Carbohydrate Research 346 (2011) 715–721

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Preparation of D-galactofuranosyl nitromethanes: a revision and a new approach

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ARTICLE INFO

Article history:
Received 11 March 2009
Received in revised form 29 January 2011
Accepted 4 February 2011
Available online 1 March 2011

Keywords:
Anhydronitroalditol
Glycosyl nitromethane
1-Deoxy-2-*O*-methyl-1-nitroalditol beta-elimination
1-Deoxy-1-nitrohept-1-enitol
Tautomerization
Aldose mutarotation

ABSTRACT

Sodium methoxide-promoted methanolysis of 7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol peracetate rapidly and nearly quantitatively accumulates 7-deoxy-6-*O*-methyl-7-nitro-L-*glycero*-L-*galacto*-heptitol. The prolonged treatment then provides 76% of D-galactofuranosyl nitromethanes and finally results in the equilibrium of 77% of β-D-galactopyranosyl nitromethane and 7–9% of three other tautomeric D-galactosyl nitromethanes. Thermal treatment of 7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol in boiling water peaks at a 58% content of D-galactofuranosyl nitromethanes and ends in a similar equilibrium mixture of four D-galactosyl tautomers. The relevant kinetic parameters of the latter transformation are determined by a curve fitting using the nonlinear least-squares Marquardt–Levenberg algorithm.

1. Introduction

Recently, efficient syntheses of *C*-glycofuranosyl compounds, especially those of the D-*galacto* and D-*arabino* configurations, have become more desirable.[1–3] The reason for this is that an extensive search for new, specific agents that are active against mycobacterial pathogens has emerged with the appearance of strains resistant to classical drugs.[4,5] Their cell wall polysaccharides, containing both D-galactofuranose and D-arabinofuranose, which are endemic to the pathogenic microorganisms,[6–8] have been identified as possible target structures for the development of new drugs for treating these diseases.[9–13] Easily available glycofuranosyl nitromethanes could be a convenient starting material in this respect as well.

As exemplified by the D-galactosyl species, Figure 1 shows the present state of synthetic methods for the preparation of all four tautomeric forms of glycosyl nitromethanes **7**–**10**, which are based on the thermally induced β-elimination of the C-2-OH group from the tautomeric, *aci*-nitro form of 1-deoxy-1-nitroalditols **4** and **5**.[14,15] However, these approaches have never been optimized for capturing the first, primarily formed five-membered ring glycofuranosyl nitromethanes **7** and **8** as the kinetic products of the cyclization of the intermediate 1,2-dideoxy-1-nitroald-1-enitol **6** and, until now, have been exploited mostly for preparation of the thermodynamically favored equatorial pyranosyl anomer **10**. Even the catalytically induced elimination of the pertinent C-2-OH group at ambient temperature in the L-fucose-derived 1-deoxy-1-nitroalditols has not been reported to provide the corresponding 6-deoxy-L-galactofuranosyl nitromethanes as primary cyclization products.[16] The prevalence of ribofuranosyl nitromethanes in the near-equilibrium reaction mixture,[17] due to obvious steric reasons in the ribopyranosyl ring, is the only known exception among the methods for the preparation of glycosyl nitromethanes. Using the desired D-*galacto* model, which also implicitly encloses the homomorphic L-*arabino* structure, we report a new, non-thermodynamic approach to the synthesis of glycofuranosyl nitromethanes. We also report a reinvestigation of the classic, thermally induced β-elimination of nitroalditol **2**, which, under the properly selected reaction conditions, can also provide preparatively interesting yields of D-galactofuranosyl nitromethanes **7** and **8**.

2. Results and discussion

2.1. Et_3N-catalyzed methanolysis of 1,2-dideoxy-1-nitro-D-*galacto*-hept-1-enitol peracetate (11)

The recently described acid-catalyzed methanolysis of 1,2-dideoxy-1-nitro-L-*arabino*-hexenitol peracetate, which does not stop at the stage of anticipated glycofuranosyl nitromethanes but proceeds further with the formation of the corresponding methanal dimethyl acetals,[3] has primarily excluded the acidic

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doi:10.1016/j.carres.2011.02.007

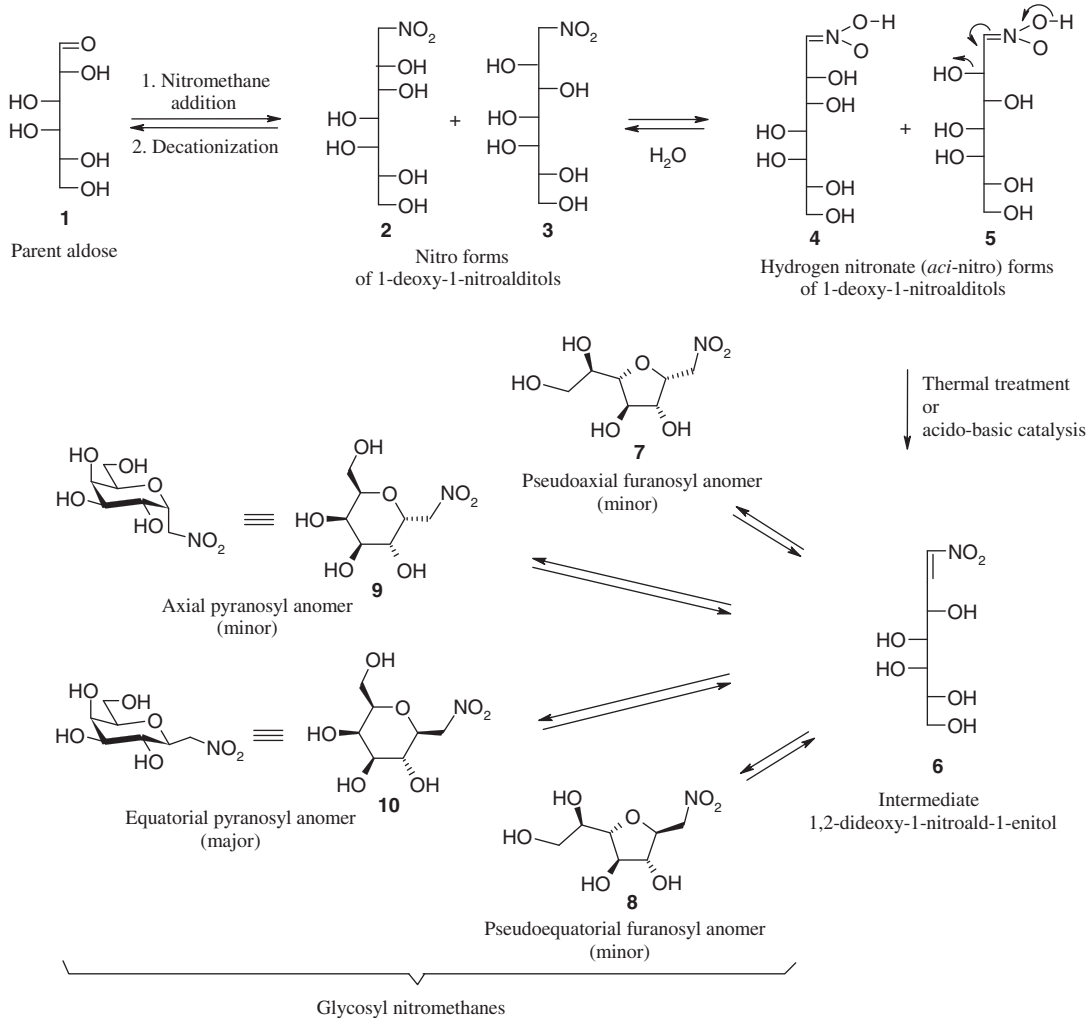
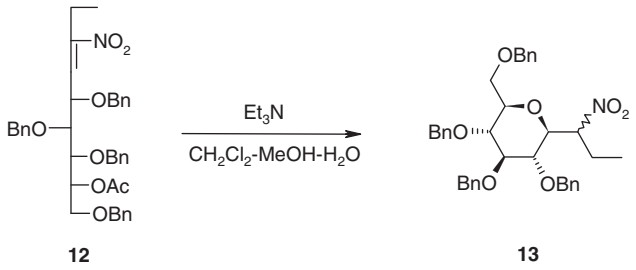


