ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 2, pp. 235–241. © Pleiades Publishing, Ltd., 2014.
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N-Glycosides of 4-Aminostyrene

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Received May 27, 2013

Abstract—Glycosylation of 4-aminostyrene with α-D-glucopyranose, α,β-D-mannopyranose, L-rhamnopyranose, and α,β-L-arabopyranose in alcoholic medium has been studied. 4-Aminostyrene *N*-glycosides like 1-(4-vinylphenyl)amino-1-deoxy-D-glucopyranose, 1-(4-vinylphenyl)amino-1-deoxy-β-D-mannopyranose, 1-(4-vinylphenyl)amino-1-deoxy-β-L-rhamnopyranose, and 1-(4-vinylphenyl)amino-1-deoxy-L-arabopyranose were synthesized and characterized for the first time.

DOI: 10.1134/S1070363214020133

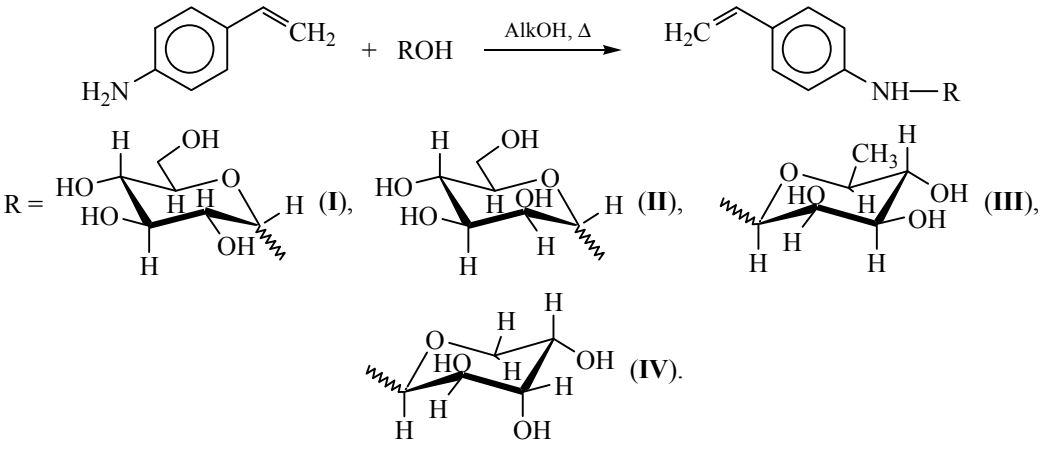
Carbohydrate-containing polymers having saccharide residues in the side chain and exhibiting valuable properties, for instance, biological activity: immunomodulating [1], antitumor [2], etc., which are suitable for preparation of new drugs and medical materials are prepared mainly by homo- and copolymerization of vinyl monomers, saccharides containing groups with double carbon-carbon bonds in their structure. Among these monomers esters and amides of unsaturated acids are the most widespread, and more rarely the unsaturated alcohol ethers are applied [3].

At the same time practically no data concerning the *N*-glycosides of vinyl-containing amines and no descriptions of their synthesis are reported. The only exclusions are short reports [4–6] and a paper [7] describing glycosylation of allylamine and the structure of its *N*-glycosides. Creating of new group of monomers opens new pathway to the synthesis of polyfunctional *N*-glycosides having in their structure wide variety of saccharide residues in controlled ratio and amounts, and exhibiting biological activity.

Hence, development of methods for preparation of *N*-glycoside monomers from vinyl-containing amines undoubtedly is an actual problem.

The aim of this work was the investigation of glycosylation of 4-aminostyrene with α-D-glucopyranose, α,β-D-mannopyranose, α-L-rhamnopyranose, and α,β-L-arabopyranose in anhydrous alcoholic medium and establishing the structure of the obtained *N*-glycosides.

