DE NOVO SYNTHESIS OF RACEMIC *ALTRONO*LACTAM AND *ARABINONO*LACTAM AZASUGARS

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Dedicated to Professor Yoshio Ban, *in memoriam.*

Abstract. - Starting from the known peracetylated piperidinose derivatives (**7a**) and (**7b**), the corresponding *altrono-* and *arabinono-*lactams (**4**) and (**5**) were obtained in a straightforward way. A selective two-step hydrolysis of the anomeric acetoxy groups gave the free hydroxyls (**8a**) and (**8b**) which were oxidised to the δ-lactams (**9a**) and (**9b**), respectively. Deprotection of these latter compounds led to the target molecules.

Introduction. - The enzymatic glycosidase mechanism of pyranosic polysaccharides is believed to involve a transient type **A** half-chair oxocarbonium ion, which is stabilized by a complementary carboxylate anion of an active site catalytic residue.[1,2] Structural aza-analogues of these glycosyl cations represent an attractive synthetic target for the design of potent glycoprocessing inhibitors.[3,4] δ-Lactam azasugars like D-mannonolactam (**1**) and its D-rhamnose analogue (**2**), once protonated in the active site of the appropriate enzyme, should meet the conformational and electrostatic requirements as potential glycosidase inhibitors.[5] And indeed they do, since both **1** and **2** are better inhibitors of α-mannosidase than DMJ (**3**), **1** being more powerful than the corresponding 6-deoxy compound (**2**) (*Scheme 1*). One may therefore surmise that the half-chair conformation of the lactams resembles more closely the structure of the transition state[2] for the enzymatic cleavage of the anomeric mannopyranoside. As to L-*rhamnono*lactam, *i.e.* (*ent*-**2**), it did not show any significant inhibition of any glycosidase, since its structure lacks the key stereochemical features at C(2), C(3) and C(4)

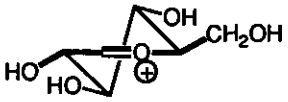
which are required for mannosidase inhibition (D-series).[5]

We describe herein the *de novo* synthesis of racemic *altrono*lactam (**4**) and of *arabinono*lactam (**5**) from the corresponding 1,2-dihydropyridines (**6a**) and (**6b**).

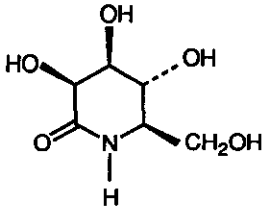
Stereospecific Synthesis of (±)-*Altrono*lactam (4) and of (±)-*Arabinono*lactam (5). In a preceding publication we described the stereospecific synthesis of the tetraacetoxy-piperidinoses (**7a**) and (**7b**) from the corresponding dihydropyridines (**6a**) and (**6b**).[6] Selective removal of the anomeric acetyl groups was performed according to Fletcher's *method* (HBr/AcOH),[7] *i.e. via the* 1-bromo intermediates which were then hydrolysed to the expected hemiaminals (**8a**) (mp 160-161 °C) and (**8b**) (mp 149-150 °C), respectively. Hemiaminal (**8b**) could also be obtained directly in a one-pot procedure when **7b** was treated with the HBr/AcOH/H_2O mixture. According to ^{1}H-nmr both hemiaminals occur as axial anomers since $J_{1,2}$=4.0 for **8a**, and $J_{1,2}$=3.6 for **8b**, a result which was anticipated for such *N-acylpiperidinoses*.[6,8,9]

Oxidation of hemiaminals (**8a**) and (**8b**) to the corresponding δ-lactams with RuO_4, as prepared from RuO_2/H_2O according to ref. 10, did not lead to any reproducible results, at least not in our hands. δ-Lactam (**9a**) was obtained when **8b** was oxidised with PCC,[11] whereas **9b** formed when **8b** was oxidised with DMSO/Ac_2O.[12] Removal of the remaining protection groups of **9a** and **9b** was performed in two steps : i) hydrogenolysis (H_2, 5%Pd/C) of the benzyloxycarbonyl groups led to δ-lactams (**10a**) and (**10b**) ; ii) reaction of these latter products with Amberlyst A-26 (OH^-) led to the crystalline racemic δ-lactams (**4**) and (**5**), respectively.

