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# Acid-catalyzed isomerization of methyl 2-deoxy-D-*arabino*-hexosides: equilibria, kinetics and mechanism

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**Abstract**

Four isomers of methyl 2-deoxy-D-*arabino*-hexosides were isolated by HPLC as chromatographically homogeneous compounds. The rates of pyranoside isomerization ($\alpha^p$ and $\beta^p$) at 40 °C and of furanoside isomerization ($\alpha^f$ and $\beta^f$) at 26 °C were determined. A mechanism has been suggested for transformations taking place during isomerization of methyl 2-deoxy-D-*arabino*-hexosides in methanolic solution catalyzed with hydrogen chloride. © 2002 Elsevier Science Ltd. All rights reserved.

*Keywords:* Methyl 2-deoxy-D-*arabino*-hexosides; Kinetic studies; Isomerization; Anomerization

## 1. Introduction

The first report on the synthesis of methyl 2-deoxy-α- and β-D-glucopyranosides appeared in 1922.[1] Hughes et al. in 1949 prepared a mixture, named by them 'α- and β-methyl-2-deoxy-D-glucofuranosides' because its optical rotation suggested another isomeric structure than that of methyl 2-deoxy-α- or β-D-glucopyranoside.[2] Bhat and Zorbach[3] reported the synthesis, isolation and purification of methyl 2-deoxy-α-D-*arabino*-hexofuranoside. The configuration of the anomeric carbon atom was established on the basis of optical rotation ($[\alpha]_D^{24}$ + 117.1°) only. The authors demonstrated also that the 'α- and β-methyl-2-deoxy-D-glucofuranosides' mixture contained ca. 30% of α- and β-pyranosides in the 1:1 ratio, ca. 35% of methyl 2-deoxy-α-D-*arabino*-hexofuranoside and ca. 35% of the starting sugar.

Capon et al. in 1962 reported important results on the isomerization of methyl β-D-glucoside in a methanolic solution of methanesulfonic acid.[4] The overall rate constant ($k_1 + k_{-1}$) for anomerization of this compound at different temperatures, based on changes of optical rotation, was determined by them. They also observed a slow change of optical rotation, which was interpreted as being due to a secondary reaction resulting in a change of the heterocyclic ring size. The composition of the 'furanoside–pyranoside' mixture was quantified on the basis of formaldehyde and formic acid concentrations arising after oxidation with sodium periodate. They determined the overall rate constant for the change in furanosidic ring size.

Extremely interesting research has recently been conducted by Swedish scientists.[5] They carried out isomerization of methyl glycosides in the presence of 4-methylmorpholine hydroborane. This compound reduces the carboxonium ions to give alditols and/or anhydroalditols. These results evidently indicated the cyclic and/or chain structures of the transition state formed during isomerization of the *O*-glycoside.

The isomerization reaction of the methyl 2-deoxy-α-D-*arabino*-hexofuranoside under conditions described by the authors, in addition in the presence of *N*-methylmorpholine borohydride, affords two 'capture' products, a chain and a cyclic alditol.[5]

In this article we report conditions for the isolation of methyl per-*O*-acetyl-2-deoxy-D-*arabino*-hexosides by HPLC and the results of kinetic studies of acid-catalyzed isomerization of *O*-deacetylated glycosides.

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## 2. Results and discussion

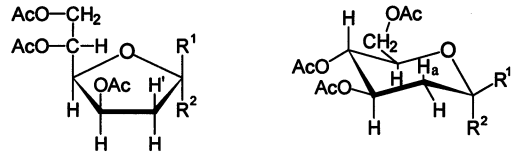
Glycosidation of 2-deoxy-D-*arabino*-hexose in absolute methanol containing catalytic amounts of hydrogen chloride was performed under two procedures described by Hughes et al.,[2] which resulted in two mixtures of products (labeled **A** and **B**). In mixture **A**, apart from small quantities of unreacted sugar, we detected two main products using the capillary gas chromatography (CGC) method. These products were isolated by HPLC as exhaustively *O*-acetylated derivatives. Their NMR spectra enabled us to identify them as methyl 3,4,6-tri-*O*-acetyl-2-deoxy-α- and β-D-*arabino*-hexopyranosides (**3** and **4**).

Again, in mixture **B** four compounds were detected. Two of these were identical with those present in sample **A**. Thus, we decided to isolate the remaining two, methyl 3,4,6-tri-*O*-acetyl-2-deoxy-α- and β-D-*arabino*-hexofuranosides (**1** and **2**). In order to determine the configuration of the anomeric carbon atom, NOE, COSY and $^{13}C$ NMR spectra of these compounds were taken. Their NMR spectra indicate that furanosides have been isolated. A NOE spectrum of compound **1** showed an interaction across the space between H-1 and H-5 and unequivocally confirmed its α configuration (Fig. 1).

Retention indices in CGC and HPLC are summarized in Table 1.

Four chromatographically homogeneous isomers after *O*-deacetylation were used for the kinetic studies of the isomerization. The concentrations of kinetically controlled products of the acid-catalyzed isomerization of the pyranosides at 40 °C are summarized in Table 2. Equilibrium mixtures contained three isomers, $\alpha^p$, $\beta^p$ and $\alpha^f$, in concentrations of 88.0, 10.5 and 1.5%, respectively. The concentrations of kinetically controlled products of the acid-catalyzed isomerization of the furanosides at 26 °C are shown in Table 3, and the equilibrium concentrations of isomers $\alpha^p$, $\beta^p$, $\alpha^f$ and $\beta^f$ were 84.0, 13.5, 2.2 and 0.3%, respectively. It is noteworthy that the very low concentration of methyl 2-deoxy-β-D-*arabino*-hexofuranoside was determined on the basis of the fixed $[\beta^f]/[\alpha^f]$ concentration ratio during the whole process of isomerization.

The kinetic curves in Figs. 2 and 3 describing temporal changes of the concentrations of products obey first-order kinetics. However, the reactions are not as simple as highlighted by the semilogarithmic relationships presented in Fig. 4. Significant deviations from the reaction of first-order are characteristic of complex reactions, i.e., two parallel reactions of first-order but running at different rates and leading to the same final product.[6] A similar pattern was observed with mutarotation of some sugars[7] and their derivatives.[8] The pyranose–furanose isomerization is usually rapid, but that of α-pyranose–β-pyranose is a slower process.[9,10]




**1**: $R^1$=H; $R^2$=$OCH_3$ **3**: $R^1$=H; $R^2$=$OCH_3$

**2**: $R^1$=$OCH_3$; $R^2$=H **4**: $R^1$=$OCH_3$; $R^2$=H

Fig. 1. Structures of methyl tri-*O*-acetyl-2-deoxy-D-*arabino*-hexosides.