Figure 1. Schematic representation of present methods of preparing glycosyl nitromethanes, as exemplified with D-galactosyl species.

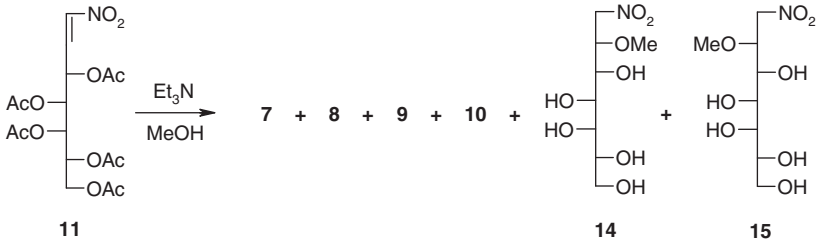


Scheme 1.

conditions for the de-O-acetylation of compound **11**. Due to the preferred Michael-like addition of the methoxide ion to 1,2-dideoxy-1-nitro-ald-1-enitol peracetates, which is a part of a well-established procedure for the preparation of 2-*O*-methyl aldoses by the Sowden procedure,[18] the classic Zemplén method does not seem applicable to the de-O-acetylation of nitroalkene **11**. Therefore, the basic reaction conditions reported by Martin et al.[19] for the de-O-acetylation of nitroalkene **12**, the product of which is cyclized into *C*-glycosyl nitro compound **13** (Scheme 1), were attempted for this purpose.

Despite the anticipation, a 3-day treatment of nitroalkene (**11**) with Et_3N as a base in a CH_2Cl_2–MeOH–H_2O solution afforded, in addition to the desired D-galactofuranosyl nitromethanes **7** and **8** and a small amount of D-galactopyranosyl nitromethanes **9** and **10**, unwanted 2-O-methylated acyclic nitroalditols **14** and **15**, characteristic of the ^{13}C NMR spectrum by their respective *O*-methyl group signals at δ 59.1 and δ 59.6, (Scheme 2; Table 1, entry *a*). With a prolonged 7-day treatment of the reaction mixture, methyl ethers **14** and **15** completely disappeared, and the content of the furanosyl derivatives **7** and **8** increased to 70% (Table 1, entry *b*). Practically the same course in the methanolysis was observed, and final yields of the individual D-galactosyl nitromethanes were obtained in a partly heterogeneous treatment of **11** with Et_3N in a starting MeOH–H_2O suspension (Table 1, entries *c* and *d*).

The disappearance of 1-deoxy-2-*O*-methyl-1-nitroheptitols **14** and **15**, which temporarily appeared in the reaction mixture and formed by the Et_3N-catalyzed addition of MeOH to the starting nitroalkene **11**, proceeds via Et_3N-catalyzed β-elimination of their 2-*O*-methyl group from the respective nitronates **16** and **17** under final formation of D-galactosyl nitromethanes **7**–**10** via the competitive ring-closure reactions of the intermediate nitroalkene **6** (Scheme 3). The newly observed elimination of the 2-*O*-methyl group from the 1-deoxy-2-*O*-methyl-1-nitroalditol derivatives is similar to the base-catalyzed elimination of the 3-O-substituent from 3-O-substituted aldoses, which is a generally well-known transformation in carbohydrate chemistry and is an another manifestation of certain similarities in the reactivity of the compounds containing nitro and carbonyl groups.



Scheme 2.

Table 1
Composition[a] of the reaction mixture obtained upon treatment of 1,2-dideoxy-1-nitro-D-*galacto*-hept-1-enitol peracetate (**11**) with Et_3N at rt

Entry	Reaction time (d)	Solvent mixture	Compound (%)					
			7	**8**	**9**	**10**	**14**	**15**
a	3	A	15	20	2	5	53	5
b	7	A	30	40	10	20	—	—
c	3	B	24	29	2	3	38	4
d	7	B	31	37	10	22	—	—

A, in a CH_2Cl_2–MeOH–H_2O; B, in a MeOH–H_2O mixture.
[a] Determined from the ^{13}C NMR spectra on the basis of the peak height measurements of similar mixtures of known composition.