Synthesis route of 4-aminostyrene *N*-glycosides: 1-(4-vinylphenyl)amino-1-deoxy-D-glucopyranose **I**, 1-(4-vinylphenyl)amino-1-deoxy-β-D-mannopyranose **II**, 1-(4-vinylphenyl)amino-1-deoxy-β-L-rhamnopyranose **III**, and 1-(4-vinylphenyl)amino-1-deoxy-L-arabopyranose **IV** is presented in the scheme.



Influence of parameters of the process on the yield of *N*-glycoside **II**

D-Mannose excess, mol %	Concentration of 4-aminostyrene in starting solution, $c\times10^3$, g/mL	Reaction time, min	Yield, %
0.005 (25.0)	79.43	30	52.0
0	230.00	53	19.3[a]
0.0043 (21.6)	111.77	13	72.5[b]

[a] At the end of the process 1.3 mL of solvent was added, and the reaction mixture was heated to boiling. [b] The crystallized mass was heated to boiling.

As is known, the rate of glycosylation depends on the nucleophilicity of amine and the configuration of the saccharide. Yield of *N*-glycosides significantly depends also on the nature of reaction medium. In the study of the glycosylation of aliphatic amines, for example, allylamine, with aldohexoses in primary aliphatic alcohols [7] it was found that the rate of the reaction, the yield of target products, and the occurrence of by-processes under the other equal conditions strongly depend on the nature of alcohol. It was shown also that hexoses containing equatorial hydroxy group in the position 4 demonstrate the highest reactivity.

4-Aminostyrene, the aromatic amine, has significantly lower nucleophilicity than the aliphatic primary amines. Therefore it is presumable that it is would be less reactive towards the saccharides. But it has been shown in the investigation of its glycosylation with monosaccharides in alcohols that one of the main factors influencing the process is the configuration of the saccharide, and not the nucleophilicity of the amine.

For example, the reaction of α,β-D-mannopyranose with 4-aminostyrene proceeds as easily as with allylamine, but unlike the latter case, the yield of *N*-glycoside is strongly affected by the excess of monosaccharide.

As seen from the table, at stoichiometric ratio of reagents a low yield of the product is observed even at their higher concentration. Higher yield of 1-(4-vinylphenyl)amino-1-deoxy-β-D-mannopyranose is obtained at the excess of α,β-D-mannopyranose and in reaction proceeding in a large amount of solvent. Evidently in less concentrated starting alcoholic solution of 4-aminostyrene the reaction proceeds faster due to fast elimination of obtaining *N*-glycoside from the surface of starting saccharide, and the excess of the latter compensates the influence of lower concentration of reacting substances due to the increase in the specific surface. Therefore at the increased availability of the D-mannose surface and its simultaneous growth the reaction time decreases, and the yield of the product significantly rises. Many monosaccharides are insoluble in alcohols. In particular, α,β-D-mannose and α-D-glucose are insoluble in anhydrous methanol and ethanol even at boiling. Nevertheless, in the case of glycosylation of 4-aminostyrene with α,β-D-mannopyranose the latter dissolves virtually completely including the excess of monosaccharide. This unreacted monosaccharide does not crystallize from the solution obtained after crystallization of the main part of *N*-glycoside and its removal. No such effect was observed in the glycosylation of allylamine.

At treating pure 4-aminostyrene with α-D-glucopyranose in alcoholic medium no glycosylation occurs. For example, heating a mixture of reagents under the inert atmosphere at 70°C in anhydrous methanol or its mixture with anhydrous ethanol for 4–5 h only dissolution of major part of starting monosaccharide and its anomerization were observed. From the solution of reaction mixture besides the starting amine only the mixture of anomers of D-glucopyranose was always isolated. β-Anomer is formed in the amounts comparable with α-anomer. These results were obtained while performing at least ten experiments with starting solutions of different composition. Hence, the change in the relative configuration of monosaccharide, in this case in going from the axial location of hydroxyl at C^2 to the equatorial one its reactivity decreases. The same effect was observed in the glycosylation of allylamine [7]. The mechanism of formation of stable oversaturated alcoholic solutions of D-mannopyranose in the course of the synthesis of *N*-glycoside **II** or of α,β-D-glucopyranose in the course of isomerization of α-anomer is not sufficiently clear, but it may be suggested that it is similar in both cases.

