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A Straightforward Synthesis of (±) 5-Amino-5,6-Dideoxyallose, of its Bisulfite β-Anomer, and of its 1-Deoxy Derivative.

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Abstract. - Diels-Alder cycloaddition of (E,E)-hexadienal dimethylacetal **3** with the benzyloxycarbonylnitroso dienophile **4**, followed by catalytic osmylation, hydrogenolysis, and treatment with SO_2, led stereospecifically to the sole β-anomer of allopiperidinose bisulfite derivative **7**. Saponification of **7** and thence catalytic hydrogenation gave in high yield the 1-deoxyallopiperidine derivative **9**.

The naturally occurring nojirimycin, *i.e.* 5-amino-5-deoxy-D-glucopyranose, was isolated and identified way back in 1967.[1] At that time it was the sole representative of sugars containing a nitrogen atom in the ring. Nojirimycin is noteworthy for its physiological properties, in particular as a glycosidase inhibitor.[1] Similarly its bisulfite,[2] and foremost, its 1-deoxy derivative DNJ,[3] also are glycosidase inhibitors.

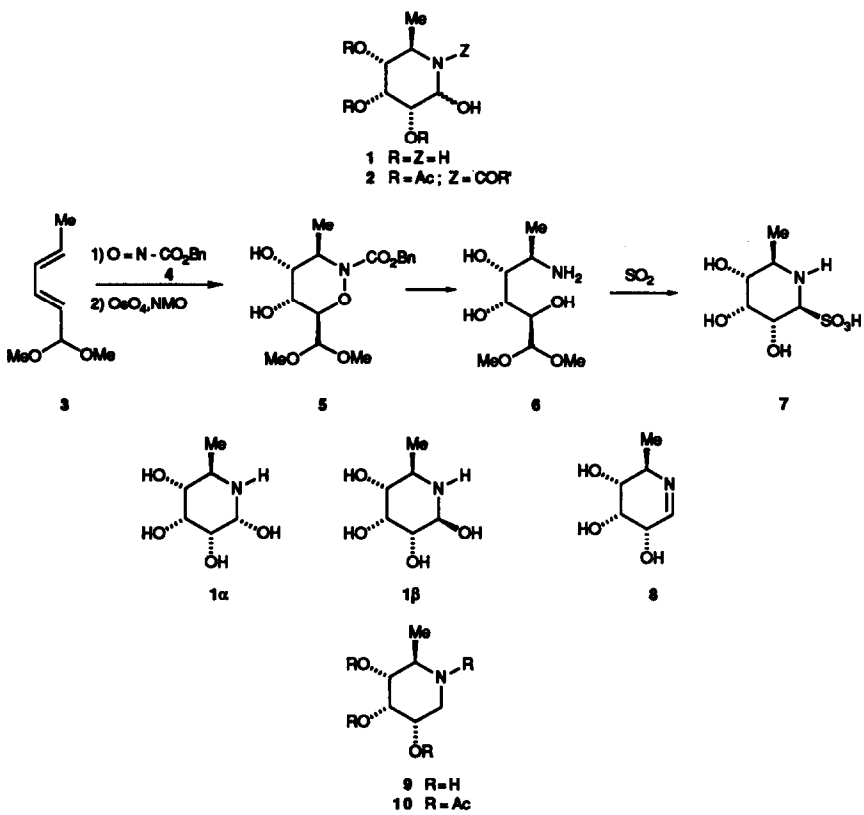
This type of physiological property has also been observed with manno-nojirimycin,[4] anti with galactostatine ;[5] as to allo-nojirimycin, its synthesis has been described recently. [6]

During the last 25 years a large number of 1-deoxyaminosugars have been isolated from natural sources ; they derive either from piperidines, from pyrrolidines, from pyrrolizines, or from octahydroindolizines.[7] Since these molecules inhibit glycoprotein processing, they have potential antihuman immunodeficiency virus (HIV) activity,[7] and led to a scramble towards the synthesis of similar target molecules.

