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Studies on the chemistry of sodium nitronates and nitronic esters derived from 5-glyco-4-nitro-1-cyclohexenes

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Abstract—Reactions of sodium nitronates derived from 5-glyco-4-nitro-1-cyclohexenes with D-*galacto* or D-*manno* sugar side-chains have been investigated. With acetic anhydride/pyridine, these salts suffered an intramolecular cyclization affording high yields of tetraacetylated isoxazoline *N*-oxides. Treatment of the latter compounds with sodium methoxide yielded, either the corresponding deacetylated derivative or a bicyclic oxime, depending on the configuration of the sugar side-chain. Furthermore, unstable nitronic acid **13** has been isolated by recrystallization of nitronate **10** in dimethylsulfoxide, as well as by reaction of this substance with cold aqueous sulfuric acid. By refluxing with trimethyl phosphite, the *N*-oxides **14** and **16** led to isoxazolines which, like their precursors, could be considered as acyclic *C*-nucleosides.

1. Introduction

The diverse reactions of nitro compounds, nitronate salts and nitronic esters with acids have been under study for over a century.[1] In particular, in the past two decades, the synthetic use of aliphatic nitro compounds has rapidly expanded.[2] In spite of this extensive background, nitronic acid derivatives have seldom been employed in organic synthesis, and this situation is in sharp contrast to that of carboxylic acid derivatives which are highly important substances. This lack of application of nitronic acids themselves and some of their derivatives could mainly be attributed to the lability of these compounds.[1] Moreover, reactions using the somewhat more stable nitronate salts have been conducted under aqueous acidic media, which are the typical conditions of Nef reactions.[3] However, little attention has been paid to other nonaqueous protocols.

On the other hand, assuming the need for efficient and specific methods for the preparation of alkyl nitronates, several authors have reported on the use of these derivatives, both chiral and achiral, for the stereo- and regioselective construction of highly functionalized molecules.[1d,4] In this sense, we have previously reported a simple procedure in which chiral nitro sugar derivatives, via their corresponding nitronate salts, are used in stereoselective Michael addition reactions,[5] as well as for the synthesis of chiral cyclic nitronic esters (2-isoxazoline-*N*-oxides).[6]

The purpose of this paper is to present in full details the preparation and reactivity of sodium nitronates derived from 5-glyco-4-nitro-1-cyclohexenes, as well as a further extension of our work to the synthesis of 2-isoxazolines, an important class of heterocycles with various synthetically useful functionalities masked in the ring.[7] The new isoxazolines and their *N*-oxides could be considered as *C*-nucleoside analogs,[8] a class of compounds that have generated considerable interest in view of their anticancer,[9a] antiviral[9b,c] and/or antibiotic[9d] properties.

2. Results and discussion

As the starting materials, we used pentaacetylated *trans*-5-glyco-4-nitro-1-cyclohexenes **1**, **2**, and **5**; their preparation being accomplished by asymmetric Diels–Alder cycloadditions between sugar-derived 1-nitroalkenes and isoprene[10] or 2,3-dimethyl-1,3-butadiene.[11] Then, following the same methodology as for related *trans*-6-glyco-5-nitro-2-norbornene derivatives,[12] we intended deacetylation of the above cited adducts, by treatment of methanolic solutions of these with a catalytic amount of 2 M sodium methoxide in methanol. In contrast with those results,[13] we observed here that after addition of one drop of the base, the pH values in the solutions changed in a few minutes from clearly alkaline to slightly alkaline (pH 8–9). Monitoring of these processes by TLC (1:1 hexane/AcOEt) showed that spots corresponding to the respective starting materials were progressively replaced by others with lower mobility in such a way that, after 3 h at room temperature, stabilization of the reaction mixtures was achieved. In this point, ^{1}H NMR spectra revealed the complete absence of each one of the pentaacetates and the presence of their respective

Keywords: sugars; nitro compounds; nitronate salts; nitronic acid; isoxazolines; oximes.

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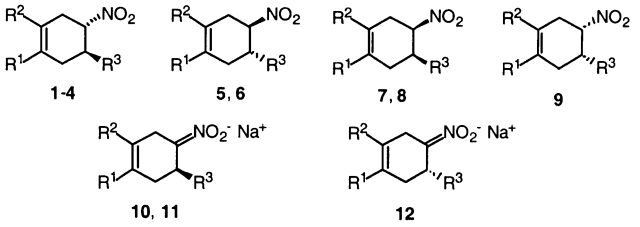
deacetylated derivatives and their C-4 epimers (ratio ca. 1:1), together with small quantities (less than 10%) of other partially deacetylated products. These results indicate that, on treatment with a catalytic amount of sodium methoxide, compounds **1**, **2** and **5** suffer two competitive processes, i.e. deacetylation of their sugar side-chains and formation of carbanions at C-4, in a comparable extent; then, reprotonation of both diastereomeric faces of these carbanions in the almost neutral reaction media would led to *cis*- and *trans*-mixtures of epimers.[14] Concerning the 1:1 ratios of these, we have observed no changes after prolonged periods of time, thus indicating that the composition of the mixtures should reflect the relative stabilities of the products; in this sense, we have performed PM3 semi-empirical calculations[15] for epimeric deacetylated **3** and **7**, finding that the former resulted more stable by only 0.5 kcal mol^{-1}.

The different behaviour between cyclohexenes and nitro-norbornenes against the base, that is, their different acidities, could be attributed to the greater geometrical limitations in angles of the carbanions that would be formed from the more strained [2.2.1] systems.