Table 1
Retention times of the methyl per-*O*-acetyl-2-deoxy-D-*arabino*-hexoside isomers in CGC and HPLC

| | $t_R$ (CGC) (min) | $t_R$ (HPLC) (min) |
|---|---|---|
| α-Furanoside ($\alpha^f$, **1**) | 12.47 | 13.30 |
| β-Furanoside ($\beta^f$, **2**) | 13.57 | 8.80 |
| α-Pyranoside ($\alpha^p$, **3**) | 14.32 | 11.69 |
| β-Pyranoside ($\beta^p$, **4**) | 14.67 | 9.83 |

Table 2
Percentage concentrations of kinetically controlled products of the methyl 2-deoxy-α- and β-D-*arabino*-hexopyranosides isomerization [a]

| Time (min) | $\alpha^p$ | $\beta^p$ | $\alpha^f$ | $\beta^p$ | $\alpha^p$ | $\alpha^f$ |
|---|---|---|---|---|---|---|
| 0 | 100 | 0 | 0 | 100 | 0 | 0 |
| 1 | 98.0 | 2.0 | 0 | 52.2 | 46.4 | 1.4 |
| 3 | 92.7 | 7.3 | 0 | 34.2 | 64.0 | 1.8 |
| 5 | 92.0 | 7.2 | 0.8 | 30.1 | 62.4 | 6.5 |
| 10 | 90.9 | 8.0 | 1.1 | 23.8 | 72.3 | 3.9 |
| 15 | | | | 15.5 | 82.3 | 1.9 |
| 30 | 86.9 | 11.5 | 1.6 | 15.3 | 83.3 | 1.5 |
| 60 | 88.6 | 9.4 | 2.0 | 10.2 | 88.3 | 1.4 |
| 120 | 88.0 | 10.3 | 1.7 | 11.4 | 88.5 | 1.3 |

[a] 0.143 M methanolic solution of HCl at 40 °C.

Fig. 4 explicitly shows that the isomerization of pyranosides is a classic two-step process with such a complex transformation.

Following a short period of rapid variations in reactant concentrations, a slow stage of attaining equilibrium of the $\alpha^p \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \beta^p$ anomerization begins. The straight-line portion of curve **a** (Fig. 4) describes a stage of slow transformation rate of $\alpha^p$ with the simultaneous formation of the $\beta^p$ isomer. The slope of straight line **a** (Fig. 4) is equal to rate constant $k^p_{-\alpha}(s) = k^p_{\beta}(s) = 0.0603\ min^{-1}$. Again, the rate constant of $\alpha^p$ formation from $\beta^p$ (straight line **b** in Fig. 4) is close to the value of $k^p_{-\alpha}(s)$, namely $k^p_{-\beta}(s) = k^p_{\alpha}(s) = 0.0609\ min^{-1}$. Thus, the mean rate constant for interconversion of the α,β-pyranosides calculated from Eq. (1) (see Section 3) is $0.0606\ min^{-1}$, and it can be assumed that it is simple

Table 3
Percentage concentrations of kinetically controlled products of isomerization of methyl 2-deoxy-α- and β-D-*arabino*-hexofuranosides [a]

| Time (min) | $\alpha^f$ | $\alpha^p$ | $\beta^p$ | $\beta^f$ | $\beta^f$ | $\alpha^p$ | $\beta^p$ | $\alpha^f$ |
|---|---|---|---|---|---|---|---|---|
| 0 | 100 | 0 | 0 | 0 | 100 | 0 | 0 | 0 |
| 1 | 76.5 | 7.5 | 3.5 | 12.4 | 17.9 | 2.8 | 2.2 | 77.1 |
| 3 | 73.9 | 9.7 | 4.4 | 12.0 | 9.9 | 6.8 | 4.2 | 79.2 |
| 5 | 68.5 | 10.9 | 7.2 | 13.4 | 9.8 | 9.9 | 5.4 | 74.9 |
| 7 | 64.7 | 14.2 | 9.3 | 11.8 | 9.9 | 11.8 | 5.9 | 72.4 |
| 10 | 54.6 | 19.4 | 13.6 | 12.4 | 9.4 | 14.9 | 8.5 | 66.2 |
| 15 | 56.1 | 19.5 | 14.8 | 9.6 | 8.2 | 22.7 | 10.3 | 58.8 |
| 20 | | | | | 6.7 | 28.8 | 13.0 | 51.5 |
| 30 | 24.1 | 48.3 | 24.2 | 3.4 | 5.0 | 44.0 | 16.0 | 35.0 |
| 40 | | | | | 4.4 | 48.4 | 17.2 | 30.0 |
| 60 | 14.9 | 62.9 | 20.1 | 2.1 | 2.7 | 62.3 | 18.7 | 16.2 |
| 120 | 2.9 | 81.9 | 15.2 | 0.0 | 0.0 | 82.1 | 14.5 | 3.4 |
| 240 | | | | | 0.0 | 86.1 | 12.0 | 2.2 |

[a] 0.143 M methanolic solution of HCl at 26 °C.

reversible reactions, $k^p_{-\alpha}(s) = k^p_{-\beta}(s) = k_1 + k_{-1} = 0.0606\ min^{-1}$ or $7.06 \times 10^{-3}\ dm^3/(mol \times s)$, because the reaction was catalyzed with hydrogen chloride ($c = 0.143$ M). Thus, since that $k_1/k_{-1} = 0.119$ (Table 4), then $k_1 = 7.51 \times 10^{-4}\ dm^3/(mol \times s)$ and $k_{-1} = 6.31 \times 10^{-3}\ dm^3/(mol \times s)$.

The slow stage of the anomerization is preceded by a rapid stage that also led to inversion of the anomeric carbon atom configuration. Owing to the high rate and small number of the data points for the first stage of the reaction, $k$ constants calculated from Eq. (2) (see Section 3) are certainly of low precision. They are, however, highly different and allow one to reach conclusions about the course of the reaction. Thus, isomer $\beta^p$ is formed from isomer $\alpha^p$ with the rate expressed by $k^p_{-\alpha} = k^p_\beta = 0.304\ min^{-1}$, and more than a half of the equilibrium quantity of $\alpha^p$ is formed from $\beta^p$ at a rate constant $k^p_{-\beta} = k^p_\alpha = 1.43\ min^{-1}$.

