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Carbohydrate Research 341 (2006) 2019–2025
Carbohydrate RESEARCH

Extension of the Nef reaction to *C*-glycosylnitromethanes

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Received 9 January 2006; received in revised form 5 April 2006; accepted 10 April 2006
Available online 22 June 2006

Abstract—Acid-catalysed methanolysis of 3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-L-*arabino*-hex-1-enitol proceeds via a cascade set of consecutive reactions resulting in its regiospecific conversion to a mixture of α- and β-*C*-L-arabinofuranosylmethanal dimethyl acetals and a mixed internal methyl acetal. Structures of the final products of the overall process provide unique evidence that a kinetically controlled, five-membered-ring closure precedes a six-membered-ring closure in reversible systems capable of giving both five-membered and six-membered all-sp^3-atom rings. Determination of the reaction intermediate enabled extension of the Nef reaction to *C*-glycosylnitromethanes. Protonated *aci*-nitro forms of *C*-glycosylnitromethanes that are resistant to the Nef reaction in aqueous acidic media undergo a modified Nef reaction in acidified methanol, and the corresponding *C*-glycosylmethanal dimethyl acetals with α-L-arabinopyranosyl, β-D-glucopyranosyl, β-D-galactopyranosyl, β-D-mannopyranosyl and β-L-rhamnopyranosyl configurations were obtained in moderate yields.

Keywords: Nef reaction; Anhydronitroalditol; Glycosylnitromethane; 2,6-Anhydroaldose dimethyl acetal; Ring-closure reaction; 1-Deoxy-1-nitro-hex-1-enitol

1. Introduction

Recent advances in transformations of the nitromethyl group of *C*-glycosylnitromethanes to an array of versatile functional groups, such as aldehydes,[1,2] aldehyde oximes,[3] methyl groups via aldehyde diethyl dithioacetals,[4] carboxylic acids,[5] or amines,[6] suggest the additional application of the compounds for synthesis of more complex *C*-glycosyl compounds. However, the present methods for the preparation of *C*-glycosylnitromethanes afford only incomplete assortments of possible and preparatively interesting isomers, since with the exception of the pyrano-equatorial anomer, the presence of the other anomers in equilibrium reaction mixtures is rather very minor. The reason is that the methods are based on the thermally or catalytically induced β-elimination of the C-2 OH group from a tautomeric, *aci*-nitro form of 1-deoxy-1-nitroalditol.[7–9] These approaches do not allow capture of the first, primarily formed five-membered-ring *C*-glycofuranosylnitromethanes as the kinetic products of the cyclisation of the intermediate 1,2-dideoxy-1-nitro-1-enitol, because, due to fast and reversible, simultaneously occurring interconversions, they are largely transformed to the thermodynamically favoured pyrano-equatorial anomers. The only known exception to this general behaviour of *C*-glycosylnitromethanes, due to obvious steric reasons in the ribopyranosyl ring, is a preferred formation of *C*-ribofuranosylnitromethanes.[10]

Recently, efficient syntheses of *C*-glycofuranosyl structures (other than the ribo or 2-deoxyribo structures) have become more and more desired. The reason is an extensive search for new, specific agents, especially

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doi:10.1016/j.carres.2006.04.050

for those active against the mycobacterial pathogens that are resistant to existing drugs, and namely, that the occurrence of D-galactofuranose in nature is specific to mycobacteria, protozoa and fungi.[11–13] Thus, compounds that mimic D-galactofuranose could interfere with the enzyme-catalysed pathways processing D-galactofuranose and become the targets for new drug development against pathogenic species of microorganisms. Therefore, we have attempted the elaboration of a non-equilibrium method of preparation of *C*-glycosylnitromethanes that should provide non-thermodynamic *C*-glycofuranosylnitromethanes exemplified in this paper with an attempted preparation of anomeric *C*-L-arabinofuranosylnitromethanes from easily available 3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-1-nitro-L-*arabino*-hex-1-enitol by its acid-catalysed O-deacetylation at rt. The reason, which has stipulated the choice of this model compound for investigation of its behaviour under the conditions of acid-catalysed O-deacetylation, was the simplicity of the model system as well as the fact that L-*arabino*-furanoid structure is homomorphic with the highly desired D-*galacto*-furanoid structure. The paper describes new findings that were developed from this attempted experiment, which led to the extension of the Nef reaction to *C*-glycosylnitromethanes. This work has been reported, in part, in meeting abstracts and in a review.[14–16]

