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Nitrone in L-lyxose series: cycloaddition way for the synthesis of new C-α-fucosides

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Abstract—Nitrone **3** analogue of 5-deoxy-L-lyxose was derived from D-ribose. Its reduction with aqueous SO_2 gave the corresponding 4-amino-sugar **2**, a potent α-L-fucosidase inhibitor. 1,3-Dipolar cycloaddition of **3** with alkenes allowed the synthesis of acetohydroxamic acid and ethane–phosphonate derivatives. Hydroxy-ethane derivative **15** is a nanomolar α-L-fucosidase inhibitor.
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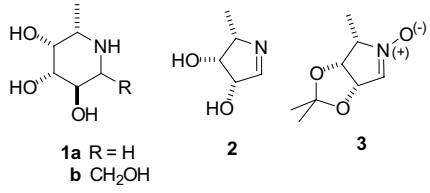
1. Introduction

L-Fuco-nojirimycin derivatives **1a**,**b** are among the most potent inhibitors[1–4] of α-L-fucosidase with K_i values in the nanomolar range. In a previous work[5] we have shown that the more simple pyrrolidine amino-L-lyxose **2** is a very good fucose mimic since it inhibits the same enzyme with a K_i value of 10 nM. In the present study, we describe the synthesis of new derivatives of our parent compound **2**, substituted at the position C-2. To achieve this goal, we have investigated new synthetic methods, which led to the nitrone derivative **3**. Cycloadditions of **3** with various dienophiles followed by chemical modifications gave rise to a series of new substituted C-2 derivatives (Scheme 1).



Scheme 1.

2. Synthesis of nitrone 3

Crystalline protected benzyl D-riboside **5** was obtained from D-ribose **4** in ca. 50% yield.[6] Its 5-*O*-mesylate was reduced with $AlLiH_4$ into **6a**. The anomeric benzyl group of **6a** was difficult to reduce by catalytic hydrogenolysis (5% Pd–C in EtOH or EtOH/AcOH), but a clear and reproducible reaction occurred with sublimated **6a** in EtOH containing 5% formic acid at 30 °C and gave 5-deoxy-D-ribose derivative **6b**[7] as 90:10 mixture of anomers (three steps from D-riboside **5**, 80% yield, Scheme 2).

The method of Holzapfel and Crous[8] was followed for the conversion of protected sugar **6b** into nitrone **3**. Thus oxime **7a** was obtained as 60:40 *E*/*Z* mixture by classic oximation[6] of **6b**. Then treatment with ClSi *t*-$BuMe_2$ in pyridine provided **7b**. Mesylation of the alcohol at C-5 and subsequent *O*-desilylation with NBu_4F gave nitrone **3** together with the cyclic oxime **8** in a 90:10 ratio in dry acetonitrile at 80 °C with 1.5 equiv $NBu_4F{\cdot}3H_2O$ and 1.5 equiv NEt_3. Under other conditions such as CsF, dry NBu_4F at 20 °C or at 50 °C led to 1:1 mixtures of **3** and **8**. Thus, nitrone **3** was also prepared in 45% yield from 5-deoxy-D-ribose **6b**. An original and simple reduction/hydrolysis of the preceding nitrone **2** with SO_2 in water at 20 °C overnight led to the 4-amino-4,5-dideoxy-L-lyxose and was isolated in 62% yield as its crystalline sulfite adduct **9**. The amino-sugar **3** was obtained in water solution by SO_2-elimination with $Ba(OH)_2$.[5]