Both constant rates can be related to direct elementary reactions ($\alpha^p \rightarrow \beta^p$ and $\beta^p \rightarrow \alpha^p$) because product concentrations are very low at the beginning, and the reversible reaction does not attain sufficient rate in accordance with the mass action law. However, since $k^p_{-\alpha} + k^p_{-\beta} \gg k_1 + k_{-1}$ and the $k^p_\beta/k^p_\alpha$ ratio is 0.21, being greater than the equilibrium constant, the $k^p_{-\alpha}$ and $k^p_{-\beta}$ constants reveal another pathway of anomerization of the pyranosides during the fast stage of the reaction. Furthermore, data of Table 2 show that a small quantity of the $\alpha^f$ appears also during the isomerization of both pyranosides. The furanoside formation rate is approximately equal to the rate of pyranoside isomerization, $k^f_\alpha = 0.34$ and $1.44\ min^{-1}$ for the isomerization of the $\alpha^p$ and $\beta^p$ isomer, respectively. This suggests that the rapid stage of the pyranoside anomerization proceeds via the furanoid form analogously to the methyl glycoside formation from D-xylose.[11] In our

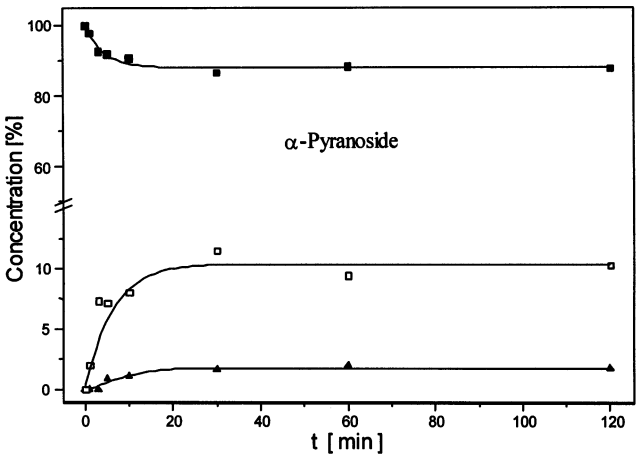



Fig. 2. Isomerization of methyl 2-deoxy-α-D-*arabino*-hexopyranoside. ■, $\alpha^p$; □, $\beta^p$; ▲, $\alpha^f$.

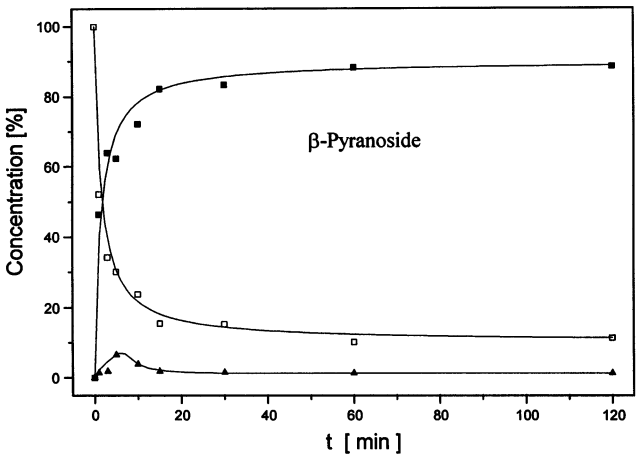



Fig. 3. Isomerization of methyl 2-deoxy-β-D-*arabino*-hexopyranoside. ■, $\alpha^p$; □, $\beta^p$; ▲, $\alpha^f$.

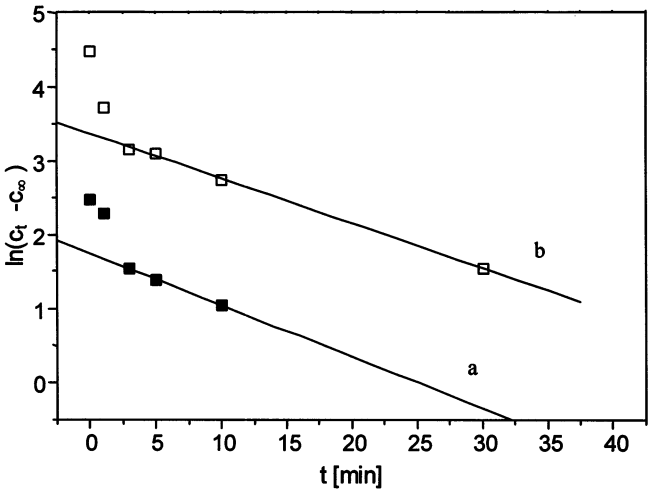



Fig. 4. Deviations from the first order reaction rate for the $\alpha^p \rightleftarrows \beta^p$ anomerization (■) and $\beta^p \rightleftarrows \alpha^p$ (□). Straight line **a**: $y = 0.0603(\pm 0.0015)x + 1.5144(\pm 0.0104)$, $r = 0.9998$; straight line **b**: $y = 0.0609(\pm 0.0016)x + 3.376(\pm 0.02556)$, $r = 0.9993$.

Table 4
Equilibrium constants $K$ for the isomerization reactions

| | Equilibrium | $K$ (40 °C) | $K$ (26 °C) |
|---|---|---|---|
| $K_1$ | $\alpha^p \rightleftarrows \beta^p$ | 0.119 | 0.161 |
| $K_2$ | $\beta^p \rightleftarrows \beta^f$ | ~0.015 | 0.022 |
| $K_2K_3$ | $\beta^p \rightleftarrows \alpha^f$ | 0.143 | 0.163 |
| $K_{-3}$ | $\alpha^f \rightleftarrows \beta^f$ | | 0.137 |
| $K_{-3}K_{-4}$ | $\alpha^p \rightleftarrows \beta^f$ | | 0.0036 |
| $K_{-4}$ | $\alpha^p \rightleftarrows \alpha^f$ | 0.017 | 0.026 |

case, the rapid stage of $\beta^p$ anomerization is inhibited before completion of the anomerization process and then in the curve of $\alpha^f$ formation a small maximum appears (Fig. 3). These findings lead to the assumption that at the beginning of the rapid stage of isomerization, the irreversible reaction $\beta^p \rightarrow \alpha^f \rightarrow \alpha^p$ occurs,[8] and as soon as the concentration of $\alpha^f$ reaches a sufficient level, the first stage of the reaction becomes reversible: $\beta^p \rightleftarrows \alpha^f \rightarrow \alpha^p$. Formation of $\beta^p$ is quicker than $\alpha^p$, thus further progress of the reaction slows down before attaining the $\beta^p \rightleftarrows \alpha^p$ equilibrium.