2. Results and discussion

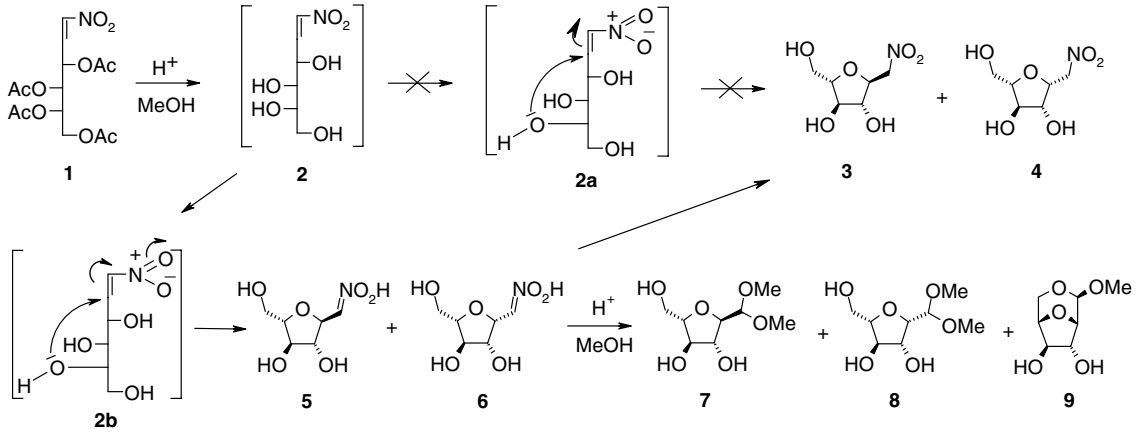
2.1. Acid-catalysed methanolysis of 3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-1-nitro-L-*arabino*-hex-1-enitol

In our attempts to obtain the anomeric *C*-L-arabinofuranosylnitromethanes **3** and **4** on treatment of 3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-1-nitro-L-*arabino*-hex-1-enitol (**1**) with 0.1–0.3 M HCl in anhydrous methanol at rt, we found that, instead of the expected nitro derivatives **3** and **4**, a mixture of acetal derivatives **7**–**9** was formed in combined 65–78% yields (Scheme 1).

The mixture of reaction products **7**–**9** was easily purified by deionisation with a mixture of a strongly acidic cation-exchange resin in the H^+ form and a strongly basic anion-exchange resin in the OH^- form, followed by an additional passing of the resulting solution through a column of the latter resin in the OH^- form. The acetal derivatives **7**–**9** were then resolved by flash chromatography on silica gel using an ammonia-containing solvent mixture.

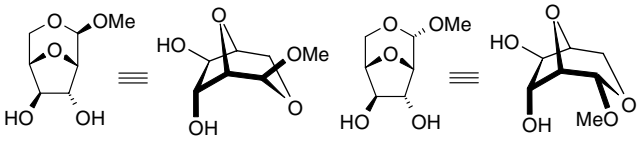
Structures of acetals **7**–**9** were established mainly by ^1H and ^{13}C NMR (including COSY, HETCOR and NOESY) spectral analyses. The chemical shifts of their C-1 carbon atoms occur at δ 96–106, characteristic for acetal carbon atoms. Also characteristic were the chemical shifts of their acetal methyl groups occurring at δ 53–56. Each of the two dimethyl acetals **7** and **8** contained in their NMR spectra two signals for the acetal methyl groups, while only one acetal methyl group signal was present in the spectrum of **9**, indicating that its second acetal linkage was internal, apparently from C-6, which was upfield shifted to δ 64.4. Furanoid carbohydrate structures have very characteristic chemical shifts of the last ring carbon atom that occur well above δ 80; and the respective values for derivatives **7**–**9** were observed at δ 85.4, 88.4 and 83.4. The ^1H NMR spectra also indicated furanoid structures for compounds **7**–**9**; these were apparent from the values of all vicinal coupling constants of hydrogen atoms linked to the ring carbon atoms.

The β-L-arabinofuranosyl structure is obvious for the mixed internal methyl acetal **9** since the opposite α-L-arabinofuranosyl configuration does not allow formation of such a thermodynamically stable internal acetal ring. Based on this consideration, the β-L-arabinofuranosyl configuration was ascribed to dimethyl acetal **8**, which is interconvertible with **9** in acidified methanol. In standard glycoside terminology, the mixed acetal **9**



Scheme 1.

can be viewed as methyl 2,5-anhydro-α-L-glucoseptanoside. Due to an anomeric effect in methyl 2,5-anhydro-β-L-glucoseptanoside (**10**) and a simultaneous 1,3-parallel interaction of its methoxyl group with the C-3 OH group, the formation of **9** is apparently much more favoured than the formation of the opposite β-anomeric septanoside **10**, the presence of which in the interconvertible, thermodynamic mixture of acetals **8** and **9** was not observed. The respective α- and β-glycosyl configurations of dimethyl acetal derivatives **7** and **8** are supported by characteristic H–H contacts in their ^{1}H–^{1}H NOESY spectra.



