KINETICS OF METHYLATION OF METHYL 5-DEOXY-α/β-D-XYLOFURANOSIDES

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Received May 10, 2004
Accepted June 30, 2004

Dedicated to Professor Miloslav Černý on the occasion of his 75th birthday.

The kinetics of methylation of methyl 5-deoxy-α-D-xylofuranoside (**1**), methyl 5-deoxy-β-D-xylofuranoside (**2**) and their partly methylated derivatives with methyl iodide in the presence of sodium hydroxide in acetonitrile was studied. The reaction rate was independent of the base concentration during the first half-time only and the methylation proceeded as a first-order reaction. The rate constants of all side and consecutive reactions were calculated and the influence of both polar and steric effect is discussed. The methylation of **1** was highly regioselective giving almost exclusively 5-deoxy-2-*O*-methyl-α-D-xylofuranoside.
Keywords: Regioselectivity; Rate constants; Partial methylation; Methyl pentofuranoside; Kinetics; Pentofuranosides; Glycosides; Carbohydrates; Methylated saccharides.

Methylation has been extensively used in structural investigations of complex saccharides[1]. The methylated monosaccharides obtained on methylation and hydrolysis of polysaccharides are usually analyzed by GC/MS technique[2] and the identification is frequently based on a comparison with authentic standards[3]. Therefore, considerable attention has been paid to the preparation of partly methylated monosaccharides. For studies of optimization of experimental conditions for the *O*-alkylation, it is essential to have an insight into the regularities governing the regioselectivity of methylation. So far, a great attention has been focused on the partial reactivity of the secondary hydroxy groups of methyl 2,6-dideoxy-[4] or 4,6-dideoxyhexopyranosides[5], 2-deoxypentopyranosides[6], and xylopyranosides[7]. The simplest furanosides, i.e. methyl tetrofuranosides, have been subjected to partial methylation as well[8].

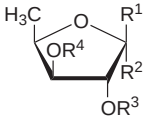
Continuing our study on the chemistry and stereochemistry of 5-deoxypentofuranosides[9], we report the kinetic and synthetic results for the methylation of methyl 5-deoxy-α-D-xylofuranoside (**1**), methyl

5-deoxy-β-D-xylofuranoside (**2**), and their respective monomethyl ethers with methyl iodide in the presence of sodium hydroxide in acetonitrile medium.

RESULTS AND DISCUSSION

Synthesis

The title compounds **1** and **2** were synthesized by a known procedure[9]. For the preparation of 2-*O*-methyl ethers **3** and **6**, 5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose[9] was converted to 3-*O*-benzoyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose[10] followed by acid methanolysis in situ and then a mixture of methyl glycosides **9** and **10** was transformed without separation to the corresponding 2-*O*-methyl derivatives **11** and **12** by methylation with diazomethane. The protective 3-*O*-benzoyl group was then removed and separation on silica gel afforded pure **3** and **6** in overall yields of 25 and 26%, respectively. The 3-*O*-methyl ethers **4** and **7** were obtained by acid methanolysis of 3-*O*-methyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose[11] followed by separation on silica gel. Total methylation of **1** and **2** using methyl iodide with sodium hydroxide in acetonitrile produced the required di-*O*-methyl ethers **5** and **8**. The new compounds **3**–**8** were characterized by MS and NMR data. The fragmentation pathway of all compounds **3**–**8** (Table I) was analogous to the fragmentation of methyl ethers of furanosides[12]. Loss of the C-1 methoxy group from the molecular ion gave *m/z* 145 (**5** and **8**) or *m/z* 131 (**3**, **4**, **6**, and **7**) and the most important peak attributed to the 5-deoxyfuranoside structure was found at *m/z* 116 (**5** and **8**) and *m/z* 102 (**3**, **4**, **6**, and **7**). Chemical shifts and vicinal coupling constants of the ^{1}H and ^{13}C nuclei of compounds **3**–**8** confirmed the proposed structures as well (Table II). In accordance with literature data[13], the signal of proton on the carbon bearing the methoxy group is shifted upfield compared with that[9] of the corresponding diol **1** or **2**.



