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Transglucosidation of methyl and ethyl D-glucofuranosides by alcoholysis

Karl-Jonas Johansson,[c] Peter Konradsson,[a,*] Zygmunt Trumpakaj[b]

[a]*Department of Chemistry, Linköping University, S-581 83 Linköping, Sweden*
[b]*Department of Chemistry, University of Gdansk, PL-80-952 Gdansk, Poland*
[c]*Arrhenius Laboratory, Department of Organic Chemistry, Stockholm University, S-106 91 Stockholm, Sweden*

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Abstract

The acid catalyzed ethanolysis of methyl 5-*O*-methyl-α- and -β-D-glucofuranoside and the analogous methanolysis of ethyl 5-*O*-methyl-α- and -β-D-glucofuranoside have been investigated. For all four reactions, the primarily formed transglycosylation product was a single glycoside that had the opposite anomeric configuration to the starting material. This strongly indicates that a D-glucose methyl ethyl acetal is first formed and is then ring closed by a nucleophilic attack by HO-4, giving either the starting material or a transglycosylation product with the opposite anomeric configuration. Low percentages of the methyl ethyl acetals and of dimethyl acetals were also observed in the reaction product during the methanolysis reactions.

Keywords: Transglucosylation; Kinetics; Mechanistic studies

1. Introduction

From the observation that the dimethyl acetals of D-glucose and D-galactose undergo ring closure to furanosides concurrent with their hydrolysis in aqueous acid, and that these reactions were considerably faster than the hydrolysis of D-glyceraldehyde dimethyl acetal, Capon and Thacker[1] draw the conclusion that ring closure of the sugar acetals was a concerted reaction, and that HO-4 provided nucleophilic assistance. The corresponding methanolyses of the sugar acetals were also assumed to be concerted processes.

A detailed kinetic study of the anomerization of the methyl D-glucofuranosides in acidic methanol was performed by Kaczmarek et al.[2] They showed that D-glucose dimethyl acetal is formed during this reaction, and discussed its possible role as an intermediate in the anomerization reaction.

In the present investigation, we have studied the transglucosidation of methyl 5-*O*-methyl-α- and -β-D-glucofuranoside in ethanolic acid, and of ethyl 5-*O*-methyl-α- and -β-D-glucofuranoside in methanolic acid.

2. Results and discussion

In order to avoid formation of pyranosides, the methyl and ethyl α- and -β-D-glucofuranosides were methylated in the 5-position. The starting material for all the glucofuranosides was 5-*O*-methyl-α-D-glucofuranosylurono-6,3-lactone (**1**).[3] On treatment with methanol or ethanol and boron trifluoride etherate in

* Corresponding author.
E-mail address: petko@ifm.liu.se (P. Konradsson).

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trimethyl or triethyl orthoformate, the methyl (**2**) and ethyl (**4**) 5-*O*-methyl-α-D-glucofuranosidurono-6,3-lactone, respectively, were obtained. An analogous reaction, starting from methyl-α-D-glucofuranosylurono-6,3-lactone, has been reported.[4] The corresponding methyl (**3**) and ethyl (**5**) 5-*O*-methyl-β-D-glucofuranosidurono-6,3-lactones were prepared by methanolysis or ethanolysis of **1**, respectively, followed by chromatography on silica gel. Reduction of **2**, **3**, **4**, and **5** with lithium aluminum hydride in THF yielded the desired glucosides, namely, methyl (**6**) and ethyl (**8**) 5-*O*-methyl-α-D-glucofuranoside and methyl (**7**) and ethyl (**9**) 5-*O*-methyl-β-D-glucofuranoside.

The methyl D-glucofuranosides were dissolved in 0.6 M ethanolic camphorsulfonic acid (CSA), and the ethyl D-glucofuranosides in 0.6 M methanolic camphorsulfonic acid. The solutions were kept at 0 °C, samples were withdrawn at intervals, neutralized with Dowex 1X4-200 resin, concentrated, and acetylated. The acetylated products were analyzed by GC and by GC–EIMS. In addition to the D-glucofuranosides, low percentages of methyl ethyl (**10**) and dimethyl acetal (**11**) were observed at the beginning and end, respectively, of the methanolysis experiments, and identified from their mass spectra. Typical ions were those derived from C-1, namely *m*/*e* 89 and 75, respectively. The acetates of the mixed acetals obtained on methanolysis of the ethyl α- and β-glucofuranoside had different retention times on GC, but had almost identical mass spectra. It was not, however, possible to determine the relative proportions of the non-cyclic acetals with sufficient accuracy to include them in the kinetic analysis.

