Synthesis, Characterization, and Crystal Structure of Sodium (Methyl α-D-Mannopyranosid)uronate Monohydrate

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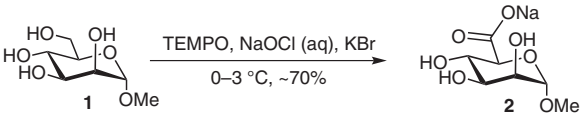
Abstract: TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl)-mediated oxidation of methyl α-D-mannopyranoside with sodium hypochlorite gave sodium (methyl α-D-mannopyranosid)uronate, which was obtained as a crystalline monohydrate in ~70% yield without chromatography. Its purity was proved by NMR spectroscopy, a newly developed HPLC method, combustion analysis, and X-ray crystallography. The crystal structure, solved from synchrotron diffraction data in space group $P2_12_12_1$, revealed that the packing of the uronate molecules is connected by an extensive network of hydrogen bonds, and that the Na^+ ion is coordinated by six oxygen ligands from one water and three surrounding sugar molecules.

Key words: mannuronic acid, oxidation, chemoselective methylation, TEMPO, HPLC

In connection with other work in this laboratory, a need arose for a convenient intermediate toward derivatives of methyl α-D-mannopyranosiduronic acid. As with other glycosides of hexuronic acids, older preparations of such compounds involve multistep synthesis[1,2] through oxidation of variously protected derivatives of methyl α-D-mannopyranoside (**1**). Isolation of products in these situations is usually straightforward because the desired product can be readily isolated from crude reaction mixtures by extraction into organic solvent and purification by chromatography. Unprotected glycosides can be oxidized catalytically (O_2/Pt) but results vary considerably.[3–5] In this way, for example, potassium (methyl α-D-mannopyranosid)uronate was obtained in 57.7% yield from **1** but attempts to oxidize phenyl-α- and -β-D-glucosides failed.[6] Unprotected alkyl glycosides have been selectively oxidized at the primary position also with calcium[7] or sodium hypochlorite in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO),[8] the method being based on the work by Semmelhack and co-workers.[9] Alkali metal salts of uronic acids are important intermediates to alkyl uronates, which are starting points toward more complex derivatives in these series. Here we describe the application of the method[8] for the preparation of sodium (methyl α-D-mannopyranosid)uronate (**2**), which is now described and fully characterized through its crystalline monohydrate **3** for the first time. Compared to protocols toward mannuronate intermediates developed earlier, the advantage of the one described here lies in that it does not require a precious metal catalyst or protection and deprotection of intermediates, and gives the desired product in higher yield. In addition, the newly developed HPLC method, which allows assessing the presence or absence of salts in product **2**, may be generally applicable in the uronic acid series.

When the TEMPO-promoted oxidation with sodium hypochlorite was applied to **1** (Scheme 1), we initially experienced difficulties in separating large amount of salts from the desired product.



Scheme 1 Oxidation of methyl α-D-mannopyranoside (**1**) with TEMPO

Previous reports on oxidation of unprotected hexopyranosides in this way lack relevant information regarding the above, as they describe the isolation of product of oxidation as the corresponding ester,[10] acid,[11] or do not offer sufficient experimental details.[4,12] Also, assessing the degree of purity (absence of salts) of the sodium uronate during various stages of purification was not straightforward at first because, for obvious reasons, TLC or NMR spectroscopy could not be used for this purpose. Since **3** does not show strong rotary power and decomposes before melting temperature, these techniques do not provide adequate evidence of purity. TLC on normal-phase silica gel of a sample of **2** that contained salts showed, after charring, a single compact spot, but purification by preparative chromatography using the same medium was inconsistent. Eventually, guided by the excellent review by Tojo and Fernandez,[8] we developed a protocol allowing isolation of crystalline **3** in good yield (~70%) without chromatography. It involves termination of the oxidation reaction by addition of HCl to slight acidity, and conversion of excess of the acid and most of salts present to NaCl, some of which could be precipitated and filtered off. Pure **3** could be obtained readily from the filtrate by crystallization (see experimental section). Purity of the material obtained, which was confirmed by X-ray and combustion analysis, could be confidently proved also by a reverse-phase HPLC method that we have developed (Figure 1). Samples of **3** containing various amounts of NaCl (e.g., B, C, or D, Figure 1) are eluted from a C18 column as two

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peaks, one co-eluting with a sample of NaCl (Figure 1, A) and the other with material that gave correct combustion analysis figures for **3** (Figure 1, G). That **3** was a monohydrate was confirmed by X-ray analysis. Presence of ~1% NaCl in **3** can be readily seen by our HPLC analysis (Figure 1, D). HPLC analysis of the crystalline material isolated here (two crops, combined yield, ~70%) showed that the amount of NaCl present was negligible (Figure 1, E and F), evidence for which was provided by each crop passing the test of purity by combustion analysis (see experimental section) as confidently as the recrystallized material that was subjected to the X-ray crystal structure analysis.