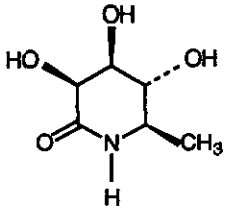
Glycosidase inhibitory assays with δ-lactams (**4**) and (**5**) remain to be made.



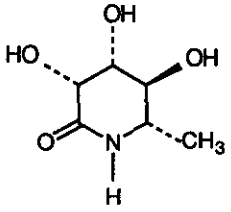
A (D- gluco)



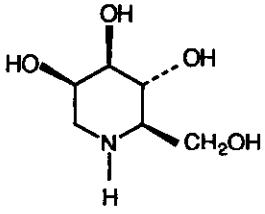
1 (D-manno)



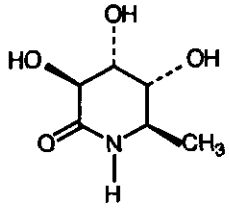
2 (D-rahmno)



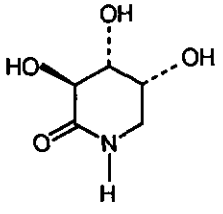
ent-2 (L-rhamno)



3 (DMJ)

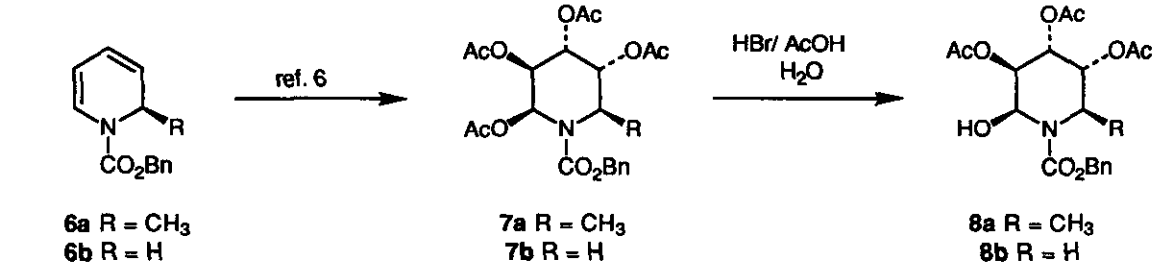


4 (altro)



5 (arabino)

Scheme 1



6a R = CH_3
6b R = H

7a R = CH_3
7b R = H

8a R = CH_3
8b R = H

9a R = CH_3
9b R = H

10a R = CH_3
10b R = H

8a

Scheme 2

ACKNOWLEDGEMENTS

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EXPERIMENTAL PART

General. - Flash chromatography (FC) was performed on silica gel (Merck 60 ; 230-400 mesh) and tlc on silica gel HF_{254} plates (Merck) which were revealed with a solution of $KMnO_4$ (2 g) and Na_2CO_3 (4 g) in H_2O (100 ml) followed by heating. Mp : *Kofler* hot bench or *Büchi-SMP-20* apparatus, corrected ; ir spectra (cm^{-1}) : *Nicolet 205.* ^1H-nmr spectra were recorded at 250 MHz and ^{13}C-nmr spectra at 62.9 MHz on a *Bruker AC-F-250* apparatus using double-irradiation techniques ; internal references : tetramethylsilane (TMS) (δ = 0.00) and CD_3OD (δ = 3.30 ppm) for ^1H-nmr, and $CDCl_3$ (δ = 77.00 ppm) and CD_3OD (δ = 49.02 ppm) for ^{13}C-nmr. Microanalyses were carried out by the "Service Central de Microanalyses" of the CNRS at Vernaison.

Reagents : Amberlyst A-26 (OH^- form) was prepared from its chloride precursor A-26 (Cl^- form) by adding 1 N aq. NaOH and letting the ion exchange occur for 1 h.