Keywords: Nitrone; 1,3-Dipolar addition; Amino sugar; Fucosidase inhibitors; Phosphonate.
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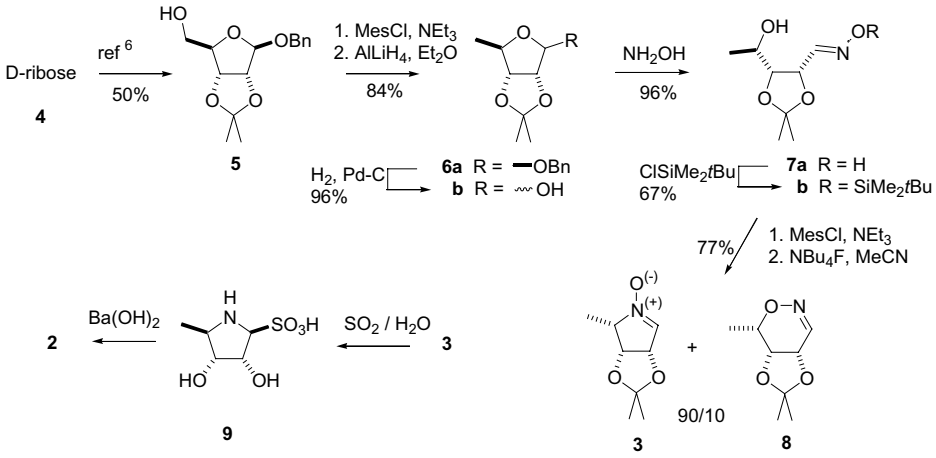
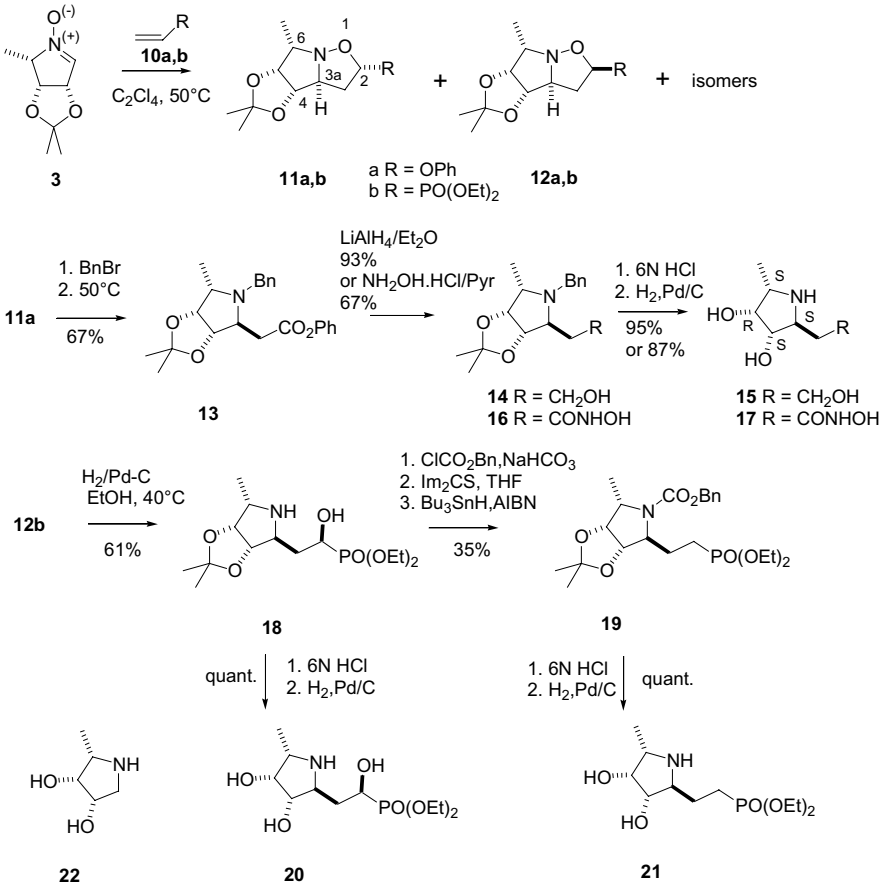


Scheme 2.

3. Cycloaddition of nitrone 3 and transformation of the adducts

Nitrone **3** reacted easily in C_2Cl_4 at 50 °C with alkenes **10a**,**b** to give cycloadducts **11a**,**b** and **12a**,**b** quantitatively in various proportions. With vinyl phenyl ether **10a**,[9] the cycloaddition was regiospecific and led to a 85/15 mixture of diastereoisomers *exo* **11a** and *endo* **12a**, the major isomer **11a** being isolated by crystallisation in 85% yield. Vinylphosphonate **10b,** which has never been used as a dienophile before, led with nitrone **3** to the four possible adducts in 30/52/13/6 ratio with an acceptable regioselectivity, the main isomers being diastereoisomers **11b** and **12b**. The major isomer **12b** was isolated by chromatography in ca. 50% yield (Scheme 3).