The overall yield of oxidation could be somewhat increased by chemoselective methylation[13] of the material remaining in the mother liquor after crystallization of **3**, to give the corresponding methyl ester. Methyl (methyl α-D-mannopyranosid)uronate (**4**) was previously synthesized and characterized.[14–17] Our material produced ^{1}H and ^{13}C NMR data (see experimental section), which agreed with those found in a not readily accessible source.[17]

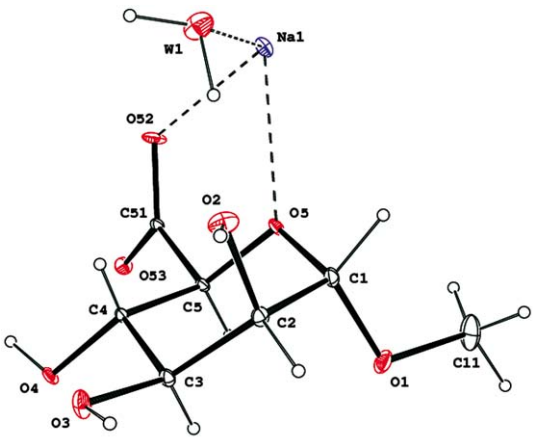

Figure 2 ORTEP plot of the molecule **3** with anisotropic displacement ellipsoids at 50% probability

Sodium (methyl α-D-mannopyranosid)uronate monohydrate (**3**) crystallized in the space group $P2_12_12_1$ with one molecule in the asymmetric unit and one accompanying molecule of water. The crystal structure was solved from

