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Synthesis of α- and β-D-glucopyranuronate 1-phosphate and α-D-glucopyranuronate 1-fluoride: Intermediates in the synthesis of D-glucuronic acid from starch

André Heeres [a], Henk A. van Doren [a,*], Kees F. Gotlieb [b], Ido P. Bleeker [c]

[a] *Netherlands Institute for Carbohydrate Research TNO, Rouaanstraat 27, NL-9723 CC Groningen, The Netherlands*

[b] *Wildervankstraat 12, NL-9648 LC Wildervank, The Netherlands*

[c] *AVEBE B.A., Avebeweg 1, NL-9607 PT Foxhol, The Netherlands*

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Abstract

The title uronates were prepared by 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) catalysed sodium hypochlorite oxidation of α- and β-D-glucopyranosyl phosphate (α-/β-Glc-1-*P*) and α-D-glucopyranosyl fluoride (α-Glc-1-F). Quantitative recovery of the TEMPO catalyst was achieved by azeotropic distillation of a small part of the reaction mixture. Also, a heterogeneous catalyst system was prepared by immobilisation of 4-oxo-tetramethyl-1-piperidinyloxy (OTEMPO) on amino-functionalized silica. The protected uronates were hydrolysed to yield D-glucuronate. Since α- and β-Glc-1-*P* and α-Glc-1-F can be obtained from starch in one step, D-glucuronic acid is now available from starch in a convenient three-step sequence. © 1997 Elsevier Science Ltd.

Keywords: α-D-Glucopyranuronate 1-phosphate; β-D-Glucopyranuronate 1-phosphate; α-D-Glucopyranuronate 1-fluoride; NaOCl-TEMPO oxidation; Catalyst immobilization; D-Glucuronic acid

1. Introduction

There is rapidly growing interest in the utilization of renewable raw materials such as carbohydrates. Environmental problems associated with the use of a number of synthetic products in terms of biodegradability and biocompatability, as well as the projected long-term limitations on the exploitation of fossil feedstocks, play an important role in this respect.

Over the past decades, the routes towards several hydrolysis products of starch have been optimized; nowadays, glucose, maltose, and, to a lesser extent, the cyclodextrins are synthesized enzymatically on a very large scale. D-Gluconic acid, prepared by fermentative oxidation of glucose, is a commercially available product whilst its sodium salt is used as a

* Corresponding author. Fax: +31 50 3128891; e-mail: havdoren@noord.bart.nl.

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metal chelating agent. D-Glucono-δ-lactone has pharmaceutical applications and it is also used as acidulant in food processing [1].

In contrast to D-gluconic acid, D-glucuronic acid and its lactone are not produced on an industrial scale. D-Glucuronic acid is of considerable biochemical significance [2]. Moreover, it is an interesting intermediate for fine chemicals such as D-glucaric acid and L-ascorbic acid [1].

Unfortunately, the synthesis of D-glucuronic acid by acid hydrolysis of polyglucuronic acid, obtainable by oxidation of starch or cellulose, proceeds slowly and leads to undesired side products [3]. To our knowledge, no enzymes capable of hydrolyzing the (1 → 4) bond of poly-D-glucuronic acid have been reported.

An alternative route for the synthesis of D-glucuronic acid is the selective oxidation of the primary hydroxyl group of anomerically-substituted glucose derivatives. The hemiacetal functionality of glucose is very reactive and has to be protected to prevent oxidation to aldonic and aldaric acids. Oxidation of these anomerically-protected monosaccharides has been performed with oxidation systems such as Pt/O_2, N_2O_4 or $KMnO_4$ [4–6].

Very recently, sodium hypochlorite oxidation catalyzed by 2,2,6,6-tetramethyl-1-pipe ridinyloxy (TEMPO) has proven to be a mild and efficient system to oxidize protected aldoses or polysaccharides to (poly)uronic acids [7–14].