It was found that under other equal conditions 4-aminostyrene can undergo glycosylation with D-glucose simultaneously with 1-amino-4-ethylbenzene. For example, heating a mixture containing 70 mol % of 4-aminostyrene and 30 mol % of 1-amino-4-ethylbenzene together with D-glucopyranose in a mixture of anhydrous methanol and ethanol at 70°C

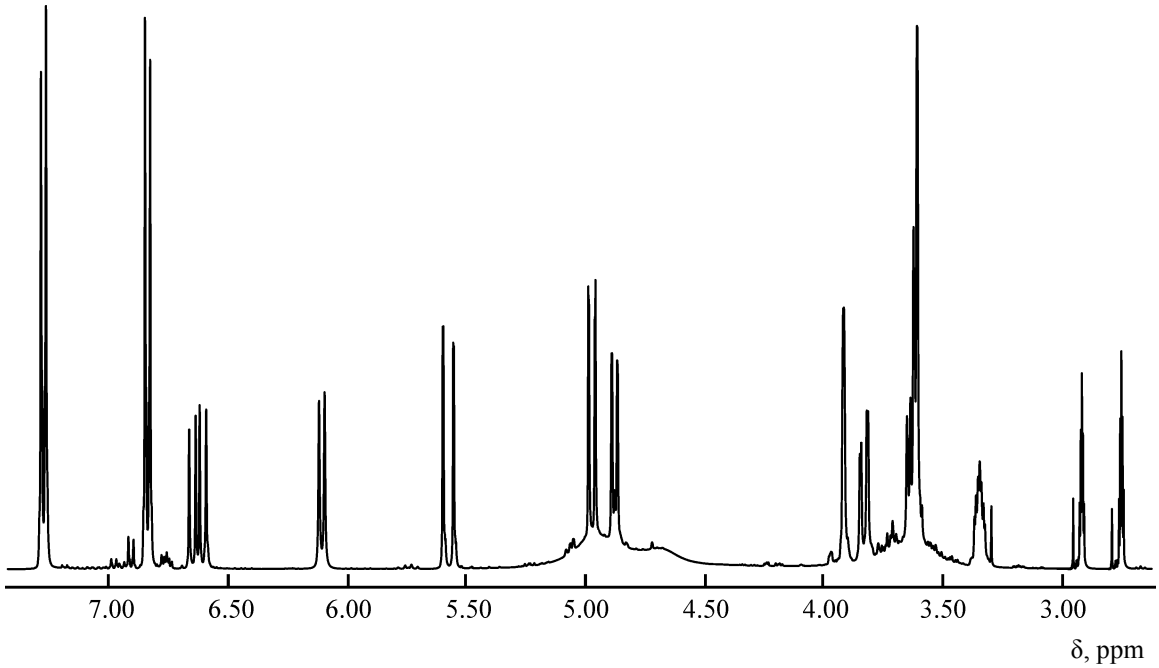


Fig. 1. ^{1}H NMR spectrum of *N*-glicoside **II**.

for 5 h leads to the formation of two *N*-glycosides among which 1-(4-vinylphenyl)amino-1-deoxy-D-gluco-pyranose **I** is the prevailing product.

Structure of *N*-glycosides **I-IV** was established using ^{1}H and ^{13}C NMR spectroscopy including correlation methods HSQC and HMBC. Relative configuration of compounds at the anomeric C^{1} atom was established from the value of $J_{H^1-H^2}$ coupling constant in the ^{1}H NMR spectrum. The signal of the corresponding H^{1} atom was found from the cross-peak belonging to the coupling of $^{1}H^{1}$ and $^{13}C^{1}$ nuclei.