	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
1	H	OCH_3	H	H	**7**	OCH_3	H	H	CH_3
2	OCH_3	H	H	H	**8**	OCH_3	H	CH_3	CH_3
3	H	OCH_3	CH_3	H	**9**	H	OCH_3	H	Bz
4	H	OCH_3	H	CH_3	**10**	OCH_3	H	H	BZ
5	H	OCH_3	CH_3	CH_3	**11**	H	OCH_3	CH_3	Bz
6	OCH_3	H	CH_3	H	**12**	OCH_3	H	CH_3	BZ

Kinetic Measurement

Methyl iodide (in molar ratio to the model compound 64:1) and sodium hydroxide in acetonitrile[4–8] were chosen as a methylation system. First, the concentration of sodium hydroxide was optimized. In general, high amounts of sodium hydroxide increased both the permethylation yield and conversion of the starting **1** (Table III) in agreement with the results pub-

TABLE I
Relative abundance of fragments in mass spectra of methyl ethers **3**–**8**

m/z	**3**	**4**	**5**	**6**	**7**	**8**
145	–	–	5.0	–	–	3.5
131	7.5	7.0	1.0	4.5	5.0	–
117	1.0	2.5	5.0	1.0	1.0	3.5
116	–	–	14.0	0.5	–	13.5
113	5.0	–	2.0	0.5	–	1.5
102	31.0	36.5	9.5	31.5	31.5	8.5
101	11.0	17.0	100.0	13.5	18.5	100.0
99	0.5	–	0.5	0.5	–	–
87	100.0	100.0	2.0	100.0	100.0	2.0
85	17.5	20.0	49.0	20.0	19.0	66.0
75	4.5	9.0	10.5	5.0	10.0	66.0
73	11.0	8.0	13.5	14.0	12.5	13.5
71	26.0	37.0	6.0	26.0	41.0	16.0
70	55.0	36.0	0.5	49.0	48.0	1.0
69	11.5	12.5	4.0	11.5	16.0	4.0
61	28.0	16.0	1.0	12.0	17.0	1.0
59	22.0	21.5	6.0	23.5	28.0	6.0
57	35.5	30.0	4.0	33.5	25.0	5.0
55	16.5	10.0	12.5	13.5	12.5	16.0
53	4.5	5.0	5.0	4.0	6.0	4.5
45	44.5	32.5	43.5	46.0	36.0	53.0
43	31.0	34.5	7.5	25.0	35.5	12.5
42	22.5	18.5	1.5	19.5	19.5	6.0
33	15.5	13.0	5.5	15.5	16.5	7.0

TABLE II
^{1}H and ^{13}C NMR data for methyl ethers **3**–**8**

Parameter	**3**	**4**	**5**	**6**	**7**	**8**
			Chemical shift δ, ppm			
H1	4.93 d	4.92 d	4.91 d	4.84 s	4.76 d	4.79 d
H2	3.73 dd	4.15 dd	3.75 dd	3.75 s	4.20 dd	3.74 dd
H3	4.30 dd	3.60 dd	3.84 dd	3.95 d	3.63 dd	3.64 dd
H4	4.36–4.30m	4.36–4.29m	4.39–4.32 m	4.38–4.32 m	4.46–4.40 m	4.38–4.31 m
H5	1.24 d	1.22 d	1.22 d	1.32 d	1.28 d	1.28 d
H–O	2.50 bs	2.85 bs	–	2.73 bs	2.65 bs	–
CH_3	3.44, 3.49	3.44, 3.48	3.41, 3.43, 3.46	3.38, 3.43	3.41, 3.43	3.41 (6H), 3.43
C1	100.9	102.1	100.8	106.8	110.0	108.3
C2	88.7	77.4	87.0	89.7	80.2	89.5
C3	75.8	87.4	84.9	74.9	87.2	85.5
C4	74.8	75.2	74.2	79.9	77.6	77.6
C5	15.5	15.1	15.7	15.8	16.5	16.4
CH_3	55.8, 59.1	56.2, 58.4	55.7, 58.9 (2C)	55.5, 58.2	56.3, 59.0	56.2, 58.4, 58.8
			Coupling constants $^{3}J_{H,H}$, Hz			
1,2	4.4	4.7	4.4	~0	2.4	1.3
2,3	4.5	2.3	5.3	~0	3.3	3.0
3,4	4.8	5.2	6.6	4.1	5.7	5.6
4,5	6.1	6.5	6.5	6.6	6.7	6.6

