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AN EFFICIENT AND FACILE THREE-STEP SYNTHESIS OF 5-AMINO-5-DEOXY-D-PENTONOLACTAMS FROM UNPROTECTED D-PENTONO-1,4-LACTONES.

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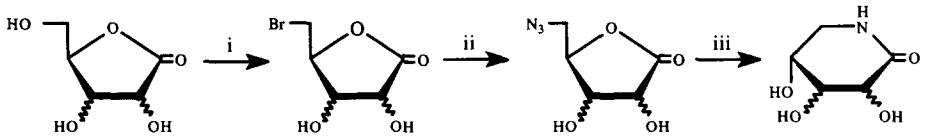
Abstract: Regioselective bromination of D-pentono-1,4-lactones with $SOBr_2$ in DMF led to 5-bromo-5-deoxy derivatives. These intermediates were treated with LiN_3 and hydrogenated to give 5-amino-5-deoxy-D-pentonolactams in 60-83% overall yield. © 1997 Elsevier Science Ltd.

The 5-amino-5-deoxy-aldonolactams constitute a new group of inhibitor of glycosidases[1] and are obtained from corresponding monosaccharides by azidation at C-5 followed by oxidation at C-1 and reduction.[2-4] All these syntheses require tedious protection-deprotection steps and lead, in the case of pentonolactams, to substantially lowered yields. Hence, starting from D-arabinose, 5-amino-5-deoxy-D-arabinonolactam was synthesized in a 13 steps process,[2] and 5-amino-5-deoxy-D-xylonolactam was synthesized in 8 steps from D-xylose in 18% overall yield.[3] Recently, the four 5-amino-5-deoxy-D-pentonolactams were obtained from corresponding pentoses in 8 steps in 30-38% overall yield.[4]

We report herein an efficient transformation of unprotected D-pentono-1,4-lactones, to unprotected 5-amino-5-deoxy-pentonolactams in a three-step transformation, *via* the 5-bromo derivatives as advantageous key intermediates (Scheme 1).



i) $SOBr_2$, DMF; ii) LiN_3, DMF; iii) H_2-Pd/C, EtOH.

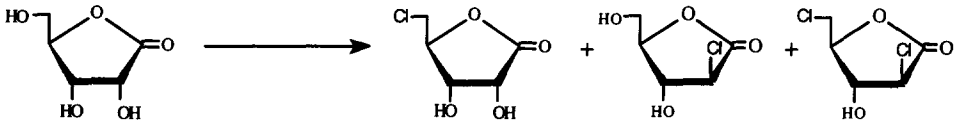
Scheme 1

We have previously described the preparation of 5-halogeno-5-deoxy-D-pentono-1,4-lactones from D-pentono-1,4-lactones in good yield (75-95%)[5] by mean of SOX_2 (X=Br, Cl) in DMF.

We have shown that regioselective halogenation reaction at the primary hydroxyl group of pentono-1,4-lactones required the presence of DMF. In the case of chlorination, it is well known that the reaction between thionyl chloride and DMF leads to Vilsmeier and Haack salt (VHs).[6]

This salt was used for chlorination of D-ribono-1,4-lactone to confirm its implication as chlorinating agent (Table 1).

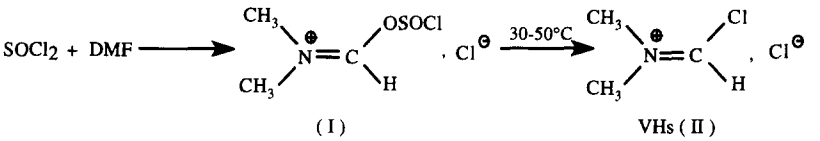
Table 1 : Chlorination of D-ribono-1,4-lactone in DMF



Entry	Reagent (eq.)	Conditions		Yield %	
1	VHs 1.2	20°C, 24h	36*	-	-
2	VHs 1.2	50°C, 24h	54*	11	5
3	VHs 2	20°C, 24h	63*	10	8
4	$SOCl_2$ 2	20°C, <1min	95	-	-

* D-ribono-1,4-lactone was recovered.

