Tetrahedron Letters,Vol.23,No.18,pp 1909-1912,1982 0040-4039/82/181909-04$03.00/0
Printed in Great Britain

A FACILE THREE-STEP SYNTHESIS OF A RACEMIC 4,5-DIAMINO-4,5-DIDEOXY-α-D,β-L-LYXOPYRANOSE. (1)

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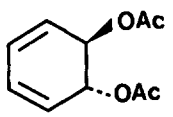
Dedicated to Professor Tetsuji KAMETANI on the occasion of his 65. Birthday.

SUMMARY. Diels-Alder cycloaddition of nitrosobenzene to 1-methoxycarbonyl-1,2-dihydropyridine led in high yield to the endocyclic hydroxylamine adduct 5, which was successively oxydized with potassium permanganate and hydrogenolyzed to give the new aminosugar 4,5-dideoxy-5-methoxycarbonylamino-4-phenylamino-α-D,β-L lyxopyranose 7.

Over the last twenty years the number of natural rare sugars has increased rapidly, providing problems of structure elucidation and synthesis (2). Aminosugars in particular play an ever-increasing role in various fields, such as aminoglycosidic antibiotics, antitumor agents and structural biopolymers in bacterial membranes (3). Most carbohydrate chemists undertake chemical modifications of naturally occurring, and therefore optically active sugars, in order to invert asymmetric centers and/or to replace one or several hydroxyl groups by other functions. Paulsen and Todt have reviewed piperidino- and pyrrolidinosugars, which have been obtained by chemical means, starting from natural carbohydrates only (4). An alternative methodology, albeit seldom used is the total synthesis of carbohydrate derivatives which may be difficult to prepare from natural sugars.

One approach to the synthesis of racemic aminocyclitols is the regiospecific, stereoselective, and if possible stereospecific, functionalization of cyclic conjugated dienes by means of Diels-Alder cycloadditions with nitroso compounds. This first step is followed by hydroxylation of the resulting bicyclic olefin and by reduction of the hydroxylamine N-O bond. Belleau and Au-Young have initiated this approach using acyclic conjugated dienes (5); then Kresze and his coworkers undertook a systematic investigation with 1,3-cyclohexadienes (6-8).

Starting from trans-5,6-diacetoxy-1,3-cyclohexadiene 1 and p-chloronitrosobenzene, for example, these authors prepared the inosamine derivative 3 via the bicyclic adduct 2 (8).



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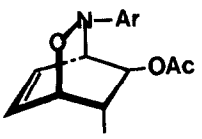

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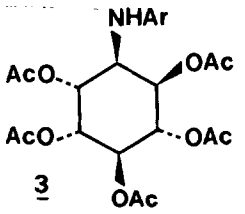

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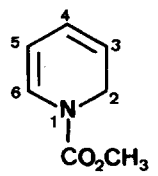
Ar = C_6H_4 p-Cl

We describe here a synthetic sequence based on a similar approach, but instead of a carbohomocyclic diene, the starting educt is a heterocyclic conjugated diene. Reaction of nitrosobenzene with N-carbomethoxy-1,2-dihydropyridine 4 (9) led to the formation of a product (86%) which could not be recristallized, but was homogeneous by TLC. During the course of our investigations Knaus et al. published the synthesis of compound 5 using the same approach; however these authors did not proceed any further toward the synthesis of the corresponding aminosugars (10). Cis-hydroxylation of 5 at -25° with $KMnO_4$ in neutral water-ethanol solution led to a cristalline compound, mp 164°, to which we assigned structure 6; no other product could be isolated. Although olefin cis-hydroxylations with $KMnO_4$ are usually favoured in basic medium (11,12), we obtained the best yields (50%) in a neutral solution. This yield could not be improved, either in a basic medium, or by using $KMnO_4$ and triethylbenzylammonium chloride in CH_2Cl_2 (13), or by the catalytic OsO_4 method in the presence of ter-butyl-hydroperoxide in acetone (14). ^1H and ^{13}C NMR spectra are in good agreement with the postulated structure 6. In particular $^1J_{(C,H)}$ (172 Hz) for C-1 can only fit with a sp^3 carbon atom bound to an oxygen atom and to a nitrogen atom; it is significantly larger than $^1J_{(C,H)}$ of C-4 (155 Hz). This clearly indicates (18) that the molecular skeleton, as indicated by structure 6, is correct and that it is not the other regioisomer. The configurations of the hydroxyl- C-7 and C-8 atoms could be ascertained unambiguously by ^1H NMR analysis of the monocyclic aminosugar 7 (vide infra). Catalytic hydrogenolysis of the endocyclic N-O bond of 6 over Pd/C led to the crystalline compound 7 (70%), mp 146-147°. 360 MHz ^1H NMR of this product, as measured at 50°C, yielded simultaneously the conformation of the piperidine ring and the configurations of all four asymmetric centers of 7, showing no change of configuration (Figure 1 and Table 1).