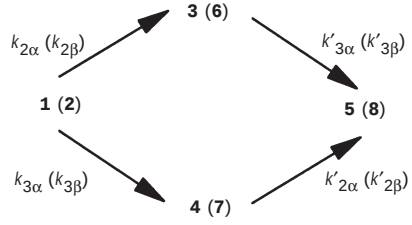
TABLE III
The composition (in mole %) of the reaction mixture in partial methylation of glycoside **1**[a]

Molar ratio **1**/NaOH	**1**	**3**	**4**	**5**	**3** + **4**
1/0.7	31.8	55.0	7.1	6.1	62.1
1/1.4	20.2	65.9	6.2	7.7	72.1
1/2.6	15.1	66.6	6.2	12.1	72.8
1/7.1	5.4	67.9	2.8	23.9	70.7

[a] Reaction time 60 min, molar ratio CH_3I/1 = 64.

lished for a combination of methyl iodide, alkalimetal hydroxide and dimethyl sulfoxide[14]. Furthermore, the methylation rate of the starting **1** was constant up to 40% conversion and independent of the initial content of sodium hydroxide as indicated by the linear time dependence of logarithm of the concentration, this being evidence of the first-order reaction (Fig. 1). The deviation from a straight line was observed first for the lowest content of base suggesting a complex role of the hydroxide consisting in: (i) ionization of the hydroxy group of glycoside, (ii) blocking of hydrogen iodide, (iii) retaining water, and (iv) nucleophilic substitution of methyl iodide. For further experiments, 1.3 equivalent of sodium hydroxide per mol of replaceable hydrogen was used and the reaction was followed within two half-times.

The first-order rate constant (Scheme 1) for the methylation of each of compounds **1**–**4**, **6**, and **7** was calculated as the slope of a linear time dependence of logarithm of molar concentration of the compound investi-



SCHEME 1

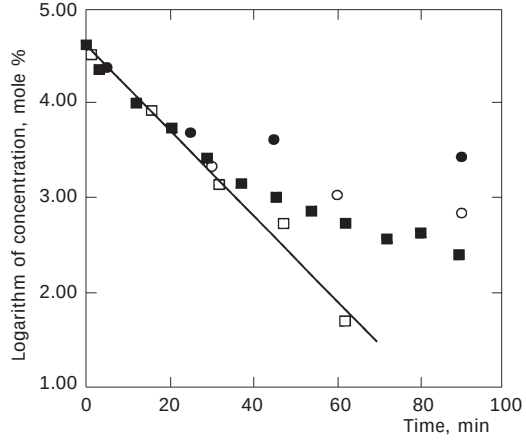


FIG. 1

The effect of NaOH on methylation of α-glycoside **1**; molar ratio **1**/NaOH: 0.7 (●), 1.4 (○), 2.6 (■), 7.1 (□)

gated (Table IV). In the case of α-glycoside **1** and β-glycoside **2** (Fig. 2), the respective hydroxy group at C-2 reacted more than three times faster than that at C-3 ($k_{2\alpha}/k_{3\alpha}$ = 3.6, $k_{2\beta}/k_{3\beta}$ = 3.0). These ratios agree well with those found in the series of methyl 4,6-dideoxyhexopyranosides[5] and methyl threofuranosides[8]. It seems that the negative induction effect of the hemiacetal grouping determines the regioselectivity in the first stage of the reaction, increasing the acidity of the 2-OH group. When comparing the