(±) Benzyl ester of [2*R-(2α,3α,4β,5β,6α)]-2-hydroxy-3,4,5-tri-*O*-acetyl-6-methyl-piperidine-1-carboxylic acid (8a).** - A solution of 33 % HBr/AcOH (10 ml) was added at 0 °C to **7a** (1.00 g, 2.15 mmol) and the mixture was stirred for 15 min at 0 °C. Ice water was added till the solution became colourless. After stirring for 5 min the solution was extracted with $CHCl_3$ (2 x 30 ml). The organic phase was washed with sat. aq. $NaHCO_3$, dried over

$MgSO_4$ and evaporated. The yellowish residue was purified by FC (AcOEt/cyclohexane 5:5) to give an oil which crystallised in AcOEt/iPr_2O (492 mg, 54 %). mp 160-161 °C (AcOEt/iPr_2O). Ir(KBr) : 3370, 1747, 1681, 1438, 1423, 1374, 1344, 1321, 1288, 1243, 1227, 1140, 1122, 1098, 1071. ^{1}H-Nmr ($CDCl_3$, 338 K) : 7.36-7.29 (m, 5 arom. H) ; 6.08 (dd, J=4.0, 3.3, H-C(2)) ; 5.60 (dd, J=11.0, 3.0, H-C(4)) ; 5.28 (dd, J=3.0, 2.3, H-C(5)) ; 5.27 (dd, J=11.0, 4.0, H-C(3)) ; 5.17 and 5.20 (AB syst., J=12.3, C*H*$_2$Ph) ; 4.37 (qd, J=7.4, 2.3, H-C(6)) ; 2.60 (br s, O*H*) ; 2.08, 2.04, 1.98 (3s, 3 x CO*CH*$_3$), 1.44 (d, J=7.4, *CH*$_3$-C(6)). ^{13}C-Nmr ($CDCl_3$) : 169.9 (2 x *C*OCH$_3$) ; 169.8 (*C*OCH$_3$) ; 155.6 (*C*O$_2$) ; 136.1, 128.6, 128.3, 127.9 (6 C arom.) ; 76.4 (C(2)) ; 71.8 (C(3)) ; 68.7 (C(5)) ; 68.0 (*C*H$_2$Ph) ; 65.4 (C(4)) ; 52.4 (C(6)) ; 20.7, 20.6, 20.5 (CO*C*H$_3$) ; 18.8 (*C*H$_3$-C(6)). Anal. Calcd for $C_{20}H_{25}NO_9$: C 56.73, H 5.95, N 3.31. Found : C 56.9, H 6.0, N 3.4.

(±) Benzyl ester of [2*R-(2α,3α,4β,5β]-2-hydroxy-3,4,5-tri-*O*-acetylpiperidine-1-carboxylic acid (8b)**. - To a stirred heterogeneous solution of **7b** (1.67 g, 3.74 mmol) in H_2O (18 ml) at 5-10 °C was added slowly a solution of 33 % HBr/CH_3CO_2H (20 ml) over a period of 80 min. The mixture became quasi homogeneous and was warmed to room temperature. To this mixture was added rapidly H_2O (100 ml) whereby **8b** precipitated as a colourless solid. Filtration and drying gave analytically pure **8b** (1.21 g, 79 %); mp : 149-150°C. Ir(KBr) : 3500, 1748, 1683, 1667, 1445, 1375, 1320, 1272, 1244, 1221, 1197, 1151, 1132, 1103, 1071, 1033. ^{1}H-Nmr ($CDCl_3$, 335 K) : 7.32 (m, 5 arom. H) ; 6.06 (br d, J=3.6, H-C(2)) ; 5.38 (dd, J=10.4, 3.2, H-C(4)) ; 5.33 (ddd, J=3.2, 2.9, 1.6, H-C(5)) ; 5.21 and 5.12 (AB syst., J=12.4, *C*H$_2$Ph) ; 5.20 (dd, J=10.4, 3.6, H-C(3)) ; 4.14 (ddd, J=14.6, 2.9, 1.1, Heq - C(6)) ; 3.47 (dd, J=14.6, 1.6, H$_{ax}$-C(6)) ; 2.53 (br s, H-O) ; 2.08 (s, CO*CH*$_3$) ; 1.98 (s, 2 x CO*CH*$_3$). ^{13}C -Nmr ($CDCl_3$) : 170.0, 169.9, 169.8 (*C*OCH$_3$) ; 155.1 (*C*O$_2$) ; 136.2, 128.6, 128.3, 128.0 (6 C arom.) ; 75.7 (C(2)) ; 69.1 (C(2)) ; 68.1 (C(4) + C(5)) ; 67.9 (*C*H$_2$Ph) ; 41.2 (C(6)) ; 20.6, 20.6,

20.5 (CO*CH3*). Anal. Calcd for $C_{19}H_{23}NO_9$: C 55.74, H 5.66, N 3.42. Found : C 55.7, H 5.8, N 3.3.