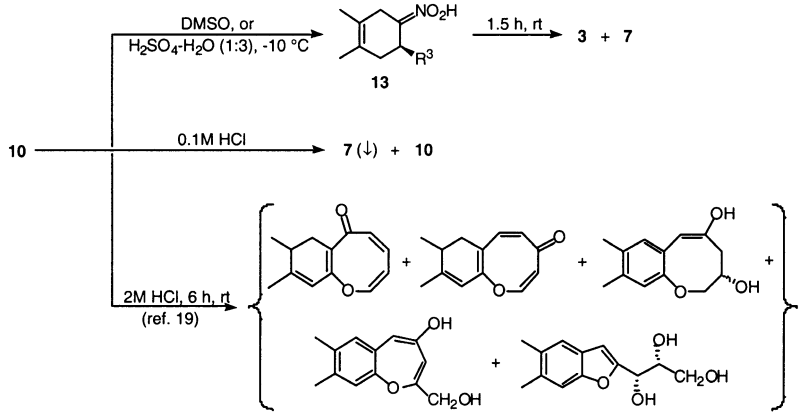
By treatment with a small excess of 2 M sodium methoxide, solutions in either acetone or methanol of *trans*-5-(penta-*O*-acetyl-pentitol-1-yl)-4-nitro-1-cyclohexenes **1**, **2** or **5** led, in each case, to a white precipitate (91% to quantitative yields) that was identified as the corresponding deacetylated sodium nitronate **10**, **11** or **12**. On the other hand, by using an identical procedure, these same products were obtained in similar yields from methanolic solutions of deacetylated derivatives (**3**, **4** and **6**) of the above cited nitrocyclohexenes, or from their epimers at C-4 (**7**, **8** and **9**).[10,11] The new nitronates appeared to be stable compounds that could be recrystallized from methanol/water, and did not decompose after long time of storage in desiccator. Their structures were in agreement with their elemental analyses, showing the typical yellowish colouration indicating the presence of sodium in the combustion test with platinum wire; IR spectra showed, as characteristic bands, those at ca. 3500–3000 cm^{-1} (OH), 1600–1570 cm^{-1} (C=N) and 1140–1120 cm^{-1} (C–O).

With deuterium oxide as solvent we found that, besides the absence of the signals of H-4, the main differences between ^{1}H NMR spectra of the salts and those of their deacetylated precursors, were the downfield shifts that exhibited some of the corresponding protons in the former; as expected, the major displacements were observed for protons close to the carbanionic center at C-4; also, the unsaturated character of this carbon was evident from its chemical shift (130.3–127.4 ppm), which was in the same region where the olefinic C-1 and C-2 (125.5–115.2 ppm) appeared.

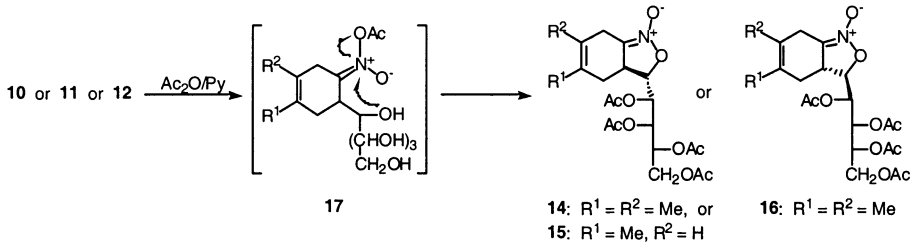


1: $R^1 = R^2 = Me$, R^3 = D-*galacto*-$(CHOAc)_4$-CH_2OAc
2: $R^1 = Me$, $R^2 = H$, R^3 = D-*galacto*-$(CHOAc)_4$-CH_2OAc
3, 7, 10: $R^1 = R^2 = Me$, R^3 = D-*galacto*-$(CHOH)_4$-CH_2OH
4, 8, 11: $R^1 = Me$, $R^2 = H$, R^3 = D-*galacto*-$(CHOH)_4$-CH_2OH
5: $R^1 = R^2 = Me$, R^3 = D-*manno*-$(CHOAc)_4$-CH_2OAc
6, 9, 12: $R^1 = R^2 = Me$, R^3 = D-*manno*-$(CHOH)_4$-CH_2OH

After several days at room temperature, NMR spectra of deuterium oxide solutions of nitronates **10**, **11** and **12** did not show any changes, thereby indicating that no deuterium addition had occurred under these conditions. On the contrary, as it is depicted in Scheme 1 for **10**, NMR spectra in DMSO-d_6 solutions were time-dependent and, after ca. 1.5 h at room temperature they showed, almost exclusively, signals that could be assigned to deacetylated *trans* (**3**) and *cis* (**7**) nitro compounds, without any further evolution.[16] Moreover, compound **10** could be recrystallized from DMSO, affording a crystalline material whose ^{1}H NMR spectrum was identical to the product isolated by direct treatment of **10** with dilute H_2SO_4 at −10°C (Scheme 1). The latter appears to be consistent with the formation of the corresponding nitronic acid **13** from which **3** and **7** arise. Compound **13** appeared to be a rather unstable[1] substance that even in solid state darkened in a few minutes; also, by polarimetric measurements in water, we could observe that, in a period of 90 min at room temperature, the initial value of −20° was changing to 0°. Spectroscopic data of **13** were clearly distinct from those of their nitro tautomers;[10,11] thus, an IR absorption at 1655 cm^{-1} was indicative of the presence of the C=N group; the ^{1}H NMR spectrum of a



Scheme 1.



Scheme 2.

freshly prepared solution of this substance in DMSO-d_6 exhibited a D_2O-exchangeable broad singlet (6.33 ppm), being assigned to C=N–O*H* proton;[17] in addition, the allylic character of H-5 and H-3a,3b was evident from their chemical shifts, that were at lower fields than for the corresponding protons in *trans* and *cis* nitro compounds **3** and **7** ($\Delta\delta$=1.15–0.23 ppm).

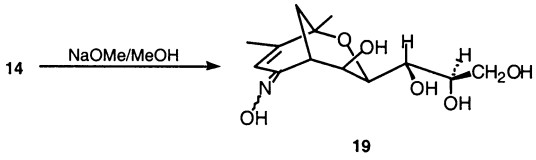
It is noteworthy that, on recrystallization of D-*galacto* nitronate **10** from 0.1 M HCl, the product that crystallized (28% yield) was the pure *cis*-4-nitro-5-(D-*galacto*-pentitol-1-yl)-1-cyclohexene **7**[18] remaining, almost exclusively, unaltered salt in dissolution (Scheme 1). Similarly, D-*manno* nitronate **12** afforded a small quantity (5%) of a solid that consisted in a 1:1.6 mixture of **6** (*trans*) and **9** (*cis*); these compounds were also present in the mother liquor (ca. 1:1 ratio), together with unchanged salt as major component. These facts, indicating a partial protonation of the carbanions, should not be related with its stereochemical course; instead, from the equilibrium between the *cis*- and *trans*-nitro compounds, the solid product we isolated in each case should depend on its relative solubility in the aqueous media.