The formation of acetals **7**–**9** on treatment of **1** with acidified methanol suggests that the cyclisation of the intermediate 1,2-dideoxy-1-nitro-L-*arabino*-hex-1-enitol (**2**, Scheme 1) via an intramolecular nucleophilic attack of its hydroxyl group at C-5 onto C-2 does not proceed as a 1,2-addition (**2a**) to give expected epimeric 2,5-anhydro-1-deoxy-1-nitroalditols (*C*-glycofuranosylnitromethanes) **3** and **4**, but as a 1,4-addition (**2b**) giving rise to intermediate *C*-(L-arabinofuranosyl)methanenitronic acids **5** and **6**. The intermediates **5** and **6** formed in situ already contain an *aci*-nitro group that, on its instant protonation at the other oxygen atom of the *aci*-nitro group under the reaction conditions available, immediately becomes susceptible to the Nef reaction. Thus, the irreversible Nef reaction, running in a cascade after the reversible cyclisation and protonation steps, quenches the result of the kinetically controlled five-membered-ring-forming step, making regiospecific the overall process.

Clean conversion of nitrohexenitol **1** to acetals **7**–**9** occurred only in dilute methanolic solutions of mineral acids in the 0.1–0.3 M acid concentration range. At higher concentrations of the catalytic acid, in addition to acetals **7**–**9**, considerable amounts of acidic products were also formed that were not further investigated.

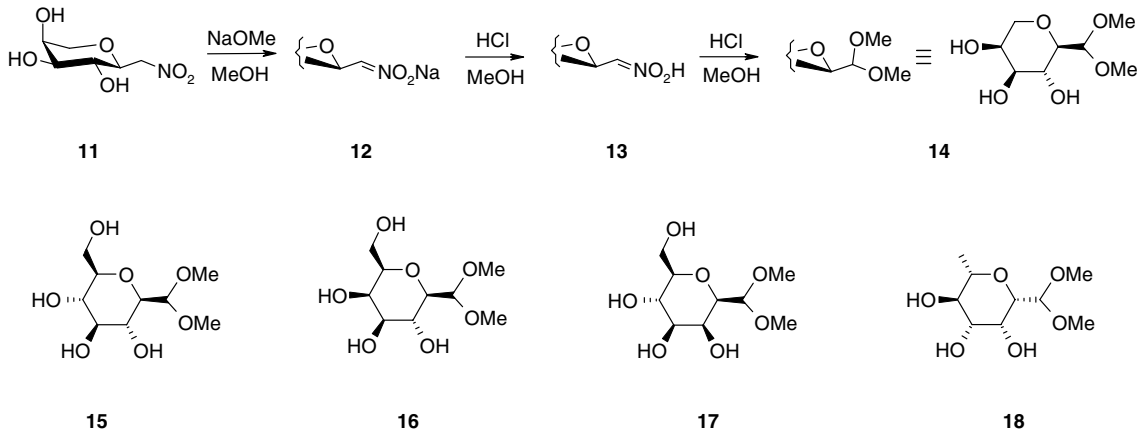
A detailed inspection of the reaction mixtures obtained at the optimum conditions revealed the presence of a very small (ca. 5%) mixture of two other compounds. Their negative DEPT ^{13}C NMR signals at δ 71.3 and 76.4 suggested that the mixture might contain *C*-L-arabinofuranosylnitromethanes **3** and **4** and that the ^{13}C peaks were those of their CH_2NO_2 carbon atoms. (The ^{13}C chemical shifts of the CH_2NO_2 carbon atoms of homomorphic *C*-D-galactofuranosylnitromethanes occur at δ 73.5 and 76.3.[17]) Because of the pK_a values (8.8–9.2) of *C*-glycosylnitromethanes,[18] this mixture could also have been removed from the reaction mixtures with the strongly basic anion-exchange resin in the OH^- form. The formation of compounds **3** and **4**, which were originally expected as the only or at least major products of deacetylation of **1** in HCl–MeOH, could be ascribed to a competitive tautomerisation of *C*-L-arabinofuranosylmethanenitronic acids **5** and **6** (Scheme 1), which is, in general, a relatively slow process.[19]

2.2. Acid-catalysed methanolysis of *C*-glycopyranosylmethanenitronates generated from ready-made *C*-glycosylnitromethanes