Experiments with the isomerization of furanosides should be performed at lower temperatures since furanosides are unstable.

Variations of concentrations of the reactants and products during isomerization of the furanosides are shown in Table 3 and Figs. 5 and 6. During the initial rapid stage of the reaction, isomer $\beta^f$ is quickly converted into isomer $\alpha^f$, followed by setting up the $\beta^f \rightleftarrows \alpha^f$ equilibrium. On the other hand, during the slow stage of isomerization of the furanosides, corresponding pyranosides are formed: $\alpha^f \rightarrow \alpha^p$ and $\beta^f \rightarrow \beta^p$.

A careful analysis of the results of these experiments allows one to suggest the interconversions presented in Scheme 1.

Accordingly to Scheme 1, the isomerization rate constant of the labile isomer $\beta^f$ calculated from Eq. (2) for the rapid stage of the reaction is:

$$k^f_{-\beta} = k_3 + k_{-3} = 2.62 \text{ min}^{-1}$$

Since $k_{-3}/k_3 = 0.137$, then $k_3 = 2.30 \text{ min}^{-1}$ and $k_{-3} = 0.315 \text{ min}^{-1}$.

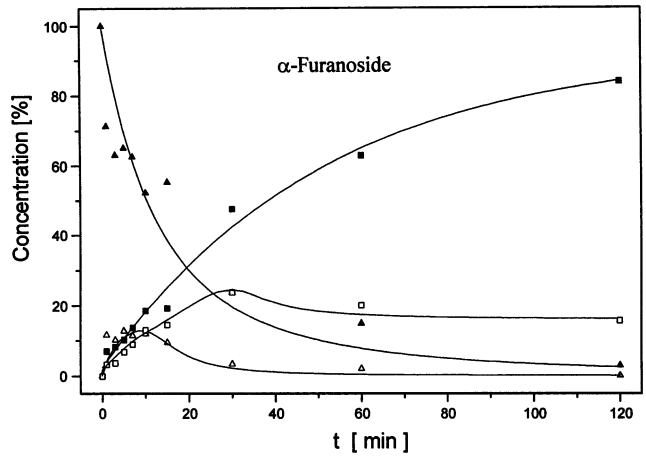



Fig. 5. Temporal variations of concentrations of the methyl 2-deoxy-α-D-*arabino*-hexofuranoside isomers. ■, $\alpha^p$; □, $\beta^p$; ▲, $\alpha^f$; △, $\beta^f$.

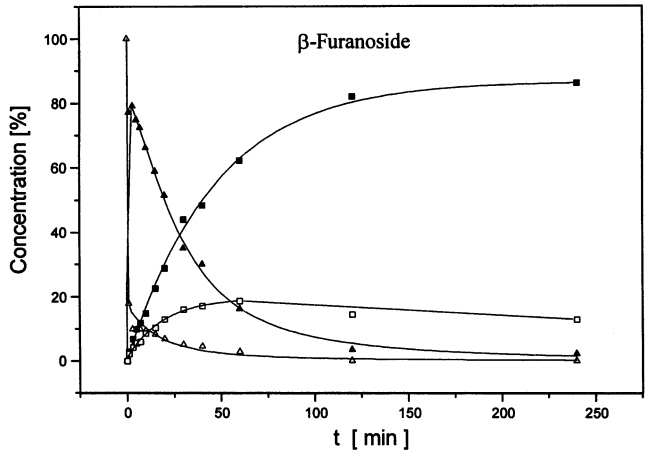



Fig. 6. Temporal variations of concentrations of the methyl 2-deoxy-β-D-*arabino*-hexofuranoside isomers. ■, $\alpha^p$; □, $\beta^p$; ▲, $\alpha^f$; △, $\beta^f$.

$$\beta^p \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \beta^f \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} \alpha^f \underset{k_{-4}}{\overset{k_4}{\rightleftarrows}} \alpha^p$$

Scheme 1. Proposed anomerization pathway for methyl 2-deoxy-D-*arabino*-hexosides.

The rate constants of the slow stage of isomerization of the furanosides, determined as slopes of straight lines **a** and **b** in Fig. 7 are: $k^{f}_{-\beta}(s) = 0.0259\ min^{-1}$ and $k^{f}_{-\alpha}(s) = 0.0300\ min^{-1}$. Since $k^{p}_{\alpha} = 0.0306\ min^{-1}$, the rate of decay of isomer $\alpha^f$ is equal to the rate of formation of pyranoside $\alpha^p$ (Fig. 8). Thus it can be assumed that $k^{f}_{-\alpha} = k^{p}_{\alpha} = k_4 + k_{-4} = 0.0303\ min^{-1}$. Hence, $k_4 = 0.0295$ and $k_{-4} = 0.000768\ min^{-1}$.

The β-pyranoside is formed at a higher rate than its α counterpart (Fig. 8). The rate of formation of $\beta^p$ is linearly related to the isomerization rate of $\beta^f$. However, the rates are unequal.

During the slow stage of isomerization, isomer $\beta^f$ remains at equilibrium with isomer $\alpha^f$:

$$\alpha^f \underset{k_3}{\overset{k_{-3}}{\rightleftarrows}} \beta^f \overset{k_{-2}}{\rightarrow} \beta^p$$

Since $k_4 \ll k_{-3}$, it can be assumed that $-d[\beta^f]/dt = k_{-2}[\beta^f] = k_{-2}k_{-3}/k_3[\alpha^f]$. Hence:

$k^{f}_{-\beta}(s) = k_{-2}k_{-3}/k_3 = 0.0259\ min^{-1}$, and then $k_{-2} = 0.189\ min^{-1}$.