(±) [3*R-(3α, 4β,5β,6α)]-3,4,5-Tri-*O*-acetyl-6-methyl-2-piperidinone (4).**

Oxidation of **8a**. - To a solution of **8a** (1.79 g, 4.23 mmol) in anh. CH_2Cl_2 (20 ml) was added PCC (1.95 g, 9.0 mmol). The mixture was stirred for 48 h at room temperature. Some more PCC (500 mg, 2.3 mmol) was added and the mixture was heated at reflux for 4 h. Filtration and evaporation of the solvent afforded crude **9a** which was recrystallised from decane leading to pure **9a** (650 mg, 36 %). ^{1}H-Nmr ($CDCl_3$, 300 K) : 7.45-7.30 (m, 5 arom. H) ; 5.58 (dd, J=10.5, 2.9, H-C(4)) ; 5.44 (t, J=2.9, H-C(5)) ; 5.43 (d, J=10.5, H-C(3)) ; 5.30 (s, *CH2*Ph) ; 4.42 (qd, J=7.0, 2.9, H-C(6)) ; 2.17, 2.12, 2.05 (2 x CO*CH3*) ; 1.48 (d, J=7.0, *CH3*-C(6)). ^{13}C-Nmr ($CDCl_3$) : 169.9, 169.8, 169.6 (*C*OCH3) ; 165.3 (*C*O2Bn) ; 153.4 (C(2)) ; 134.8, 128.6, 128.4, 128.0 (6 arom. C) ; 70.7 (C(5)) ; 69.9 (C(3)) ; 69.1 (*C*H2Ph) ; 67.1 (C(4)) ; 54.6 (C(6)) ; 20.8, 20.6, 20.5 (3 x CO*C*H3) ; 18.8 (CH3-C(6)).

N-Deprotection of **9a**. - A solution of **9a** (650 mg, 1.54 mmol) in AcOEt (15 ml) was stirred under H_2 in the presence of 5 % Pd/C (40 mg) for 2 h. Filtration and evaporation of the solvent gave a crude product which was purified by FC (AcOEt) leading to **10a** (418 mg, 94 %). ^{1}H-Nmr ($CDCl_3$) : 6.50 (H-N) ; 5.52 (dd, J=9.4, 2.6, H-C(4)) ; 5.39 (d, J=9.4, H-C(3)) ; 5.27 (td, J=2.6, 1.2, H-C(5)) ; 3.66 (qt, J=6.9, 3.0, H-C(6)) ; 2.15, 2.14, 2.07 (3s, 3 x CO*CH3*) ; 1.40 (d, J=6.9, C*H3*-C(5)).

O-Deprotection of **10a**. - A stirred solution of **10a** (418 mg, 1.46 mmol) in MeOH (3 ml) containing Amberlyst A-26 (OH^-) (200mg) was allowed to react at room temperature for 1 h. Filtration and evaporation of the solvent gave an oil which crystallised slowly leading to **4** (110 mg ; 47 %). mp 176-177 °C (solid washed with MeOH and iPr_2O). Ir (KBr) 3360, 3299, 3179,

3128, 2896, 2360, 2355, 1661, 1618, 1459, 1443, 1348, 1335. ^{1}H-Nmr (CD_3OD) : 4.03 (d, J=6.7, H-C(3)) ; 3.85 (dd, J=6.7, 2.5, H-C(3)) ; 3.75 (dd, J=5.2, 2.5, H-C(5)) ; 3.51 (qd, J=6.7, 5.2, H-C(6)) ; 1.24 (d, J=6.7, C*H*$_3$-C(6)). ^{13}C-Nmr (CD_3OD) : 173.6 (CO) ; 72.3, 72.1, 72.0 (C(3), C(4), C(5)) ; 52.1 (C(6)) ; 20.4 (*C*H$_3$-C(6)). Anal. Calcd for $C_6H_{11}NO_4$: C 44.71, H 6.88, N 8.69. Found : C 44.7, H 7.3, N 8.5.