Here, we report the efficient and simple preparation of α- and β-D-glucopyranuronate 1-phosphate and α-D-glucopyranuronate 1-fluoride. The recovery of the 2,2,6,6-tetramethyl-1-piperidinyloxy catalyst by immobilization or by azeotropic distillation of a part of the reaction mixture is also described. D-Glucuronate was obtained by hydrolysis of these uronates, thus completing the formal synthesis of D-glucuronic acid from starch.

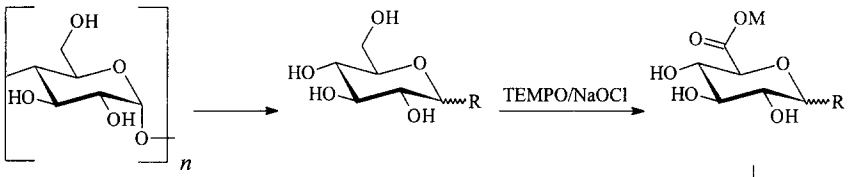
2. Results and discussion

The α and β anomers of D-glucopyranosyl phosphate (α-Glc-1-*P* and β-Glc-1-*P*) and α-D-glucopyranosyl fluoride (α-Glc-1-F) are easily accessible anomerically-protected monosaccharides. Both anomers of Glc-1-*P* can be synthesized enzymatically from starch [15,16], whereas the chemical routes to α- and β-Glc-1-*P* from glucose are cumbersome and inefficient [17–23]. α-Glc-1-F is synthesized by hydrolysis of starch in HF [24,25].

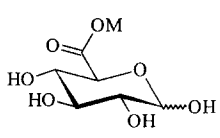
Selective oxidation of the primary hydroxyl group at C-6 of these compounds yields excellent precursors for glucuronic acid since hydrolysis of the anomeric substituents is achieved readily. The route developed, shown in Scheme 1, is a novel (chemo-enzymatic) route to D-glucuronic acid starting from starch.

Much like the starting materials, these substituted uronates may be interesting substrates for enzymatic reactions, such as chain extension of starch and in the chemical synthesis of di- and oligosaccharides [26–29].

The oxidation of α- and β-Glc-1-*P* and α-Glc-1-F with the TEMPO/hypohalite system at pH 9 and 0 °C was complete in 1–2 h. The pH was maintained at the desired value by addition of 1 M NaOH using a pH-stat. Lower yields were obtained when the oxidation was performed at ambient temperature, probably due to a decrease in selectivity of the oxidation system at higher temperatures.



	R	M
1	α-OPO_3M_2	Na,K
2	β-OPO_3M_2	Na
3	α-F	K



Scheme 1. Routes for the synthesis of D-glucuronate from starch.

Whilst oxidized polysaccharides, such as polyglucuronic acid, can easily be separated from the sizable amounts of salts formed during oxidation, by dialysis or precipitation in aqueous methanol or ethanol, mono- or di-saccharide derivatives are not so easily separated from inorganic salts [8,13,14]. After oxidation of dipotassium α-Glc-1-*P* ($2K^+ \cdot C_6H_{11}O_9P^{2-} \cdot 2H_2O$ [30]) with TEMPO/hypohalite, **1** crystallized from the reaction mixture by addition of methanol. The yield (about 85%) could not be calculated exactly because the uronate was a mixture of sodium and potassium salts. After cation exchange of the crude α-D-glucopyranuronate 1-phosphate, the tris potassium ($3K^+ \cdot C_6H_8O_{10}P^{3-} \cdot 5H_2O$) and the tris sodium ($3Na^+ \cdot C_6H_8O_{10}P^{3-} \cdot 6.5H_2O$) salts **1** could be isolated by crystallization from H_2O–methanol.

β-Glc-1-*P* is usually isolated as its dicyclohexylammonium or barium salt [31]. The dicyclohexylammonium salt could not be oxidized with the TEMPO/hypohalite system due to inactivation of the catalyst by the amino functionality of the ammonium salt [32]. After cation-exchange (Dowex H^+) and neutralization with 1 M NaOH, crude disodium β-Glc-1-*P* was oxidized. The reaction was complete within 2 h (no more acid was formed) and, after addition of methanol, an oil precipitated. After decantation of the mother liquor the crude oil of **2** crystallized partially (compare Marsh [33]).