NMR spectra confirming the structure of 1-(4-vinylphenyl)amino-1-deoxy-β-D-mannopyranose are presented in Figs. 1−3.

In the ^{1}H NMR spectrum (Fig. 1) signals of protons of D-mannose residue are located in the range 3.2–4.9 ppm. H^{1} anomeric proton is characterized by a doublet of doublets at 4.87–4.89 ppm (*J* 9.4 Hz). High value of coupling constant $J_{H^1-H^2}$ shows that the anomeric center of saccharide **II** has β-configuration. Signal of the vinyl group protons appear in the range 4.9–6.7 ppm. Geminal protons give two doublets at 4.9–5.7 ppm, and vicinal proton is characterized by a quartet at 6.63 ppm. Doublet of the proton of secondary amino group is observed at 6.11 ppm (*J* 9.4 Hz). Two intense downfield doublets belong to the protons of the aromatic ring.

^{13}C NMR spectrum (Fig. 2) unambiguously shows that this compound is present as one anomer, has a six-member heteroring, and in the course of glycosylation no formation of admixtures of other isomers occurs. Signals of the pyranose ring carbon atoms C^{2-5} are located in the upfield region. The signal corresponding to the exocyclic atom C^{6} is observed at δ_C 63.10 ppm. The signal of the anomeric atom C^{1} is located at 83.05 ppm, and in the range 114–149 ppm the set of signals of aglycone appears. Signals of carbon atoms in the positions 3, 4, and 5 of the aromatic ring overlap and give two peaks at 128.04 and 128.30 ppm respectively.

In the reaction of 4-aminostyrene with L-rhamnopyranose and L-arabinose no complications are observed. In the case of L-rhamnose *N*-glycoside **III** is formed in good yield. From the spectral data presented in Fig. 3 it follows that this compound also exists in the pyranose form.

In the ^{13}C NMR spectrum a set of signals of C^{1-5} carbon atoms appears in the range 71–84 ppm. The signal of the anomeric proton H^{1} gives a doublet of doublets at 4.88-4.91 ppm (*J* 9.8 Hz), consequently the anomeric center of the saccharide **III** has also β-configuration. The exocyclic atom C^{6} is characterized by an upfield signal. The other cross-peaks excluding the signals of solvent correspond to the coupling of ^{1}H and ^{13}C atoms of aglycone.

