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Direct conversion of 1-deoxy-1-nitroalditols to methyl glycofuranosides

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Abstract

Treatment of the sodium nitronate forms of 1-deoxy-1-nitrohexitols with methanolic sulfuric or hydrochloric acid at −30 °C leads to their regiospecific conversion to the corresponding methyl glycofuranosides. The reaction exhibits more pronounced stereoselectivity for 1-deoxy-1-nitroalditols with the 2,3-*erythro* configuration than with the 2,3-*threo* substrates and *cis* methyl glycofuranosides are the major products. The observed stereoselectivity indicates the lysis of the protonated aci-nitro form which is a two-step process consisting of nucleophilic addition to the protonated carbon–nitrogen double bond followed by the bimolecular nucleophilic substitution of the nitrogen-containing residue.

Keywords: Nef reaction; Stereoselectivity; 1-Deoxy-1-nitroalditol; Nitronate; Ring-closure reaction; Intramolecular nucleophilic addition; Walden inversion; Methyl glycofuranoside

Methyl glycofuranosides are important starting compounds for the synthesis of more complex structures containing glycofuranosyl building blocks.[1] In particular, D-galactofuranose and D-arabinofuranose-containing cell surface oligosaccharides endemic to pathogenic microorganisms, such as *Mycobacteria*,[2] have attracted attention to the development of new approaches for the treatment and prevention of diseases caused by these pathogens.[3]

Two general groups of methods for the synthesis of methyl glycofuranosides have been known for a long time. The first group is based on kinetically controlled Fischer glycosidation of free aldoses in methanolic hydrogen chloride.[4] In the course of the reaction, the concentration decrease of the starting aldose is associated with a rapid, but temporary formation of furanosides, which slowly isomerize to pyranosides.[5] This method is also stereoselective and preferentially provides 1,2-*trans* methyl glycofuranosides. In the presence of calcium or strontium ions, which form tridentate complexes with the methoxy and hydroxyl groups, 1,2-*cis* glycosides are the major products.[6] In place of the acid catalyst, especially on a preparative scale, a strongly acidic-cation exchange resin is used in order to avoid a troublesome removal of acid. Mostly, however, methyl glycopyranosides are also present in the reaction mixtures to some extent such that their separation is necessary.[7]

The other group of methods is based on the starting aldose dithioacetals and, in spite of the unpleasant preparation of the starting compounds, these are considered to be the most convenient for the synthesis of glycofuranosides.[8] The procedure involves transformation into a monothioacetal which is then treated with a thiophilic promoter.[9] Due to the acyclic structure of the starting compounds and the neutral conditions for the decomposition of their thioacetal group they provide the desired five-membered ring glycosides unambiguously.[8] The process has also been extended to the synthesis of furanose-containing disaccharides.[10]

The conversion of the nitronate forms of aliphatic nitro compounds into carbonyl compounds is a very common transformation. Although the original Nef procedure, first described in 1894,[11] involves strong acid-catalyzed hydrolysis of nitronates, many alternative, non-hydrolytic