Along these lines we describe herein a simple and straightforward stereospecific synthesis of the piperidinose (±) 5-amino-5,6-dideoxyallose **1**, of its bisulfite **7** and of its 1-deoxy derivative **9**. In passing it should be mentioned that a series of 6-deoxyaldohexoses occur as natural products, *e.g.* L-rhamnose and L-fucose.[8]

(E,E)-Hexadienal-dimethylacetal **3** had been shown to undergo Diels-Alder cycloaddition with a series of acylnitroso dienophiles. The primary adducts were transformed stereospecifically into N-acyl 6-deoxyallo-nojirimycin derivatives **2**.[9] To cite but one example, N-benzyloxycarbonylnitroso dienophile **4** - which was obtained by *in situ* oxidation of the corresponding hydroxamic acid with tetra-n-propylammonium periodate - reacted with **3** to give a major D.A. cycloadduct in excellent yield. Catalytic osmylation (in the presence of N-methylmorpholine N-oxide, or NMO) of this latter one led to the *cis*-diol **5** whose hydrogenolysis

(H_2, Pd/C) gave the acyclic aminoallose dimethylacetal **6**.[9] When a solution of **6** in water was reacted with SO_2 for 3 d at 40°C (the bisulfite **7** (β-anomer) was formed in 90 % yield as colourless crystals (m.p. 146-147°C). Saponification of **7** in water using a small excess of $Ba(OH)_2$ at r.t. gave (±) 6-deoxyallonojirimycin **1** - *i.e.* (±)5-amino-5,6-dideoxyallose - as an equilibrium of the piperidinose anomers **1**(α) (37 %), and **1**(β) (53 %), as well as the imine **8** (10 %), as determined by ^{1}H-NMR in D_2O at 27°C. In acidic medium **1** undergoes easily the "Amadori rearrangement", *i.e.* a functional isomerisation which had already been observed with some other piperidinoses.[10] Catalytic hydrogenation (5 % Pd/C ; r t ; overnight) of the **1**(α)/**1**(β)/**8** mixture led quantitatively to the sole aminotriol **9**, *i.e.* to (±) 1,6-dideoxyallonojirimycin which was characterized as its tetracetyl derivative **10** (m.p. 120-121°C).

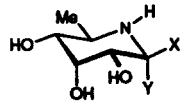


Structural and conformational analyses of the newly synthesized products - **1(α), 1(β), 7-9** - were performed by ^{1}H-NMR (see ***Table***). One notices in particular that the piperidinose derivatives appear in their $^4C_1$ conformation which is imposed by the equatorial orientation of the CH_3-C(5) group. The β-anomers appear with a large $^3J_{1,2}$ (trans-diaxial H-atoms), the α-anomers with the expected long-rang $^4J_{1,3}$ coupling constants (see ***Table***).

Table. - ^{1}H NMR spectral data of allopiperidinose derivative **7, 1α, 1β,** and **8** in D_2O at 250 MHz at 300 K. δ in ppm, J in Hz, internal standard TBDS.

	H-1	H-2	H-3	H-4	H-5	Me	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,Me}$
7	4.23	4.11	4.18	3.68	3.49	1.43	10.6	-	2.5	2.5	10.6	6.4
1α	4.58	3.63	4.04	3.21	3.17	1.12	3.5	1.3	3.1	2.4	10.0	6.0
1β	4.36	3.32	4.05	3.25	2.92	1.10	8.8	-	3.0	3.0	10.2	6.4
8[a)]	7.52	4.02	4.20	3.51	3.47	1.30	2.0	0.9	3.7	~3	9.0	6.6

a) $J_{1,5}$ = 2.2 Hz



7 X = SO_3H ; Y = H
1β X = OH ; Y = H
1α X = H ; Y = OH

Let us compare the α/β anomer ratio of allopyranose (α/β = 18:70 at 40°C)[11] with the one observed with 6-deoxyallopiperidinose **1**, *i.e.* α/β = 37:53 (see above). The observed increase of the ratio is due to the replacement of the ring oxygen atom by a nitrogen. This means that the so-called anomer-effect is stronger with piperidinoses than with the corresponding pyranoses by *ca.* 0.6 kcal.mol^{-1}. This magnitude is similar to the one which had been determined for nojirimycin (a piperidinose) as compared to glucopyranose.[12]

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