By using increased concentrations of the acid, we could observe (^{1}H NMR) a progressive complication in the reaction media and, with 2 M HCl, we obtained a mixture of products arising from a Nef reaction, followed by intramolecular cyclization of the intermediate glycocyclohexenones (Scheme 1).[19]

On the other hand, when nitronates **10**, **11** or **12** were dissolved in pyridine and treated with acetic anhydride for 1.5 h at room temperature they gave, after pouring on ice-water, 80–90% yields of tetraacetylated isoxazoline *N*-oxides **14**, **15** or **16**, respectively (Scheme 2). These compounds, that may be considered as cyclic nitronic esters, were stable solids with elemental analyses and spectroscopic data in agreement with their proposed structures; thus, there was absence of IR bands for hydroxyl or nitro groups, whereas those for nitronic esters ($\nu_{C=N}$, 1650–1670 cm^{-1}) and for carbonyl esters ($\nu_{C=O}$, 1740–1750 cm^{-1}) were evident. ^{1}H NMR spectra showed four singlets (ca. 2.1 ppm) attributable to methyl acetates. When compared with their respective (deacetylated) nitronates, we observed the characteristic downfield *acylation shifts*[20] that exhibited protons on the sugar backbones, with the sole exception of H-3 (H-1′ in **10**, **11** and **12**) which underwent a lesser downfield shift; the latter suggests that the first hydroxyl group in the sugar side-chain remains deacetylated and it is therefore involved in the cyclization step leading to **14**–**16**; an additional support to this fact could be deduced from ^{13}C NMR spectra, where C-3 signals on isoxazoline *N*-oxides appeared at clearly lower field than the signals of C-1′ in their corresponding precursors.

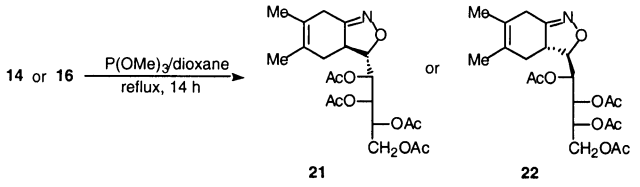
As it was discussed previously,[6] transformation of the sodium salts **10**–**12** into the isoxazoline-*N*-oxides **14**–**16** could be explained by supposing the formation of an intermediate acetic nitronic anhydride **17** (Scheme 2), in which the acetate group on the nitrogen would suffer an intramolecular nucleophilic displacement from the hydroxyl group at C-1. Although very little is known about nitronic anhydrides, mainly as a result of their instability,[1a] some of them have been either isolated[21–23] or postulated as intermediates[24] in various types of reactions; thus, in a related precedent with the processes here described, Miyashita et al.[22] have reported that in the boron trifluoride-promoted hydrolysis of a series of acetic nitronic anhydrides, the acetoxy group on the nitrogen is intramolecularly displaced by a δ-carbonyl oxygen.

In order to obtain their respective deacetylated derivatives, compounds **14** and **16** were treated with a catalytic amount of sodium methoxide in methanol; however, although the latter led quantitavely to the expected deacetylated isoxazoline *N*-oxide **18** (see Section 3.1.10), this was not parallel with what occurred when starting from **14**; instead, the only product in this case (90% yield) was a bicyclic oxime **19** (Scheme 3) that was additionally characterized through its penta-*O*-acetyl derivative **20** (see Section 3.1.9). Explanations about the formation of **19**, as well as a justification for the different behaviour of **14** and **16** against sodium methoxide have been provided.[6]



Scheme 3.

Following the procedure described by Foucaud et al.,[25] the reaction of isoxazoline *N*-oxides **14** and **16** with trimethyl phosphite in dioxane yielded the corresponding isoxazolines **21** and **22** (Scheme 4). After refluxing for 14 h, ^{1}H NMR spectra of the crude reaction mixtures revealed about 90% conversion into the reduced products, also appearing a small quantity of the starting materials together with unidentified by-products.[26] Isolation of **21** and **22** was performed by preparative TLC, their structures being demonstrated by IR, NMR and high resolution mass spectra. Thus, whereas strong IR bands were observed for carbonyl acetate groups



Scheme 4.

(1740–1750 cm^{-1}), those for C=N (1640–1670 cm^{-1}) appeared much more weaker than the same for their precursors. Although proton resonances of **21** and **22** differ very little from those of **14** and **16**, significative divergences were found between ^{13}C NMR spectra; as could be expected, the larger differences were encountered for carbons bonded to nitrogen (C-7a), which appeared more deshielded in isoxazolines than in the respective *N*-oxides by about 44 ppm.

Summarizing the above results, efficient and easy syntheses of optically pure heterocyclic compounds have been achieved from stable nitronate salts of 5-glyco-4-nitro-1-cyclohexenes. The major advantage of the methods described in this paper relies on the simple reaction conditions which have been used; furthermore, the syntheses demonstrate the versatility of these sodium nitronates, readily available in optically pure form, for the preparation of molecules with potential pharmacological activity.

3. Experimental

3.1. General

Solvents were evaporated under reduced pressure below 40°C bath temperature. Melting points were determined with an Electrothermal 8100 apparatus and are uncorrected. Optical rotations were obtained at 20±2°C with a Perkin–Elmer 241 polarimeter. Infrared spectra were recorded in the range 4000–600 cm^{-1} with Perkin–Elmer 399 or Midac FT-IR spectrophotometers. NMR spectra were recorded at 20°C on a Bruker spectrometer AM 400 (400.13 MHz for ^1H, 100.62 MHz for ^{13}C) with TMS or residual $CHCl_3$/DMSO as internal standards. NMR assignments were confirmed by homonuclear double-resonance experiments, and DEPT. Chemical shifts are reported in ppm and coupling constants are reported in Hz. Mass spectra were recorded on a VG Autospec spectrometer. TLC was performed on precoated plates of silica gel 60 GF254 (Merck), with visualisation of spots by UV light or iodine vapour, and the solvent systems specified. Preparative thin layer chromatography (p.TLC) was carried out on 0.20 mm Merck silica gel 60F_{254} plates. Elemental analyses were determined by the Servicio de Microanálisis of our department.