Isomer $\beta^f$ can be converted into $\beta^p$ via the acyclic cation and the rate of formation of $\beta^p$ is: $d[\beta^p]/dt = k_{-5}[S^{\beta}H^+]$. If $k_{-5} \gg k_{-2}$,[12] then $k^{p}_{\beta} = k_{-2}k_{-5}/(k_5 + k_{-5}) = 0.0919$ (Fig. 8) i$k_5 = k_{-5}$ and hence, as previously, $k_{-2} = 0.184\ min^{-1}$.

Based on Scheme 1 we can assume, that the rapid stage in the reaction of $\alpha^p$ isomer (the most stable one), could be expressed as $k^{p}_{-\alpha} = k_4 + k_{-4} = 0.304\ min^{-1}$. Since $k_{-4}/k_4 = 0.017$, thus $k_4 = 0.299\ min^{-1}$ and $k_{-4} = 0.00508\ min^{-1}$. In turn, for the $\beta^p$ isomer: $k^{p}_{-\beta} = k_2 + k_{-2} = 1.43\ min^{-1}$. We were not able to determine experimentally the value $k_2/k_{-2}$ because of too little concentration of $\beta^f$ at 40 °C. However, if we accept the analogous logarithmic dependence $\log k = f(1/T)$ for the reactions $\beta^p \rightleftarrows \beta^f$ and $\alpha^p \rightleftarrows \alpha^f$, then $K_2$ (40 °C) ≅ 0.015, and $k_2$ and $k_{-2}$ are 0.02 and 1.41 $min^{-1}$, respectively. If the slow stage of isomerization of the pyranosides proceed via the same way of transformation, i.e., in accordance with Scheme 1, the rate constant $k^{p}_{-\beta}(s)$ will be $K_2K_3k_4 = 0.043\ min^{-1}$. This calculated value is not markedly smaller than those experimentally found (0.060 $min^{-1}$).

Experimental rate constants and the calculated constants of the elementary reactions are collected in Tables 5 and 6, respectively. They determine the transformation rates of particular isomers and decline in the following series: $k_3 > k_{-3} > k_{-2} > k_4 > k_2 > k_{-4} > k_{-1} > k_1$.

Based on data given in Table 6 we calculated approximate values of activation parameters for some reaction steps at 26 °C. Values of $\Delta H^{\#}_2$, $\Delta H^{\#}_{-2}$, $\Delta H^{\#}_4$ and $\Delta H^{\#}_{-4}$ are: 21.1, 26.3, 30.2 and 24.5 kcal/mol, respectively. Approximate values of $\Delta S^{\#}_2$, $\Delta S^{\#}_{-2}$, $\Delta S^{\#}_4$ and $\Delta S^{\#}_{-4}$ are: −3.08, 21.9, 31.2 and 5.00 cal/(mol K),

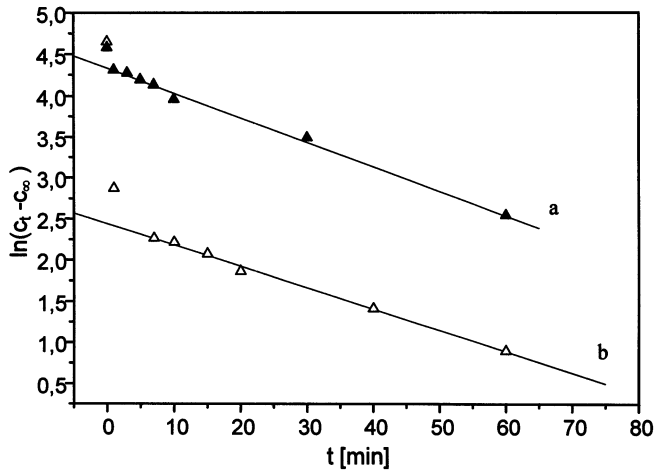



Fig. 7. Deviations from the first-order reaction for isomerization of methyl 2-deoxy-α-D-*arabino*-hexofuranoside (▲) and methyl 2-deoxy-β-D-*arabino*-hexofuranoside (△). Straight line **a**: $y = -0.030(\pm 0.001)x + 4.329(\pm 0.020)$, $r = 0.9986$; straight line **b**: $y = -0.026(\pm 0.001)x + 2.441(\pm 0.024)$, $r = 0.9982$.

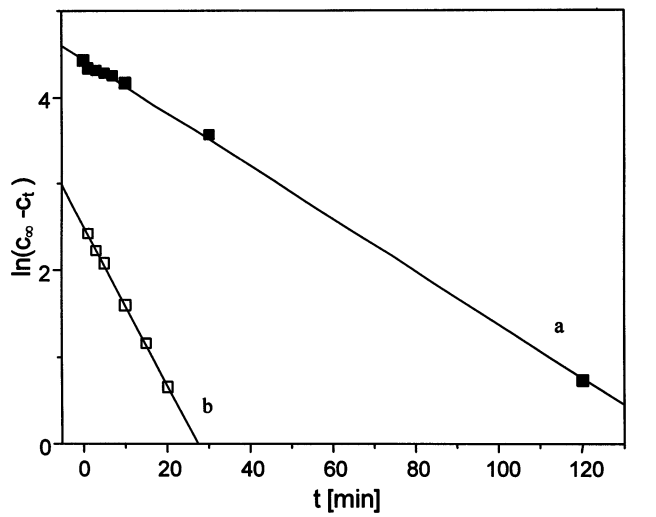



Fig. 8. Rate constants of formation of methyl 2-deoxy-α-D-*arabino*-hexopyranoside (■) and methyl 2-deoxy-β-D-*gluco*-pyranoside (□) from β-furanoside. Straight line **a**: $y = -0.0306(\pm 0.0004)x + 4.4379(\pm 0.0183)$, $r = 0.9994$; straight line **b**: $y = -0.0919(\pm 0.0013)x + 2.5271(\pm 0.0145)$, $r = 0.9996$.