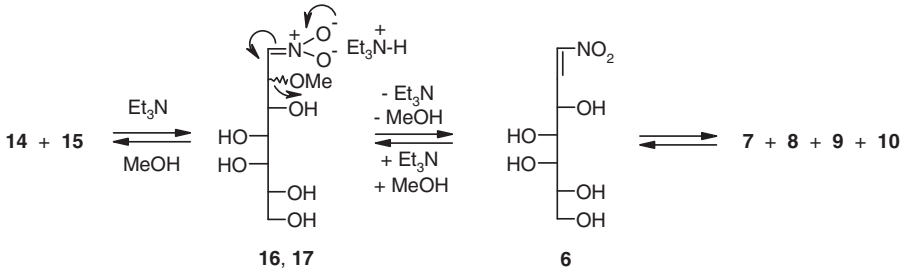
2.2. Sodium methoxide-catalyzed methanolysis of 7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol peracetate (18)

The finding from the above section substantiated a detailed analysis of the formation of D-galactofuranosyl nitromethanes **7** and **8** directly from 7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol peracetate (**18**, Scheme 4) under treatment with sodium methoxide. Compound **18** is easily available by crystallization from an aqueous solution of an epimeric 1-deoxy-1-nitroheptitol mixture obtained by the nitromethane synthesis from D-galactose, followed by per-O-acetylation of the crystalline epimer **2**.

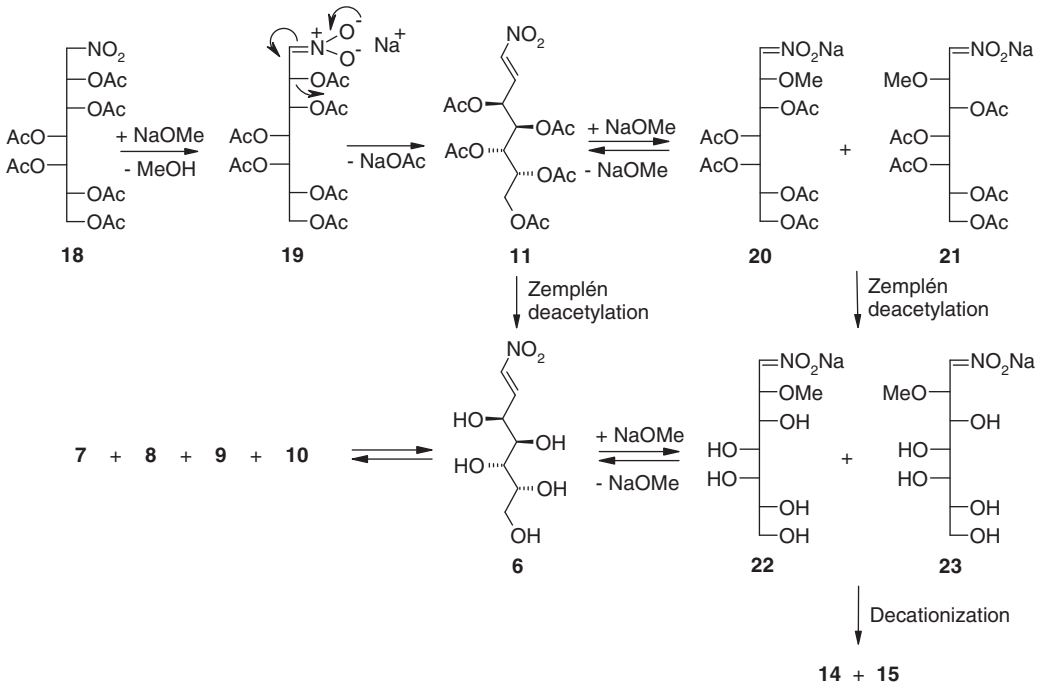
Thus, the treatment of nitroalkene **18** with 1 M NaOMe in MeOH at rt with a 3.2-mol excess of the base led to a fast dissolution of the starting compound. Remarkably, after 5 min, the reaction mixture contained compound **14** only (Table 2, Fig. 2). Soon after, the amount of compound **14** decreased due to the appearance of *O*-methyl epimer **15** and D-galactofuranosyl nitromethanes **7** and **8**. The highest contents, ~34% and ~42%, of the respective compounds **7** and **8** in the reaction mixture were reached within 30–36 h. After a 30-day treatment, the distribution of the respective D-galactosyl nitromethanes **7**–**10** in the reaction mixture became constant at a ratio of 7:7:9:77.

Two moles and a catalytic amount of NaOMe were necessary to effect the conversion of the per-O-acetylated compound **18** to the sodium nitronate forms of *O*-methyl derivatives **14** and **15**, which accompany and/or precede the formation of nitroalkene **6**, the direct intermediate of the anomeric and tautomeric D-galactosyl nitromethanes **7**–**10** (Scheme 4). The first mole of methoxide was used for the deprotonization of **18** to form nitronate **19**. The generation of the conjugate base **19** was a prerequisite to the following β-elimination of its 2-*O*-acetyl group (as sodium acetate) to provide the still per-O-acetylated nitroalkene **11**, which was immediately able to consume the second mole of sodium methoxide via a Michael-like addition, giving the sodium nitronate forms of the acetylated *O*-methyl ethers **20** and **21**. Apparently, all of these transformations, due to the relatively high acidity of the nitroalditol CH_2NO_2 group (pK_a = 8.8–9.2),[20] are substantially faster than the catalytic Zemplén de-O-acetylation of the other *O*-acetyl groups of **18**.

The first stages of the transformation of the starting compound **18** are supported by the diastereoisomeric excess (de) of >90% of epimer **14**, which later, after the de-O-acetylation of 3-*O*-acetyl group, significantly dropped. The bulkier 3-*O*-acetyl group of nitroalkene **11** stereoselectively differentiates the methoxide addition to its *Si* face more than the less bulky 3-OH group of nitroalkene **6** (i.e., from below the plane of the double bond of the respective nitroalkenes **11** and **6**, Scheme 4). Thus, in addition to the expected D-galactofuranosyl nitromethanes **7** and **8** and the appearance of D-galactopyranosyl nitromethanes **9** and **10**, methyl ethers **14** and **15**, in their respective sodium nitronate forms **22** and **23**, were temporarily accumulated in the reaction mixture as well. A probable reason for this rather unexpected behavior is that the methoxide ion, despite its intermolecular action, efficiently competes with a neutral, intramolecularly acting 5-OH group in their Michael-like additions to the double bond of nitroalkene **6** due to its strong anionic nucleophilicity. Thus, the addition interference of methoxide considerably delays the kinetically preferred five-membered ring closure of nitroalkene **6** to D-galactofuranosyl nitromethanes **7** and **8** so that their maximum content in the reaction mixture is reached only when considerable amounts of thermodynamically preferred D-galactopyranosyl nitromethanes **9** and **10** are already present. The observation of these complex transformations also explains only the moderate yields of 1-deoxy-2-*O*-methyl-1-nitroalditols in the original procedure developed by Sowden et al.,[18] as after the chosen 30-min treatment of the corresponding per-O-acetylated nitroalkene under otherwise comparable reaction



Scheme 3.