At room temperature, VHs (1.2 eq.) led to 5-chloro-5-deoxy-D-ribono-1,4-lactone in only 36% yield. To improve this yield, the increase in temperature (50°C entry 2) or equivalent number of VHs (2 eq. entry 3) led to a mixture of 5-chloro, 2-chloro, and 2,5-dichloro derivatives (Table 1). Replacement of VHs by $SOCl_2$ (2 eq. entry 4) at room temperature provided the 5-chloro-5-deoxy-D-ribono-1,4-lactone instantaneously in 95% yield. We have attributed this very interesting result to an iminium salt intermediate (I) (Scheme 2).[6,7] To confirm this hypothesis we have added the D-ribono-1,4-lactone to a solution of $SOCl_2$ in DMF kept for 2 hours at 55°C and we recovered the result observed with the VHs (Entry 2).

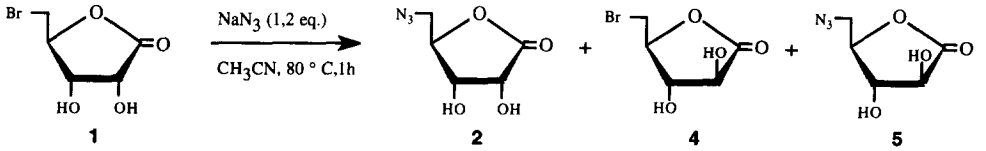


(I) VHs (II)

Scheme 2

This mechanistic approach allowed us to propose the participation of brominated iminium salt analogous to (I) for the regioselective bromination, with $SOBr_2$ in DMF (Scheme 1, step i).

Treatment of 5-bromo-5-deoxy-D-ribono-1,4-lactone **1** with NaN_3 (1.2 eq.) in CH_3CN at 80°C, for 1 h, gave the 5-azido-5-deoxy-D-ribono-1,4-lactone **2**[4] (72%) contaminated with a small amount of the C-2 epimeric azido lactone **5** (7%) and 5-bromo-5-deoxy-D-arabinono-1,4-lactone **4** (9%). The configuration of **5** was confirmed by conversion of the 5-bromo-5-deoxy-D-arabinono-1,4-lactone **4** into **5** (Scheme 3).



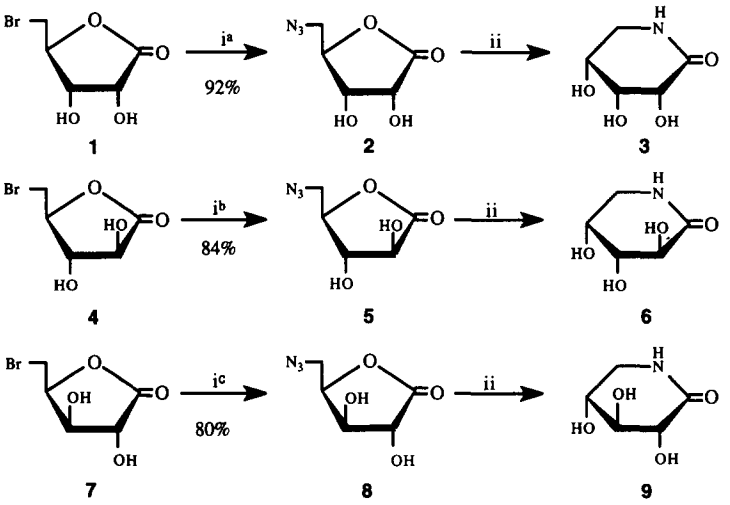
Scheme 3

In DMF, with NaN_3 (1.2 eq.) at 80 ° C for 1h, we obtained only **2** and **5** in 88/12 ratio. Similar epimerisation was reported by Lundt et *al*, when 2,5-dibromo-2,5-dideoxy-D-xylono and 2-bromo-2,6-dideoxy-L-gulono-1,4-lactones were treated with NaN_3 in DMF, acetonitrile or acetone.[8]

When the reaction was performed with LiN_3 (1.2 eq.) in DMF, at 80 ° C for 1h, the 5-azido derivative **2** was obtained as the sole product in 92% yield. A longer reaction time induced epimerisation at C-2.

The reduction of the 5-azido-lactone was then investigated for access to 5-amino-5-deoxy-D-ribonolactam. We previously reported that catalytic hydrogen transfer was a very rapid method to reduce the azido group into amino group.[9] When 5-azido-5-deoxy-D-ribono-1,4-lactone was treated with ammonium formate (2.5 eq.) as hydrogen donor in the presence of palladium on charcoal in AcOEt at 70 ° C, the 5-amino-5-deoxy-D-ribonolactam **3**[10] was obtained in 80% yield. Catalytic hydrogenation of **2**, (H_2-Pd/C, ethanol, room temperature) produced quantitatively the desired 5-amino-5-deoxy-D-ribonolactam **3** (Scheme 4).