Table 5
Experimental rate constants ($min^{-1}$) in 0.143 M methanolic HCl

| 40 °C | 26 °C |
|---|---|
| $k^{p}_{-\beta} = 1.43$ | $k^{f}_{-\beta} = 2.62$ |
| $k^{p}_{-\alpha} = 0.304$ | $k^{f}_{-\beta}(s) = 0.0259$ |
| $k^{p}_{-\alpha}(s) = 0.0603$ | $k^{f}_{-\alpha}(s) = 0.0300$ |
| $k^{p}_{-\beta}(s) = 0.0609$ | $k^{p}_{\alpha} = 0.0306$ |
| $k^{f}_{\alpha}$ (from $\alpha^p$) = 0.34 | $k^{p}_{\beta} = 0.0919$ |
| $k^{f}_{\alpha}$ (from $\beta^p$) = 1.44 | |

Table 6
Elementary rate constants

| Constant | $\frac{k}{\text{min}^{-1}}$ (40 °C) | $\frac{k}{\text{min}^{-1}}$ (26 °C) | $\frac{k}{\text{dm}^3/(\text{mol}\times\text{s})}$ (40 °C) | $\frac{k}{\text{dm}^3/(\text{mol}\times\text{s})}$ (26 °C) |
|---|---|---|---|---|
| $k_1$ | $6.44\times10^{-3}$ | | $7.51\times10^{-4}$ | |
| $k_{-1}$ | $5.42\times10^{-2}$ | | $6.32\times10^{-3}$ | |
| $k_2$ | $\sim2.1\times10^{-2}$ | $4.10\times10^{-3}$ | $2.45\times10^{-3}$ | $4.78\times10^{-4}$ |
| $k_{-2}$ | 1.41 | $1.86\times10^{-1}$ | $1.64\times10^{-1}$ | $2.17\times10^{-2}$ |
| $k_3$ | | 2.30 | | $2.68\times10^{-1}$ |
| $k_{-3}$ | | $3.15\times10^{-1}$ | | $3.67\times10^{-2}$ |
| $k_4$ | $2.99\times10^{-1}$ | $2.95\times10^{-2}$ | $3.48\times10^{-2}$ | $3.44\times10^{-3}$ |
| $k_{-4}$ | $5.08\times10^{-3}$ | $7.68\times10^{-4}$ | $5.92\times10^{-4}$ | $8.95\times10^{-5}$ |

respectively, and values of $\Delta G^{\#}$ given in the same order are as follows: 22.0, 19.8, 20.9 and 23.0 kcal/mol. These values correspond well to the stability of studied compounds ($\alpha^p > \beta^p > \alpha^f > \beta^f$).

A complete cycle of transformation of four methyl 2-deoxy-D-*arabino*-hexosides in methanol containing hydrogen chloride is presented in Scheme 2.

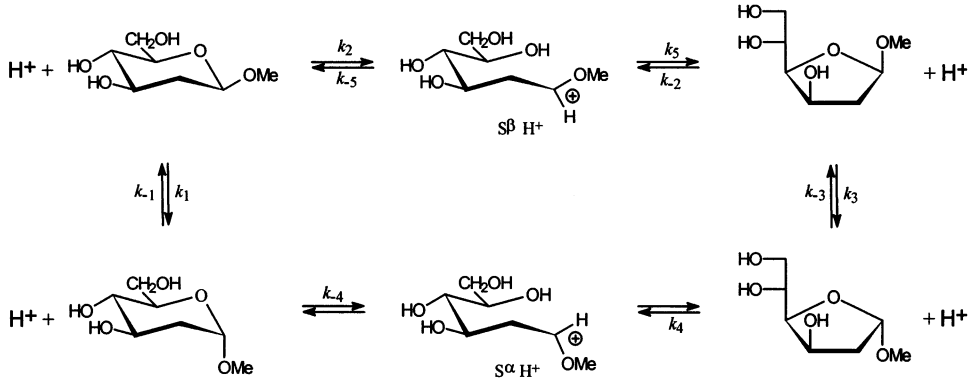
In the presence of an excess of strong acid, the isomerization reactions proceed via appropriate cations. Anomerization of furanosides $\beta^f \rightleftarrows \alpha^f$ is the most rapid and the easiest process. The rate of this reaction is more than ten times faster than the rate of furanoside → pyranoside isomerization via an acyclic carboxonium cation ($k_3/k_{-2} = 12.4$ and $k_{-3}/k_4 = 10.7$). One can assume that anomerization of furanosides goes via an electrophilic attack of a solvated proton on the glycosidic oxygen atom and subsequent cyclic carboxonium ion formation. The presence of such cations was documented during isomerization of other glycosides.[5,13] On the other hand, protonation of the heterocyclic oxygen atom in the furanoside molecules leads to ring cleavage. Very high values of $\Delta S^{\#}_{-2}$ and $\Delta S^{\#}_4$ confirm the statement mentioned above. Nevertheless, high values of activation enthalpy ($\sim 28$ kcal/mol) do not favor this reaction.

The fast process of anomerization of the pyranosides is a consequence of the heterocyclic oxygen protonation. Cleavage of the pyranoid ring needs enthalpy of activation $\sim 23$ kcal/mol, and very low values of the $\Delta S^{\#}_2$ and $\Delta S^{\#}_{-4}$ (close to zero) could suggest that the structures of transition states and substrates are similar. Thus, one can suppose that the pseudoacyclic cations keep their starting conformations and easily undergo the following transformations: $S^{\alpha}H^+ \rightarrow \alpha^f$ and $S^{\beta}H^+ \rightarrow \beta^f$. However, the results obtained do not provide any evidence for the $S^{\alpha}H^+ \rightleftarrows S^{\beta}H^+$ interconversion.

The slow process of anomerization of the pyranosides could be caused by a cyclic carboxonium ion formation. However, the transformation $\beta^p \rightleftarrows \alpha^f \rightarrow \alpha^p$ is more probable, i.e., after rapid preliminary equilibration, the final equilibrium state $\alpha^p \rightleftarrows \beta^p$ is slowly reached.

## 3. Experimental

*General methods.*—All HPLC separations were performed using a VISTA 5500 (Varian) HPLC chromatograph equipped with a Kromasil $C_8$ column (5 μm packing material, $4.6\times250$ mm) from Eka–Nobel




Scheme 2. Transformations of the methyl 2-deoxy-D-*arabino*-hexoside isomers in methanolic hydrogen chloride solution.