Scheme 4.

Table 2
Composition[a] of the reaction mixture obtained upon treatment of 7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol peracetate (**18**) with 3.2 equiv of NaOMe/MeOH at rt

Reaction time (h)	Compound (%)					
	7	**8**	**9**	**10**	**14**	**15**
1/12	—	—	—	—	>95	—
1/4	10	10	—	—	68	12
1/2	15	15	—	—	60	10
6	25	30	5	5	32	3
24	33	41	9	13	6	—
30	34	42	9	15	2	—
36	34	42	10	16	—	—
48	33	40	10	17	—	—
72	29	34	13	22	—	—
168	15	20	15	50	—	—
720	7	7	9	77	—	—

[a] Determined from the ^{13}C NMR spectra.

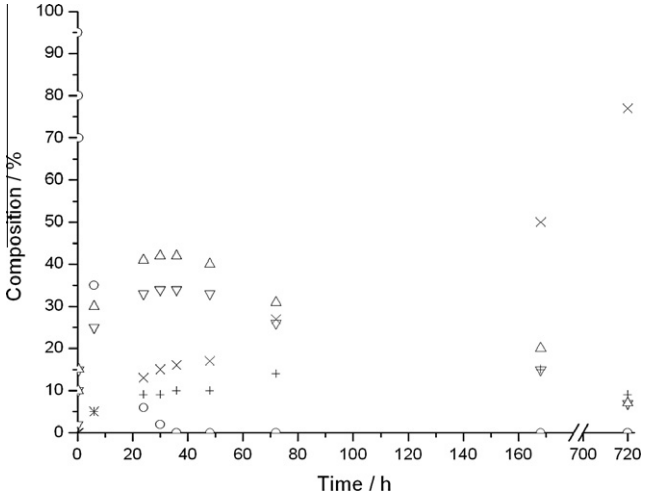


Figure 2. Time dependence of the composition of the reaction mixture obtained by the treatment of 7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol peracetate (**18**) with 1 M NaOMe in MeOH at rt under a 3.2-mol excess of the base, determined from the ^{13}C NMR spectra. ○, 7-deoxy-6-*O*-methyl-7-nitro-L-*glycero*-L-*galacto*-heptitol (**14**) and its epimer **15**; ▽, α-D-galactofuranosyl nitromethane (**7**); △, β-D-galactofuranosyl nitromethane (**8**); +, α-D-galactopyranosyl nitromethane (**9**); ×, β-D-galactopyranosyl nitromethane (**10**).

conditions, a part of the expected methoxy derivatives had to be eliminated and cyclized to the pertinent glycosyl nitromethanes.

For preparation of the individual D-galactofuranosyl nitromethanes **7** and **8**, the reaction was quenched with water and a cation exchange resin after 36 h of treatment. Following per-O-acetylation, chromatography indicated 15% and 38% yields of α-D-galactofuranosyl nitromethane peracetate (**24**) and β-D-galactofuranosyl nitromethane peracetate (**25**). Fractional crystallization of the decationized 36-h reaction mixture offered another possible value, giving 25% of the crystalline compound **7**.

2.3. Thermally induced β-elimination of 7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol (2)

A similar analysis was then performed for the classic, thermally induced β-elimination of acyclic 1-deoxy-1-nitroalditols, namely by heating compound **2** in water. In this case, due to a convenient resolution of selected, non-overlapping signals of all the components of the reaction mixture, a more exact ^{1}H NMR analysis was possible in addition to the cognate ^{13}C NMR measurements. The data obtained for the individual components did not mutually differ by more than 3%, which justified the relevance of the ^{13}C NMR results discussed in the previous section. The desired D-galactofuranosyl nitromethanes **7** and **8** were also preferentially formed in this case, although to a lower total extent (maximum ca. 58% in 8–10 h, Fig. 3) when starting **2** was still present at <10%. The thermodynamic equilibrium of all four D-galactosyl nitromethanes **7**–**10** in the corresponding ratio 4:4:3:89 was then reached after 4 days of reflux and was different from that obtained under basic conditions (7:7:9:77).

Assuming a steady-state approximation for the acyclic intermediate **6**, kinetic Scheme 5 can be analytically solved by providing

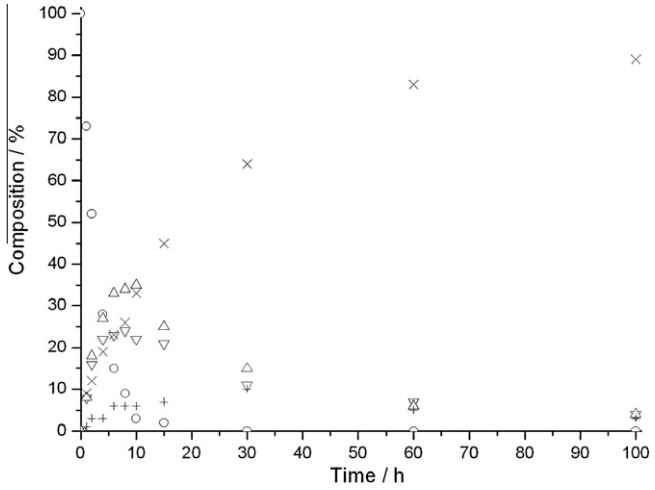


Figure 3. Time dependence of composition of reaction mixture obtained by refluxing 7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol (**2**, ○) in a 5% aqueous solution, as determined from ^{1}H NMR spectra; ▽, α-D-galactofuranosyl nitromethane (**7**); △, β-D-galactofuranosyl nitromethane (**8**); +, α-D-galactopyranosyl nitromethane (**9**); ×, β-D-galactopyranosyl nitromethane (**10**).