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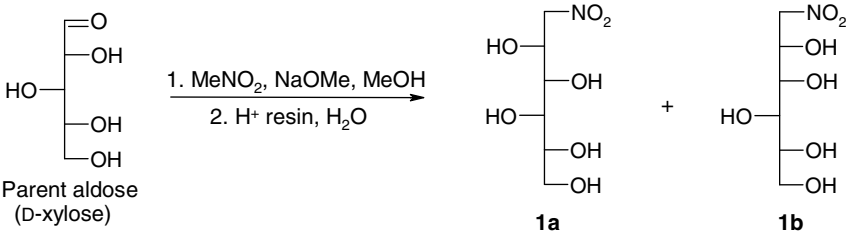
procedures have been developed since.[12] This was mostly due to the harsh conditions of the conversion (pH<1), but also because of the failure of the acid-catalyzed hydrolysis of the nitronate group alone. Hydrolysis failures were reported for some multifunctional group compounds, where the starting nitro derivatives were recovered.[13–15] However, a Nef-type strong acid-catalyzed methanolysis of the nitronate forms of *C*-glycosylnitromethanes[16] as well as of some other non-sugar nitro compounds,[12,15] which resist the Nef reaction in water, proceeds smoothly and dimethyl acetals or ketals of the corresponding carbonyl compounds were the products. The acid-catalyzed methanolysis of nitronates was first used because of the increasing solubility of, and consequently the yields of products from nitronates of hydrophobic, medium and high molecular weight nitro compounds.[17] Here, we report a simple and general method for the preparation of methyl glycofuranosides, which is based on a strong acid-catalyzed methanolysis of the nitronate forms of 1-deoxy-1-nitroalditols.[18] The starting nitro compounds, the nitronates of which are intermediates of the Sowden procedure for the preparation of aldoses, can be easily obtained by decationization of the nitronates, followed by the separation of their epimers by fractional crystallization,[19] or by chromatography on cation exchange resins in the La^{3+} or Ca^{2+} forms.[20] Some are also available commercially. Scheme 1 illustrates this general method for preparing 1-deoxy-1-nitrohexitols from the parent aldopentoses by the nitromethane synthesis, as exemplified by the preparation of 1-deoxy-1-nitro-D-*ido*-hexitol (**1a**) and 1-deoxy-1-nitro-D-*gulo*-hexitol (**1b**) from D-xylose.

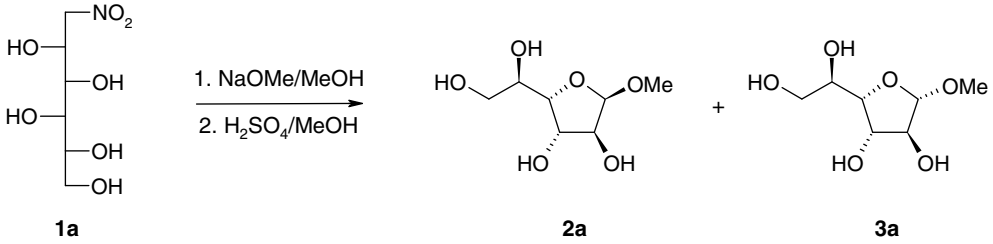
One-pot treatment[21] of a methanolic solution of 1-deoxy-1-nitro-D-*ido*-hexitol (**1a**, Scheme 2) with sodium methoxide followed with methanolic sulfuric or hydrochloric acid at −30 °C resulted in its quantitative conversion to a mixture of the corresponding methyl D-idofuranosides **2a** and **3a**.[22]

Under the same conditions of kinetic control, similar behaviour was observed for other 1-deoxy-1-nitrohexitols and the corresponding mixtures of anomeric methyl hexofuranosides, not containing remarkable amounts of any other sugar compounds (by ^{1}H NMR), were obtained in combined ~90% yields (Table 1). All the products were characterized by ^{1}H and ^{13}C NMR spectral data and specific rotation, and by comparison with known methyl hexofuranosides.[6,23] The analysis of the composition of the reaction mixtures revealed that in all the cases the 1,2-*cis* methyl hexofuranosides were the major anomers. Moreover, the predominance of the 1,2-*cis* anomers was significantly higher in the group of 2,3-*cis* hexofuranosides (entries b, d, f and h) than with the 2,3-*trans* hexofuranosides (Table 1, entries a, c, e and g). The observed stereoselectivities using this method, which can be considered a modified Nef solvolysis, are opposite to the stereoselectivities obtained using the Fischer glycosidation,[5] and are very indicative of the lysis mechanism of the protonated nitronate group.