The serendipitous observation of the acid-catalysed methanolysis of the *C*-L-arabinofuranosyl-to-*aci*-nitromethyl linked groups generated in situ from compound **1**, which provides methyl acetal-protected aldehydic derivatives **7**–**9**, then implied a simple extrapolation of this modification of the Nef reaction to ready-made *C*-glycosylnitromethanes. Thus, as shown for the conversion of *C*-(α-L-arabinopyranosyl)nitromethane (**11**) to *C*-α-L-arabinopyranosylmethanal dimethyl acetal (**14**, Scheme 2) obtained in a 58% yield, the starting *C*-glycosylnitromethanes were first transformed to their sodium nitronate forms **12** upon treatment with sodium methoxide. Subsequent treatment of nitronates **12** with an excess of a methanolic solution of hydrogen chloride led to acid-catalysed methanolysis of the intermediate *aci*-nitro forms **13**. Analogous two-step treatment of other easily available *C*-glycosylnitromethanes led also to moderate (50–62%) yields of dimethyl acetal-protected *C*-glycosylmethanals, namely those with β-D-glucopyranosyl (**15**), β-D-galactopyranosyl (**16**), β-D-mannopyranosyl (**17**) and β-L-rhamnopyranosyl (**18**) configurations (Scheme 2). A similar nitro group to dimethyl acetal transformation has been earlier reported for preparation of higher molecular weight, non-sugar aldehydes.[20]

The structures of pyrano-equatorial glycosylmethanal dimethyl acetals **14**–**18** were proved by their ^{1}H and ^{13}C NMR spectra. The chemical shifts of their C-1 carbon atoms were observed in the range of δ 103–106, which is characteristic for occurrence of acetal carbon atoms, as compared to the former values (δ 77–78) of the nitromethyl groups in their *C*-glycosylnitromethane precursors. The values of their $J_{2,3}$ proton–proton coupling constants prove that the original pyrano-equatorial configuration of the glycopyranosyl moieties remained unchanged.

Unlike the acid-catalysed methanolysis of 3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-1-nitro-L-*arabino*-hex-1-enitol, acid-catalysed methanolysis of *C*-glycosylmethanenitronates generated from ready-made *C*-glycosylnitromethanes did not lead to their complete transformation to the corresponding *C*-glycosylmethanal dimethyl acetals,



Scheme 2.

and a part of the starting material remained unchanged. The reason for this result was a limited solubility of the sodium nitronate forms of starting *C*-glycosylnitromethanes. In the presence of water, the nitronates did not undergo methanolysis at all, and only the starting material was recovered. More diluted methanolic solutions of the sodium nitronate forms of *C*-glycosylnitromethanes were a possible compromise that, however, then required a proportionally higher molar excess of the catalytic acid to ensure its optimum concentration for the transformation required, and a greater amount of anion-exchange resin necessary for removal of the acid. This led to an inevitable greater loss of product. But in this way, the yield of acetal **15** was increased to 75–80%. Attempts to utilise a phase-transfer catalyst, either in a solid phase using a strongly basic anion-exchange resin or in a liquid phase using tetrabutylammonium ions, both with methoxide counter ions, for generating the necessary nitronates before the treatment with methanolic hydrogen chloride, gave no conversion of starting *C*-glycosylnitromethanes. Consideration of increasing the solubility of the nitronate form of the substrate using derivatives of *C*-glycosylnitromethanes that are stable in basic media led to use of the sodium nitronate form of 4,6-*O*-benzylidene-β-D-glucopyranosylnitromethane. In this way, the yield of acetal **15** was increased to 84%.

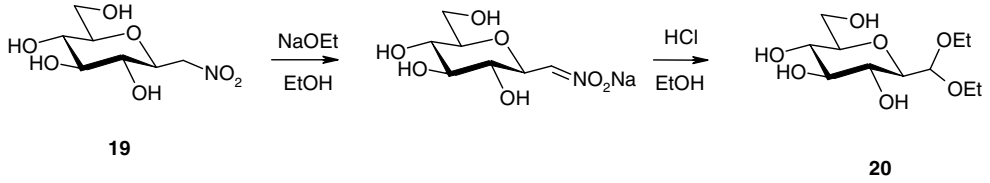
Ethanol instead of methanol can be used for the acid-catalysed solvolysis of *C*-glycosylmethanenitronates to the corresponding glycosylmethanal diethyl acetals. Thus, β-D-glucopyranosylmethanal diethyl acetal (**20**, Scheme 3) was obtained in a 56% yield from glycosylnitromethane **19**. Also in this case, the ^{1}H and ^{13}C NMR spectral analysis unambiguously supported the glycosylmethanal diethyl acetal structure of compound **18** with a retained β-D-glucopyranosyl configuration of its glycosyl moiety.