3.1.1. Sodium salt of 1-*C*-[(4*S*,5*S*)-1,2-dimethyl-4-nitro-1-cyclohexen-5-yl]-D-*galacto*-pentitol (10). To a solution of 1,2,3,4,5-penta-*O*-acetyl-1-*C*-[(4*S*,5*S*)-1,2-dimethyl-4-nitro-1-cyclohexen-5-yl]-D-*galacto*-pentitol **1**[11] (1.00 g, 1.94 mmol) in methanol (15 mL) was added dropwise a solution of 2 M sodium methoxide in methanol (1 mL, 2.00 mmol). In a few moments, there was apparition of a white crystalline product and the reaction mixture was cooled at 0°C for 6 h. Then, the solid was filtered, washed on the filter with cold methanol and recrystallized from methanol/water; yield: 0.62 g (98%); mp 228–230°C; R_f 0.70 (3:1 AcOEt/EtOH); $[\alpha]_D$=+5.4° (*c* 0.55, H_2O); ν_{max} (KBr) 3090, 2870, 1585, 1420, 1300, 1130, 1070, 1040, 1020 cm^{-1}; ^1H NMR (D_2O) δ 4.01 (t, 1H, $J_{3',4'}\sim J_{4',5'}$=6.3 Hz, $J_{4',5''}$=1.0 Hz, H-4′), 3.90 (d, 1H, $J_{1',5}$=9.7 Hz, H-1′), 3.80–3.70 (m, 2H, H-2′, H-3′), 3.73 (dd, 1H, H-5′), 3.69 (dd, $J_{5',5''}$=9.5 Hz, H-5″), 3.61 (dd, 1H, $J_{5,6a}$=5.2 Hz, $J_{5,6b}\sim$1 Hz, H-5), 3.18 (d, 1H, H-3a), 2.91 (d, 1H $J_{3a,3b}$=22.2 Hz, H-3b), 2.39 (br d, 1H, H-6a), 2.07 (d, 1H, $J_{6a,6b}$=17.2 Hz, H-6b), 1.75 (s, 3H, Me), 1.72 (s, 3H, Me); ^{13}C NMR (D_2O) δ 129.3 (C-4), 124.4, 123.8 (C-1, C-2), 72.3, 71.1, 70.2 (C-1′, C-2′, C-3′, C-4′), 64.1 (C-5′), 38.3 (C-5), 33.1, 32.5 (C-3, C-6), 19.1, 18.4 (Me-1, Me-2). Anal. calcd for $C_{13}H_{22}NO_7Na\cdot H_2O$: C, 45.21; H, 7.00; N, 4.05. Found: C, 45.43; H, 6.89; N, 4.01.

3.1.2. Sodium salt of 1-*C*-[(4*S*,5*S*)-1-methyl-4-nitro-1-cyclohexen-5-yl]-D-*galacto*-pentitol (11). Following the same procedure described above for the preparation of **10**, treatment of a solution of **2**[10] (0.38 g, 0.76 mmol) in methanol (6 mL) with 2 M sodium methoxide in methanol (0.8 mL, 0.40 mmol) led to the title compound as a white solid (0.24 g, quantitative): mp 166–168°C (from methanol/water); R_f 0.68 (3:1 AcOEt/EtOH); $[\alpha]_D$=+24.7° (*c* 0.90, H_2O); ν_{max} (KBr) 3300, 2950, 1580, 1440, 1275, 1140, 1015, 1080 cm^{-1}; ^1H NMR (D_2O) δ 5.51 (br s, 1H, H-2), 4.01 (t, 1H, $J_{3',4'}\sim J_{4',5'}$=6.3 Hz, $J_{4'',5''}$=1.0 Hz, H-4′), 3.93 (d, 1H, $J_{1',5}$=10.0 Hz, H-1′), 3.80–3.65 (m, 4H, H-2′, H-3′, H-5′, H-5″), 3.66 (dd, 1H, $J_{5,6a}$=5.8 Hz, $J_{5,6b}\sim$1 Hz, H-5), 3.22 (dd, 1H, H-3a), 2.94 (d, 1H, $J_{3a,3b}$=22.7 Hz, H-3b), 2.37 (br d, 1H, H-6a), 2.07 (d, 1H, $J_{6a,6b}$=17.4 Hz, H-6b), 1.74 (s, 3H, Me-1); ^{13}C NMR (D_2O) δ 130.3 (C-4), 125.5 (C-1), 115.2 (C-2), 69.3, 68.3, 67.4 (C-1′, C-2′, C-3′, C-4′), 61.2 (C-5′), 35.2 (C-5), 28.1, 24.7 (C-3, C-6), 20.5 (Me-1). Anal. calcd for $C_{12}H_{20}NO_7Na$: C, 46.00; H, 6.43; N, 4.47. Found: C, 45.77; H, 6.64; N, 4.22.

3.1.3. Sodium salt of 1-*C*-[(4*R*,5*R*)-1,2-dimethyl-4-nitro-1-cyclohexen-5-yl]-D-*manno*-pentitol (12). Following the same procedure described above for the preparation of **10**, compound **5**[11] (1.00 g, 1.94 mmol) led to the title compound as a white solid (0.58 g, 91%): mp 173–175°C (from methanol/water); R_f 0.70 (3:1 AcOEt/EtOH); $[\alpha]_D$=+5.4° (*c* 0.84, H_2O); ν_{max} (KBr) 3400, 2900, 1585, 1430, 1150, 1120, 1010 cm^{-1}; ^1H NMR (D_2O) δ 3.93 (d, 1H, $J_{1',5}$=3.1 Hz, $J_{1',2'}$=9.0 Hz, H-1′), 3.88 (dd, 1H, $J_{4',5'}$=1.9 Hz, $J_{5',5''}$=11.8 Hz, H-5′), 3.79 (m, 2H, H-3′, H-4′), 3.66 (dd, 1H, $J_{4',5''}$=5.1 Hz, H-5″), 3.56 (m, 2H, H-2′, H-5), 3.15 (d, 1H, H-3a), 3.00 (d, 1H, $J_{3a,3b}$=22.5 Hz, H-3b), 2.59 (dd, 1H, $J_{5,6a}$=5.5 Hz, H-6a), 2.15 (d, 1H, $J_{5,6b}\sim$1 Hz, $J_{6a,6b}$= 17.6 Hz, H-6b), 1.71 (s, 3H, Me), 1.69 (s, 3H, Me); ^{13}C NMR (D_2O) δ 127.4 (C-4), 124.4, 122.4 (C-1, C-2), 76.3 (C-1′), 71.2, 70.3, 69.2 (C-2′, C-3′, C-4′), 63.3 (C-5′), 36.1 (C-5), 34.2, 33.7 (C-3, C-6), 18.2, 17.9 (Me-1, Me-2). Anal. calcd for $C_{13}H_{22}NO_7Na$: C, 47.70; H, 6.77; N, 4.28. Found: C, 47.85; H, 6.70; N, 4.04.