The oxidation product of α-Glc-1-F, α-D-glucopyranuronate 1-fluoride (**3**), could not be separated from the inorganic salts by crystallization. For purification we used an anion-exchange resin with potassium acetate as the eluting buffer, and the mono potassium salt **3** ($K^+ \cdot C_6H_8O_6F^- \cdot H_2O$) was crystallized as the monohydrate from H_2O–ethanol–acetone in 65% yield.

Table 1 shows the NMR data of compounds **1–3**. The coupling constants ($^3J_{HH}$ 9–10 Hz) of the synthesized uronates are consistent with a $^4C_1$ pyranose conformation for all three compounds. The $^3J_{PH}$, $^4J_{PH}$, $^2J_{PC}$ and $^3J_{PC}$ coupling constants of **1** and **2** are almost equal to those of the starting compounds α-Glc-1-*P* ($^3J_{PH}$ 7.5 Hz, $^4J_{PH}$ 1.8 Hz, $^2J_{PC}$ 5.3 Hz, $^3J_{PC}$ 5.3 Hz) and β-Glc-1-*P* ($^3J_{PH}$ 7.7 Hz, $^4J_{PH}$ 0 Hz, $^2J_{PC}$ 3.7 Hz, $^3J_{PC}$ 6.6 Hz). The $^2J_{PC}$ and $^3J_{PC}$ coupling constants are dependent on the pH [34]. The coupling constants of α-D-glucopyranuronate 1-fluoride are almost equal to those of α-Glc-1-F ($^2J_{FH}$ 53.2 Hz, J_{FC} 222 Hz, $^2J_{FC}$ 25.0 Hz). It can be concluded that the oxidation of the primary hydroxyl function at C-6 of compounds **1–3** has very little influence on the conformation of the compounds in solution.

Table 2
Yields of repeated oxidations of α-Glc-1-*P* with NaOCl in the presence of immobilized OTEMPO and recovered TEMPO (by azeotropic distillation)

	Immobilized OTEMPO	Recovered TEMPO
1st cycle	~ 65% [a]	~ 85%
2nd cycle	~ 75%	~ 86%
3rd cycle	~ 35%	~ 77%

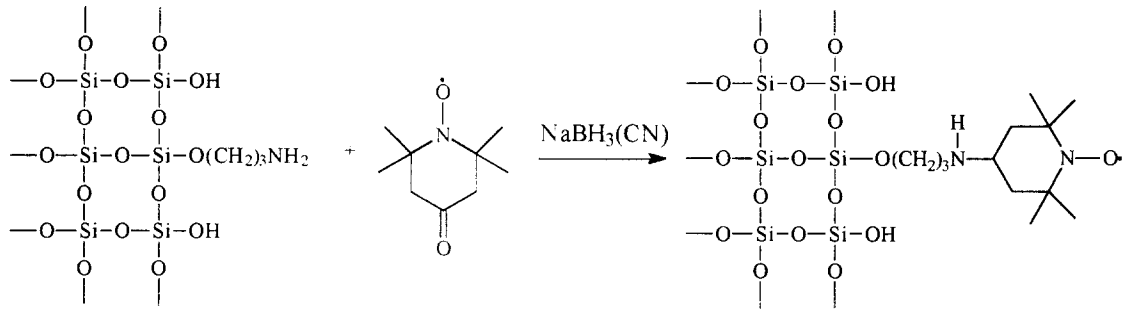
[a] Exact yields can not be calculated due to the fact that a mixture of cations will be present.