TABLE IV
The first-order rate constants for methylation of glycosides

Compound	10^4 k, s^{-1}	Standard deviation 10^4, s^{-1}	Correlation coefficient
1	$(k_{2\alpha} + k_{3\alpha})^a$ = 6.40	0.30	0.9902
3	$k'_{3\alpha}$ = 0.81	0.08	0.9307
4	$k'_{2\alpha}$ = 2.10	0.09	0.9811
2	$(k_{2\beta} + k_{3\beta})^b$ = 8.90	0.30	0.9964
6	$k'_{3\beta}$ = 1.90	0.04	0.9954
7	$k'_{2\beta}$ = 2.20	0.09	0.9826

[a] From the initial rates of the formation of both **3** and **4**: $k_{2\alpha}$ = 5.01 × 10^{-4} s^{-1}, $k_{3\alpha}$ = 1.39 × 10^{-4} s^{-1}. [b] From the initial rates of the formation of both **6** and **7**: $k_{2\beta}$ = 6.65 × 10^{-4} s^{-1}, $k_{3\beta}$ = 2.25 × 10^{-4} s^{-1}.

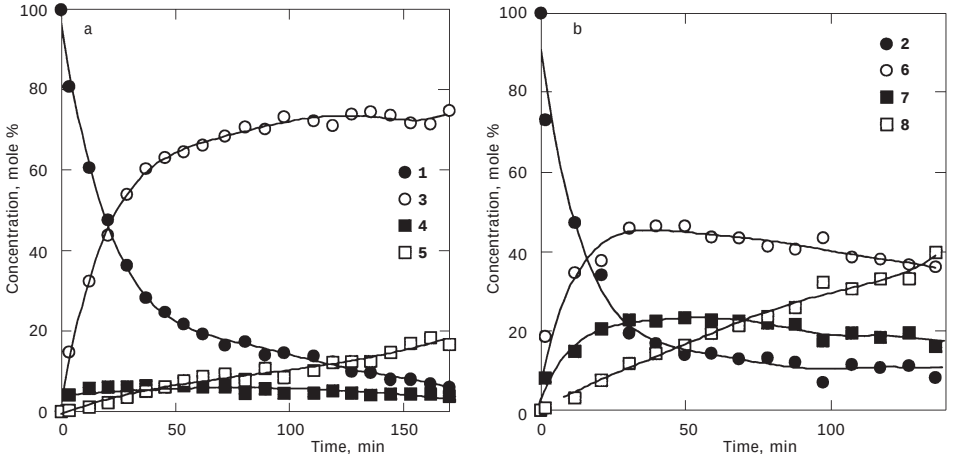


FIG. 2
Time dependence of composition of the reaction mixture in methylation of α-glycoside **1** (a) and β-glycoside **2** (b)

rate constants of both glycosides **1** and **2** in the methylation at the position 2 (Table IV), the higher reactivity of **2** ($k_{2\beta}/k_{2\alpha}$ = 1.3) could be attributed to steric effects. Surprisingly, the reactivity of the 3-OH group in **2** was also enhanced ($k_{3\beta}/k_{3\alpha}$ = 1.6) although the influence of the anomeric center or steric hindrance was expected to be approximately equal in both **1** and **2**. This might be explained by the existence of internal hydrogen bonds[8], which caused the changes in nucleophilicity of the oxygen of the hydroxy groups involved. The strong intramolecular hydrogen bond C3–O–H···O1 in the β-anomer **2** (Table V) increases nucleophilicity of the O-3 atom, whereby the inductive effect of the acetal group is partially compensated. In contrast, the five-membered intramolecular hydrogen bond C2–O–H···O1 in the α-anomer **1** (Table V) activates the 2-OH group and thus the inductive effect of the acetal group is enhanced. For this reason the ratio k_2/k_3 measured for β-anomer **2** (3.0) is lower than that found for α-anomer **1** (3.6).