The new method of preparation of the dialkyl acetal-protected glycosylmethanal derivatives directly from *C*-glycosylnitromethanes significantly increases the synthetic attractiveness of these easily available *C*-glycosyl compounds and is very simple in comparison with other methods of preparation of glycosylmethanals. In addition, the new findings arising from the acid-catalysed solvolysis of the hydrogen-nitronate forms of the nitroalditol derivatives have numerous consequences for further development of the Nef and other relative reactions.

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 obtained using a Fisons EA-1108 instrument. pH measurements were made using a Radiometer Standard pH Meter PHM-82 and a universal thermostated EA 880 AB-H vessel. 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]. TLC



Scheme 3.

was run on Merck silica gel 60 F254 precoated aluminium plates; detection was effected by spraying the chromatograms with 10% ethanolic sulfuric acid and charring them on a hot plate. Flash chromatography was performed using an Acros silica gel (0.037–0.075 mm). For chromatographic separations, the following solvent mixtures (volume ratios) were used: S_1, butan-1-ol–propan-2-ol–water–25% aq ammonia 8:4:2:1; S_2, ethyl acetate–butan-1-ol–MeOH–water 16:3:3:4. Starting *C*-α-L-arabinopyranosylnitromethane,[7] *C*-β-D-glucopyranosylnitromethane,[8] *C*-β-D-galactopyranosylnitromethane,[8] *C*-β-D-mannopyranosylnitromethane,[21] *C*-β-L-rhamnopyranosylnitromethane,[6b] were prepared according to the published procedures.

3.2. Acid-catalysed methanolysis of 3,4,5,6-tetra-*O*-acetyl-1,2-dideoxy-1-nitro-L-*arabino*-hex-1-enitol (1)

3,4,5,6-Tetra-*O*-acetyl-1,2-dideoxy-1-nitro-L-*arabino*-hex-1-enitol,[7] (0.5 g, 1.4 mmol) was dissolved in a 0.1 M solution of HCl in MeOH (50 mL, made of acetyl chloride and anhyd MeOH) and left to stand at rt for 60 h. Then Dowex 1 X-4 in the OH^- form (25 mL) was added and the mixture was stirred for 5 min. The resin was removed by filtration and washed with water (3 × 10 mL). The combined neutral filtrate was evaporated under reduced pressure. The residue (0.25 g) was dissolved in water (5 mL), passed through a column (25 × 1.6 cm) of Dowex 1 X-4 (100–200 mesh) in the OH^- form, and the column was washed with water (200 mL). Finally, the combined eluted solution was concentrated on a rotary evaporator, and the residue was fractionated by flash chromatography on silica gel using eluent S_1. Evaporation of individual fractions under reduced pressure followed by drying in vacuo over a solid NaOH gave compounds **7**, **8** and **9**.

3.2.1. 2,5-Anhydro-L-mannose dimethyl acetal (7, *C*-α-L-arabinofuranosylmethanal dimethyl acetal). Yield 86 mg (29%); $[\alpha]_D^{20}$ −44.5 (*c* 1, H_2O); R_f 0.48 (S_1); ^1H NMR (D_2O), δ 4.56 (d, 1H, $J_{1,2}$ 6.0 Hz, H-1), 4.17 (t, 1H, $J_{3,4}$ 5.7 Hz, H-3), 4.05 (dd, 1H, $J_{4,5}$ 5.3 Hz, H-4), 3.87–3.93 (m, 1H, H-5), 3.88 (t, 1H, $J_{2,3}$ 5.6 Hz, H-2), 3.74 (dd, 1H, $J_{5,6a}$ 3.3 Hz, $J_{6a,6b}$ 12.5 Hz, H-6a), 3.68 (dd, 1H, $J_{5,6b}$ 5.1 Hz, H-6b), 3.51, 3.49 (2s, 6H, 2OMe); NOE contacts: H-1,3; H-2,4; ^{13}C NMR (D_2O), δ 105.6 (C-1), 84.1 (C-5), 82.6 (C-2), 78.6 (C-3), 77.6 (C-4), 61.9 (C-6), 56.9, 56.1 (2OMe); ^{13}C NMR (MeOH-d_4), δ 105.9 (C-1), 86.2 (C-5), 85.1 (C-2), 79.6 (C-3), 79.1 (C-4), 63.2 (C-6), 55.9, 54.9 (2OMe). Anal. Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 45.84; H, 8.04.