Catalyst recovery.—For commercial applications of the TEMPO/hypohalite system, it is important to recover the catalyst. Also, nitroxide radicals are suspected to be toxic and, therefore, removal from the final products is necessary [35]. We found that TEMPO can be recovered quantitatively by azeotropic distillation of a part of the reaction mixture. No loss in activity was observed and the selectivity (see Table 2) remains high [36]. Recovery of TEMPO in this way is very useful in batch oxidations of homogeneous and heterogeneous systems, such as native starch, cellulose, etc. [37]. Other stable nitroxide radicals, such as 4-oxo-2,2,6,6-tetramethyl-1-piperidinyloxy (OTEMPO) and 4-hydroxy-2,2,6,6-te-

Table 1
^1H NMR chemical shifts (δ, ppm) and coupling constants (*J*, Hz) for **1–3**

Compound	H-1	H-2	H-3	H-4	H-5	C-1	C-2	C-3	C-4	C-5	C-6
1	5.30	3.35	3.62	3.32	3.99	93.0	71.4	71.5	71.5	72.4	176.6
2	4.86	3.29	3.52	3.45	3.72	96.3	73.7	74.6	71.2	74.9	175.5
3	5.49	3.44	3.54	3.35	3.85	106.7	70.3	71.7	70.6	73.4	175.0
	$J_{L,H1}$ [a]	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{L,C1}$	$J_{L,C2}$		other:	$J_{L,H2}$	$J_{L,C5}$
1	7.3	3.4	9.5	9.5	9.9	4.9	7.3			1.8	
2	~ 7.6	~ 7.6	9–10	9–10	9–10	4.9	6.1				
3	53.1	< 1	9.2	9.9	9.9	224	25.0				2.4

[a] L = P (in **1** and **2**) or F (in **3**).



Scheme 2. Immobilization of 4-oxo-2,2,6,6-tetramethyl-1-piperidinyloxy (OTEMPO) on aminopropyl silica.

tramethyl-1-piperidinyloxy (4-HO-TEMPO) could not be recycled by azeotropic distillation.

Another promising method for the recovery of the nitroxide radical is immobilization on a carrier. Immobilization of nitroxide radicals on polymers and their use in oxidation reactions have been described in the literature [38,39]. After the oxidations, the catalyst can be recovered by filtration. The immobilization of stable nitroxide radicals on a carrier is especially useful in continuous processes (Scheme 2).

We immobilized OTEMPO on aminopropyl silica by reductive amination with $NaBH_3CN$. Although the procedure clearly needs to be optimized (see Table 2), α-Glc-1-*P* is oxidized by the resulting heterogeneous catalyst to give **1** in reasonable yields. The immobilized catalyst can be re-used in subsequent oxidation reactions. Loss in activity and yield of **1** was observed in the third cycle.

Hydrolysis to D-*glucuronate.*—To obtain D-glucuronic acid, hydrolysis of compounds **1** and **2** has been performed with acid, Dowex H^+ and enzymatically with phosphatase [40–42]. We tested an enzymatic route, using the enzyme fytase (EC 3.1.3.26), for the hydrolysis of both isomers of D-glucopyranuronate 1-phosphate. Fig. 1 shows that the hydrolysis of α anomer **1** proceeds much slower than the hydrolysis of β anomer **2** (not optimized). A

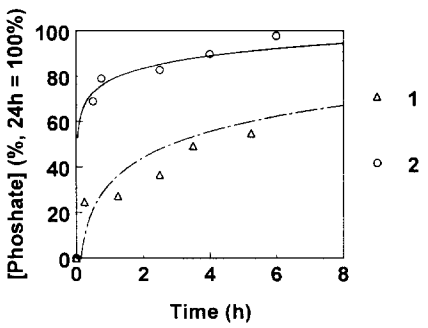


Fig. 1. Hydrolysis of compounds **1** and **2** with fytase.

possible explanation is the formation of a hydrogen bridge between the phosphate substituent and the carboxylic acid group in the case of **1**, which decreases the rate of the enzymatic hydrolysis [41].

The separation of potassium D-glucuronate from free phosphate (and **1**) was accomplished by column chromatography on an anion-exchange column using 0.5 M potassium acetate as the eluent.