expressions for the time dependence of the composition (molar fraction) of furanosyl compounds $y(F)$ as a sum of **7** and **8** and that of pyranosyl compounds $y(P)$ as a sum of **9** and **10**:

$$y(F) = \frac{K_{FP}\cdot(1-k)\cdot k_{NA} - k\cdot k_{-F}}{K_{FP}\cdot(k\cdot k_{-F} - k_{NA}) + k\cdot k_{-F}}\left(e^{-k_{NA}\cdot t} - e^{-k_0\cdot t}\right) + \frac{1-e^{-k_0\cdot t}}{1+K_{FP}}$$

$$y(P) = 1 - e^{-k_{NA}\cdot t} - y(F)$$

$$k = \frac{k_P}{k_F + k_P};\quad k_0 = k\cdot k_{-F}\left(\frac{1}{K_{FP}} + 1\right),$$

where t is time, K_{FP} denotes the equilibrium constant of the conversion of furanosyl to pyranosyl compounds $K_{FP} = \sum[P]/\sum[F]$, k_{NA} is the rate constant of the decomposition of the starting nitroalditol **2**, k_F and k_P represent the rate constants of the furanosyl and pyranosyl compounds production from the acyclic intermediate, respectively, and k_{-F} and k_{-P} are the rate constants of the corresponding reverse reactions.

The above expressions nicely fit the experimental data (Fig. 4) using the measured values for $K_{FP} = 92/8 = 11.5$ and $k_{NA} = 0.32\ h^{-1}$ (both at 100 °C). The nonlinear least-squares Marquardt–Levenberg algorithm yields values for the parameters k and k_{-F}: $k = 0.23 \pm 0.02$ and $k_{-F} = 0.19 \pm 0.03\ h^{-1}$. These values can be used to estimate the ratio of the rate constants for furanosyl and pyranosyl productions from the acyclic intermediate, which produce $k_F/k_P = 1/k - 1 \approx 3.3$; they can also be used to estimate the reverse rate constant of pyranosyl formation, which produces $k_{-P} \approx 4.9 \times 10^{-3}\ h^{-1}$.

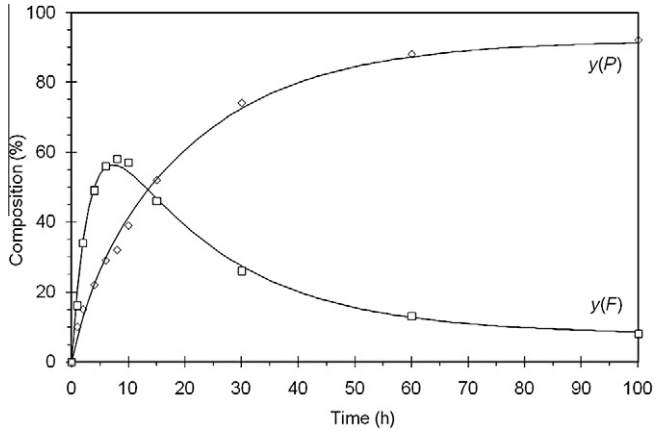
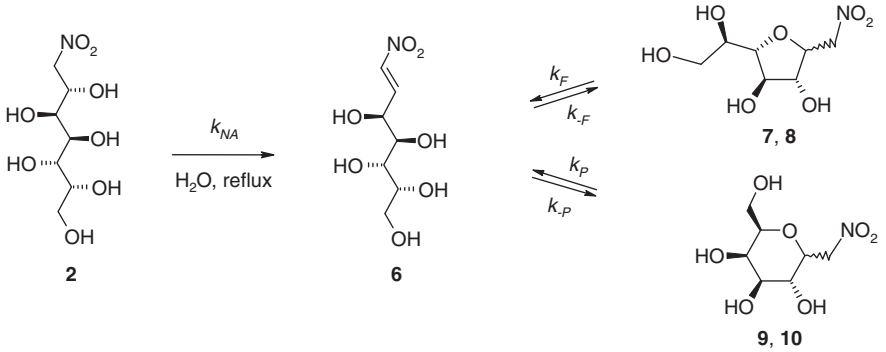


Figure 4. Graphical representation of the analytical solution of kinetic Scheme 5, expressed as the time dependence of the composition of the reaction mixture; $y(F)$ is the sum of furanosyl compounds **7** and **8**, and $y(P)$ is the sum of pyranosyl compounds **9** and **10**, both expressed as molar fractions.

Because the intermediate of the mutual interconversion of both anomeric glycopyranosyl nitromethanes and both anomeric glycofuranosyl nitromethanes, as demonstrated here by the D-galactosyl nitromethanes, is 1,2-dideoxy-1-nitroald-1-enitol of the general formula $HOCH_2–(CHOH)_n–CH{=}CHNO_2$, the ring-chain tautomeric behavior of glycosyl nitromethanes is analogous to the behavior of aldoses. Comparison of the nitroalkene structure with the general structure of acyclic aldoses $HOCH_2–(CHOH)_n–CH{=}O$ indicates that both structures, expressed by the generic formula $HOCH_2–(CHOH)_n–CH{=}X$, differ only in the functional moiety =X, which is =O for aldoses and $=CHNO_2$ for glycosyl nitromethanes. The distinct characteristics of these moieties, which after cyclization of the intermediates become the respective OH and CH_2NO_2 groups, are responsible for the diverse proportions of the anomeric structures in the respective equilibrium mixtures of aldoses and glycosyl nitromethanes. The distinctions are striking, mainly in pyranoid structures, where the anomeric and the other structural effects are quite manifest. Thus, the proportions of α- and β-pyranoid anomers for all aldoses are within the same order of magnitude. On the other hand, the percentages of the axial pyranosyl anomer in the equilibrium mixtures of glycosyl nitromethanes are very low in comparison with the pertinent concentrations of the equatorial pyranosyl anomers, which are generally well above 50%. Additionally, the proportions of furanoid anomers in the equilibrium mixtures of the most common glycosyl nitromethanes are usually comparable with the proportion of the axial pyranosyl anomer. Despite the differences in the composition of the final equilibrium mixtures of these two groups of compounds, the presented tautomerization of 1-nitro-1,2-dideoxy-D-*galacto*-hept-1-enitol and four



Scheme 5.