3.2.2. 2,5-Anhydro-L-glucose dimethyl acetal (8, *C*-β-L-arabinofuranosylmethanal dimethyl acetal). Yield 90 mg (31%); $[\alpha]_D^{20}$ −16.0 (*c* 1, H_2O); R_f 0.58 (S_1); ^1H NMR (D_2O), δ 4.66 (d, 1H, $J_{1,2}$ 7.5 Hz, H-1), 4.12 (dd, 1H, $J_{2,3}$ 3.7 Hz, $J_{3,4}$ 1.4 Hz, H-3), 4.08 (dd, 1H, $J_{4,5}$ 3.1 Hz, H-4), 4.04 (dd, 1H, H-2), 3.88–3.92 (m, 1H, H-5), 3.70–3.77 (m, 2H, H-6a, H-6b), 3.51, 3.49 (2s, 6H, 2OMe); NOE contacts: H-2,3; H-4,6; ^{13}C NMR (D_2O), δ 103.7 (C-1), 87.0 (C-5), 81.0 (C-2), 79.4 (C-4), 77.6 (C-3), 62.8 (C-6), 56.6, 55.1 (2OMe); ^{13}C NMR (MeOH-d_4), δ 104.1 (C-1), 88.4 (C-5), 81.7 (C-2), 80.1 (C-4), 78.2 (C-3), 63.5 (C-6), 55.8, 53.5 (2OMe). Anal. Calcd for $C_8H_{16}O_6$: C, 46.15; H, 7.75. Found: C, 46.14; H, 7.84.

3.2.3. Methyl 2,5-anhydro-α-L-glucoseptanoside (9). Yield 48 mg (19%); $[\alpha]_D^{20}$ −80.5 (*c* 1, H_2O); R_f 0.53 (S_1); ^1H NMR (D_2O), δ 4.67 (d, 1H, $J_{1,2}$ 1.0 Hz, H-1), 4.40 (br d, 1H, H-4), 4.20–4.31 (m, 2H, H-2, H-3), 4.00–4.06 (m, 1H, H-5), 3.79 (dd, 1H, $J_{5,6a}$ 2.9 Hz, $J_{6a,6b}$ 11.9 Hz, H-6a), 3.62 (dd, 1H, $J_{5,6b}$ 1.1 Hz, H-6b), 3.53 (s, 3H, OMe); ^{13}C NMR (D_2O), δ 96.2 (C-1), 83.4 (C-5), 80.5 (2C, C-3, C-4), 78.9 (C-2), 64.0 (C-6), 56.0 (OMe); ^{13}C NMR (MeOH-d_4), δ 96.7 (C-1), 84.1 (C-5), 81.7 (C-2), 81.2 (C-3), 79.9 (C-4), 64.4 (C-6), 55.5 (OMe). Anal. Calcd for $C_7H_{12}O_5$: C, 47.72; H, 6.87. Found: C, 47.58; H, 7.11.

3.3. Preparation of *C*-glycopyranosylmethanal dimethyl acetals by acid-catalysed methanolysis of *C*-glycopyranosylmethanenitronates generated from ready-made *C*-glycopyranosylnitromethanes

A mixture of a powdered *C*-glycosylnitromethane (2 mmol) and a 0.1 M solution of NaOMe in MeOH (30 mL) was stirred at rt under argon for 16 h. Then, a 0.5 M solution of HCl in MeOH (22 mL) was added, and the mixture was stirred for an additional 1 h. Next water (50 mL), a strongly basic anion-exchange resin in the OH^- form (30 mL) and a strongly acidic cation-exchange resin in the H^+ form (10 mL) were added, and the mixture was stirred for 5 min. The ion-exchanger mixture was removed by filtration and washed with water (3 × 10 mL). The combined filtrate and washing was passed through a column (25 × 1.6 cm) of Dowex 1 X-4 (100–200 mesh) in the OH^- form, and the column was washed with water (30 mL). The combined solutions eluted from the column were evaporated under reduced pressure and gave the corresponding *C*-glycopyranosylmethanal dimethyl acetal. The raw product, which according to its ^{13}C NMR spectrum did not contain any impurity, was still purified by flash chromatography on silica gel using eluent S_2. A part of starting *C*-glycosylnitromethane (ca. 0.6 mmol) was recovered by a 15 min treatment of the mixture of the ion-exchange resins used for deionisation of the reaction mixture with crushed solid carbon dioxide in water at 5 °C, removal of the resins by filtration, and final evaporation of the filtrate in vacuo.