3. Experimental

General methods.—α-Glc-1-*P* was prepared by the method described by Hokse [15]. β-Glc-1-*P* was prepared by a procedure described by Fitting [43] and Doudoroff [43]. α-Glc-1-F was a gift from Hoechst (Frankfurt, Germany). TEMPO, OTEMPO and 4-HO-TEMPO were purchased from Aldrich. Bio-Sil NH_2 90 15–35 was purchased from Bio-Rad, and $NaBH_3CN$ from Merck. The NaOCl solutions were obtained from Akzo Nobel (The Netherlands). Fytase (EC 3.1.3.26) was a gift from AVEBE (Foxhol, The Netherlands). ^1H and ^{13}C NMR spectra were recorded on a 300 MHz Varian VTR-300 spectrometer. The pH-stat, a Titration Controller 1200 equipped with a Titronic T110 buret, was purchased from Schott Geräte. HPLC was performed with Gilson 305 and 302 pumps, a Marathon autosampler, and a Dionex ED 40 Au-electrode. The CarboPac PA-1 column (250 × 4 mm i.d.) was eluted with a gradient of 0.1 M NaOH (eluent A) and 0.1 M NaOH/0.6 M NaOAc (eluent B) [%B = 5% (0 min), %B = 35% (10 min), %B = 60% (20 min), %B = 100% (25–27 min), %B = 5% (28–35 min)]. Column chromatography was performed on Dowex 1 × 8 (200–400 mesh) or Dowex 5 × 8 (20–50 mesh), purchased from Fluka. Detection of carbohydrates was effected by spraying plates of silica with 20% H_2SO_4 in MeOH, followed by heating with a hot gun. Detection of phosphate was effected by the method of Chen et al. [44].

Elemental analyses were performed at the Microanalytical Department of the University of Groningen.

α-D-Glucopyranuronic acid 1-phosphate, mixed tris(alkali metal)salt (**1**).—TEMPO (0.10 g, 0.64 mmol) was added to a solution of dipotassium α-Glc-1-*P* ($2\ K^+ \cdot C_6H_{11}O_9P^{2-} \cdot 2H_2O$) (4.86 g, 13.6 mmol) in H_2O (40 mL). The solution was cooled to 0 °C and 1 M NaOH was added to reach the desired pH of 9.0. To this solution, 12.0 mL NaOCl (active $[Cl_2] = 148$ g/L) was added slowly. The pH was controlled with a pH-stat by adding portions of 1 M NaOH. After 1.5 h the reaction was complete (no acid formation) and the mixture was allowed to come to room temperature. The product crystallized from the mixture after addition of MeOH to obtain **1** (5.55 g, 85%).

A portion of **1** (0.50 g) was subjected to cation-exchange column chromatography (Dowex 5 × 8, 20–50 mesh, K^+ form) and then crystallized from H_2O–MeOH to obtain 0.35 g (not optimized) of the tripotassium form of **1** ($3\ K^+ \cdot C_6H_8PO_{10}^{3-} \cdot 5H_2O$). Anal. Calcd for $C_6H_{18}PO_{15}K_3$: C, 15.06; H, 3.79; P, 6.47. Found: C, 15.01; H, 3.87; P, 6.42.

Another portion of **1** (0.50 g) was subjected to cation-exchange column chromatography (Dowex 5 × 8, 20–50 mesh, Na^+ form) and then crystallized from H_2O–MeOH to obtain 0.32 g (not optimized) of the trisodium form of **1** ($3\ Na^+ \cdot C_6H_8PO_{10}^{3-} \cdot 6.5H_2O$). Anal. Calcd for $C_6H_{21}PO_{16.5}Na_3$: C, 15.76; H, 4.63; P, 6.78. Found: C, 15.71; H, 4.66; P, 6.76.

β-D-Glucopyranuronic acid 1-phosphate, trisodium salt (**2**).—The dicyclohexylammonium form of β-Glc-1-*P* ($2\ C_6H_{14}N^+ \cdot C_6H_{11}O_9P^{2-} \cdot EtOH \cdot H_2O$) (5.98 g, 11.5 mmol) was, at 4 °C, subjected to cation-exchange column chromatography (Dowex 5 × 8, 20–50 mesh, H^+ form). The eluent was neutralized with 1 M NaOH and concentrated to about 40 mL. After the addition of TEMPO (0.05 g, 0.32 mmol), the solution was cooled to 0 °C and 1 M NaOH was added to reach the desired pH of 9.0. Then, 10.0 mL NaOCl ($c = 148$ g/L) was added slowly. The pH was controlled with a pH-stat by adding portions of 1 M NaOH. After 2 h, the reaction was complete and the mixture was allowed to warm to room temperature. Attempts to crystallize the product from the mixture by addition of MeOH yielded an opaque oil. After decantation the oil solidified partially to provide **2** (3.47 g, 80%).