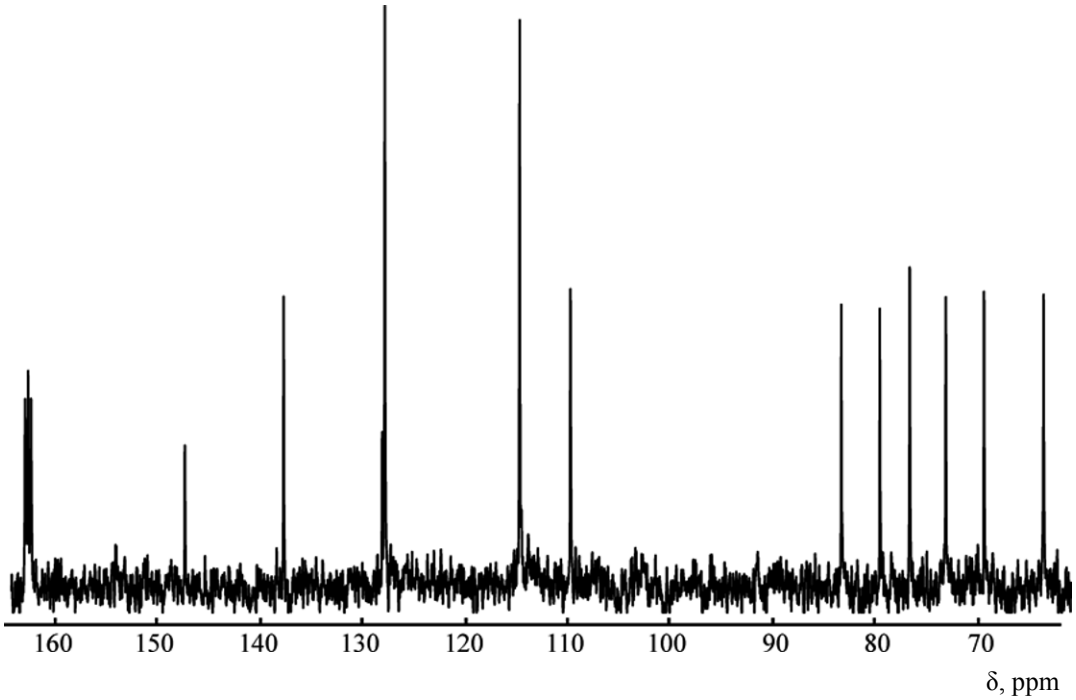


Fig. 2. ^{13}C NMR spectrum of *N*-glycoside **II** in DMF-d_7.

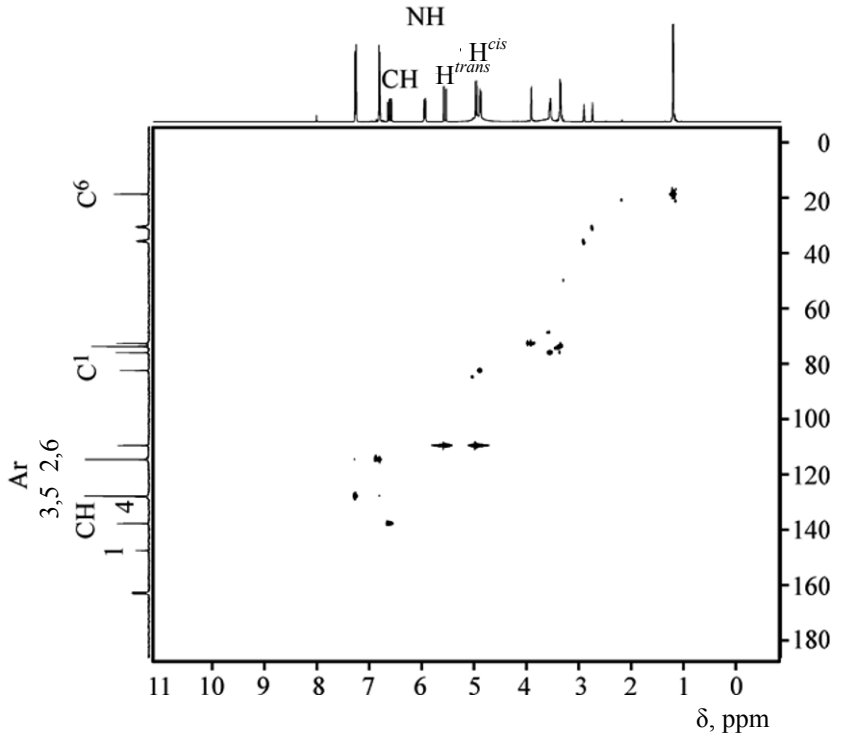


Fig. 3. HSQC ^{1}H–^{13}C NMR spectrum of 1-(4-vinylphenyl)amino-1-deoxy-β-L-rhamnopyranose (DMF-d_7).

In the course of the reaction of 4-aminostyrene with α,β-L-arabinose in anhydrous methanol several isomers of *N*-glycoside are formed. Analysis of HSQC NMR data, in particular, ^{13}C NMR spectra, permits a conclusion that the product of glycosylation may exist as β-anomer of *N*-arabinopyranoside **IV** as well as a mixture of isomers including its α- and β-anomers containing the admixture of furanose forms. The trend

in N-arabinoside to form several isomers is evidently due to the absence of substituent at C^5 atom of the carbohydrate part of the molecule.