(±) [3*R-(3α,4β,5β)]-3,4,5-Tri-*O*-acetyl-2-piperidinone (5).**

Oxidation of **8b**. - To a stirred solution of **8b** (409 mg, 1.00 mmol) in anhydr. DMSO (4 ml, 56 mmol) at room temperature under Ar was added dropwise Ac_2O (15 ml, 159 mmol). After stirring for 16 h EtOH (10 ml) was added, stirring was continued for 30 min and the solution treated with H_2O (20 ml). After stirring for 20 min the mixture was extracted with $CHCl_3$ (2 x 15 ml). Drying of the organic phase with $MgSO_4$, filtration and evaporation of the solvent gave a mixture (375 mg) of **9b** and **7b** (77/23 (nmr), 69 % and 21 % resp.) which was used without any purification. ^{1}H-Nmr of **9b** ($CDCl_3$) : 7.45-7.30 (m, 5 arom. H) ; 5.60 (ddd, J=3.4, 2.9, 2.4, (H-C(5)) ; 5.48 (d, J=10.4, H-C(3)) ; 5.35 (dd, J=10.4, 2.9, H-C(4)) ; 5.30 (s, C*H*$_2$-Ph) ; 4.14 (dd, J=14.4, 3.4, H-C(6)) ; 3.76 (dd, J=14.4, 2.4, H-C(6)) ; 2.16, 2.13, 2.06 (3s, 3 x CO*CH*$_3$).

N-Deprotection of **9b**. - A mixture of **9b** and **7b** (1.025 g ; 77/23) in AcOEt (8ml) was stirred under H_2 in the presence of an excess of 5%Pd/C (30 mg) for 2 h. After removal of the catalyst and evaporation of the solvent, the residue was purified by FC (AcOEt). The major product (**10b**) was collected (370 mg, 71 % with respect to **9b**). ^{1}H-Nmr ($CDCl_3$) : 5.84 (br s, H-N) ; 5.54 (dt, J=3.0, 2.4, H-C(5)) ; 5.46 (d, J=10.0, H-C(3)) ; 5.38 (dd, J=10.0, 2.4, H-C(4)) ; 3.65 (dd, J=13.7, 2.4, H-C(6)) ; 3.44 (dt, J=13.7, 3.0, H-C(6)) ; 2.16 (s, 2 x CO*CH*$_3$) ; 2.07 (s, CO*CH*$_3$).

O-Deprotection of ***10b***. - Procedure as for **10a** : From **10b** (360 mg, 0.88 mmol) in MeOH (15 ml) with Amberlyst A26 (OH^-) (1.5 g) **5** was obtained (115 mg, 50 %) as a resin which

crystallised slowly, mp 162-164 °C (solid washed with MeOH and iPr_2O). Ir(KBr) : 3400-3230, 1648, 1497, 1414, 1335, 1310, 1254, 1132, 1111, 1091, 1062. ^{1}H-Nmr (CD_3OD) : 4.11 (td, J=3.8, 2.4, H-C(5)) ; 4.10 (d, J=8.4, H-C(2)) ; 3.78 (dd, J=8.4, 2.4, H-C(3)) ; 3.38 (dd, J=13.0, 3.5, H-C(6)) ; 3.25 (dd, J=13.0, 3.8, H-C(6)). ^{13}C-Nmr (CD_3OD) : 174.4 (*C*O) ; 73.8, 71.5, 68.0 (C(3), C(4), C(5)) ; 46.0 (C(6)). HR-ms calcd for $C_5H_9NO_4$: 147.05315 ; found : 147.0530. Anal. Calcd for $C_5H_9NO_4$: C 40.81, H 6.17, 9.52. Found: C 40.6, H 6.5, N 9.3.

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