Potassium α-D-glucopyranuronate 1-fluoride (**3**).—TEMPO (0.04 g, 0.26 mmol) was added to a solution of α-Glc-1-F (1.82 g, 10 mmol) in H_2O (40 mL), and after cooling to 0 °C, 1 M NaOH was added to reach the desired pH of 9.0. Then, 11 mL NaOCl ($c = 148$ g/L) was added slowly. The pH was controlled with a pH-stat by adding portions of 1 M NaOH. After 2 h, the reaction was complete and the mixture was concentrated to about 5–10 mL. The residue was subjected to anion-exchange column chromatography (Dowex 1 × 8, 200–400 mesh, OAc^- form) and after elution with water (150 mL) and 0.5 M KOAc, the carbohydrate-containing fractions were concentrated and the product was crystallized from H_2O–EtOH–acetone to obtain **3** (1.85 g, 65%) as the monohydrate. Anal. Calcd for $C_6H_{10}O_7KF$: C, 28.57; H, 4.00; F, 7.53. Found: C, 28.30; H, 4.02; F, 7.41.

Oxidation of α-Glc-1-P with recovered TEMPO.—TEMPO (0.11 g, 0.70 mmol) was added to a solution of α-Glc-1-*P* ($2\ K^+ \cdot C_6H_{11}O_9P^{2-} \cdot 2H_2O$) (4.44 g, 11.6 mmol) in H_2O (50 mL), and after cooling to 0 °C, 1 M NaOH was added to reach the desired pH of 9.0. Then, 12.0 mL NaOCl ($c = 148$ g/L) was added slowly, while maintaining a constant pH. After 1.5 h, the reaction was complete and the mixture was concentrated under reduced pressure on a closed rotary evaporator until the residue had become colorless. After the addition of MeOH and crystallization, 4.63 g of **1** was isolated.

The distillate, about 20 mL, which contained the TEMPO catalyst, was replenished with H_2O to a volume of 50 mL and the procedure was repeated with α-Glc-1-*P* ($2\ K^+ \cdot C_6H_{11}O_9P^{2-} \cdot 2H_2O$) (4.16 g, 11.2 mmol) and NaOCl (11.5 mL, $c = 148$ g/L). After 1 h, the reaction was complete and the mixture was distilled under reduced pressure until the residue had become colorless. After addition of MeOH and crystallization, 4.49 g of **1** was isolated.

The distillate was replenished with H_2O to 50 mL and the procedure was repeated with α-Glc-1-*P* ($2\ K^+ \cdot C_6H_{11}O_9P^{2-} \cdot 2H_2O$) (4.20 g, 11.2 mmol) and NaOCl (11.5 mL, $c = 148$ g/L). After 1 h, the reaction was complete and the mixture was allowed to come to room temperature. The product crystallized from the reaction mixture after addition of MeOH to obtain **1** (4.04 g).

Immobilization of OTEMPO (4-oxo-2,2,6,6-tetramethyl-1-piperidinyloxy) on aminopropyl silica.—OTEMPO (0.54 g, 3.2 mmol) was added to a suspension of 5.00 g Bio-Sil NH_2 90 (15–35) in 50 mL MeOH. After 1 h, $NaBH_3CN$ (0.20 g, 3.2 mmol) was added and the mixture was stirred for 7 days. After filtration and washing with MeOH, 5.11 g of immobilized OTEMPO was isolated.

Oxidation of α-Glc-1-P with immobilized OTEMPO.—Immobilized OTEMPO (0.52 g) was

added to a solution of α-Glc-1-*P* (2 $K^+ \cdot C_6H_{11}O_9P^{2-} \cdot 2H_2O$) (2.17 g, 5.82 mmol) in 30 mL H_2O. At room temperature, 1 M NaOH was added to reach the desired pH of 9.0. To this solution, NaOCl (5.6 mL, $c = 148$ g/L) was added slowly. The pH was controlled with a pH-stat by adding portions of 1 M NaOH. After 3 h, the reaction was complete (acid formation had ceased). Filtration and crystallisation by the addition of MeOH yielded 1.78 g of **1**.