As shown in Scheme 3, for the conversion of 1-deoxy-1-nitro-D-*manno*-hexitol (**1d**) to methyl D-mannofuranosides **2d** and **3d**, the first step involves activation of the nitro form via deprotonated nitronate **4d**. After acidification, the C-4-OH group intramolecularly attacks the double bond of the protonated nitronate **5d** from the least hindered *Si* face. The same preference of the *Si* face attack is apparent also for 1-deoxy-1-nitrohexitols with D-*ido*, D-*talo* and D-*altro* configurations (entries a, f and g), while preferential intramolecular addition in the nitronates with remaining D-*gulo*, D-*gluco*, D-*galacto* and D-*allo* configurations (Table 1, entries b, c, e and h) proceeds mainly from the *Re* face. Moreover, the 2,3-*erythro* arrangement of the

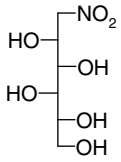
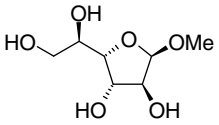
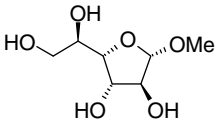
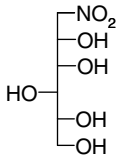
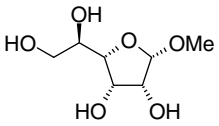
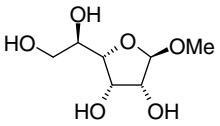
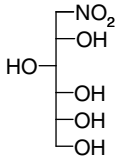
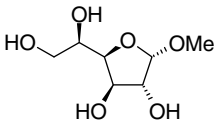
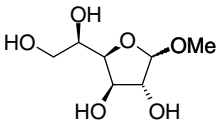
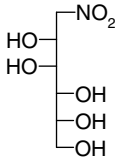
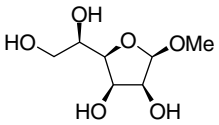
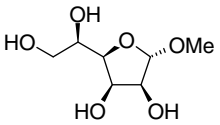
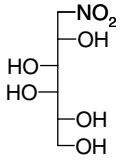
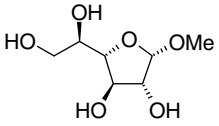
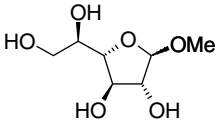
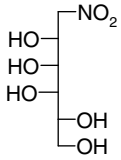
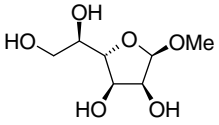
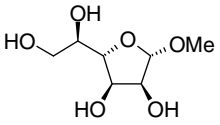
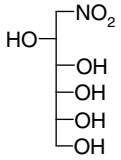
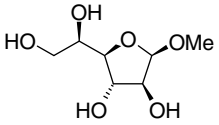
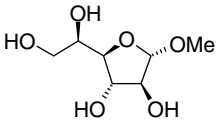
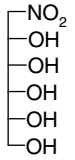
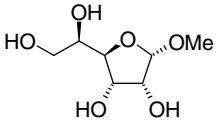
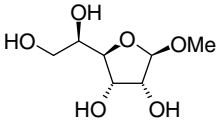


Scheme 1.