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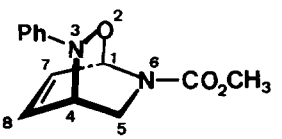

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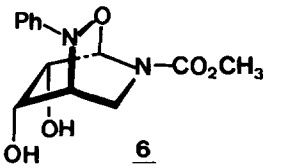

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Table 1 360 MHz ^1H NMR spectrum of 7 measured at 50°C in D_6 acetone and D_2O.

	δ (ppm)	i,j	$J_{i,j}$(Hz)
H-1	5.72	1,2 1,5eq	2.5 0.5
H-2	4.05	2,3	3
H-3	3.92	3,4	10
H-4	3.69	4,5ax 4,5eq	11 5
H-5eq	4.18	5eq,4	5
H-5ax	2.88	5ax,5eq	13.5
CO_2CH_3	3.72		
H arom.	6.76(o) 7.13(m) 6.63(p)		

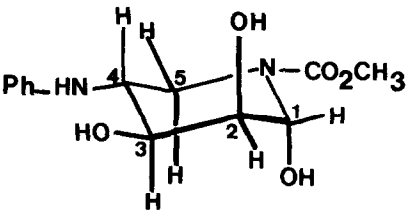

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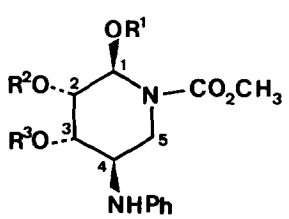
Figure 1

Table 1 clearly indicates that the piperidine ring of 7 is in a chair conformation, the phenylamino substituent being equatorial. That 7 occurs as the axial anomers (α-anomer for the D enantiomer) follows from the coupling constant ($^4J_{H,H}$= 0.5 Hz) between H-1 and H-5eq. When measured at RT the NMR spectrum of 7 shows broadened bands, because of a coalescence process, partially due to inhibition of free rotation around the N-CO bond of the urethane moiety (4). The methylglycoside 8 was obtained by treatment of 7 in dry MeOH in the presence of p-toluenesulfonic acid. Its high field ^1H NMR spectrum, at 50°C, was very similar to the spectrum of 7. At 0°C the spectrum led to the splitting of all but two bands into two signals each of approximatively equal intensity. This clearly indicates the existence of an equilibrium between the two urethane rotamers. NMR spectroscopic analyses (360 ans 400 MHz ^1H NMR) of the methyl-glycoside-diacetate 9, mq 168-169°, and of the triacetate 10, mp 164°, corroborate the above structural, configurational and conformational assignments, made for 7. We note in particular that the D-enantiomer occurs in the C(1)-type chair conformation (15) : the bulky phenylamino group prevents this stable conformation -which nevertheless bears two axial hydroxyl groups- from flipping over to the other chair conformation, in which Ph-NH would be axially oriented.

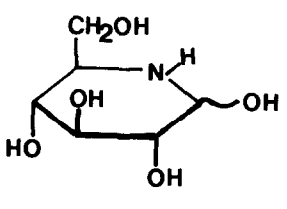


7 $R^1=R^2=R^3=H$

8 $R^1=CH_3$ $R^2=R^3=H$

9 $R^1=CH_3$ $R^2=R^3=Ac$

10 $R^1=R^2=R^3=Ac$



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The conformation of the D enantiomer of 7, as represented in Figure 1, fits also with the anomer effect which Paulsen has observed and generalized (4).

To our knowledge 4,5-diamino-4,5-dideoxylyxose itself has neither been found in nature nor synthesized previously. Indeed piperidino-sugars are rare products, nojirimicine being one of the few known examples -if not the only one- in this series (16, 17). We shall now turn our attention to other heterocyclic dienes as well as to other nitroso dienophiles, an approach which should lead ultimately to free amino functions and to new aminosugars.

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(18) ^{13}C NMR of 6 measured in CD_3OD : δ 81.29 ppm for C-1 and 59.52 ppm for C-4

(Received in France 20 February 1982)