From these results, the ratio of the initially formed glucosides could be determined, as exemplified for the transglucosidation of ethyl 5-*O*-methyl-α-D-glucofuranoside (Scheme 1). In this scheme, α-Et stands for the ethyl 5-*O*-methyl-α-D-glucofuranoside (**8**), etc. the k_1 and $(k_2 + k_3)$ represent the rate constants for the initial formation of β-Me and that of for the equilibration of the initial formed product, respectively.

The analytical solutions of the differential equation system (gained form Scheme 1)

$$\mathrm{d}f_1/\mathrm{d}t = -k_1 f_1$$

$$\mathrm{d}f_2/\mathrm{d}t = k_1 f_1 - k_2 f_2 + k_3 f_3$$

$$\mathrm{d}f_3/\mathrm{d}t = k_2 f_2 - k_3 f_3 \quad (1)$$

has the following analytical solution

$$f_1(t) = f_1(0)\exp(-k_1 t) \quad (1a)$$

$$f_2(t) = f_1(0)\{A - B\exp(-k_1 t) - C\exp[-(k_2 + k_3)t]\} \quad (1b)$$

$$f_3(t) = f_1(0)\{1 - A - (1 - B)\exp(-k_1 t) + C\exp[-(k_2 + k_3)t]\} \quad (1c)$$

where

$$A = \frac{k_3}{k_2 + k_3}, \qquad B = \frac{k_3 - k_1}{k_2 + k_3 - k_1},$$

$$C = A - B \quad (1d)$$

At long time ($t \to \infty$)

$$f_{2\mathrm{eq}}/f_{3\mathrm{eq}} = k_3/k_2 = A/(1 - A) \quad (1e)$$

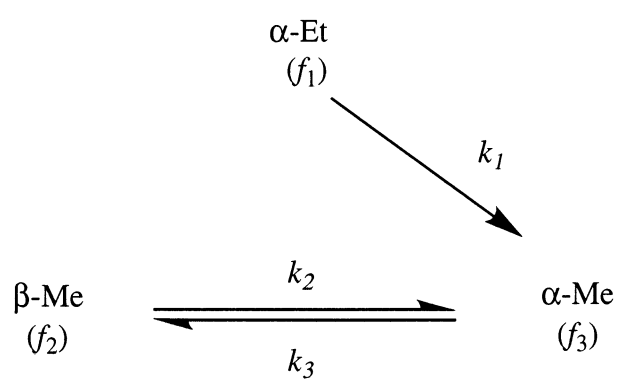
At short time ($k_j t < 1$)

$$f_2(t) = f_1(0)[k_1 t - k_1(k_1 + k_2)t^2/2 + \ldots] \quad (1f)$$

$$f_3(t) = f_1(0)[k_1 k_2 t^2/2 - k_1 k_2(k_1 + k_2 + k_3)t^3/6 + \ldots] \quad (1g)$$

Eqs. (1f) and (1g) indicate that initially formed product (β-Me) is proportional to t, and initially formed product (α-Me) is proportional to t^2. All k_1, k_2 and k_3 rate constants can be estimated in similar way as in our proceeding paper (Figs. 1–4).[5]

The results of the transglucosidation experiments are summarized in Tables 1–4, and the final results in Table 5.



Scheme 1. Transglucosidation of ethyl 5-*O*-methyl-α-D-glucofuranoside in methanolic CSA.

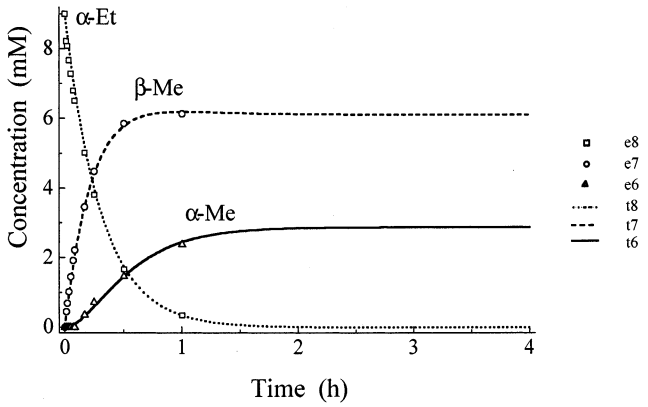


Fig. 1. Transglucosidation of ethyl 5-*O*-methyl-α-D-glucofuranoside in methanolic CSA. e6–e8 correspond to experimental points and t6–t8 to theoretical curves.