In the methylation to the second degree, the introduced methyl group mostly decreased the reactivity of a vicinal hydroxy group (Fig. 3). Thus, the 2-*O*-methyl ether **3** was alkylated at position 3 slower than diol **1** ($k_{3\alpha}/k'_{3\alpha}$ = 1.7) because steric hindrance of the 3-OH group is not compensated by the intramolecular hydrogen bond C2–O–H···O1 in **3** (Table V). When comparing the rate constants of methylation at position 2 of 3-*O*-methyl ether **4** and diol **1**, the decrease is substantially higher ($k_{2\alpha}/k'_{2\alpha}$ = 2.4) probably again due to the steric effect. The coupling constants of **4** (Table II) and the magnitude of the frequency shift of the internal hydrogen bond vi-

TABLE V
IR stretching OH vibrations (in cm^{-1}) of glycosides **1**–**4**, **6**, and **7**

Glycoside	Free OH	Intermolecular H-bonded[a]	Intramolecular H-bonded[b]	$\Delta\nu^c$, cm^{-1}
1	3627.7	3473.2	3557.2[d]	70.5
3	3627.1	3473.9	–	–
4	–	–	3562.9[d]	64.8
2	3627.3	3450.8	3536.4[e]	90.9
6	–	–	3534.7[e]	92.6
7	3622.7	3442.3	–	–

[a] 0.2 M solution. [b] 0.02 M solution. [c] The difference of the absorption wavenumbers of the free OH and the intramolecular H-bonded OH. [d] O2–H···O1. [e] O3–H···O1.

bration (Table V) suggest that the substitution of C-3 induced a remarkable conformational change resulting in a pseudoaxial character of the 2-OH group. For comparison, the etherification of an equatorial hydroxy group of 2,6-dideoxyhexopyranosides was enhanced three times with respect to an axial hydroxy group[5d].

The methylation of 3-OH in both β-diol **2** and 2-*O*-methyl ether **6** proceeded at the same rate ($k_{3\beta}/k'_{3\beta}$ = 1.0). In this case, the steric effect of the vicinal substitution on the conformational equilibrium is negligible as the coupling constants of both **2** and **6** (Table II; for diol **2**, $J_{1,2} = J_{2,3} \approx 0$ Hz, $J_{3,4}$ = 4.3 Hz, $J_{4,5}$ = 6.6 Hz, lit.[9]) are virtually identical. Moreover, the strength of the internal hydrogen bond is comparable in both compounds **2** and **6** (Table V). In contrast, the etherification of the 3-OH group in diol **2** led to a distinct decrease in the methylation rate of the neighboring 2-OH group ($k_{2\beta}/k'_{2\beta}$ = 3.0). When considering possible reasons, the steric 1,3-interaction of methoxy groups at C-1 and C-3 in the 3-*O*-methyl ether **7** and its influence on the furanoside ring conformation should be taken into account as discussed above (Table II).

From the preparative point of view, partial methylation of diol **1** is the most advantageous for synthesis of methyl 5-deoxy-2-*O*-methyl-α-D-xylofuranoside (**3**), which was obtained in more than 60% yield.