Hence, the process of glycosylation of 4-aminostyrene with aldoses was investigated, and it was found that most reactive are saccharides having the equatorial location of hydroxy group on C^4 and axial on C^2 atom. The presence of substituent at C^5 influences the stability of carbohydrate part of molecule and its configuration. The interaction of starting substances, intermediates, reaction products, and solvent with one another is observed. It is expressed in such effects, as glycosylation proper, in particular, with D-glucose, anomerization of starting monosaccharides and their unusual solubility. Finally note that 1-(4-vinylphenyl)-amino-1-deoxy-D- and L-saccharides, synthesized and characterized for the first time, are successfully used as new vinyl monomers.

EXPERIMENTAL

NMR spectra were registered on a Bruker Avance II 400 spectrometer (400.1 MHz ^{1}H, 100.6 MHz ^{13}C) in DMF-d_7 (δ 8.03 ppm, CDO), and in D_2O (δ 4.78 ppm, HDO suppression). UV spectra were registered on a LOMO SF-256 UVI spectrophotometer. Elemental analysis data were obtained on a Vario Elemental C,H,N,S analyzer. TLC was carried out on Silufol UV 254 plates (elution with MeOH, development with I_2).

Anhydrous methanol and ethanol were prepared by treating commercial product with excess CaH_2, distillation, and repeated distillation with small amount of sodium. Diethyl ether was purified from admixtures and boiled over sodium. Anhydrous monosaccharides of "chemically pure" grade were used. Synthesis of starting 4-aminostyrene was described previously [8–12].

1-(4-Vinylphenyl)amino-1-deoxy-D-glucopyranose I. A mixture, 0.33 g, of 4-aminostyrene (70 mol % or 69.9 wt %, 1.9 mmol) with 1-amino-4-ethylbenzene (30 mol %), was treated with 0.001 g of hydroquinone, 0.005 g of sodium bisulfite, 2.5 mL of anhydrous methanol, 2.5 mL of anhydrous ethanol, and 0.75 g of finely pulverized α-D-glucopyranose. After that the reaction mixture was heated under argon at 70°C for 5 h with intermittent stirring. After the reaction was complete the solution was decanted from the precipitate of D-glycose, and the suspended material was filtered off. The residual D-glucose was twice washed with anhydrous ethanol, and then with anhydrous diethyl ether. After drying in air 0.23 g of substance was obtained. All filtrates were combined, and the solvent was removed in a vacuum. The syrup-like residue was treated with 50 mL of anhydrous diethyl ether, and fine crystalline precipitate began to form. The suspension was decanted, the hygroscopic residue was quickly filtered off, washed with anhydrous diethyl ether, and immediately placed in a vacuum dessicator over P_4O_{10}. The residue was triturated in the anhydrous diethyl ether, the obtained suspension was filtered off, the crystals were washed with anhydrous diethyl ether and dried in a vacuum over P_4O_{10}. A mixture of *N*-glycosides was obtained as a fine crystalline powder, yield 0.60 g, mp 80.5–83°C. It contained 53.4 mol % of *N*-glycoside **I**. From the obtained mixture 1-(4-vinylphenyl)amino-1-deoxy-D-glucopyranose was isolated by column chromatography. ^{1}H NMR spectrum (D_2O), δ, ppm: 3.35–4.75 m (11H, H^{1-6}, $OH^{2-4,6}$), 4.5–7.0 d (1H, NH), 5.10 d.d (1H, *cis*-H, *J* 11.1 Hz), 5.54 d.d (1H, *vic*-H, *J* 11.0 Hz), 6.82 d (2H, 2,6-Ar, *J* 8.4 Hz), 7.35 d (2H, 3,5-Ar, *J* 8.5 Hz).

