocalyx boutiqueanus* [2], is known as a potent inhibitor of yeast α-glucosidase, as a potential AIDS virus replication inhibitor[6] and exhibits several other biological activities.[7a]

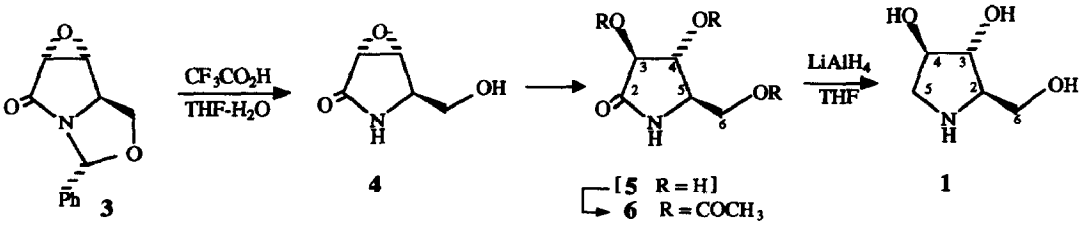



**1** **3** **2**

Therefore, much efforts have been directed to synthesize the compound **1**, structurally related to sugar, from carbohydrates.[3,7] Some other routes developed to achieve the same goal involved the use of aldolases to catalyze aldol condensations, prior to reductive amination and cyclization to the pyrrolidine ring.[8] In addition, a synthesis of 1,4-dideoxy-1,4-imino-D-arabinitol **1** from (*S*)-pyroglutamic acid **2** has already been described.[9] As part of a program to synthesize several bioactive molecules using (*S*)-pyroglutamic acid **2** as a chiral precursor[10], a straightforward diastereoselective synthesis of **1** from the epoxy pyrrolidone **3**[10b,11] is described here.

The high regioselectivity that we observed in the oxirane ring opening of **3** by hydride ion[10b], led us to check its regioselective opening by other nucleophiles, as well. Thus, the epoxy lactam **3** could be a valuable intermediate in the synthesis of several natural products, particularly the aqueous acidic hydrolysis of **3** could lead to a direct precursor of (2*R*, 3*R*, 4*R*)-2-hydroxymethyl-3,4-dihydroxypyrrolidine **1**.

This step could be achieved in one-pot together with the deprotection of both primary alcohol and nitrogen atom of **3** ($CF_3CO_2H$-THF-$H_2O$, 80°C) to afford the trihydroxylated lactam **5**, through the 3,4-epoxy-5-hydroxymethyl-pyrrolidin-2-one **4**.[12] The water soluble crude polyhydroxylated pyrrolidone **5** was directly converted (excess $Ac_2O$, pyridine, r.t., 24 h.) to its triacetate **6**[13], isolated chromatographically in 43% yield from **3**.




The configurations of **6** were assigned by $^1H$ NMR. The doublet at 5.46 ppm (1H, $J_{3,4}$ = 6 Hz) was attributed to the proton H-3, whereas the proton H-4 gives rise to a doublet of doublet at 5.28 ppm ($J_{3,4} = J_{4,5}$ = 6 Hz). The NOE observed between H-3 and H-5 and between H-4 and H-6 support the indicated configurations. The lactam **6** was reduced by an excess of $LiAlH_4$ in refluxing THF (4h.) to afford 1,4-dideoxy-1,4-imino-D-arabinitol **1** (74%).[14] This simple scheme could be applied to the commercially available (*R*)-pyroglutamic acid to obtain the enantiomer 1,4-dideoxy-1,4-imino-L-arabinitol, which has been reported to be a potent inhibitor of the cytopathic effect of AIDS virus at non-cytotoxic concentrations.[6]

The use of the epoxy pyrrolidone **3** in further syntheses is under current investigation in our laboratory.

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11. A very recent synthesis of (2*S*,3*S*)-3-hydroxyproline from **3** prompted us to disclose our own results : Herdeis, C.; Hubmann, H.P.; Lotter, H. *Tetrahedron Asymmetry* **1994**, *5*, 119-128.
12. Previously characterized as its acetate, see reference 10b.
13. **6** : mp : 79-81°C ; $[\alpha]_D^{30}$ = +45 (c = 0.78, $CHCl_3$) ; IR : 1742 $cm^{-1}$; $^1H$ NMR [250 MHz, $CDCl_3$, d = 0 : TMS, J (Hz)] : 6.32 (bs, 1H, NH), 5.46 (d, 1H, J = 6, H-3), 5.28 (dd, 1H, J = J' = 6, H-4), 4.48 (dd, 1H, J = 12, J' = 3.5, Ha-6), 4.04 (dd, 1H, J = 12, J' = 6, Hb-6), 3.78 (m, 1H, H-5), 2.17 (s, 3H, $CH_3$), 2.12 (s, 3H, $CH_3$), 2.11 (s, 3H, $CH_3$) ; $^{13}C$ NMR (75 MHz, $CDCl_3$) : 170.81 (CO), 170.24 (CO), 170.00 (CO), 169.46 (CO), 74.10 (CHO), 74.07 (CHO), 63.75 ($CH_2O$), 55.62 (CHN), 20.71 ($CH_3$) ; MS (m/z) : 274 ($M^{+\cdot}$ + H), 213, 200, 171 (100%), 140, 98 ; Anal. calcd for $C_{11}H_{15}NO_7$ : C, 48.35 ; H, 5.53 ; N, 5.13. Found : C, 48.36; H, 5.28 ; N, 5.17.
14. **1** (hydrochloride) $[\alpha]_D^{33}$ = +30 (c = 0.41, $H_2O$) ; comparison of $^1H$ NMR (300 MHz), $^{13}C$ NMR (75 MHz, $D_2O$), and CIMS data.[3]


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