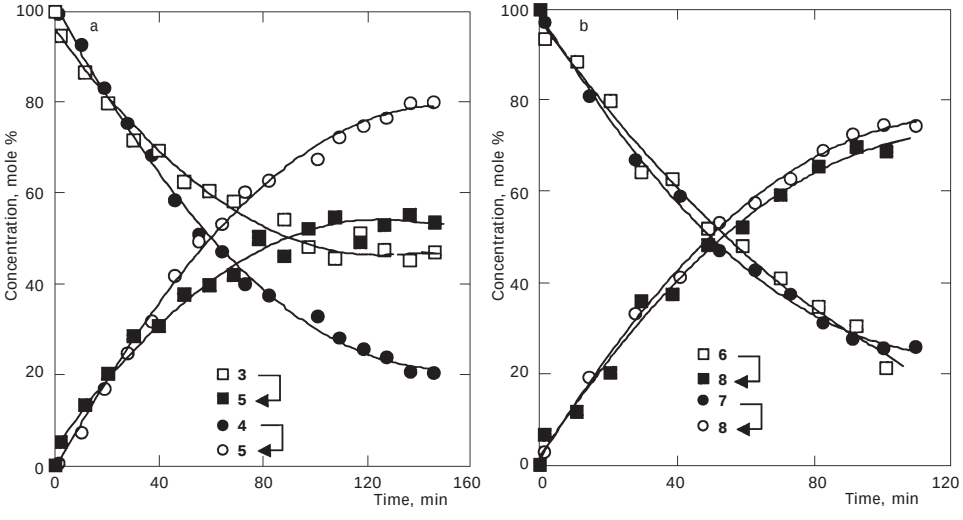


FIG. 3

Time dependence of composition of the reaction mixture in methylation of methyl ethers **3** and **4** (a) and methyl ethers **6** and **7** (b)

In conclusion, a detailed insight into the kinetics of methylation of model compounds having a flexible furan ring with two *trans*-oriented hydroxy groups demonstrates unambiguously that the electronic character of the acetal group controlled the regioselectivity in the first stage of reaction. Furthermore, this primary effect can be altered by additional steric or polar interactions. Once a methyl group is introduced at position 3, it will decrease the rate of further methylation due to steric hindrance of a vicinal hydroxy group. The fact that internal hydrogen bonds can influence considerably the rate of methylation in particular during the second stage of reaction suggests that also a neutral hydroxy group can act as a weak nucleophile.

EXPERIMENTAL

Optical rotations were measured on a JASCO Model DIP-370 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were determined with a Kofler hot block and are uncorrected. NMR data (δ, ppm; *J*, Hz) were extracted from spectra measured in solutions of $CDCl_3$ (Me_4Si as an internal standard) at 25 °C with a Bruker AMX3 400 spectrometer (^{1}H at 400 MHz, ^{13}C at 100 MHz). Assignment of signals was provided by 2D homonuclear and heteronuclear correlated spectra or based on APT experiments. Mass spectra were recorded on a JEOL DX 303 instrument using an EI technique at 70 eV. Column chromatography was performed on 100–160 μm silica gel (Lachema Brno, Czech Republic), and TLC on 10–40 μm silica gel according to Stahl (Merck, Germany). TLC spots were visualized by spraying with 1% $Ce(SO_4)_2$ in 10% H_2SO_4 and subsequent mineralization. Solutions were concentrated under reduced pressure with a bath temperature below 40 °C. All solvents were dried before use.

Analyses were performed with a Hewlett–Packard 5890 A instrument equipped with a flame-ionization detector. A fused silica capillary column (50 m × 0.32 mm i.d.) with chemically bonded methyl phenyl silicone (5%, film thickness 0.5 μm) was used with nitrogen as a carrier gas at a flow rate of 1.2 ml/min (split 1:50). Temperature: column, 110 °C; detector, 230 °C; injector, 200 °C. The following retention times were obtained: **1**, 6.08 min; **2**, 7.00 min; **3**, 7.25 min; **4**, 4.98 min; **5**, 5.80 min; **6**, 5.17 min; **7**, 7.19 min; **8**, 5.46 min. The relative response factors were determined using a solution of **2** (5.1 mg/ml), **6** (5.1 mg/ml), and **8** (5.5 mg/ml) in CH_3OH; their values were 1.000, 1.161, and 1.502, respectively.

The Kinetics of Methylation

The kinetics measurements were carried out in minivials with a magnetic stirrer (100 r.p.m.) placed in an oil bath thermostatted at 25 ± 0.1 °C. To a 0.03 M solution (2 ml) of a glycoside in CH_3CN was added finely powdered NaOH (1.3 equivalent per mol of replaceable H) and the vial was closed with a septum. After initial stirring at 25 °C (5 min), CH_3I (300 μl) was injected with a syringe. Aliquots of the reaction mixture (0.5 μl) were withdrawn through the septum and directly analyzed by GLC. The reported value of each rate constant is the average of two determinations.