3.1.4. 1-*C*-[(5*S*)-1,2-Dimethyl-4-*aci*nitro-1-cyclohexen-5-yl]-D-*galacto*-pentitol (13). To a solution of compound **10** (0.12 g, 0.35 mmol) in water (1 mL) was added dropwise a

3:1 mixture of H_2SO_4/H_2O at −10°C until the apparition of a crystalline product. This solid was rapidly filtered and dried (0.05 g, 45%), showing mp 99–101°C (decomp.); R_f 0.48 (AcOEt); $[\alpha]_{546}$ varied from −20° to 0° in 90 min (*c* 0.37, H_2O); ν_{max} (KBr) 3400, 3300, 3220, 3150, 2960, 2920, 2850, 1655, 1100, 1040 cm^{-1}; ^1H NMR (freshly prepared solution in DMSO-d_6) δ 6.33 (br s, 1H, N–O*H*), 4.70–4.10 (m, 5H, 5OH), 3.75–3.20 (m, 7H, H-5, H-1′, H-2′, H-3′, H-4′, H-5′, H-5″), 2.94 (d, 1H, $J_{3a,3b}$=22.5 Hz, H-3a), 2.75 (d, 1H, H-3b), 2.07 (br d, 1H, H-6a), 1.89 (d, 1H, $J_{6a,6b}$=8.2 Hz, H-6b), 1.62 (s, 3H, Me), 1.60 (s, 3H, Me). A progressive change in this spectrum could be observed; thus, after 90 min at room temperature, those signals corresponding to previously described[11] *trans*- and *cis*-5-glyco-4-nitro-1-cyclohexenes (**3** and **7**, respectively) were preponderant.

3.1.5. (3*S*,3a*S*)-3-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*lyxo*-tetritol-1-yl)-5,6-dimethyl-(3,3a,4,7)-tetrahydrobenzisoxazoline *N*-oxide (14). A suspension of the sodium salt of 1-*C*-[(4*S*,5*S*)-1,2-dimethyl-4-nitro-1-cyclohexen-5-yl]-D-*galacto*-pentitol **10** (0.50 g, 1.53 mmol) in pyridine (5 mL) and acetic anhydride (3 mL) was stirred at room temperature until dissolution (ca. 1.5 h). Then, the mixture was poured onto ice cold water (200 mL), yielding the title compound (0.53 g, 81%) as a white solid which was filtered and washed on the filter with cold water: mp 152–154°C (from 96% EtOH); R_f 0.40 (1:1 hexane/AcOEt); $[\alpha]_D$=+88.0° (*c* 0.54, $CHCl_3$); ν_{max} (KBr) 2980, 2960, 2920, 2860, 1745, 1670, 1660, 1365, 1200, 1055, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.51 (dd, 1H, $J_{1',2'}$= 9.2 Hz, $J_{2',3'}$=2.0 Hz, H-2′), 5.34 (ddd, 1H, H-3′), 5.25 (dd, 1H, H-1′), 4.36 (dd, 1H, $J_{3,3a}$=7.7 Hz, $J_{3,1'}$=2.3 Hz, H-3), 4.25 (dd, 1H, $J_{3',4'}$=5.6 Hz, $J_{4',4''}$=11.6 Hz, H-4′), 3.91 (dd, 1H, $J_{3',4''}$=7.1 Hz, H-4″), 3.17 (m, 1H, H-3a), 2.97 (br d, 1H, $J_{7a,7b}$=21.4 Hz, H-7a), 2.86 (br d, 1H, H-7b), 2.35 (dd, 1H, $J_{3a,4a}$=7.1 Hz, $J_{4a,4b}$=15.8 Hz, H-4a), 2.17 (m, 1H, $J_{3a,4b}$=7.1 Hz, H-4b), 2.16 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.71 (s, 3H, Me), 1.67 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 170.4, 170.3, 170.1, 169.2 (O–*C*O–CH_3), 124.4, 122.7 (C-5, C-6), 115.3 (C-7a), 79.0 (C-3), 68.5, 68.1 (C-1′, C-2′, C-3′), 61.8 (C-4′), 41.8 (C-3a), 36.5 (C-4), 29.4 (C-7), 20.7, 20.6 (O–CO–*C*H_3), 19.3, 18.8 (Me-5, Me-6). Anal. calcd for $C_{21}H_{29}NO_{10}$: C, 55.38; H, 6.42; N, 3.07. Found: C, 55.03; H, 6.40; N, 3.04.