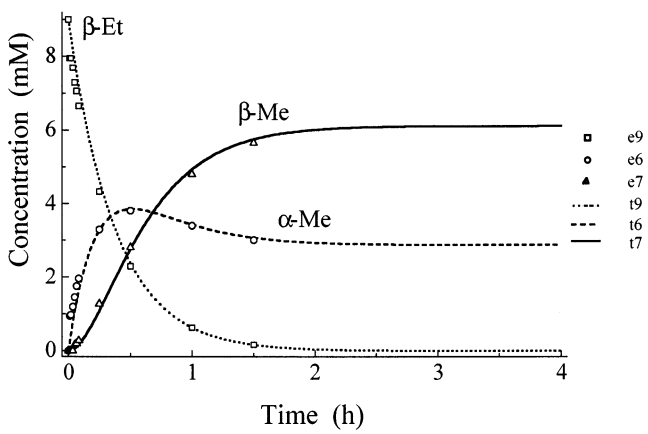


Fig. 2. Transglucosidation of ethyl 5-*O*-methyl-β-D-glucofuranoside in methanolic CSA. e6, e7, e9 correspond to experimental points and t6, t7, t9 to theoretical curves.

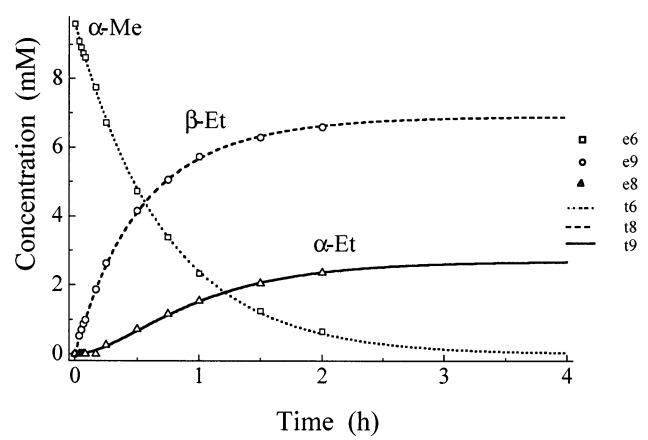


Fig. 3. Transglucosidation of methyl 5-*O*-methyl-α-D-glucofuranoside in ethanolic CSA. e6, e8, e9 correspond to experimental points and t6, t8, t9 to theoretical curves.

For all four transglucosidation reactions, the only glucoside formed as a primary product was that with the inversed anomeric configuration relative to the starting material. This indicates that a methyl ethyl acetal with inversed configuration at C-1 is the first product formed. Ring closure, by attack of HO-4, could proceed in two ways, either with formation of the starting material or with formation of the anomeric transglucosidation product. The latter then reacts further to give an anomeric mixture of glucosides. The reaction sequence is exemplified in Scheme 2 for the methanolysis of ethyl 5-*O*-methyl-α-D-glucofuranoside (**8**).

In contradistinction, both anomers, with a slight predominance of the product with inversed anomeric configuration, are initially formed on the alcoholysis of the methyl and ethyl 4-*O*-methyl-α- and β-D-glucopyranosides,[5] indicating that these reactions proceed via a cyclic intermediate.

In conclusion, the results of the present study are in full agreement with those of Capon and Tucker[1] and of Kaczmarek et al.[2] On methanolyses of different methyl aldofuranosides under reducing conditions[6] only non-cyclic alditols were formed, also indicating a non-cyclic intermediate. The results further demonstrate that the transglucosidation in the examples studied proceeds exclusively or almost exclusively via intermediate, non-cyclic acetals.