The reaction of 5-bromo-5-deoxy-D-arabinono-1,4-lactone **4** with 1.2 eq. of LiN_3 afforded the 5-azido-5-deoxy derivative **5**[4] in 84% yield after 2 h. The longer reaction time could be explained by the stereoelectronic repulsion, for the favored conformation of **4** (Scheme 4), between the C-2 hydroxyl group and the attacking nucleophile at C-5, as assumed in the case of halogenation of pentonolactones with SOX_2 (X=Br, Cl).[5] Hydrogenation of **5** with H_2-Pd/C produced quantitatively 5-amino-5-deoxy-D-arabinonolactam **6**.[10] Azidation of 5-bromo-5-deoxy-D-xylono-1,4-lactone yielded 80% of **8**[4] for 3 h. In this case, an interaction between the azide ion and the C-3 hydroxyl group presumably occurred and reduced the reaction rate. Hydrogenation of **8** produced quantitatively the lactam **9**.[10] Overall yields for the transformation of D-xylono, D-arabinono, and D-ribono-1,4-lactones into corresponding 5-amino-5-deoxy-D-pentonolactams are 60%, 71%, 83% respectively.



i) LiN_3 1.2 eq., DMF. a) 1h. b) 2h. c) 3h

ii) H_2, Pd/C, EtOH, rt, 3h, quantitative yield.

Scheme 4

In conclusion, we developed a new and direct three steps synthesis of 5-amino-5-deoxy-D-ribono, arabinono- and xylonolactams from corresponding pentono-1,4-lactones in 60-83% overall yield.

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10. NMR data and physical characteristics for products 3^4, 6^4, and 9^4:

For **3**: mp 240-242 ° C; $[\alpha]_D$ +33.0 (c 0.4; H_2O); IR (KBr): 1639 cm^{-1} (CONH.); ^1H NMR (300 MHz, D_2O): δ 4.20-4.26 (m, 3H, H-2, H-3, H-4), 3.31 (dd, 1H, H-5, $J_{4,5}$ = 6.8 Hz), 3.40 (dd, 1H, H-5', $J_{4,5'}$ = 6.8 Hz, $J_{5,5'}$ = 11.8 Hz); ^{13}C NMR (75 MHz, D_2O): δ 175.7 (C-1); 73.3; 70.5; 67.0 (C-2, C-3, C-4); 44.8 (C-5).

For **6**: mp 181-182 ° C; $[\alpha]_D$ -60.0 (c 0.7; H_2O); IR (KBr): 1649 cm^{-1} (CONH.); ^1H NMR (300 MHz, D_2O): δ 4.22 (d, 1H, H-2, $J_{2,3}$ = 8.6 Hz), 3.95 (q, 1H, H-3, $J_{3,4}$ = 2.5 Hz), 4.26 (m, 1H, H-4, $J_{4,5'}$ = 2.7 Hz), 3.53 (dd, 1H, H-5, $J_{4,5}$ = 2.9 Hz), 3.33 (dd, 1H, H-5', $J_{5,5'}$ = 13.9 Hz); ^{13}C NMR (75 MHz, D_2O): δ 175.7 (C-1), 71.7 (C-2), 74.0 (C-3), 69.2 (C-4), 47.2 (C-5).

For **9**: mp 177-178 ° C; $[\alpha]_D$ +6.0 (c 1.0; H_2O); IR (KBr): 1634 cm^{-1} (CONH.); ^1H NMR (300 MHz, D_2O): δ 4.01 (d, 1H, H-2, $J_{2,3}$ = 9.2 Hz), 3.69 (t, 1H, H-3, $J_{3,4}$ = 9.0 Hz), 3.93 (m, 1H, H-4, $J_{4,5'}$ = 8.9 Hz), 3.49 (dd, 1H, H-5, $J_{4,5}$ = 5.6 Hz), 3.12 (dd, 1H, H-5', $J_{5,5'}$ = 12.4 Hz); ^{13}C NMR (75 MHz, D_2O): δ 175.7 (C-1), 73.6 (C-2), 77.0 (C-3), 69.9 (C-4), 46.2 (C-5).

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