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STEREOSPECIFIC DOUBLE GLYCOLISATION OF 1,2-DIHYDROPYRIDINES WITH OsO_4. SYNTHESIS OF (±) AMINOARABINOSE- AND OF (±) AMINOALTROSE DERIVATIVES [1].

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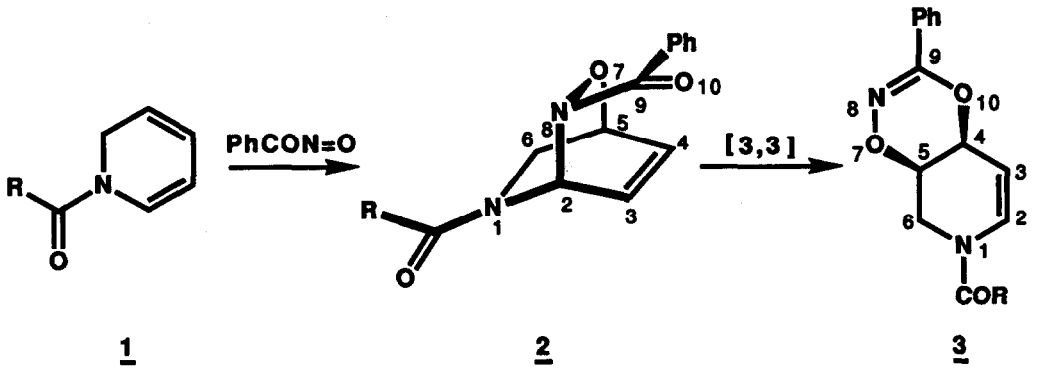
Summary. - Double glycolisation of 1,2-dihydropyridines **1** led stereospecifically and in good yield to the corresponding (±) aminoarabinose- and (±) aminoaltrose derivatives **5**. Hydrogenolysis of the N-benzyloxy carbonyl piperidinose **5b** gave directly the 1-desoxy derivative **7a**.

In two preceding publications we reported the total synthesis of aminoallose-, aminoribose- and aminolyxose derivatives [2,3]. In all these instances the key step was a Diels-Alder cycloaddition of acylnitroso dienophiles RCON=O, either with conjugated dienals in their acetal form [2], or with 1,2-dihydropyridines [3]. The primary cycloadducts were then submitted to *cis* glycolisation and thence to hydrogenolysis (of the N-O bond) leading thereby to the above cited aminosugars.

We describe herein two novel methodologies which permitted the stereospecific synthesis of (±) aminoarabinose-, and of (±) aminoaltrose derivatives, 1,2-dihydropyridines being the starting material. In the first one we took advantage of the known hetero-Cope rearrangement of the primary Diels-Alder cycloadducts **2** to their isomers **3** [4], followed by cis-glycolisation and reductive destruction of the dioxazine ring. In the second approach we describe the newly discovered stereospecific double glycolisation of 1,2-dihydropyridines with OsO_4, which represents a one-pot and higher yield alternative to the above described methodology.

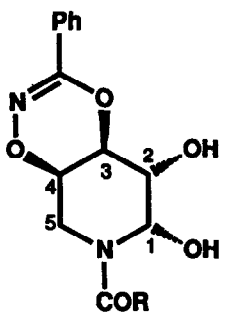
The hetero-Cope rearrangement approach. - Reaction of 1,2-dihydropyridines **1a** and **1b** with *in situ* generated benzoylnitroso dienophile [5] led instantaneously and regiospecifically to the cycloadducts **2a** (70 % [3, 4]) and **2b** (unstable product ; 60 %). Hetero-Cope rearrangement of **2a** and **2b** was achieved best in the presence of large amounts of silicic acid in CH_2Cl_2 solution, and gave stereospecifically the corresponding dioxazines **3a** (75 % [4]) and **3b** (mp : 84 -86° ; 64 %) [6]. Cis-glycolisation of these latter products occurred *anti* with respect to the dioxazine ring and led to **4a** (mp : 194-195° ; 95 %) and to **4b** (mp : 167-168° ; 98 %), respectively. The relative configuration of **4a** and **4b** could be established unequivocally by ^{1}H-NMR ; *e.g.* $J_{2,3}$=9.5 Hz which is characteristic for two vicinal trans diaxial H-atoms. Reductive destruction of the dioxazine ring was difficult to achieve : hydrogenolysis with Pd/C, or with $Pd(OH)_2$/C, or with PtO_2 did not operate at all. Only Raney nickel permitted to cleave the dioxazine moiety of the diacetate of **4a** and led in poor yield, after peracetylation, to the tetraacetate **6a** (mp : 151-153° ; 30 %) which is an arabinose derivative. Clearly a better and simpler methodology was needed.