D-galactosyl nitromethanes is a valuable model for the complete mutarotation of aldoses and other reducing sugars, which still remains to be studied in fundamental carbohydrate chemistry.

3. Experimental

3.1. General methods and materials

Melting points were measured on a Kofler stage. Optical rotations were measured with a Perkin–Elmer 141 polarimeter at 20 °C. Microanalyses were performed using a Fisons EA-1108 instrument. NMR spectra were recorded at 295 K on a Bruker AVANCE DPX 300 spectrometer [300.13 MHz and internal sodium (trimethylsilyl)propionate-*2,2,3,3-d*$_4$, δ 0.00 for ^{1}H; 75.47 MHz and internal MeOH, δ 50.15 for ^{13}C]. Mass spectra were obtained with a Shimadzu-Kratos Analytical MALDI TOF IV instrument (matrix 2,5-dihydroxybenzoic acid). Paper chromatography (PC) was performed on a Whatman 1 using descending elution with the upper layer of the S_1 solvent mixture *n*-BuOH–EtOH–H_2O 5:1:4 (v/v) and visualization with alkaline silver nitrate. TLC was run on Merck 60 F254 silica gel precoated aluminum plates; the detection was effected by spraying the chromatograms with 10% ethanolic sulfuric acid and charring them on a hot plate. Flash chromatography was performed using Acros silica gel (37–75 μm) and the solvent mixture S_2, hexanes–EtOAc 5:2 (v/v).

3.2. Et_3N-catalyzed methanolysis of 1,2-dideoxy-1-nitro-D-*galacto*-hept-1-enitol peracetate (11)

(a) Compound **11** (0.1 g, 0.23 mmol) was dissolved in CH_2Cl_2 (1 mL), and an 8:2:1 (volume ratio) mixture of MeOH–H_2O–Et_3N (2 mL) was added. The solution was kept at rt for 3 and 7 days, respectively. Then the solvents were evaporated at diminished pressure and temperature below 40 °C and submitted to ^{13}C NMR evaluation of the reaction mixtures against similar mixtures of known composition (Table 1).

(b) A mixture of powdered compound **11** (0.1 g, 0.23 mmol) in an 8:2:1 mixture of MeOH–H_2O–Et_3N (3 mL) was stirred at rt for 3 and 7 days, respectively, and the final reaction solution was further processed as described above.

3.3. Sodium methoxide-catalyzed methanolysis of 7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol peracetate (18)

Compound **18** (0.1 g, 0.2 mmol) was stirred in a mixture of anhydrous MeOH (2.4 mL) and 1 M NaOMe in MeOH (0.64 mL) at rt. After the given time (Table 2), Amberlite IR 120, H^+ form (1 mL) was added to the mixture and filtered. The neutral filtrate was evaporated, and the composition of the reaction mixture was submitted to ^{13}C NMR analysis.

3.4. 7-Deoxy-6-*O*-methyl-7-nitro-L-*glycero*-L-*galacto*-heptitol (14)

Finely powdered compound **18** (1.05 g, 2.1 mmol) was suspended by stirring in anhydrous MeOH (26 mL), and 1 M NaOMe in MeOH (6.7 mL) was added. After 5 min of vigorous stirring at rt, Amberlite IR 120, H^+ form (10 mL) was added to the mixture and filtered. The resin was washed with water (3 × 10 mL). The combined neutral filtrates were concentrated on a rotary evaporator under reduced pressure, and the residue was crystallized from ethanol.

Yield 0.5 g (92%), mp 170–172 °C (EtOH), $[\alpha]_D^{20}$ −4.0 (*c* 1, H_2O), R_{Gal} 4.13 (S_1). ^{1}H NMR (D_2O) δ: 5.03 (dd, 1H, $J_{6,7}$ = 3.5 Hz, $J_{7,7'}$ = 13.2 Hz, H-7), 4.79 (dd, 1H, $J_{6,7'}$ = 7.1 Hz, H-7′), 4.12 (dt, 1H, $J_{5,6}$ = 7.4 Hz, H-6), 3.96–4.02 (m, 2H, H-2, H-5), 3.82 (d, 1H, $J_{3,4}$ = 9.6 Hz, H-4), 3.66–3.70 (m, 3H, H-1, H-1′, H-3), 3.49 (s, 3H, CH_3). ^{13}C NMR (D_2O) δ: 79.45 (C-6), 76.86 (C-7), 71.01 (C-2), 70.17 (C-3), 69.32 (C-4), 69.19 (C-5), 64.18 (C-1), 59.12 (OCH_3). MALDI-TOFMS: *m/z* 257.5 $[M+H]^+$. Anal. Calcd for $C_8H_{17}NO_8$: C, 37.65; H, 6.71; N, 5.49. Found: C, 37.93; H, 6.57; N, 5.74.

3.5. D-Galactofuranosyl nitromethane peracetates 24 and 25

Compound **18** (0.25 g, 0.5 mmol) was stirred in a mixture of anhydrous MeOH (6 mL) and 1 M NaOMe in MeOH (1.6 mL) at rt for 36 h. Then Amberlite IR 120, H^+ form (5 mL) was added to the mixture and filtered. The resin was washed with water (3 × 5 mL). The combined filtrates were concentrated in a rotary evaporator under reduced pressure. The foam-dry residue was dissolved in MeOH (2 mL) and added dropwise into Ac_2O (15 mL) containing concentrated H_2SO_4 (two drops) at 30 °C. After 24 h, the reaction mixture was poured into ice and water (100 mL), and the mixture was stirred for 5 h. The resulting solution was extracted with $CHCl_3$ (3 × 30 mL), and the extract was washed with water until neutral, dried (Na_2SO_4) and evaporated, yielding a mixture of peracetates of compounds **7**–**10**, which were separated by flash chromatography.