(Sweden) for analytical runs and an Ultrasphere ODS column (5 μm packing material, 10 × 250 mm) from Beckman (USA) for semipreparative runs. Constant flowrates were 1 and 4.5 mL/min, respectively. The products were detected at $\lambda = 226$ nm. The 8:17 MeCN–water solvent system for analytical separations and another MeCN–water system (linear gradient from 18.4 to 32% run over 90 min) for semipreparative separations were used. A small portion of the sample **A** or **B** was injected into a Vega 6180 (Carlo Erba) capillary gas chromatograph equipped with a cold 'on column' injector and a flame ionization detector (FID). Gas flowrates for FID were 50 and 90 mL/min for hydrogen and air, respectively. Hydrogen (2 mL/min) was used as the carrier gas. Separation of the mixture was achieved with a DB-23 fused-silica capillary column (60 m × 0.258 mm i.d., 0.15 μm film thickness) from J&W Scientific (Folsom, CA, USA) using a temperature program from 140 to 160 °C at 4 °C/min, 160 to 200 °C at 6 °C/min, 200 to 240 °C at 8 °C/min (held for 10 min). The FID system was held at 260 °C. All 500 MHz $^1$H NMR spectra were recorded in $CDCl_3$ with $Me_4Si$ as an internal standard using a Varian Unity Plus 500 spectrometer. Optical rotations were measured with a JASCO J-20 spectropolarimeter.

*Kinetics studies—Solvent purification.*—Methanol was first dried over $Na_2SO_4$ and then with magnesium methoxide and distilled.[14]

*Catalyst.*—A methanolic solution of hydrogen chloride was prepared by bubbling dry hydrogen chloride through purified MeOH. The concentration of the stock solution was determined by titration.

*Sample preparation.*—Four starting solutions were prepared by dissolution of compound $\alpha^p$ or $\beta^p$ or $\alpha^f$ or $\beta^f$ (8 mg) in 4 mL of purified MeOH. Four sets of ampoules with the same amounts of starting isomer ($\alpha^p$ or $\beta^p$ or $\alpha^f$ or $\beta^f$) were prepared by taking 50 mL of the starting solution. Then the solvent was removed under a $N_2$ stream. To each ampoule containing 0.1 mg of appropriate isomer, 200 μL of 0.143 M methanolic solution of hydrogen chloride was added, and the vial was tightly closed. Two sets of ampoules containing pyranosides ($\alpha^p$ and $\beta^p$) were held at 40 ± 0.1 °C, and two other sets containing furanosides ($\alpha^f$ and $\beta^f$) were held at 26 ± 0.1 °C. The reaction, after appropriate time, was quenched by adding one drop of 25% aq ammonia (the solution was alkaline). Next, solvents were removed under a $N_2$ stream at rt. The dry residue was exhaustively O-acetylated with 1:1 pyridine–$Ac_2O$ at rt for 24 h. Then solvents were removed under a nitrogen stream, and the dry residue was dissolved in 100 μL of $CHCl_3$ and analyzed with CGC.

*Calculations.*—Rate constants, $k$, were calculated with the least-squares method from the following equation:

$$\ln|c_t - c_\infty| = -kt + \ln|c_0 - c_\infty| \quad (1)$$

where $t$ is the reaction time in min, $c_0$ is the starting concentration of the solution, $c_t$ is the concentration after $t$ minutes, and $c_\infty$ is the isomer concentration at equilibrium. With complex reactions, the rate of the slow stage(s) was calculated from Eq. (1), whereas that of the fast reaction from Eq. (2)

$$k = \frac{1}{t} \ln \frac{c_0 - c_0(s)}{c_1 - c_1(s)} \quad (2)$$

where $c_0$ is the initial concentration, $c_1$ is the concentration measured after 1 min, $c_0(s)$ and $c_1(s)$ are, respectively, appropriate quantities calculated from Eq. (1) back to $t = 0$ and $t = 1$ min of the slow stage of the reaction.[6–8] All rate constants were determined at the fixed HCl concentration (0.143 M). The precision of calculation of the rate constants from Eq. (1) was determined by standard deviations calculated from the following expression:

$$\sigma_n = \sqrt{\frac{\Sigma x^2 - \frac{(\Sigma x)^2}{n}}{n-1}}$$

*Syntheses.*—The anomeric mixture of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-D-*arabino*-hexosides (sample **A**) was obtained under the procedure of Hughes et al.[2] (heating at 45 ° C during 1 h) from 1 g (6 mmol) of 2-deoxy-D-*arabino*-hexose. The resulting oil (1.3 g) was exhaustively *O*-acetylated with 1:1 $Ac_2O$–pyridine at ambient temperature during 24 h. Then the volatile components were removed under reduced pressure. CGC analysis revealed two main components. The crude product (1.59 g) was decolorized by passing its solution in 9:1 $CCl_4$–acetone through a short column with Kieselgel MN 60, $\mu < 0.08$. A sample of the solution, after concentration to a dense syrup under reduced pressure, was separated by semipreparative HPLC.

*Methyl tri*-O-*acetyl-2-deoxy-α*-D-arabino-*hexopyranoside* **3**.—741 mg, $[\alpha]_D^{22}$ +118.8° (*c* 0.8, MeOH); $^1$H NMR ($CDCl_3$) $\delta$ 4.87 (dd, 1 H, $J_{1,2}$ 1.4, $J_{1,2a}$ 3.4 Hz, H-1); 2.26 (m, 1 H, $J_{2,2a}$ 13.1, $J_{2,3}$ 5.4 Hz, H-2); 1.84 (m, 1 H, $J_{2a,3}$ 11.5 Hz, H-2a); 5.31 (m, 1 H, $J_{3,4}$ 9.7 Hz, H-3); 5.02 (t, 1 H, $J_{4,5}$ 9.7 Hz, H-4); 3.96 (m, 1 H, $J_{5,6}$ 4.5, $J_{5,6'}$ 2.4 Hz, H-5); 4.33 and 4.09 (dd, 2 H, $J_{6,6'}$ 12.2 Hz, H-6 and H-6′); 3.37 (s, 3 H, $OCH_3$); 2.04–2.12 (3s, each 3 H, OAc); $^{13}$C NMR: $\delta$ 98.00 (C-1), 34.86 (C-2), 69.01 (C-3), 67.65 (C-4), 69.20 (C-5), 62.33 (C-6), 54.87 ($OCH_3$), 20.95–20.72 (OAc), 170.74–169.88 (C=O).