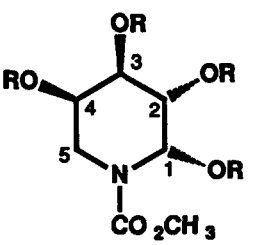
Scheme 1



1 2 3

a) R = OMe ; b) R = OBn





4 a R = OMe
4 b R = OBn

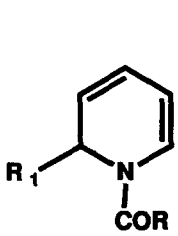
5 a R = H
6 a R = Ac

Stereospecific double glycolisation of 1,2-dihydropyridines with OsO_4. - When 1,2-dihydropyridine **1a** was left to react with catalytic amounts of OsO_4 in acetone/water (9:1 v/v) solution in the presence of an excess of N-methylmorpholine oxide (NMO) for 12 h at r.t., tetrol **5a** (mp : 171.5-172.5 ° ; 85 %) was formed **stereospecifically**. It was characterized as its tetraacetate **6a** which was identical with the one described above. Likewise, and using the same methodology, dihydropyridines **1b** and **1c** led stereospecifically to the expected aminoarabinose **5b** (mp : 168-170° ; 65 %) and to the aminoaltrose **5c** (resin ; 73 %) ; both tetrols were characterized by their tetraacetates **6b** (mp : 127.5-128.5°) and **6c** (mp : 138-139°). These tetrols **5** were obtained pure by deacetylation of the corresponding tetraacetates **6** using *Amberlyst A-26* [7].

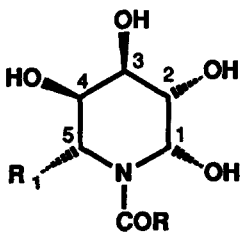
The relative configuration and dominant conformation of these aminosugars could be ascertained unambiguously by 400 MHz ^{1}H-NMR. In particular the tetraacetate of the aminoaltrose **6c** occurred in its chair conformation [$J_{1,2}$=4.0 ; $J_{2,3}$=11.0 ; $J_{3,4}$=3.0 ; $J_{4,5}$=1.6 ; $J_{1,5}$=0.6], as

indicated in the perspective view **A** (**Scheme 2**), the AcO-C(1) and Me-C(5) groups being axially oriented. We had already described and discussed a similar conformation for an aminoallose derivative (a piperidinose) in which both OH-C(1) and Me-C(5) were axially oriented [2].

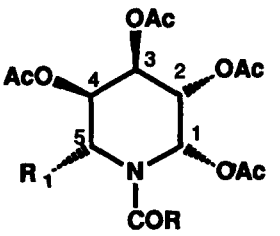
Scheme 2



1

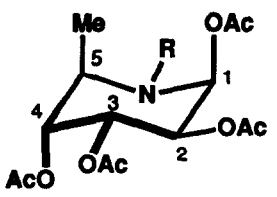


5



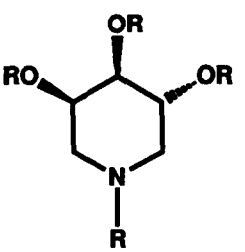
6

a) R = OMe ; R_1 = H ; b) = OBn ; R_1 = H ; c) R = OBn ; R_1 = Me



A

R = CO_2Bn



7a R = H
7b R = Ac

To the best of our knowledge this type of stereospecific double glycolisation of conjugated dienes with OsO_4 had not yet been described. It represents a simple methodology which has some obvious implications in organic synthesis. According to Natsume N-acyl 1,2-dihydropyridines seem to undergo double glycolisation with $KMnO_4$ but do not lead to any defined product(s) [8]. Polyhydroxylation of 1,2-dihydropyridines with catalytic amounts of OsO_4 has been performed ; in the presence of $NaIO_4$ though. As a consequence this latter reagent led to destructive cleavage of the postulated tetrol intermediates which, for that reason, could not be isolated [9].

Hydrogenolysis of the N-benzyloxycarbonyl aminosugar **5b** led in a one-pot multistep process (hydrogenolytic debenzylation ; decarboxylation ; dehydration to the corresponding cyclic imine ; hydrogenation of this latter one) to the 1-desoxy compound **7a** (resin ; 91 %) which was characterized as its tetraacetyl derivative **7b** (mp : 102-103°). Similar multistep hydrogenolyses of of piperidinose derivatives have already been described [10, 11]. Product **7a** is analogous to some well-known 1-desoxypiperidinose derivatives, like DNJ and DMJ, which are powerful and specific glycosidase inhibitors and whose chemotherapeutic potential has been recognized [12].

Compound **7a** was submitted to some physiological tests and found to be devoid of any anti-HIV properties.

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