3.1.6. (3*S*,3a*S*)-3-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*lyxo*-tetritol-1-yl)-5-methyl-(3,3a,4,7)-tetrahydrobenzisoxazoline-*N*-oxide (15). Following the same procedure described above for the preparation of tetrahydrobenzisoxazoline *N*-oxide **14**, compound **11** (0.14 g, 0.44 mmol) led to the title compound as a white solid (0.11 g, 57%): mp 143–145°C (from 96% EtOH); R_f 0.35 (1:1 hexane/AcOEt); $[\alpha]_D$=+110.9° (*c* 0.65, $CHCl_3$); ν_{max} (KBr) 2960, 2920, 2860, 1745, 1670, 1660, 1365, 1240, 1200, 1060, 1040, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.52 (dd, 1H, $J_{1',2'}$= 9.3 Hz, $J_{2',3'}$=2.1 Hz, H-2′), 5.42 (br s, 1H, H-6), 5.34 (ddd, 1H, H-3′), 5.25 (dd, 1H, H-1′), 4.37 (dd, 1H, $J_{3,3a}$= 8.2 Hz, $J_{3,1'}$=2.0 Hz, H-3), 4.25 (dd, 1H, $J_{3',4'}$=5.5 Hz, $J_{4',4''}$=11.5 Hz, H-4′), 3.92 (dd, 1H, $J_{3',4''}$=7.1 Hz, H-4″), 3.23 (m, 1H, $J_{3a,4b}$=7.0 Hz, H-3a), 3.04 (br d, 1H, $J_{7a,7b}$= 21.9 Hz, H-7a), 2.93 (br d, 1H, H-7b), 2.34 (dd, 1H, $J_{3a,4a}$=7.0 Hz, $J_{4a,4b}$=16.2 Hz, H-4a), 2.18 (m, 1H, H-4b), 2.16 (s, 3H, OAc), 2.12 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.73 (s, 3H, Me-5); ^{13}C NMR ($CDCl_3$) δ 170.4, 170.3, 170.1, 169.2 (O–*C*O–CH_3), 132.7 (C-5), 117.2 (C-6), 114.5 (C-7a), 79.2 (C-3), 68.5, 68.1, 67.9 (C-1′, C-2′, C-3′), 61.8 (C-4′), 41.8 (C-3a), 34.8 (C-4), 23.9 (C-7), 23.4 (Me-5), 20.7, 20.6 (O–CO–*C*H_3). Anal. calcd for $C_{20}H_{27}NO_{10}$: C, 54.41; H, 6.16; N, 3.17. Found: C, 54.32; H, 6.15; N, 3.20.

3.1.7. (3*R*,3a*R*)-3-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)-5,6-dimethyl-(3,3a,4,7)-tetrahydrobenzisoxazoline *N*-oxide (16). Following the same procedure described above for the preparation of **14**, compound **12** (0.12 g, 0.37 mmol) led to the title compound as a white solid (0.09 g, 54%): mp 146–148°C (from 96% EtOH); R_f 0.40 (1:1 hexane/AcOEt); $[\alpha]_D$=−119.2° (*c* 0.49, $CHCl_3$); ν_{max} (KBr) 2990, 2920, 2860, 1740, 1660, 1365, 1250, 1210, 1060, 1040, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.51 (dd, 1H, $J_{1',2'}$=2.4 Hz, $J_{2',3'}$=8.7 Hz, H-2′), 5.39 (dd, 1H, H-1′), 5.09 (ddd, 1H, H-3′), 4.29 (t, 1H, $J_{3,3a}\sim J_{3,1'}$=7.6 Hz, H-3), 4.25 (dd, 1H, $J_{3',4'}$=2.8 Hz, H-4′), 4.09 (dd, 1H, $J_{3',4''}$=5.0 Hz, $J_{4',4''}$=12.5 Hz, H-4″), 3.32 (m, 1H, $J_{3a,4a}\sim J_{3a,4b}$=7.0 Hz, H-3a), 2.98 (br d, 1H, $J_{7a,7b}$=21.5 Hz, H-7a), 2.90 (br d, 1H, H-7b), 2.25 (m, 2H, H-4a, H-4b), 2.14 (s, 3H, OAc), 2.13 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.71 (s, 3H, Me), 1.66 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 170.7, 170.0, 169.2 (O–*C*O–CH_3), 124.3, 122.7 (C-5, C-6), 115.4 (C-7a), 78.5 (C-3), 70.0, 68.1 (C-1′, C-2′, C-3′), 61.7 (C-4′), 43.0 (C-3a), 37.3 (C-4), 29.4 (C-7), 20.8, 20.7 (O–CO–*C*H_3), 19.3, 18.8 (Me-5, Me-6). Anal. calcd for $C_{21}H_{29}NO_{10}$: C, 55.38; H, 6.42; N, 3.07. Found: C, 55.42; H, 6.42; N, 3.07.

3.1.8. 7-En-(4*S*)-4-hydroxy-(3*R*)-3-[(1′*S*,2′*R*)-1′,2′,3′-trihydroxypropyl]-1,8-dimethyl-2-oxabicyclo[3.3.1]nonan-6-one oxime (19). To a solution of compound **14** (1.00 g, 2.19 mmol) in methanol (12.5 mL) was added dropwise 2 M sodium methoxide in methanol (0.8 mL). The reaction mixture was stirred for 1.5 h at room temperature and the solvent evaporated, yielding the title compound as a white solid that was recrystallized from methanol (0.57 g, 90%): mp 137–139°C; R_f 0.50 (5:1 AcOEt/EtOH); $[\alpha]_D$=+158.9° (*c* 0.48, H_2O); ν_{max} (KBr) 3400, 3300, 2970, 2940, 2900, 2860, 1630, 1340, 1030 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.85 (s, 1H, =N–O*H*), 6.07 (br s, 1H, H-7), 4.64 (d, 1H, $J_{4,OH}$= 4.9 Hz, OH-4), 4.35 (t, 1H, $J_{3',OH}$=4.8 Hz, OH-3′), 3.99 (d, 1H, $J_{1',OH}$=7.6 Hz, OH-1′), 3.83 (d, 1H, $J_{2',OH}$=7.0 Hz, OH-2′), 3.65 (m, 1H, $J_{3,1'}$=8.1 Hz, $J_{1',2'}$=1.5 Hz, H-1′), 3.61 (m, 1H, $J_{4,5}$=2.3 Hz, $J_{3,4}$=1.5 Hz, H-4), 3.55 (m, 1H, H-2′), 3.45–3.25 (m, 4H, H-3, H-3′, H-3″, H-5), 2.05 (dd, 1H, $J_{9syn,9anti}$=12.5 Hz, $J_{9syn,5}$=2.4 Hz, H-9*syn*), 1.36 (dd, 1H, $J_{9anti,5}$=3.3 Hz, H-9*anti*), 1.73 (s, 3H, Me-8), 1.20 (s, 3H, Me-1); ^{13}C NMR (DMSO-d_6) δ 155.5 (C-6), 139.8 (C-8), 124.7 (C-7), 70.7, 70.6, 69.6, 67.6 (C-1, C-4, C-1′, C-2′), 63.0 (C-3′), 62.2 (C-3), 34.1 (C-5), 31.7 (C-9), 25.0 (Me-1), 18.1 (Me-8). Anal. calcd for $C_{13}H_{21}NO_6$: C, 54.34; H, 7.37; N, 4.87. Found: C, 53.88; H, 7.49; N, 4.72. CI MS *m/z* (rel. int.): 288 (MH^+, 44), 272 (M−CH_3, 20), 270 (M+H−H_2O, 5), 253 (M−2OH, 3), 238 (M−2OH−CH_3, 6), 167 (37), 150 (19), 137 (83), 120 (100). HRMS (CI) calcd for $C_{13}H_{21}NO_6$+H: 288.1447. Found $(M+H)^+$ 288.1439.