3.5.1. 1,2,4,5-Tetra-*O*-acetyl-3,6-anhydro-7-deoxy-7-nitro-D-*glycero*-L-*galacto*-heptitol (α-D-galactofuranosyl nitromethane 1,2,4,5-tetraacetate, 24)

Yield 30 mg (15%), R_f = 0.31 (S_2), $[\alpha]_D^{20}$ +12.0 (*c* 1, $CHCl_3$); Ref. 21: $[\alpha]_D^{20}$ +18.5 (*c* 1.5, $CHCl_3$). ^{1}H NMR (acetone-d_6) δ: 5.44 (dd, 1H, $J_{5,6}$ = 4.1 Hz, $J_{4,5}$ = 1.4 Hz, H-5), 5.38 (ddd, 1H, $J_{1,2}$ = 4.0 Hz, $J_{1',2}$ = 7.0 Hz, $J_{2,3}$ = 5.8 Hz, H-2), 5.16 (dd, 1H, $J_{3,4}$ = 3.2 Hz, H-4), 4.84–4.91 (m, H-6, H-7), 4.73 (dd, 1H, $J_{6,7'}$ = 9.4 Hz, $J_{7,7'}$ = 14.3 Hz, H-7′), 4.36 (dd, 1H, $J_{1,2}$ = 4.0 Hz, $J_{1,1'}$ = 12.0 Hz, H-1), 4.09–4.16 (m, 2H, H-1′, H-3), 1.98, 2.07, 2.09, 2.13 (4s, 12H, CH_3). ^{13}C NMR (acetone-d_6) δ: 171.98, 171.74, 171.38, 171.22 (4CO), 84.56 (C-3), 79.76 (C-4), 78.57 (C-5), 78.46 (C-6), 76.48 (C-7), 71.76 (C-2), 64.55 (C-1), 21.80, 21.86, 21.90, 22.06 ($4CH_3$).

3.5.2. 1,2,4,5-Tetra-*O*-acetyl-3,6-anhydro-7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol (β-D-galactofuranosyl nitromethane 1,2,4,5-tetraacetate, 25)

Yield 74 mg (38%), R_f = 0,28 (S_2), $[\alpha]_D^{20}$ +6.0 (*c* 1, $CHCl_3$); Ref. 21: $[\alpha]_D^{20}$ +6.0 (*c* 1.5, $CHCl_3$). ^{1}H NMR (acetone-d_6) δ: 5.36 (dt, 1H, $J_{1,2}$ = 7,0 Hz, $J_{2,3}$ = 4,6 Hz, H-2), 5.23 (t, 1H, $J_{3,4}$ = 2.8 Hz, H-4), 5.19 (t, 1H, $J_{4,5}$ = 3.0 Hz, H-5), 4.92 (t, 2H, $J_{6,7}$ = 4.3 Hz, H-7, H-7′), 4.80 (dd, 1H, $J_{5,6}$ = 5.2 Hz, H-6), 4.33 (dd, 1H, H-5), 4.28 (dd, 1H, $J_{1,2}$ = 4.4 Hz, $J_{1,1'}$ = 11.9 Hz, H-1), 4.15 (dd, 1H, H-1′), 1.98, 2.07, 2.09, 2.11 (4s, 12H, $4CH_3$). ^{13}C NMR (acetone-d_6) δ: 171.92, 171.85, 171.66, 171.60 (4CO), 84.07 (C-3), 82.23 (C-6), 80.38 (C-4), 80.19 (C-5), 78.37 (C-7), 71.94 (C-2), 64.23 (C-1), 21.77, 21.89, 21.91, 22.07 ($4CH_3$).

3.6. D-Galactopyranosyl nitromethane peracetates 26 and 27

Yield 35 mg (18%, 1:2). R_f = 0.28 (S_2).

3.6.1. 1,3,4,5-Tetra-*O*-acetyl-2,6-anhydro-7-deoxy-7-nitro-D-*glycero*-L-*galacto*-heptitol (α-D-galactopyranosyl nitromethane 1,2,4,5-tetraacetate, 26)

^{1}H NMR (acetone-d_6) δ: 5.59–5.61 (m, 1H), 5.50–5.57 (m, 1H), 5.37–5.48 (m, overlap), 5.13–5.19 (m, 1H), 4.63–4.67 (m, overlap), 4.32–4.35 (m, 1H, H-7), 4.24 (dd, 1H, overlap, H-7′), 2.14, 2.16, 2.26, 2.29 (4s, 12H, $4CH_3$). ^{13}C NMR (acetone-d_6) δ: 171.82, 171.76, 171.44, 171.23 (4CO), 74.54, 71.80, 71.23, 69.43, 69.06, 68.57 (C-2–C-7), 62.74 (C-1), 21.74, 21.83, 21.85, 21.92 ($4CH_3$).

3.6.2. 1,3,4,5-Tetra-*O*-acetyl-2,6-anhydro-7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol (β-D-galactopyranosyl nitromethane 1,2,4,5-tetraacetate, 27)

^{1}H NMR (acetone-d_6) δ: 5.63 (dd, 1H, $J_{2,3}$ = 0.9 Hz, H-3), 5.45 (dd, 1H, $J_{3,4}$ = 3.5 Hz, H-4), 5.28 (t, 1H, $J_{4,5}$ = 9.9 Hz, H-5), 5.02 (dd, 1H, $J_{7,7'}$ = 13.5 Hz, $J_{6,7}$ = 2.3 Hz, H-7), 4.77 (dd, 1H, $J_{6,7'}$ = 9.4 Hz, H-7′), 4.64 (dt, 1H, $J_{5,6}$ = 9.6 Hz, H-6), 4.43 (dt, 1H, $J_{1,2}$ = 6.5 Hz, H-2), 4.25 (dd, 2H, H-1, H-1′), 2.11, 2.13, 2.23, 2.30 (4s, 12H, 4CH_3). ^{13}C NMR (acetone-d_6) δ: 171.89, 171.76, 171.71, 171.40 (4CO), 78.21 (C-7), 76.58 (C-6), 76.24 (C-2), 73.45 (C-4), 69.74 (C-3), 68.57 (C-5), 63.31 (C-1), 21.74, 21.75, 21.77, 21.91 (4CH_3).