3.3.1. 2,6-Anhydro-L-mannose dimethyl acetal (14, *C*-α-L-arabinopyranosylmethanal dimethyl acetal). Yield 0.25 g (58%); $[\alpha]_D^{20}$ −16.0 (*c* 1, MeOH); R_f 0.45 (S_1), 0.32 (S_2); ^{1}H NMR (MeOH-d_4), δ 4.58 (d, 1H, $J_{1,2}$ 3.2 Hz, H-1), 3.89 (dd, 1H, $J_{5,6a}$ 2.3 Hz, $J_{6a,6b}$ 12.5 Hz, H-6a), 3.80 (m, 1H, H-5), 3.73 (t, 1H, $J_{3,4}$ 9.3 Hz, H-3), 3.53 (dd, 1H, $J_{5,6b}$ 1.2 Hz, H-6b), 3.39–3.52 (m, 7H, H-4, 2OMe), 3.21 (dd, 1H, $J_{2,3}$ 9.3 Hz, H-2); ^{13}C NMR (MeOH-d_4), δ 104.9 (C-1), 80.9 (C-2), 75.5 (C-4), 71.2 (C-6), 70.3 (C-5), 69.2 (C-3), 56.0 (2OMe). Anal. Calcd for $C_8H_{16}O_6$: C, 46.15; H; 7.75. Found: C, 46.14; H, 8.02.

3.3.2. 2,6-Anhydro-D-*glycero*-D-*gulo*-heptose dimethyl acetal (15, *C*-β-D-glucopyranosylmethanal dimethyl acetal). Yield 0.3 g (62%); $[\alpha]_D^{20}$ +3.5 (*c* 2, MeOH); R_f 0.27 (S_2); ^{1}H NMR (MeOH-d_4), δ 4.59 (d, 1H, $J_{1,2}$ 1.5 Hz, H-1), 3.82 (dd, 1H, $J_{6,7a}$ 1.6 Hz, $J_{7a,7b}$ 12.0 Hz, H-7a), 3.63 (dd, 1H, $J_{6,7b}$ 5.4 Hz, H-7b), 3.50, 3.48 (2s, 6H, 2OMe), 3.32–3.40 (m, 3H, H-2, H-3, H-4), 3.18–3.26 (m, 2H, H-5, H-6); ^{13}C NMR (MeOH-d_4), δ 105.1 (C-1), 82.1 (C-6), 80.1 (C-2), 79.7 (C-4), 71.9 (C-3), 71.4 (C-5), 63.1 (C-7), 56.8, 56.3 (2OMe). Anal. Calcd for $C_9H_{18}O_7$: C, 45.37; H, 7.61. Found: C, 45.70; H, 7.83.

3.3.2.1. Preparation of 15 from *C*-(4,6-*O*-benzylidene-β-D-glucopyranosyl)nitromethane.[22] A solution of the title nitromethane derivative (0.4 g, 1 mmol) in 1,2-dimethoxyethane (6 mL) was mixed with a 1 M solution of NaOMe in MeOH (1.7 mL) and stirred at rt under argon for 10 min. The suspension was mixed with a 0.24 M solution of HCl in MeOH (8 mL), and the resulting solution first was left to stand at rt for 1 h and then, after addition of MeOH (15 mL), was heated under reflux for 2 h. After cooling to rt, a strongly basic anion-exchange resin in the OH^- form (10 mL) and a strongly acidic cation-exchange resin in the H^+ form (5 mL) were added, and the mixture was stirred for 5 min. Following removal of the resins by filtration, evaporation of the filtrate and aq washing solutions (3 × 10 mL) in vacuo, flash chromatographic purification of the residue on silica gel with eluent S_2, evaporation of the pertinent chromatographic fraction, and drying the residue over solid NaOH in vacuo gave compound **15** (0.20 g, 84%).

3.3.3. 2,6-Anhydro-D-*glycero*-L-*manno*-heptose dimethyl acetal (16, *C*-β-D-galactopyranosylmethanal dimethyl acetal). Yield 0.25 g (52%); mp 117–118 °C (MeOH); $[\alpha]_D^{20}$ +26.0 (*c* 2, MeOH); R_f 0.22 (S_2); ^{1}H NMR (MeOH-d_4), δ 4.60 (d, 1H, $J_{1,2}$ 2.9 Hz, H-1), 3.83 (dd, 1H, $J_{4,5}$ 3.5 Hz, $J_{5,6}$ 1.0 Hz, H-5), 3.76 (dd, 1H, $J_{6,7a}$ 7.3 Hz, $J_{7a,7b}$ 11.6 Hz, H-7a), 3.69 (t, 1H, $J_{3,4}$ 9.5 Hz, H-3), 3.63 (dd, 1H, $J_{6,7b}$ 4.8 Hz, H-7b), 3.49, 3.48 (2s, 6H, 2OMe), 3.40–3.47 (m, 2H, H-4, H-6), 3.28 (dd, 1H, $J_{2,3}$ 9.4 Hz, H-2); ^{13}C NMR (MeOH-d_4), δ 105.3 (C-1), 80.8 (C-6), 80.6 (C-2), 76.3 (C-4), 70.8 (C-5), 69.2 (C-3), 63.1 (C-7), 56.2 (2OMe); ^{13}C NMR (D_2O), δ 104.5 (C-1), 79.6 (C-6), 79.4 (C-2), 74.9 (C-4), 70.0 (C-5), 68.2 (C-3), 62.3 (C-7), 57.6, 56.9 (2OMe). Anal. Calcd for $C_9H_{18}O_7$: C, 45.37; H, 7.61. Found: C, 45.35; H, 7.70.