In a related reaction, (1-*O*-methyl-D-glucitol-1-yl)-*N*-*p*-nitroaniline was formed on treatment of methyl α-D-glucofuranoside with

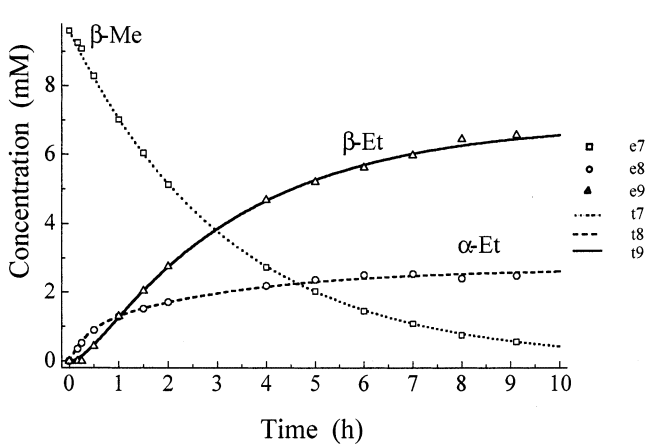


Fig. 4. Transglucosidation of methyl 5-*O*-methyl-β-D-glucofuranoside in ethanolic CSA. e7–e9 correspond to experimental points and t7–t9 to theoretical curves.

Table 1
Methanolysis of ethyl 5-*O*-methyl-α-D-glucofuranoside in 0.6 M methanolic CSA at 0.0 ± 0.1 °C

Time (s)	α-Et (mM)	Me Et acetal (mM)	β-Me (mM)	Di Me Acetal (mM)	α-Me (mM)
0	9.0	0.0	0.0	0.0	0.0
46	8.2	0.33	0.45	0.0	0.0
74	8.1	0.24	0.69	0.0	0.0
121	7.7	0.31	1.0	0.0	0.0
183	7.3	0.27	1.5	0.0	0.0
253	6.8	0.28	1.9	0.0	0.0
302	6.5	0.27	2.2	0.0	0.0
606	5.0	0.18	3.5	0.0	0.35
900	3.8	0.0	4.5	0.0	0.71
1816	1.7	0.0	5.9	0.0	1.5
3608	0.34	0.0	6.1	0.13	2.4

Table 2
Methanolysis of ethyl 5-*O*-methyl-β-D-glucofuranoside in 0.6 M methanolic CSA at 0.0 ± 0.1 °C

Time (s)	β-Et (mM)	Et Me acetal (mM)	α-Me (mM)	Di Me acetal (mM)	β-Me (mM)
0	9.0	0.0	0.0	0.0	0.0
40	7.9	0.11	0.95	0.0	0.0
70	7.9	0.088	0.97	0.0	0.0
128	7.7	0.12	1.2	0.0	0.0
180	7.3	0.11	1.5	0.0	0.16
241	7.1	0.00	1.8	0.0	0.19
300	6.7	0.11	2.0	0.0	0.27
899	4.3	0.0	3.3	0.11	1.3
1804	2.3	0.0	3.8	0.086	2.8
3600	0.63	0.0	3.4	0.16	4.8
5403	0.16	0.0	3.0	0.17	5.7

p-nitroaniline in methanolic hydrogen chloride under mild conditions.[7] The absolute configuration at C-1 was not determined but is most probably (**S**), as in **9**.

3. Experimental

General methods.—Methanol was distilled over Mg/I_2 and kept over 3 Å molecular sieves. Ethanol (99.5%) was dried over powdered 3 Å molecular sieves. CSA was recrystallized from EtOAc and dried under reduced pressure over P_2O_5. Titrations with 0.5 M NaOH of freshly prepared 1 M CSA in MeOH or EtOH and of the same solutions that had been kept at 50 °C for 3 days (MeOH) or for 5 days (EtOH) showed no difference. ^{13}C NMR spectra of 1 M CSA in CD_3OD, kept in a sealed NMR tube, and of the same sample refluxed for 7 days were identical.

TLC was performed on 0.25 mm precoated silica-gel plates (E. Merck, silica-gel 60 F_{254})

Table 3
Ethanolysis of methyl 5-*O*-methyl-α-D-glucofuranoside in 0.6 M ethanolic CSA at 0.0 ± 0.1 °C

Time (s)	α-Me (mM)	β-Et (mM)	α-Et (mM)
0	9.6	0.0	0.0
120	9.1	0.52	0.0
180	8.9	0.69	0.0
238	8.7	0.87	0.0
294	8.6	0.98	0.0
600	7.7	1.9	0.0
899	6.7	2.6	0.26
1799	4.7	4.2	0.72
2699	3.4	5.1	1.2
3608	2.3	5.7	1.5
5400	1.3	6.3	2.1
7214	0.65	6.6	2.4