The filtered catalyst was re-used and suspended in 30 mL H_2O. α-Glc-1-*P* (2 $K^+ \cdot C_6H_{11}O_9P^{2-} \cdot 2H_2O$) (2.18 g, 5.85 mmol) was added to the solution. The pH was adjusted to 9 with 1 M NaOH. Then, NaOCl (5.6 mL, $c = 148$ g/L) was added slowly, and the pH was kept constant by addition of 1 M NaOH. After 4 h, the reaction was complete. Filtration and crystallization by the addition of MeOH resulted in 2.03 g of **1**.

The procedure was repeated with α-Glc-1-*P* ($2K^+ \cdot C_6H_{11}O_9P^{2-} \cdot 2H_2O$) (2.18 g, 5.85 mmol) and NaOCl (5.6 mL, $c = 148$ g/L). After 24 h, the reaction was complete. Filtration and crystallisation afforded 0.95 g of **1**.

*Enzymatic hydrolysis of α- and β-*D*-glucopyranuronate 1-phosphate.*—To solutions of 0.40 g of compounds **1** and **2** in 20 mL H_2O was added, at pH 5.5, 1 mL fytase (EC 3.1.3.26). Samples were taken from the mixture and the amount of free phosphate was determined with the method of Chen et al. [44].

D-*Glucuronate.*—To a solution of α-D-glucopyranuronate 1-phosphate (0.40 g, 0.85 mmol) in H_2O (20 mL), was added, at pH 5.5, 1 mL fytase (EC 3.1.3.26). After 24 h, the mixture was heated to 100 °C and centrifuged. The remaining solution was subjected to anion-exchange column chromatography (Dowex 1 × 8, 200–400 mesh, OAc^- form). After elution with 0.5 M KOAc, pH 5.3, the potassium D-glucuronate fraction, which was first eluted from the column, was concentrated to dryness. The product was washed with EtOH (30 mL) and filtered to yield 130 mg of the desired product. The product gave a single peak in HPLC with a retention time identical to that of D-glucuronate (yield about 67%).