3.3.4. 2,6-Anhydro-D-*glycero*-D-*galacto*-heptose dimethyl acetal (17, *C*-(β-D-mannopyranosyl)methanal dimethyl acetal). Yield 0.29 g (60%); $[\alpha]_D^{20}$ +5.0 (*c* 2, MeOH); R_f 0.33 (S_2); ^{1}H NMR (MeOH-d_4), δ 4.58 (d, 1H, $J_{1,2}$ 7.5 Hz, H-1), 3.94 (d, 1H, $J_{2,3}$ 2.8 Hz, $J_{3,4}$ 2.8 Hz, H-3), 3.84 (dd, 1H, $J_{6,7a}$ 2.2 Hz, $J_{7a,7b}$ 12.0 Hz, H-7a), 3.68 (dd, 1H, $J_{6,7b}$ 5.9 Hz, H-7b), 3.56 (t, 1H, $J_{4,5}$ 9.5 Hz, $J_{5,6}$ 9.5 Hz, H-5), 3.42–3.50 (m, 2H, H-2, H-4), 3.43, 3.38 (2s, 6H, 2OMe), 3.21 (ddd, 1H, H-6); ^{13}C NMR (MeOH-d_4), δ 103.6 (C-1), 82.4 (C-6), 78.4 (C-2), 76.2 (C-4), 70.4 (C-3), 68.7 (C-5), 63.0 (C-7), 56.1, 53.2 (2OMe). Anal. Calcd for $C_9H_{18}O_7$: C, 45.37; H, 7.61. Found: C, 45.64; H, 7.84.

3.3.5. 2,6-Anhydro-7-deoxy-L-*glycero*-L-*galacto*-heptose dimethyl acetal (18, *C*-β-L-rhamnopyranosylmethanal dimethyl acetal). Yield 0.27 g (61%); $[\alpha]_D^{20}$ +16.0 (*c* 1, H_2O); R_f 0.53 (S_2); ^{1}H NMR (MeOH-d_4), δ 4.59 (d, 1H, $J_{1,2}$ 7.5 Hz, H-1), 3.99 (d, 1H, $J_{2,3}$ 2.8 Hz, $J_{3,4}$ 2.8 Hz, H-3), 3.50, 3.45 (2s, 6H, 2OMe), 3.23–3.52 (m, 4H, H-2, H-4, H-5, H-6), 1.35 (d, 3H, *J* 6.0 Hz, H-7a, H-7b, H-7c); ^{13}C NMR (MeOH-d_4), δ 103.9 (C-1), 78.6 (C-6), 77.7 (C-2), 75.8 (C-4), 74.0 (C-5), 70.3 (C-3), 56.2, 54.2 (2OMe), 18.3 (C-7). Anal. Calcd for $C_9H_{18}O_6$: C, 48.64; H, 8.16. Found: C, 48.77; H, 8.22.

3.3.6. 2,6-Anhydro-D-*glycero*-D-*gulo*-heptose diethyl acetal (20, *C*-β-D-glucopyranosylmethanal diethyl acetal). Using ethanolic solutions of NaOEt and H_2SO_4 instead of the pertinent methanolic solutions and otherwise the same procedure as for preparation of *C*-glycopyranosylmethanal dimethyl acetals, the title compound was obtained from *C*-β-D-glucopyranosylnitromethane. Yield 0.3 g (56%); $[\alpha]_D^{20}$ +3.5 (*c* 2, MeOH); R_f 0.25 (S_2); ^{1}H NMR (D_2O), δ 4.76 (d, 1H, $J_{1,2}$ 2.0 Hz, H-1), 3.60–3.88 [m, 6H, H-7a, H-7b, $2CH_2$(OEt)], 3.20–3.46 (m, 5H, H-2–6), 1.24 [t, 6H, $2CH_3$(OEt)]; ^{13}C NMR (D_2O), δ 102.9 (C-1), 82.0, 80.6, 79.7, 71.9, 71.4 (C-2–6), 63.1 (C-7), 65.9, 65.3 [$2CH_2$(OEt)], 15.7 [$2CH_3$(OEt)]. Anal. Calcd for $C_{11}H_{22}O_7$: C, 49.62; H, 8.33. Found: C, 49.88; H, 8.38.

Acknowledgements

This work was supported in part by the APVT-51/039802 and VEGA-2/6129/26 grants.

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