Table 4
Ethanolysis of methyl 5-*O*-methyl-β-D-glucofuranoside in 0.6 M ethanolic CSA at 0.0 ± 0.1 °C

Time (s)	β-Me (mM)	α-Et (mM)	β-Et (mM)
0	9.6	0.0	0.0
599	9.3	0.35	0.0
900	9.1	0.52	0.0
1800	8.3	0.89	0.43
3601	7.0	1.3	1.3
5401	6.0	1.5	2.0
7199	5.1	1.7	2.8
14,398	2.7	2.2	4.7
17,999	2.0	2.4	5.2
21,599	1.5	2.5	5.6
25,200	1.1	2.5	6.0
28,800	0.75	2.4	6.4
32,836	0.55	2.5	6.6

and detection by spraying the plates with 8% aq H_2SO_4 solution, followed by heating at 250 °C. For column chromatography E. Merck silica-gel K 60 (0.040–0.063 mm) was used.

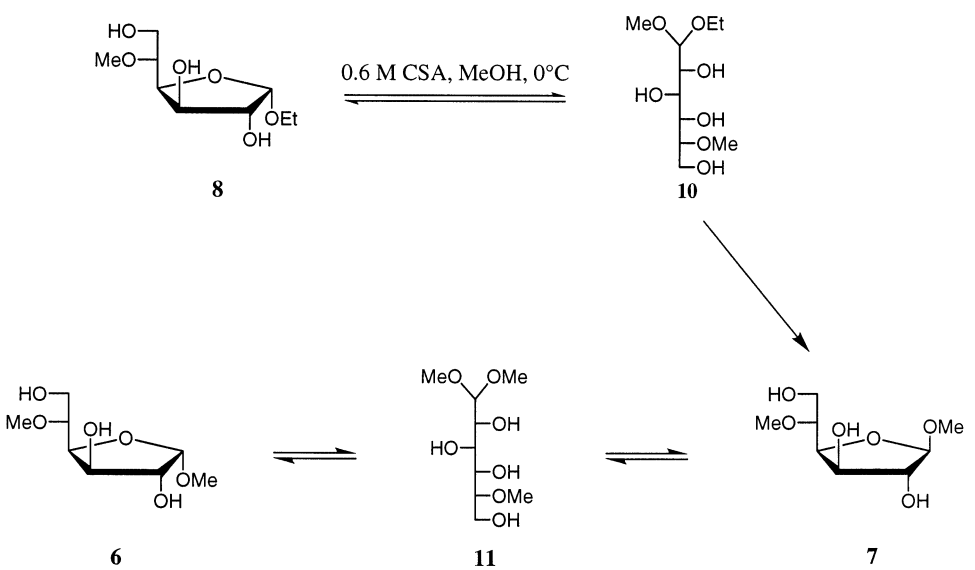
NMR spectra was recorded on a Varian Mercury 300 at 300 Hz instrument and chemical shifts were measured relative to acetone (δ 31.0 ppm, CH_3) or TMS as an internal standard. FAB-MS, in the positive mode, was performed on a JEOL SX 102 instrument, using a glycerol matrix. Optical rotations were determined with on a Perkin–Elmer 241 polarimeter. GC was conducted on an HP 5890 instrument with a flame ionization detector and hydrogen as carrier gas, using a HP-5 fused-silica capillary column. EI GC–MS was conducted on an HP 5890-HP 5970 instrument, using an HP-5MS fused-silica capillary column and helium as carrier gas.

*Methyl 5-*O*-methyl α-*D*-glucofuranosiduro-6,3-lactone* (**2**).—BF_3 etherate (1.5 mL) was added to MeOH (10 mL) and 0.2 mL

Table 5
Mean rate constants (s^{-1}) and (α/β) ratios for the initial transglucosidation reaction and for the equilibration of initially formed product, on ethanolysis of methyl 5-*O*-methyl-α- and -β-D-glucofuranoside and on methanolysis of ethyl methyl 5-*O*-methyl-α- and -β-D-glucofuranoside

Starting material	$10^4\ k_1$ (s^{-1})	$10^4\ k_2$ (s^{-1})	$10^4\ k_3$ (s^{-1})	k_2/k_3	*R*	Inversion [a] (%)
α-Me	3.9 ± 0.02	2.2 ± 0.02	5.6 ± 0.08	1/0.39	1.000	100
β-Me	0.86 ± 0.03	5.6 ± 0.15	2.2 ± 0.08	0.39	0.999	100
α-Et	9.1 ± 0.10	3.2 ± 0.10	6.7 ± 0.20	1/0.47	0.998	100
β-Et	7.4 ± 0.50	6.7 ± 0.50	3.2 ± 0.30	0.47	0.982	100

[a] Inversion (%) of configuration during the initial reaction.