The *exo* stereostructure (2*S*,3a*S*,4*S*,5*R*,6*S*) of the major adduct **11a** was determined by X-ray crystallography[15] (Fig. 1) and agrees with those of other nitrone adducts of the pyrrolidine series obtained with vinyl ethers.[10–14]



Scheme 3.

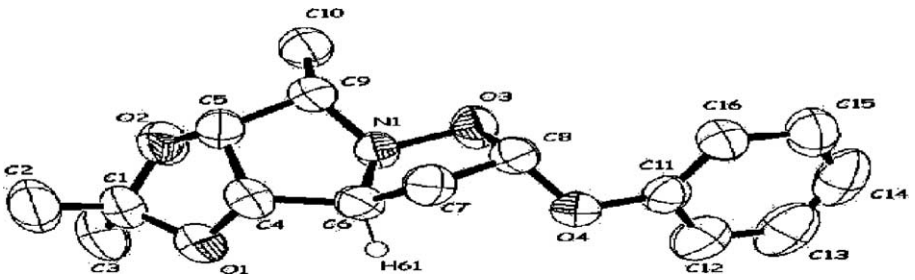


Figure 1. ORTEP view of adduct **11a**.

The ^{1}H NMR spectrum of **11a**,**b** and **12a**,**b** showed vicinal coupling constants J (H-3a, H-4) = ca. 0, confirming a *trans* relation between both protons H-3a and H-4. For the minor adduct **11b**, *exo* stereostructure was proven by the observation of strong NOE of 10% on the signal of H-6 by irradiation of H-2.

Transformation of **11a** into ester **13** was carried out according to the Bayon's method[10,11,14] (*N*-benzylation with benzyl bromide in $CHCl_3$ and subsequent thermal rearrangement at 50 °C). Phenyl ester replacement with hydroxylamine in pyridine at 30 °C[11] gave protected hydroxamic acid **16** in 50% yield. Reduction of **13** with $AlLiH_4$ in dry ether gave alcohol **14** in 61% yield.

Ring opening of phosphonate **12b** generated the pyrrolidineethylphosphonate **19** in 21% overall yield by hydrogenolysis of the N–O bond into **18**, followed by *N*-protection and then elimination of the β-hydroxy group in two steps. This implied formation of a xanthate[16–19] by reaction with thiocarbonyldiimidazole in THF and radical fragmentation with AIBN and Bu_3SnH in toluene heated under reflux.

N,*O*-Deprotection of **14**, **16**, **18, 19** by hydrolysis with 6 N HCl in EtOH followed by hydrogenolysis over Pd–C gave the corresponding diols **15**, **17**, **20**, **21** in 87–100% yield.

4. Inhibition studies

We have evaluated the C-α-fucosides **15**, **17**, **20**, **21** as inhibitors of bovine kidney L-fucosidase, a model enzyme for fucose recognition. The results are reported in Table 1. For comparison we have also reported K_i values for the amino-L-lyxose **2**[5] and the imino-L-lyxitol **22**.[5]

All inhibitors were competitive. Among the various substitutions explored in this work, it appears clearly that alcohol **15** is as potent as the amino-L-lyxose **2** with a K_i value of 8 nM. Compared with **2**, **15** is much more stable in solution.

Table 1. Bovine kidney α-L-fucosidase inhibition values (K_i in μM) for pyrrolidine-diols **15**, **17**, **20**, **21,** amino-L-lyxose **2**[5] and imino-L-lyxitol **22**[5]

Compounds	**2**	**22**	**15**	**17**	**20**	**21**
α-L-Fucosidase	0.010	0.050	0.008	5.1	0.040	0.1

5. Conclusion

Efficient conversion of (3*R*,4*R*,5*S*)-3,4-dihydroxy-5-methylpyrroline (**2**) into 2-substituted (2*S*,3*S*,4*R*,5*S*)-3,4-dihydroxy-5-methylpyrrolidine have been developed. The new C-glycosides containing the α-L-lyxofuranosides moiety are not better inhibitors of α-L-fucosidase from bovine kidney than **2**, except for **15**, which bears a 2-(hydroxymethyl) substituent.

Acknowledgements

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CCDC-233 941 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.cam.ac.uk [or from the Cambridge Crystallographic Data Center, 12 Union Road, CB2 1WZ, UK; fax (internat.) +44-1223/336-033; e-mail deposit@ccdc.cam.ac.uk].
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