*Methyl tri*-O-*acetyl-2-deoxy-β*-D-arabino-*hexopyranoside* **4**.—163 mg, $[\alpha]_D^{20}$ −27.8° (*c* 0.5, EtOH); $^1$H NMR ($CDCl_3$) $\delta$ 4.50 (dd, 1 H, $J_{1,2}$ 2.0, $J_{1,2a}$ 9.8 Hz, H-1); 2.32 (m, 1 H, $J_{2,2a}$ 12.7, $J_{2,3}$ 4.9 Hz, H-2); 1.75 (m, 1 H, $J_{2a,3}$ 11.2 Hz, H-2a); 5.04 (m, 1 H, $J_{3,4}$ 9.5 Hz,

H-3); 5.00 (t, 1 H, $J_{4,5}$ 9.5 Hz, H-4); 3.62 (m, 1 H, $J_{5,6}$ 4.6, $J_{5,6'}$ 2.4 Hz, H-5); 4.32 and 4.12 (dd, 2 H, $J_{6,6'}$ 12.2 Hz, H-6 and H-6′); 3.50 (s, 3 H, $OCH_3$); 2.04–2.10 (3s, each 3 H, OAc); $^{13}$C NMR: $\delta$ 100.54 (C-1), 36.01 (C-2), 70.55 (C-3), 69.03 (C-4), 71.92 (C-5), 62.37 (C-6), 56.90 ($OCH_3$), 20.92–20.73 (OAc), 170.70–169.85 (C=O).

The mixture of four methyl tri-*O*-acetyl-2-deoxy-D-*arabino*-hexosides (sample **B**) was obtained under the procedure of Hughes et al.[2] (at rt, during 9 min) from 0.5 g (3 mmol) of 2-deoxy-D-*arabino*-hexose. The resulting oil (0.529 g) was exhaustively *O*-acetylated as described above. CGC analysis of the mixture of per-*O*-acetylated compounds (0.895 g) showed the presence of four components. The mixture was decolorized as described above, concentrated and finally separated by semipreparative HPLC.

*Methyl tri*-O-*acetyl-2-deoxy*-α-D-arabino-*hexofuranoside* **1**.—67 mg, $[\alpha]_D^{20}$ +92.8° (*c* 0.9, EtOH); $^1$H NMR ($CDCl_3$) $\delta$ 5.20 (dd, 1 H, $J_{1,2}$ 3.4, $J_{1,2'}$ 5.4 Hz, H-1); 2.28 (m, 1 H, $J_{2,2'}$ 15.1, $J_{2,3}$ 6.1 Hz, H-2); 2.21 (m, 1 H, $J_{2',3}$ 1.5 Hz, H-2′); 5.48 (m, 1 H, $J_{3,4}$ 3.9 Hz, H-3); 4.21 (dd, 1 H, $J_{4,5}$ 9.2 Hz, H-4); 5.28 (m, 1 H, $J_{5,6}$ 2.2, $J_{5,6'}$ 5.4 Hz, H-5); 4.57 and 4.21 (dd, 2 H, $J_{6,6'}$ 12.2 Hz, H-6 and H-6′); 3.48 (s, 3 H, $OCH_3$); 2.03–2.13 (3s, each 3 H, OAc); $^{13}$C NMR: $\delta$ 104.66 (C-1), 40.90 (C-2), 72.61 (C-3), 76.74 (C-4), 68.43 (C-5), 63.78 (C-6), 55.65 ($OCH_3$), 21.11–20.94 (OAc), 170.89–169.99 (C=O).

*Methyl tri*-O-*acetyl-2-deoxy*-β-D-arabino-*hexofuranoside* **2**.—24 mg, $[\alpha]_D^{20}$ −17.3° (*c* 0.4, EtOH); $^1$H NMR ($CDCl_3$) $\delta$ 5.09 (d, 1 H, $J_{1,2}$ 5.4 Hz, H-1); 2.33 (m, 1 H, $J_{2,2'}$ 14.7, $J_{2,3}$ 5.9 Hz, H-2); 2.13 (1 H, H-2′); 5.47 (dd, 1 H, $J_{3,4}$ 4.9 Hz, H-3); 4.30 (dd, 1 H, $J_{4,5}$ 9.2 Hz, H-4); 5.32 (m, 1 H, $J_{5,6}$ 2.2, $J_{5,6'}$ 5.0 Hz, H-5); 4.67 and 4.21 (dd, 2 H, $J_{6,6'}$ 12.2 Hz, H-6 and H-6′); 3.40 (s, 3 H, $OCH_3$); 2.01–2.12 (3s, each 3 H, OAc); $^{13}$C NMR: $\delta$ 105.25 (C-1), 39.86 (C-2), 71.48 (C-3), 78.90 (C-4), 69.59 (C-5), 63.78 (C-6), 55.77 ($OCH_3$), 21.20–20.99 (OAc), 170.94–169.96 (C=O).

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## References

1. (a) Bergmann, M.; Schotte, H.; Leschinsky, W. *Ber. Dtsch. Chem. Ges.* **1922**, *55*, 158–172;
   (b) Bergmann, M.; Schotte, H.; Leschinsky, W. *Ber. Dtsch. Chem. Ges.* **1923**, *56*, 1052–1059.
2. Hughes, I. W.; Overend, W. G.; Stacey, M. *J. Chem. Soc.* **1949**, 2846–2849.
3. Bhat, K. V.; Zorbach, W. W. *Carbohydr. Res.* **1968**, *6*, 63–74.
4. Capon, B.; Loveday, G. W.; Overend, W. G. *Chem. Ind.* **1962**, 1537–1538.
5. Garegg, P. J.; Johansson, K.-J.; Konradsson, P.; Lindberg, B. *J. Carbohydr. Chem.* **1999**, *18*, 31–40.
6. Frost, A. A.; Pearson, R. S. *Kinetics and Mechanisms*; Wiley: New York, 1961; p. 162.
7. Pigman, W.; Isbell, H. S. *Adv. Carbohydr. Chem. Biochem.* **1968**, *23*, 11–57.
8. Smiataczowa, K. *Pol. J. Chem.* **1999**, *73*, 1513–1522.
9. Isbell, H. S.; Pigman, W. *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 13–65.
10. Lemieux, R. U.; Anderson, L.; Conner, A. H. *Carbohydr. Res.* **1971**, *20*, 59–72.
11. Bishop, C. T.; Cooper, F. P. *Can. J. Chem.* **1962**, *40*, 224–232.
12. Schwetlick, K. *Kinetische Methoden zur Untersuchung von Reactionmechanismen*; PWN: Warszawa, 1975; p. 66 (in Polish).
13. Bunton, C. A.; Lewis, T. A.; Lewellyn, D. R.; Vernon, C. A. *J. Chem. Soc.* **1955**, 4419–4423.
14. Vogel, A. I. *Textbook of Practical Organic Chemistry*; WNT: Warszawa, 1984; p. 219 (in Polish).