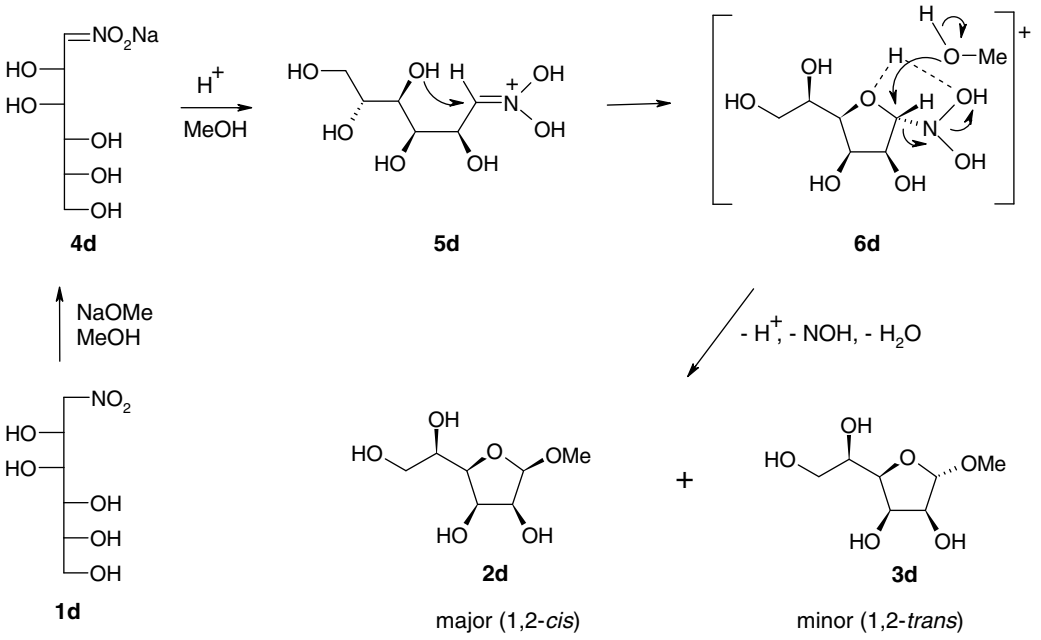


Scheme 2.

Table 1
Stereoselectivities and yields observed in the H_2SO_4 catalyzed methanolysis of the sodium nitronate forms of 1-deoxy-1-nitrohexitols at −30 °C

Entry	Nitrohexitol (**1**)	*cis*-Furanoside (**2**)	Yield (%)	*trans*-Furanoside (**3**)	Yield (%)
a			55		36
b			78		11
c			54		36
d			76		14
e			65		25
f			74		16
g			67		24
h			83		8

hydroxyl groups blocks the reaction site and thus more discrimination between the respective *Re* and *Si* faces occurs during the addition than with the 2,3-*threo* substrate and, consequently, the respective ratios of the resulting anomeric glycofuranosides differ more clearly. In the next step, methanol acts as the second, aglycon nucleophile and, with a Walden inversion at the anomeric carbon atom, substitutes the hydrated nitroxyl moiety of **6d** leading to the formation of the final methyl hexofuranosides.



Scheme 3.

The stereoselectivity of the transformation, which is controlled by the structural configurations of individual starting compounds, may even change stereospecifically as demonstrated by a 5 min treatment of **4d** with methanolic H_2SO_4 at −50 °C. The only product of this transformation was methyl β-D-mannofuranoside (**2d**) isolated in a 30% yield; the remainder was starting 1-deoxy-1-nitro-D-mannitol (**1d**). On the other hand, if the reaction temperature was increased to 0 °C, a significant amount of methyl α-D-mannopyranoside appeared in the reaction mixture. This may result from the consecutive reactions also accompanying the Fischer procedure for the preparation of glycosides.[5]

The high preference for the observed five-membered ring closure over six-membered ring closure during the methanolysis of the protonated nitronic acids of 1-deoxy-1-nitroalditols is in good agreement with a difference in the relative rate constants for closing five- and six-membered lactone rings from the respective 4-bromobutanoate and 5-bromopentanoate of about two orders.[24] However, a much more convenient model for studying the competitive ring-closure addition reactions, which are so common in carbohydrate chemistry, including those occurring in this novel preparation of methyl glycofuranosides, is strong acid-catalyzed methanolysis of 1,2-dideoxy-1-nitro-L-*arabino*-hex-1-enitol to L-arabinofuranosylmethanal dimethyl acetals.[16] This model reaction proceeds cascade-wise and thus is able to quench reactive intermediates of the cyclization step forming stable compounds. This study, applied to the starting compounds of different configurations is in progress in our laboratory.