Scheme 2. Methanolysis of methyl 5-*O*-methyl-α-D-glucofuranoside in ethanolic CSA.

of this solution was added to a solution of 5-*O*-methyl α-D-glucono-6,3-lactone[3] (2.0 g, 10.5 mmol) in trimethyl orthoformiate (50 mL, dried over Drierite). The solution was stirred for 1 h at rt and neutralized with Et_3N. After standard work up, **2** was isolated by column chromatography (15:1, $CHCl_3$–MeOH). Crystallization from EtOAc gave **2** in 20% yield. $[\alpha]_D + 169°$ (*c* 0.98, water). Mp 113–114 °C. ^{13}C NMR (D_2O) δ: 175.9 (C-6), 105.1 (C-1), 86.7 (C-3), 77.9 (C-5), 76.2 (C-2), 74.7 (C-4), 59.6 (CH_3), 56.7 (CH_3). ^1H NMR (D_2O) δ: 5.18 (1 H, d, H-1), 5.06 (1 H, t, H-4), 4.95 (1 H, d, H-3), 4.55 (1 H, d, H-5), 4.42 (1 H, d, H-2), 3.59 (3 H, s, CH_3), 3.47 (3 H, s, CH_3). Anal. Calcd for $C_8H_{12}O_6$: C, 47.06; H: 5.92. Found C, 47.09; H, 5.90.

Methyl 5-O-*methyl β*-D-*glucofuranosidurono-6,3-lactone* (**3**).—Dowex 50w- × 8 (H^+, 0.510 g) was added to a solution of 5-*O*-methyl α-D-glucono-6,3-lactone[3] (0.514 g, 2.7 mmol) in MeOH (10 mL) and kept at 50 °C. After 5 h the resin was filtered off and the solution was concentrated to dryness. Column chromatography (39:1, $CHCl_3$–MeOH) of the syrup, followed by crystallization from EtOAc–hexane gave **3** in 47% yield. $[\alpha]_D - 14°$ (*c* 0.86, water). Mp 100 °C. ^{13}C NMR (D_2O) δ: 176.0 (C-6), 110.0 (C-1), 84.6 (C-3), 77.9 (C-5), 76.9 (C-2), 76.8 (C-4), 59.5 (CH_3), 56.0 (CH_3). ^1H NMR (D_2O) δ: 5.22 (1 H, m, H-4), 5.05 (2 H, m, H-1, H-3), 4.46 (1 H, d, H-5), 4.34 (1 H, s, H-2), 3.60 (3 H, s, CH_3), 3.31 (3 H, s, CH_3). Anal. Calcd for $C_8H_{12}O_6$: C, 47.06; H: 5.92. Found C, 47.06; H, 6.04.

Ethyl 5-O-*methyl α*-D-*glucofuranosidurono-6,3-lactone* (**4**).—BF_3 etherate (1.5 mL) was added to EtOH (10 mL) and 0.2 mL of this solution was added to a solution of 5-*O*-methyl α-D-glucono-6,3-lactone[3] (2.0 g, 10.5 mmol) dissolved in triethyl orthoformiate (50 mL, dried over Drierite). The solution was stirred for 2 h and neutralized with Et_3N. After standard work up the syrup was purified by column chromatography (39:1, $CHCl_3$–MeOH). Two consecutive crystallizations from toluene gave **4** in 26% yield. ^{13}C NMR (D_2O) δ: 175.6 (C-6), 103.9 (C-1), 86.6 (C-3), 77.9 (C-5), 75.9 (C-2), 74. 6 (C-4), 65.9 (CH_2), 59.5 (CH_3), 15.0 (CH_3). ^1H NMR (D_2O) δ: 5.30 (1 H, d, H-1), 5.07 (1 H, dd, H-4), 4.95 (1 H, dd, H-3), 4.55 (1 H, d, H-5), 4.40 (1 H, dd, H-2), 3.85 (2 H, m, CH_2), 3.66 (2 H, m, CH_2), 3.58 (3 H, s, CH_3), 1.21 (3 H, t, CH_3). $[\alpha]_D +$ 147° (*c* 0.94, water). Mp 94–95°. Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H: 6.47. Found C, 49.62; H, 6.49.