Methyl 5-Deoxy-2-*O*-methyl-α-D-xylofuranoside (**3**) and
Methyl 5-Deoxy-2-*O*-methyl-β-D-xylofuranoside (**6**)

A solution of benzoyl chloride (0.6 ml, 5.2 mmol) in $CHCl_3$ (5 ml) was added dropwise at 5 °C within 1 h to a solution of 5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose[9] (400 mg, 2.3 mmol) in pyridine (10 ml). The reaction was then stopped by adding of water (1 ml) and the solvents were removed. The residue (R_F 0.8, benzene–acetone 4:1) was partitioned between $CHCl_3$ and water, the organic layer after drying (anhydrous $MgSO_4$) was concentrated to give a crude 3-*O*-benzoyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose as a syrup (780 mg). Methanolysis of this compound using Dowex W 50X8 (H^+ form, 3 ml, saturated with CH_3OH) in CH_3OH (15 ml) under reflux at 80 °C resulted in a mixture of anomers **9** and **10** (**9**: R_F 0.7, **10**: R_F 0.6, benzene–acetone 4:1) within 2 h. The resin was filtered off, washed with CH_3OH, and the combined filtrates were concentrated to a syrup (650 mg). The syrup was diluted with CH_2Cl_2 (3 ml), $BF_3{\cdot}Et_2O$ was introduced (20 μl) and a solution of CH_2N_2 in CH_2Cl_2 (20 ml) was then added dropwise at 5 °C within 1 h. The reaction was monitored by TLC (the starting mixture: R_F 0.42 and 0.35, benzene–acetone 10:1) and after additional stirring (30 min) only the spots of glycosides **11** and **12** were visible (R_F 0.68 and 0.50, benzene–acetone 10:1). The mixture was then filtered and the filtrate was washed with saturated $NaHCO_3$ and with water. After drying (anhydrous $MgSO_4$), the solvent was evaporated and the residue (560 mg) in CH_3OH (15 ml) was treated with CH_3ONa (0.2 ml, 2 M in CH_3OH). Transesterification was finished after 2 h (R_F 0.28 and 0.10, benzene–acetone 10:1), CO_2(g) was introduced to neutralize the mixture and solids were filtered off. The filtrate was concentrated and the residue (530 mg) was separated by chromatography on a silica gel (30 g, benzene) to give methyl benzoate (180 mg). Further elution (benzene–acetone 10:1) afforded the β-anomer **6** as a syrup (100 mg, 26%), $[\alpha]_D^{24}$ –65.9 (*c* 1.5, $CHCl_3$). For $C_7H_{14}O_4$ (162.2) calculated: 51.84% C, 8.70% H; found: 51.75% C, 8.60% H. Finally, the α-anomer **3** was obtained as a syrup (94 mg, 25%), $[\alpha]_D^{24}$ +144.0 (*c* 0.5, $CHCl_3$). For $C_7H_{14}O_4$ (162.2) calculated: 51.84% C, 8.70% H; found: 51.70% C, 8.64% H. MS, ^{1}H and ^{13}C NMR data are summarized in Tables I and II.

Methyl 5-Deoxy-3-*O*-methyl-α-D-xylofuranoside (**4**) and
Methyl 5-Deoxy-3-*O*-methyl-β-D-xylofuranoside (**7**)