1-(4-Vinylphenyl)amino-1-deoxy-β-D-mannopyranose II. *a*. To a solution of 2.383 g (20 mmol) of 4-aminostyrene in 30 mL of anhydrous methanol 4.504 g (25 mmol) of finely powdered α,β-D-mannopyranose was added. The reaction mixture was heated under argon for 0.5 h at 70°C with intermittent stirring. The most part of D-mannose dissolved in the course of 13–15 min, and at the end of heating the dissolution was almost complete. The solution was decanted from the insignificant amount of precipitate and left for crystallization. After several minutes the crystals formed were filtered off, washed with small amount of methanol, and dried over P_4O_{10}. *N*-glycoside, 2.45 g, was obtained as lustrous plate crystals. The rest of the product was extracted at heating with small amounts of methanol, insoluble precipitate was filtered off, and combined filtrates were concentrated in a vacuum. Fine crystalline precipitate was filtered off, washed with methanol, and dried to give 0.45 g of product **II**. One more portion of crystals, 0.13 g of white fine crystalline substance was isolated from the filtrate. This batch was crystallized from boiling methanol to give 0.025 g of *N*-glycoside. Total yield 2.925 g (52%). TLC: R_f 0.72. ^{1}H NMR spectrum, δ, ppm: 3.35 m (1H, H^5), 3.5–4.0 m (9H, $H^{2-4,6}$, $OH^{2-4,6}$), 4.88 d.d (1H, β-H^1, *J* 0.8, *J* 9.4 Hz), 4.98 d.d (1H, *cis*-H, *J* 1.1, *J* 10.9 Hz), 5.58 d.d (1H, *trans*-H, *J* 1.2, *J* 17.6 Hz), 6.11 d (1H, NH, *J* 9.4 Hz), 6.63 q (1H, *vic*-H, *J* 11.0 Hz), 6.84 d (2H, 2,6-Ar, *J* 8.6 Hz), 7.28 d (2H,

3,5-Ar, *J* 8.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 63.10 (C^6), 68.98 (C^4), 72.74 (C^3), 76.30 (C^2), 79.25 (C^5), 83.05 (C^1), 109.75 (=CH_2), 114.75 (2,6-Ar), 128.05 (3,5-Ar), 128.31 (3-Ar), 138.03 (CH=), 147.76 (1-Ar). UV spectrum, λ_{max}, nm: 274.9 (H_2O); 278.9 (MeOH). Found, %: C 59.29, H 6.92. $C_{14}H_{19}NO_5$. Calculated, %: C 59.78, H 6.81.

Filtrate obtained after isolation of the product was diluted with the excess of diethyl ether. White viscous precipitate was formed which crystallized in air. Yield 1.90 g. It was identified as a mixture of D-mannopyranose and *N*-glycoside **II** in 10 : 1 ratio.

b. To a solution of 1.38 g (11.6 mmol) of 4-aminostyrene in 6 mL of anhydrous methanol 2.09 g (11.6 mmol) of α,β-D-mannopyranose was added. The reaction mixture was stirred and heated for 53 min at 70°C under argon with intermittent stirring. After that 1.3 mL of anhydrous methanol was added, reaction mixture was heated to boiling and left for crystallization. When the crystallization was complete, the solid obtained was filtered off, washed twice with small portions of anhydrous methanol, and dried over P_4O_{10}. Yield 0.63 g (19.3%), white crystalline substance. UV spectrum (H_2O), λ_{max} 274.9 nm. From the filtrate 1.1 g of contaminated D-mannopyranose was isolated.

c. To a solution of 4-aminostyrene (1.90 g, 15.9 mmol) in 17 mL of anhydrous methanol 3.59 g (19.9 mmol) of α,β-D-mannopyranose was added. The obtained mixture was heated to 69°C with intermittent stirring for 13 min. During this period dissolution of D-mannose and subsequent crystallization of *N*-glycoside was observed. The obtained reaction mixture was heated to boiling, and after cooling the product was filtered off, twice washed with cooled anhydrous methanol, and dried in air. Residual D-mannose was boiled with filtrate, hot solution was decanted from the insoluble precipitate which was washed with anhydrous methanol, and all liquids were combined. After crystallization additional portion of the product was obtained. Total yield 3.25 g (72.5%).