3.1.9. (4*S*)-4-*O*-Acetyl-(3*R*)-3-[(1′*S*,2′*R*)-1′,2′,3′-tri-*O*-acetylpropyl]-7-en-1,8-dimethyl-2-oxabicyclo[3.3.1]-nonan-6-one oxime acetate (20). A suspension of compound **19** (0.10 g, 0.35 mmol) in pyridine (1 mL) and acetic anhydride (0.5 mL) was stirred at room temperature until dissolution (ca. 2 h). Then, the mixture was poured onto ice cold water (100 mL), extracted with methylene dichloride (3×25 mL) and washed successively with 1 M hydrochloric acid (2×25 mL), saturated aqueous sodium hydrogencarbonate (2×25 mL) and water (2×25 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated, yielding the title compound as a white solid residue which was recrystallized from 96% ethanol (0.14 g, 78%): mp 142–144°C; R_f 0.43 (1:1 hexane/AcOEt); $[\alpha]_D$=+33.9° (*c* 0.61, $CHCl_3$); ν_{max} (KBr) 3020, 2970, 2920, 2845, 1740, 1370, 1230, 1200, 1030, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.40 (br s, 1H, H-7), 5.49 (ddd, 1H, $J_{2',3'}$=6.3 Hz, $J_{2',3''}$=1.0 Hz, H-2′), 5.31 (dd, 1H, $J_{3,1'}$=9.6 Hz, $J_{1',2'}$=1.8 Hz, H-1′), 4.73 (t, 1H, $J_{4,5}\sim J_{3,4}$=2.5 Hz, H-4), 4.25 (dd, 1H, $J_{2',3'}$=4.8 Hz, $J_{3',3''}$=11.7 Hz, H-3′), 3.86 (dd, 1H, $J_{2',3''}$=7.5 Hz, H-3″), 3.68 (dd, 1H, H-3), 3.66 (m, 1H, H-5), 2.23 (s, 3H, =N–O*Ac*), 2.10 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.02 (m, 1H, H-9*syn*), 2.00 (s, 3H, OAc), 1.82 (d, 3H, $J_{Me\text{-}8,H\text{-}7}$=1.2 Hz, Me-8), 1.66 (dd, 1H, $J_{9anti,9syn}$=13.3 Hz, $J_{9anti,5}$=3.2 Hz, H-9*anti*), 1.37 (s, 3H, Me-1); ^{13}C NMR ($CDCl_3$) δ 170.4, 170.1, 169.7, 168.3 (O–*C*O–CH_3, =N–O–*C*O–CH_3), 161.3 (C-6), 147.2 (C-8), 123.4 (C-7), 71.6 (C-1), 68.7, 68.2, 67.3 (C-4, C-1′, C-2′), 63.8 (C-3), 62.5 (C-3′), 33.4 (C-5), 32.0 (C-9), 24.5 (Me-1), 21.0, 20.6, 20.5, 19.3 (O–CO–*C*H_3, =N–O–CO–*C*H_3), 18.7 (Me-8). Anal. calcd for $C_{23}H_{31}NO_{11}\cdot 1/2H_2O$: C, 54.54; H, 6.36; N, 2.76. Found: C, 54.26; H, 6.12; N, 2.55.

3.1.10. (3*R*,3a*R*)-3-(D-*arabino*-Tetritol-1-yl)-5,6-dimethyl-(3,3a,4,7)-tetrahydrobenzisoxazoline *N*-oxide (18). Following the same procedure described above for the preparation of **19**, treatment of a solution of **16** (0.30 g, 0.66 mmol) in methanol (5 mL) with 2 M methanolic sodium methoxide led to the title compound as a white solid (0.19 g, quantitative): mp 218–220°C (from methanol/water); R_f 0.50 (2:1 AcOEt/EtOH); $[\alpha]_D$=−98.8° (*c* 0.52, H_2O); ν_{max} (KBr) 3300, 2920, 2880, 1670, 1400, 1240, 1080, 1060, 1020, 1005 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.27 (t, 1H, $J_{3,3a}\sim J_{3,1'}$=6.6 Hz, H-3), 3.83 (d, 1H, $J_{1',2'}$=1.0 Hz, H-1′), 3.60 (dd, 1H, $J_{3',4'}$=2.7 Hz, $J_{4',4''}$=11.1 Hz, H-4′), 3.47 (m, 1H, H-3′), 3.43 (m, 1H, H-3a), 3.41 (dd, 1H, $J_{3',4''}$=6.5 Hz, H-4″), 3.28 (d, 1H, $J_{2',3'}$=8.7 Hz, H-2′), 2.88 (br d, 1H, H-7a), 2.74 (br d, 1H, $J_{7a,7b}$=21.3 Hz, H-7b), 2.34 (dd, 1H, $J_{3a,4a}$=7.2 Hz, $J_{4a,4b}$=16.4 Hz, H-4a), 2.15 (dd, 1H, $J_{3a,4b}$=11.1 Hz, H-4b), 1.62 (s, 3H, Me), 1.58 (s, 3H, Me); ^{13}C NMR (DMSO-d_6) δ 126.0 (C-7a), 122.7, 120.3 (C-5, C-6), 82.8 (C-3), 71.4, 71.0, 70.1 (C-1′, C-2′, C-3′), 64.0 (C-4′), 43.2 (C-3a), 37.9, 29.6 (C-7, C-4), 19.9, 19.3 (Me-5, Me-6). Anal. calcd for $C_{13}H_{20}NO_6$: C, 54.54; H, 7.04; N, 4.89. Found: C, 54.78; H, 7.11; N, 5.05.