A solution of 5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose[9] (500 mg, 3.9 mmol) in CH_3CN (3 ml) was stirred at ambient temperature with CH_3I (2 ml, 32 mmol) and powdered NaOH (150 mg, 3.6 mmol) for 3 h. The methylation was checked by TLC (starting compound: R_F 0.43; product: R_F 0.7; benzene–acetone 4:1). As the starting compound was still present, additional portion of CH_3I (1 ml, 16 mmol) and NaOH (100 mg, 2.4 mmol) were added and the stirring was continued for another 2 h. After evaporation to dryness, the residue was filtered through a short column of silica gel (20 g, toluene) to yield 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose (342 mg, 64%); its ^{1}H NMR spectrum was in agreement with that published previously[12a]. Further treatment with Dowex W 50X8 (H^+ form, 2 ml, saturated with CH_3OH) in CH_3OH (10 ml) under reflux at 80 °C gave a mixture of **4** and **7** in a ratio of 1:1 (**4**: R_F 0.54; **7**: R_F 0.39, benzene–acetone 4:1) within 2 h. The resin was filtered off, washed with CH_3OH, and the combined filtrates were concentrated to dryness. The residue (290 mg) was separated on silica gel (20 g, benzene up to benzene–acetone 10:1) to give the α-anomer **4** as a syrup (115 mg, 25%). $[\alpha]_D^{22}$ +107.3 (*c* 0.8, $CHCl_3$). For $C_7H_{14}O_4$ (162.2) calculated: 51.84% C, 8.70% H; found: 51.65% C, 8.55% H.

Further elution afforded the β-anomer **7** as a white solid (125 mg, 27%), m.p. 49 °C (Et_2O–petroleum ether), $[\alpha]_D^{22}$ –95.8 (*c* 0.7, $CHCl_3$). For $C_7H_{14}O_4$ (162.2) calculated: 51.84% C, 8.70% H; found: 51.70% C, 8.58% H. MS, ^1H and ^{13}C NMR data are summarized in Tables I and II.

Methyl 5-Deoxy-2,3-di-*O*-methyl-α-D-xylofuranoside (**5**)

A solution of glycoside **1** [9] (100 mg, 0.68 mmol) in CH_3CN (1 ml) was stirred with CH_3I (1.3 ml, 21 mmol) and powdered NaOH (100 mg, 2.4 mmol) under reflux at 40 °C. After the reaction was complete according to TLC (**1**: R_F 0.2; **5**: R_F 0.65; benzene–acetone 4:1), the mixture was concentrated and the residue separated on silica gel (20 g, benzene–acetone 4:1). Di-*O*-methyl ether **5** was obtained as a white solid (90 mg, 75%), m.p. 35 °C (Et_2O–petroleum ether), $[\alpha]_D^{19}$ +82.7 (*c* 0.8, $CHCl_3$). For $C_8H_{16}O_4$ (176.2) calculated: 54.53% C, 9.15% H; found: 54.44% C, 9.02% H. MS, ^1H and ^{13}C NMR data are summarized in Tables I and II.

Methyl 5-Deoxy-2,3-di-*O*-methyl-β-D-xylofuranoside (**8**)

Starting from diol **2** [9], the same procedure as described above for **5** yielded di-*O*-methyl ether **8** as a syrup (85 mg, 71%), $[\alpha]_D^{19}$ –80.8 (*c* 0.8, $CHCl_3$). For $C_8H_{16}O_4$ (176.2) calculated: 54.53% C, 9.15% H; found: 54.39% C, 8.92% H. MS, ^1H and ^{13}C NMR data are summarized in Tables I and II.

The Preparative Partial Methylation of Methyl 5-Deoxy-α-D-xylofuranoside (**1**)

A solution of glycoside **1** (100 mg, 0.68 mmol) in CH_3CN (20 ml) was stirred with CH_3I (2.8 ml, 44 mmol) and powdered NaOH (75 mg, 1.8 mmol) at ambient temperature. After 100 min, the reaction was stopped by evaporation and the residue was separated on silica gel (50 g, benzene–acetone 4:1). Di-*O*-methyl ether **5** was eluted first (15 mg, 12%) followed by 2-*O*-methyl ether **3** (70 mg, 65%). Optical rotation as well as ^1H NMR spectra were identical with those reported above. Minor 3-*O*-methyl ether **4** and unreacted **1** were not isolated.

The authors are indebted to colleagues from the Central Laboratories for spectral measurements and elemental analyses. This research was supported by the Ministry of Education, Youth and Sports of the Czech Republic (project No. 223300006).

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