In conclusion, we have developed a new and simple method for the preparation of methyl glycofuranosides from acyclic 1-deoxy-1-nitroalditols using strong acid-catalyzed methanolysis of their respective nitronates at −30 °C. In addition to the regiospecificity, which results from preferential five-membered ring closure, the new reaction is also stereoselective. The stereoselectivity of the reactions led to the conclusion that lysis of the protonated aci-nitro form involves a two-step process, that is nucleophilic addition to the protonated carbon–nitrogen double bond in the first step, followed by the bimolecular nucleophilic substitution of the nitrogen-containing residue in the second step.

Acknowledgements

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21. *General experimental procedure*: To a stirred solution of 1-deoxy-1-nitroalditol (2.3 mmol) in MeOH (15 mL), was added 2.5 ml of 1 M NaOMe in MeOH at room temperature. The mixture was cooled to −30 °C and mixed with 5 ml of 4.5 M H_2SO_4 in MeOH under stirring, which was continued for 30 min. The cold reaction mixture was deionized with cation and anion exchange resins (H^+, HCO_3^-), concentrated under reduced pressure and the anomeric glycofuranosides were separated by column chromatography on silica gel (37–75 μm) using 16:3:3:4 EtOAc–BuOH–MeOH–H_2O elution or on Dowex 1 X-8 (100–200 mesh), OH^- form, with H_2O elution to yield the pure products.
22. *Analytical data for novel methyl glycofuranosides (Table 1)*: *Methyl* α-D-*idofuranoside* (**3a**): $[\alpha]_D^{20}$ +62 (*c* 1, H_2O); ^{1}H NMR (300 MHz, D_2O), δ 4.89 (d, 1H, $J_{1,2} = 0.5$ Hz, H-1), 4.19 (dd, 1H, $J_{3,4} = 4.3$ Hz, $J_{4,5} = 6.7$ Hz, H-4), 4.13–4.17 (m, 2H, H-2, H-3), 3.94 (br dt, 1H, H-5), 3.73 (dd, 1H, $J_{5,6a} = 3.7$ Hz, $J_{6a,6b} = 11.8$ Hz, H-6a), 3.61 (dd, 1H, $J_{5,6b} = 6.5$ Hz, H-6b), 3.41 (s, 3H, OMe); NOE contact: H-1,3; ^{13}C NMR (75 MHz, D_2O), δ 109.4 (C-1), 83.1 (C-4), 80.8 (C-2), 75.5 (C-3), 72.2 (C-5), 63.5 (C-6), 56.3 (OMe); Elem. Anal. Calcd for $C_7H_{14}O_6$: C, 43.30; H, 7.27. Found: C, 43.04; H, 7.54; *Methyl* β-D-*idofuranoside* (**2a**): $[\alpha]_D^{20}$ −105 (*c* 1, H_2O); ^{1}H NMR (300 MHz, D_2O), δ 4.89 (d, 1H, $J_{1,2} = 4.4$ Hz, H-1), 4.27 (br dd, 1H, H-3), 4.18 (dd, 1H, $J_{2,3} = 5.6$ Hz, H-2), 4.15 (dd, 1H, $J_{3,4} = 4.1$ Hz, $J_{4,5} = 6.3$ Hz, H-4), 3.90 (m, 1H, H-5), 3.66 (dd, 1H, $J_{5,6a} = 4.6$ Hz, $J_{6a,6b} = 11.6$ Hz, H-6a), 3.60 (dd, 1H, $J_{5,6b} = 7.1$ Hz, H-6b), 3.44, (s, 3H, OMe); ^{13}C NMR (75 MHz, D_2O), δ 103.0 (C-1), 78.4 (C-4), 77.5 (C-2), 75.9 (C-3), 70.8 (C-5), 63.5 (C-6), 56.6 (OMe); Elem. Anal. Calcd for $C_7H_{14}O_6$: C, 43.30; H, 7.27. Found: C, 43.08; H, 7.49.
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