3.1.11. (3*S*,3a*S*)-3-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*lyxo*-tetritol-1-yl)-5,6-dimethyl-(3,3a,4,7)-tetrahydrobenzisoxazoline (21). To a solution of (3*S*,3a*S*)-3-(1′,2′,3′,4′-tetra-*O*-acetyl-D-*lyxo*-tetritol-1-yl)-5,6-dimethyl-(3,3a,4,7)-tetrahydrobenzisoxazoline *N*-oxide **14** (0.24 g, 0.53 mmol) in 1,4-dioxane (3 mL) was added trimethyl phosphite (0.08 mL, 0.66 mmol). After the reaction mixture had been refluxed for 14 h, its ^1H NMR spectrum showed about 90% conversion of the starting *N*-oxide into the title compound. Then, the crude mixture was evaporated and the resulting oil was subjected to p.TLC (1:3 hexane/AcOEt), affording a pure analytical sample of compound **21** (0.05 g): oil; R_f 0.60 (1:1 hexane/AcOEt);$[\alpha]_D$=+102.5° (*c* 0.48, $CHCl_3$); ν_{max} (film) 2900, 2840, 1740, 1640, 1360, 1200, 1040, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.56 (dd, 1H, $J_{1',2'}$=9.2 Hz, $J_{2',3'}$=1.8 Hz, H-2′), 5.35 (m, 1H, H-3′), 5.22 (dd, 1H, $J_{3,1'}$=2.5 Hz, H-1′), 4.26 (dd, 1H, $J_{3',4'}$=5.3 Hz, H-4′), 4.23 (dd, 1H, H-3), 3.92 (dd, 1H, $J_{4',4''}$=11.5 Hz, $J_{3',4''}$=7.2 Hz, H-4″), 3.07 (dd, 1H, $J_{3,3a}$=17.8 Hz, $J_{3a,4a}$=7.9 Hz, H-3a), 2.97 (br d, 1H, H-7a), 2.85 (br d, 1H, $J_{7a,7b}$=19.6 Hz, H-7b), 2.38 (dd, 1H, $J_{4a,4b}$=16.0 Hz, H-4a), 2.19 (m, 1H, H-4b), 2.15 (s, 3H, OAc), 2.07 (s, 6H, 2×OAc), 2.03 (s, 3H, OAc), 1.69 (s, 3H, Me), 1.64 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 170.4, 170.2, 169.3 (O–*C*O–CH_3), 159.1 (C-7a), 124.5, 123.9 (C-5, C-6), 82.4 (C-3), 69.1, 68.8, 68.2 (C-1′, C-2′, C-3′), 61.9 (C-4′), 47.2 (C-3a), 37.6 (C-4), 29.6 (C-7), 20.7 (O–CO–*C*H_3), 18.9 (Me-5, Me-6). CI MS *m*/*z* (rel. int.): 440 (MH^+, 6), 398 (M+H−C_2H_2O, 8), 380 (M−OAc, 16), 338 (M−C_2H_2O–OAc, 13), 320 (M−OAc–HOAc, 4), 259 (M−3×HOAc, 8), 192 (21), 150 (M−$C_{12}H_{17}O_8$, 100), 122 (18). HRMS (CI) calcd for $C_{21}H_{29}NO_9$+H: 440.1920. Found $(M+H)^+$ 440.1948.

3.1.12. (3*R*,3a*R*)-3-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)-5,6-dimethyl-(3,3a,4,7)-tetrahydrobenzisoxazoline (22). Following the same procedure described above for the preparation of **21**, compound **16** (0.24 g, 0.53 mmol) afforded 88% ^1H NMR yield of the title compound. A pure analytical sample of **22** (0.03 g) was obtained by p.TLC (1:3 hexane/AcOEt): oil; R_f 0.60 (1:1 hexane/AcOEt); $[\alpha]_D$=−125.5° (*c* 0.51, $CHCl_3$); ν_{max} (film) 3000, 2900, 2850, 1745, 1660, 1430, 1360, 1240, 1050, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.55 (dd, 1H, $J_{1',2'}$=2.8 Hz, $J_{2',3'}$=8.5 Hz, H-2′), 5.30 (dd, 1H, H-1′), 5.11 (m, 1H, H-3′), 4.26 (dd, 1H, $J_{3',4'}$=2.8 Hz, $J_{4',4''}$=12.4 Hz, H-4′), 4.20 (t, 1H, $J_{3,3a}\sim J_{3,1'}$=7.3 Hz, H-3), 4.10 (dd, 1H, $J_{3',4''}$=5.5 Hz, H-4″), 3.21 (m, 1H, $J_{3a,4a}\sim J_{3a,4b}$=7.6 Hz, H-3a), 2.95 (br d, 1H, $J_{7a,7b}$=20.8 Hz, H-7a), 2.93 (br d, 1H, H-7b), 2.25 (m, 2H, H-4a, H-4b), 2.17 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc), 1.69 (s, 3H, Me), 1.64 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 170.6, 170.1, 169.9, 169.3 (O–*C*O–CH_3), 159.3 (C-7a), 124.5, 124.0 (C-5, C-6), 82.4 (C-3), 70.5, 68.7, 68.2 (C-1′, C-2′, C-3′), 61.8 (C-4′), 58.5 (C-3a), 38.2 (C-4), 29.9 (C-7), 20.8, 20.7 (O–CO–*C*H_3), 19.0, 18.9 (Me-5, Me-6). CI MS *m*/*z* (rel. int.): 440 (MH^+, 18), 398 (M+H−C_2H_2O, 8), 380 (M−OAc, 17), 338 (M−C_2H_2O–OAc, 8), 320 (M−OAc–HOAc, 8), 259 (M−3×HOAc, 8), 192 (23), 150 (M−$C_{12}H_{17}O_8$, 100), 122 (24). HRMS (CI) calcd for $C_{21}H_{29}NO_9$+H: 440.1920. Found $(M+H)^+$ 440.1909.

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    Moreover, a similar D_2O-exchangeable signal was encountered at 7.68 ppm in the ^1H NMR spectrum of a DMSO-d_6 freshly prepared solution of nitronate **12**.
18. In a similar experiment with 0.1 M DCl as the solvent, the solid we obtained was the corresponding *cis*-4-nitro-5-(D-*galacto*-pentitol-1-yl)-1-cyclohexene deuterated at C-4. This compound, as well as its penta-*O*-acetyl derivative, showed ^1H NMR spectra in which the signal of H-4 was absent.
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