References

[1] H. Röper, *Starch / Stärke*, 42 (1990) 342–349.
[2] H.G. Bray, *Adv. Carbohydr. Chem.*, 8 (1953) 251–261.
[3] G. Graefe, *Starch / Stärke*, 5 (1953) 205–209.
[4] C.L. Mehltretter, *Adv. Carbohydr. Chem.*, 8 (1953) 231–249.
[5] Y. Schuurman, B.F.M. Kuster, K. van der Wiele, and G.B. Marin, *Appl. Catal. A: General*, 89 (1992) 31–68.
[6] H.E. van Dam, A.P.G. Kieboom, and H. van Bekkum, *Appl. Catal.*, 33 (1987) 361–372 and 373–382.
[7] R.V. Casciani, P.J.M. Likibi, and G.L. McGraw, Ger. Offen DE 4209869 A1 (1992), *Chem. Abstr.*, 119 (1993) 9389s.
[8] N.J. Davis and S.L. Flitsch, *Tetrahedron Lett.*, 34 (1993) 1181–1184.
[9] A.C. Besemer and A.E.J. de Nooy, NL Patent 9301549 (1993), *Chem. Abstr.*, 120 (1994) 324088n.
[10] A.E.J. de Nooy, A.C. Besemer, and H. van Bekkum, *Recl. Trav. Chim. Pays-Bas*, 113 (1994) 165–166.
[11] A.E.J. de Nooy, A.C. Besemer, and H. van Bekkum, *Tetrahedron*, 51 (1995) 8023–8032.
[12] A.E.J. de Nooy, A.C. Besemer, and H. van Bekkum, *Carbohydr. Res.*, 269 (1995) 89–98.
[13] Z. Györgydeák and J. Thiem, *Carbohydr. Res.*, 268 (1995) 85–92.
[14] K. Li and R.F. Helm, *Carbohydr. Res.*, 273 (1995) 249–253.
[15] H. Hokse, *Starch / Stärke*, 35 (1983) 101–102.
[16] A. Kamogawa, K. Yokobayashi, and T. Fukui, *Agr. Biol. Chem.*, 37 (1973) 2813–2819.
[17] P. Pale and G.M. Whitesides, *J. Org. Chem.*, 56 (1991) 4547–4549.
[18] M.A. Salam and E.J. Behrman, *Carbohydr. Res.*, 90 (1981) 83–89.
[19] D.L. MacDonald, *Carbohydr. Res.*, 3 (1966) 117–120.
[20] R.R. Schmidt, M. Stumpp, and J. Michel, *Tetrahedron Lett.*, 23 (1982) 405–408.
[21] S. Saseban and S. Neira, *Carbohydr. Res.*, 223 (1992) 169–185.
[22] C.L. Stevens and R.E. Harmon, *Carbohydr. Res.*, 11 (1969) 99–102.
[23] L.V. Volkova, L.L. Danilov, and R.P. Evstigneeva, *Carbohydr. Res.*, 32 (1974) 165–166.
[24] A.A.E. Penglis, *Adv. Carbohydr. Chem. Biochem.*, 38 (1981) 195–285.
[25] T. Tsuchiya, *Adv. Carbohydr. Chem. Biochem.*, 48 (1990) 91–277.
[26] M. Schlingmann, R. Keller, M. Wiessner, W. Treder, and J. Thiem, Ger. Offen DE 3722812 A1 (1989), *Chem. Abstr.*, 112 (1990) 75339g.
[27] M. Kreuzer and J. Thiem, *Carbohydr. Res.*, 149 (1986) 347–361.
[28] J. Thiem and M. Wiesner, *Synthesis*, (1988) 124–127.
[29] K.F. Gotlieb, P.M. Bruinenberg, J.B. Schotting, and D.J. Binnema, Eur. Pat. EP 0590736 A1 (1993), *Chem. Abstr.*, 121 (1994) 55999e.
[30] N. Narenda, T.P. Seshadri, and M.A. Viswamitra, *Acta Cryst.*, C40 (1984) 1338–1340.
[31] R.L. Whistler, M.L. Wolfrom, *Methods Carbohydr. Chem.*, 2 (1963) 224.
[32] J.M. Bobbit and M.C.L. Flores, *Heterocycles*, 27 (1988) 509–533.
[33] C.A. Marsh, *J. Chem. Soc.*, (1952) 1578–1582.
[34] J.V. O'Connor, H.A. Nunez, and R. Barker, *Biochemistry*, 18 (1979) 500–507.
[35] T.S. Straub, *J. Chem. Educ.*, 68 (1991) 1048–1049.

[36] A. Heeres, H.A. van Doren, K.F. Gotlieb, and I.P. Bleeker, NL Patent 1000396 (1995).
[37] A. Heeres, I.P. Bleeker, K.F. Gotlieb, and H.A. van Doren, NL Patent 1000495 (1995).
[38] T. Miyazawa, T. Endo, and M. Okawara, *J. Polym. Sci., Polym. Chem. Ed.*, 23 (1985) 1527–1535.
[39] T. Mizayawa and T. Endo, *J. Polym. Sci., Polym. Chem. Ed.*, 23 (1985) 2487–2494.
[40] S.A. Barker, E.J. Bourne, J.G. Fleetwood, and M. Stacey, *J. Chem. Soc.*, (1958) 4128–4132.
[41] H.E. van Dam, Thesis, TU Delft (1989).
[42] J.V. O'Connor and R. Barker, *Carbohydr. Res.*, 73 (1979) 227–234.
[43] C. Fitting and M. Doudoroff, *J. Biol. Chem.*, 199 (1952) 153–163.
[44] P.S. Chen, Jr, T.Y. Toribara, and H. Warner, *Anal. Chem.*, 28 (1956) 1756–1758.