The synthesis also gave the β anomer as a by-product in 5% yield

Ethyl 5-O-*methyl β*-D-*glucofuranosidurono-6,3-lactone* (**5**).—Dowex 50w- × 8 (H^+, 0.549 mg) was added to solution of 5-*O*-methyl α-D-glucono-6,3-lactone[3] (0.50 g, 2.6 mmol) in anhyd EtOH (10 mL and heated to 50 °C. After 5 h the ion-exchange resin was filtered of and the solution concentrated under reduced pressure. The resulting syrup was purified by column chromatography (9:1, $CHCl_3$–MeOH), and gave **5** in 71% yield. $[\alpha]_D - 21°$ (*c* 1.1, $CHCl_3$). ^{13}C NMR (D_2O) δ: 176.2 (C-6), 108.6 (C-1), 84.6 (C-3), 77.9 (C-5), 76.8 (C-2), 76.6 (C-4), 64.7 (CH_2), 59.4 (CH_3), 14.4 (CH_3). ^1H NMR (D_2O) δ: 5.21 (1 H, t, H-4), 5.16 (1 H, s, H-1), 5.05 (1 H, d, $J_{3,4}$ 4.4 Hz, H-3), 4.45 (1 H, d, H-5), 4.34 (1 H, s, H-2), 3.76 (1 H, m, CH_2), 3.59 (3 H, s, CH_3), 3.47 (1 H, m, CH_2), 1.07 (3 H, t, CH_3). Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H: 6.47. Found C, 49.38; H, 6.40.

Methyl 5-O-*methyl*-α-D-*glucofuranoside* (**6**).—A solution of **2** (128 mg, 630 mmol) and lithium aluminum hydride (62 mg, 1.6 mmol) in freshly distilled THF (10 mL) was refluxed for 1 h. A second portion of lithium aluminum hydride (31 mg, 820 mmol), was added after the solution had reached rt. After 1 h the reaction was quenched with an excess of $Na_2SO_4 \cdot 10\ H_2O$ and filtered through Celite.[8] The filtrate was concentrated under reduced pressure. Chromatography (9:1, $CHCl_3$–MeOH containing 1% Et_3N) of the syrup gave the title compound in 44% yield $[\alpha]_D$ 120° (*c* 2.04, CH_3CH_2OH). ^{13}C NMR (CD_3OD): δ 104.1 (C-1), 80.9 (C-5), 79.3 (C-2), 78.5, 77.5 (C-3 and C-4), 61.8 (C-6), 58.4 (O-CH_3), 56.1 (O-CH_3). ^1H NMR (CD_3OD): δ 4.93 (1 H, d, H-1), 4.12 (2 H, m, H-3 and H-4), 3.99 (1 H, q, H-2), 3.88 (1 H, dd, H-6′), 3.63 (1 H, dd, H-6), 3.50 (1 H, m, H-5), 3.46 (3 H, s, CH_3), 3.43 (3 H, s, CH_3). FAB-MAS Calcd for $C_8H_{16}O_6$ (M + Na) 231.0845. Found (M + Na) 231.0835.

Methyl 5-O-methyl-β-D-glucofuranoside (**7**).—A solution of **3** (126 mg, 620 mmol) and lithium aluminum hydride (53 mg, 1.4 mmol) in freshly distilled THF (10 mL) was refluxed for 1 h. The reaction was quenched with an excess of $Na_2SO_4 \cdot 10\ H_2O$ and filtered through Celite.[8] The filtrate was concentrated under reduced pressure. Chromatography (9:1, $CHCl_3$–MeOH containing 1% Et_3N) of the syrup gave the title compound in 72% yield. $[\alpha]_D$ −87° (*c* 2.35, CH_3CH_2OH). ^{13}C NMR (CD_3OD): δ 110.9 (C-1), 82.0 (C-4), 81.7 (C-2), 80.8 (C-5), 76.7 (C-3) 62.1 (C-6), 58.3 (O–CH_3), 55.6 (O–CH_3). ^1H NMR (CD_3OD): δ 4.74 (1 H, s, H-1), 4. 17 (1 H, dd, H-4), 4.03 (1 H, d, H-3), 4.00 (1 H, t, H-2), 3.95 (1 H, dd, H-6′), 3.67 (1 H, dd, H-6), 3.57 (1 H, m, H-5), 3.47 (3 H, s, CH_3), 3.34 (3 H, s, CH_3). FAB-MS Calcd for $C_8H_{16}O_6$ (M + Na) *m*/*z* 231.0845. Found (M + Na) *m*/*z* 231.0834.