1-(4-Vinylphenyl)amino-1-deoxy-β-L-rhamnopyranose III. To a solution of 1.31 g (11.0 mmol) of 4-aminostyrene in 2.0 mL of anhydrous methanol heated to 65°C 2.05 g (12.5 mmol) of finely pulverized α-L-rhamnopyranose was added. The reaction mixture was heated under argon at 65±0.5°C for 54 min. After 45 min of heating the solution began to crystallize, and at the end of heating the reaction mixture solidified. The obtained solid mass was crushed, the crystals were filtered off, washed with small amount of cooled anhydrous methanol and dried in air, and then in a vacuum over P_4O_{10}. Yield 1.64 g (56.3%), white crystalline substance decomposing while heating. TLC: R_f 0.72. ^{1}H NMR spectrum, δ, ppm: 1.21 t (3H, CH_3, *J* 5.8 Hz), 3.3–3.6 m (6H, $H^{3–5}$, $OH^{3–5}$), 3.92 d (1H, H^2, *J* 2.6 Hz), 4.90 d.d (1H, βH^1, *J* 0.6, *J* 9.8 Hz), 4.98 d.d (1H, *cis*-H, *J* 1.0, *J* 10.9 Hz), 5.57 d.d (1H, *trans*-H, *J* 1.1, *J* 17.6 Hz), 5.96 d (1H, NH, *J* 9.8 Hz), 6.63 q (1H, *vic*-H, *J* 11.0 Hz), 6.83 d (2H, 2,6-Ar, *J* 8.6 Hz), 7.28 d (2H, 3,5-Ar, *J* 8.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.68 (C^6); 72.81 (C^2); 73.84, 76.05 ($C^{3–5}$), 82.55 (C^1), 109.77 (=CH_2), 114.80 (2,6-Ar), 128.06 (3,5-Ar), 128.34 (4-Ar), 138.02 (CH=), 147.78 (1-Ar) UV spectrum (H_2O), λ_{max}, nm: 275.9.

1-(4-Vinylphenyl)amino-1-deoxy-L-arabinopyranose IV. *a*. A mixture of 0.08 g (0.67 mmol) of 4-aminostyrene, 1.0 mL of anhydrous methanol, and 0.10 g (0.67 mmol) of α,β-L-arabinose was heated at 69–70°C for 65 min under intermittent stirring. After that the insignificant amount of unreacted monosaccharide was filtered off and washed with anhydrous methanol. The filtrate was added to 50 mL of anhydrous diethyl ether, the obtained solution was evaporated in a vacuum, and the residue was several times washed with anhydrous diethyl ether. After that the residue was crushed under a layer of anhydrous diethyl ether, filtered, and dried over P_4O_{10}. Yield 0.05 g (29.7%), white crystalline hygroscopic substance melting and acquiring coloration in air. UV spectrum (MeOH), λmax, nm: 200, 279.9.

b. A solution of 1.70 g (14.3 mmol) of 4-aminostyrene in 8 mL of anhydrous methanol was heated to 65°C, and 2.25 g (15.0 mmol) of pulverized α,β-L-arabinose was added to it. After that it was heated under argon at 69°C for 39 min. The isolation of the product was carried out analogously to the previous case. The syrup obtained after removing solvents was crystallized by triturating it on a glass with intermittent washing with anhydrous diethyl ether. Yield 2.76 g (77%). ^{13}C NMR spectrum (DMF-d_7), δ_C, ppm: 66.63 (C^5); 69.45, 71.89, 74.98 (C^{2-4}); 86.41 (βC^1), 109.58 (=CH_2), 114.39 (2,6-Ar), 128.01 (3,5-Ar), 128.10 (4-Ar), 137.99 (CH=), 148.44 (1-Ar).

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