3.7. D-Galactosyl nitromethanes 7–10

Compound **18** (4.93 g, 10 mmol) was stirred in a mixture of anhydrous MeOH (120 mL) and 1 M NaOMe in MeOH (32 mL) at rt for 36 h. Then Amberlite IR 120, H^+ form (50 mL) was added to the mixture and filtered. The resin was washed with water (3 × 50 mL). The neutral combined filtrates were concentrated in a rotary evaporator under reduced pressure and again dissolved in water (100 mL) and treated with charcoal (2 g). The decolorized filtrate was again concentrated, and the syrupy residue (2.2 g) was submitted to fractional crystallization from MeOH. A part of the mother liquor (0.5 g) was separated by the Whatman 3 preparative PC and S_1 solvent mixture.[15]

3.7.1. 3,6-Anhydro-7-deoxy-7-nitro-D-*glycero*-L-*galacto*-heptitol (α-D-galactofuranosyl nitromethane, 7)

Yield 0.3 g (15%), R_{Gal} = 4.79 (S_1), mp 161–163 °C (MeOH–Me_2CO), $[\alpha]_D^{20}$ −2 (*c* 1; H_2O); Ref.[21]: mp 163–166 °C, $[\alpha]_D^{20}$ −7 (*c* 0.8, H_2O). ^{1}H NMR (D_2O) δ: 4.87 (dd, 1H, $J_{7,7'}$ = 12.5 Hz, $J_{6,7}$ = 1,9 Hz, H-7), 4.66–4.77 (m, 2H, H-6, H-7′), 4.28 (dd, 1H, $J_{4,5}$ = 2.9 Hz, H-5), 4.17 (t, 1H, $J_{3,4}$ = 3.4 Hz, H-4), 3.82–3.86 (m, 2H, H-2, H-3), 3.57–3.71 (m, 2H, H-1, H-1′). ^{13}C NMR (D_2O) δ: 85.62 (C-3), 78.69 (C-4), 77.91 (C-6), 77.67 (C-5), 75.99 (C-7), 72.08 (C-2), 63.49 (C-1).

3.7.2. 3,6-Anhydro-7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol (β-D-galactofuranosyl nitromethane, 8)

Yield 0.1 g (4.5%, by PC), R_{Gal} = 4.13 (S_1), $[\alpha]_D^{20}$ −48 (*c* 1, H_2O); Ref.[21]: mp 99–100 °C (EtOH), $[\alpha]_D^{20}$ −63.2 (*c* 0.7, H_2O). ^{1}H NMR (D_2O) δ: 4.75–4.80 (m, 2H, H-7, H-7′), 4.48 (dt, 1H, $J_{6,7}$ = 7.3 Hz, $J_{5,6}$ = 3.7 Hz, H-6), 4.05 (t, 1H, $J_{3,4}$ = 6.4 Hz, H-4), 3.97 (t, 1H, $J_{4,5}$ = 6.3 Hz, H-5), 3.88 (dd, 1H, $J_{3,4}$ = 6,4 Hz, H-3), 3.76–3.83 (m, 1H, H-2), 3.60 (dt, 2H, $J_{1,2}$ = 4.5 Hz, $J_{1,1'}$ = 12.0 Hz, H-1, H-1′). ^{13}C NMR (D_2O) δ: 83.17 (C-3), 79.89 (C-6), 78.22 (C-5), 77.71 (C-7), 77.30 (C-4), 71.80 (C-2), 63.53 (C-1).

3.7.3. 2,6-Anhydro-7-deoxy-7-nitro-D-*glycero*-L-*galacto*-heptitol (α-D-galactopyranosyl nitromethane, 9)

Yield 0.05 g (2.2%, by PC), R_{Gal} = 2.63 (S_1), $[\alpha]_D^{20}$ +145 (*c* 1, H_2O); Ref.[20]: mp 171–181 °C, $[\alpha]_D^{24}$ +88.5 (*c* 2, H_2O). ^{1}H NMR (D_2O) δ: 5.05 (dd, 1H, $J_{7,7'}$ = 11.7 Hz, H-7), 4.80–4.88 (m, 2H, H-6, H-7′), 4.12 (dd, 1H, H-5), 3.91–3.93 (m, 1H, H-2), 3.67–3.73 (m, 4H, H-1, H-1′, H-3, H-4). ^{13}C NMR (D_2O) δ: 74.34 (C-2), 74.07, 73.21 (C-6, C-7), 70.65, 69.65 (C-3, C-4), 67.74 (C-5), 61.89 (C-1).

3.7.4. 2,6-Anhydro-7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol (β-D-galactopyranosyl nitromethane, 10)

Yield 1.6 g (71%), R_{Gal} = 3.39 (S_1), mp 198–200 °C (MeOH), $[\alpha]_D^{20}$ +36 (*c* 1, H_2O); Ref. 22: mp 199.5–200.5 °C, $[\alpha]_D^{25}$ +36 (*c* 2.9. H_2O). ^{1}H NMR (D_2O) δ: 4.95 (dd, 1H, $J_{7,7'}$ = 13.5 Hz, $J_{6,7}$ = 2.6 Hz, H-7), 4.67 (dd, 1H, $J_{6,7'}$ = 8.8 Hz, H-7′), 4.02 (dt, 1H, $J_{5,6}$ = 9.6 Hz, H-6), 3.96 (d, 1H, $J_{2,3}$ = 3.3 Hz, H-3), 3.65–3.71 (m, 4H, H-1, H-1′, H-2, H-4), 3.57 (t, 1H, H-5). ^{13}C NMR (D_2O) δ: 79.73 (C-2), 77.52 (C-6), 77.41 (C-7), 74.70 (C-4), 69.92 (C-3), 68.72 (C-5), 62.09 (C-1).

3.8. Thermally induced β-elimination of 7-deoxy-7-nitro-L-*glycero*-L-*galacto*-heptitol (2)

The starting compound **2** Ref. [23] was dissolved in deionized and distilled water, and the solution was stirred and heated at an internal temperature of 100 °C. At selected time intervals (Fig. 3), appropriate volume samples were taken, cooled, and concentrated in a rotary evaporator under reduced pressure (0.5-mL samples from 0.5 g (2.07 mmol) of **2** in 10 ml of H_2O for ^{1}H NMR spectroscopy and 0.4-mL samples from 1.2 g (4.98 mmol) of **2** in 5 mL of H_2O for ^{13}C NMR spectroscopy).

Acknowledgments

This work was supported by the APVV-51-046505 and VEGA-2/0199/09 grants. The funds for the NMR measurements were provided by the Slovak State Programme Project No. 2003SP200280203.

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