Ethyl 5-O-methyl-α-D-glucofuranoside (**8**).—A solution of **4** (192 mg, 880 mmol) and lithium aluminum hydride (37 mg, 970 mmol) in freshly distilled THF (10 mL) was refluxed, after 4 h an additional proportion of lithium aluminum hydride (50 mg, 1.3 mmol) was added. After further 30 min the reaction was quenched with an excess of $Na_2SO_4 \cdot 10\ H_2O$ and filtrated through Celite.[8] The filtrate was concentrated under reduced pressure and the resulting syrup purified by column chromatograph (5:1, toluene–MeOH). Recrystallization from EtOAc and hexane gave **8** in 38% yield. $[\alpha]_D$ 104° (*c* 1.27, EtOH). ^{13}C NMR (D_2O) δ: 102.3 (C-1), 79.7 (C-5), 77.4 (C-4), 77.3 (C-2), 76.2 (C-3), 65.7 (CH_2), 60.4 (C-6), 58.0 (CH_3), 15.0 (CH_3). ^1H NMR (D_2O) δ: 5.14 (1 H, d, H-1), 4.24 (1 H, t, H-3), 4.17 (1 H, t, H-4), 4.10 (1 H, t, H-2), 3.91 (1 H, dd, H-6′), 3.80 (1 H, m, CH_2), 3.62 (2 H, m, H-6 and CH_2), 3.52 (1 H, m, H-5), 3.42 (3 H, s, CH_3), 1.18 (3 H, t, CH_3). Anal. Calcd for $C_9H_{18}O_6$: C, 48.64; H: 8.16. Found C, 48.79; H, 8.28.

Ethyl 5-O-methyl-β-D-glucofuranoside (**9**).—A solution of **5** (202 mg, 930 mmol) and lithium aluminum hydride (88 mg, 2.3 mmol) in freshly distilled THF (10 mL) was refluxed for 1 h. The reaction was quenched with an excess of $Na_2SO_4 \cdot 10\ H_2O$ and filtrated through Celite.[8] The filtrate was concentrated under reduced pressure. Chromatograph (9:1, $CHCl_3$–MeOH containing 1% Et_3N) of the resulting syrup gave the title compound in 76% yield. $[\alpha]_D$ −84° (*c* 1.85, CH_3CH_2OH). ^{13}C NMR (CD_3OD) δ: 109.5 (C-1), 81.8 (C-2 and C-4), 80.8 (C-5) 76.8 (C-3), 64.7 (CH_2), 62.1 (C-6), 58.3 (CH_3), 15.5 (CH_3). ^1H NMR (CD_3OD) δ: 4.84 (1 H, d, H-1), 4.14 (1 H, q, H-4), 4.02 (1 H, d, H-3), 4.00 (1 H, s, H-2), 3.93 (1 H, dd, H-6′), 3.77–3.49 (4 H, m, H-5, H-6 and CH_2), 3.47 (3 H, s, CH_3), 1.19 (3 H, t, CH_3). FAB-MS Calcd for $C_9H_{18}O_6$ (M + H) *m*/*z* 223.1182. Found (M + H) *m*/*z* 223.1167.

Kinetic runs.—The runs were performed in Supelco screw cap vials with PTFE/Neopren septa. Glassware were dried at 110 °C and cooled in a desiccator. The glucosides were dissolved in 1 mL of water and freeze-dried in the vials. The vials with the glucoside (10 mg) and the 0.6 M CSA in MeOH or EtOH (5 mL) were cooled in an ice-water bath before to mixing. The reactions were performed at 0 °C. Aliquots (100 mL) were withdrawn with a syringe at suitable intervals and neutralized with DOWEX 1X4-200 resin (OH^-). The solutions were concentrated, acetylated, and analyzed by GC and GC–MS. The components were identified by comparison with authentic substances or from their mass spectra. The molar proportions of the components were estimated from the areas under the GC peaks and corrected by response factors.[9]

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