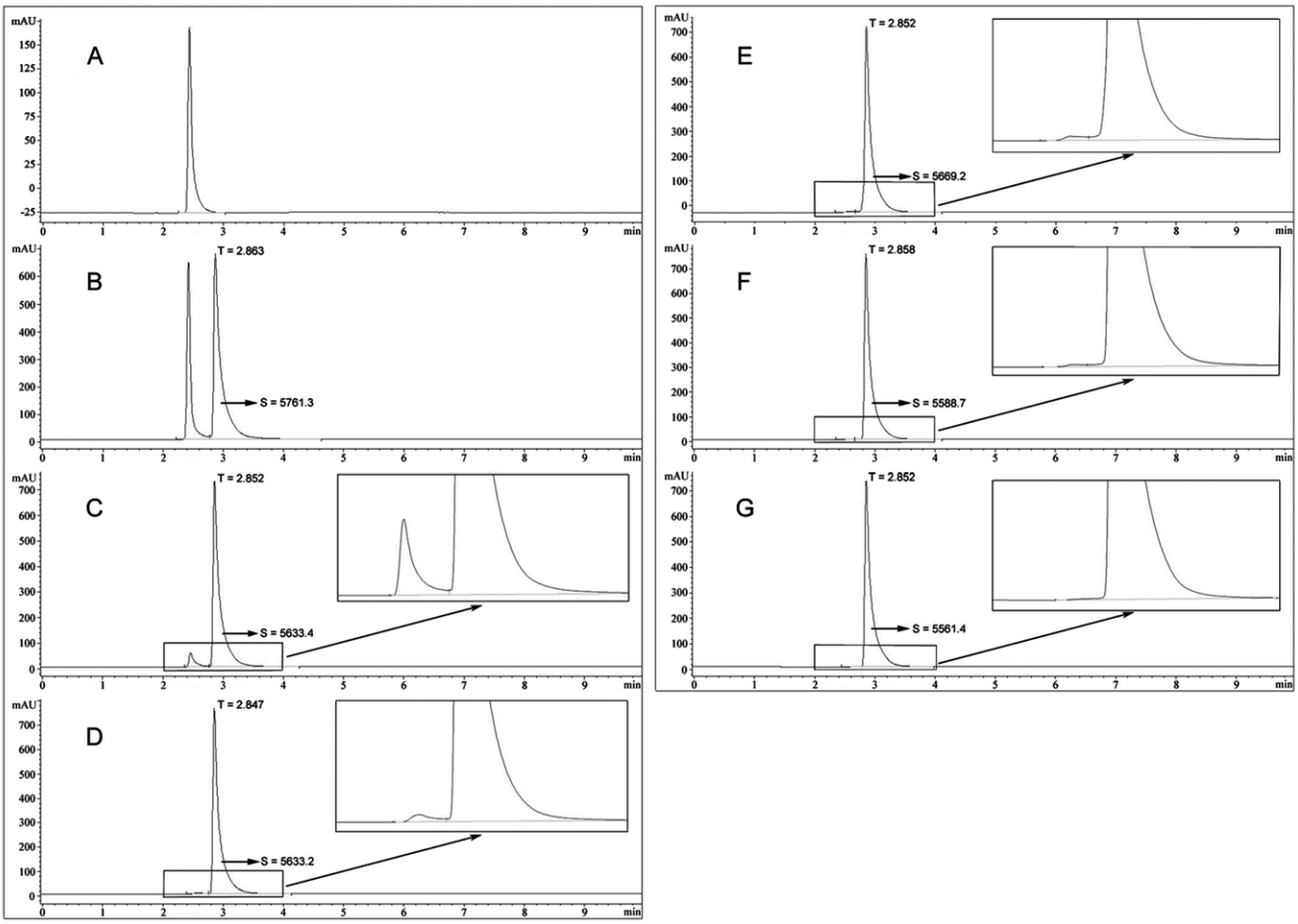

Figure 1 HPLC analysis of products of TEMPO-catalyzed, NaOCl oxidation of methyl α-D-mannopyranoside (**1**); inset shows expansion of the relevant region at sensitivity ~5 times increased. A, NaCl; B, 1:1 (w/w) NaCl/**3** mixture; C, 1:10 (w/w) NaCl/**3** mixture; D, 1:100 (w/w) NaCl/**3** mixture; E, first crop of crystals (59% yield); F, second crop of crystals (recrystallized material obtained from mother liquor after crystallization of the first crop, making the total yield to ~70%); G, analytical sample of **3** that was subjected to X-ray crystal structure analysis; S: HPLC area count; T: retention time.

the diffraction data measured at the synchrotron beam line and refined to $R1 = 0.034$ and $wR2 = 0.125$, with other details available in Table 1. The coordinate uncertainty of the non-hydrogen atoms is better than 0.002 Å. The selected geometrical parameters are shown in Table 2. The molecular structure and atom numbering scheme are presented in Figure 2.

The sugar moiety adopts a chair $^4C_1$ conformation with axially connected methoxy group at C1 and hydroxyl group at C2 and equatorially connected two hydroxyl and one carboxylate group at C3, C4, and C5, respectively. The carboxylate group is symmetric in terms of both C–O bond lengths, but its torsion angle with respect to the pyranose ring is twisted to about 90° from the ideal gauche conformation. No other crystal structures of compounds possessing the mannuronate moiety are available, but the bond lengths and angles of the carboxylate ring show typical values, close to those observed in the structures of the similar compounds, for example sodium D-glucuronate monohydrate,[18] potassium and rubidium D-glucuronate dihydrates,[19] D-galacturonic acid monohydrate,[20] and methyl 4-*O*-methyl-α-D-glucopyranuronate.[21]

All hydrogen atoms in the hydroxyl groups and the water molecule are engaged in intermolecular hydrogen bonds, with the geometry indicated in Table 3. The Na^+ ion is coordinated in the form of slightly distorted octahedron by O3 and O4 hydroxyl oxygen atoms of one sugar molecule, the ring O5 oxygen and O52 carboxylate oxygen atoms of the second molecule, the O53 carboxylate oxygen atom of the third molecule and a water oxygen atom. The coordi-

Table 1 Diffraction Data and Refinement Statistics

Empirical formula	$C_7H_{13}NaO_8$
Formula weight	248.16
Beamline	24-ID-C @ APS
Wavelength (Å)	0.61992
Crystal size (mm)	0.10 × 0.15 × 035
Temperature (K)	100
Space group	$P2_12_12_1$
Cell dimensions	
a (Å)	6.96
b (Å)	11.79
c (Å)	12.07
Volume (Å^3)	990.4
Absorption coefficient (mm^{-1})	0.19
F(000)	544
θ_{max} (°)	31.7
Index ranges	$-9 \le h \le +9, -19 \le k \le +19, -20 \le l \le +20$
Reflections measured/unique	17981/2417
Data (Friedel mates separate)	4230
Data (Friedel mates separate) [F >4σ (F)]	4180
Restraints	0
Parameters	154
R(int)	0.043
Flack parameter	0.096(59)
Final *R*1 factor [F >4σ (F)]	0.0337
Final *R*1 factor (all data)	0.0340
Final *wR*2 factor (all data)	0.1249
CSD deposition code	CCDC964974

Table 2 Selected Geometrical Parameters of **3**[a]

Bond	Distance (Å)	Bond angle	Angle (°)
C1–C2	1.5243(21)	O5–C1–C2	112.39(9)
C2–C3	1.5362(19)	C1–C2–C3	110.74(11)
C3–C4	1.5196(17)	C2–C3–C4	111.03(10)
C4–C5	1.5398(19)	C3–C4–C5	110.26(9)
C5–C51	1.5325(17)	C4–C5–O5	109.05(11)
C1–O1	1.4021(16)	C5–O5–C1	114.06(10)
C1–O5	1.4248(16)	C1–O1–C11	112.39(12)
O1–C11	1.4349(21)	C5–C51–O52	116.81(10)
C2–O2	1.4228(16)	C5–C51–O53	118.11(10)
C3–O3	1.4174(18)	O52–C51–O53	124.93(10)
C4–O4	1.4216(17)		
C5–O5	1.4340(16)		
C51–O52	1.2593(15)		
C51–O53	1.2595(16)		

Torsion angle	Angle (°)	Torsion angle	Angle (°)
O5–C1–C2–C3	50.92(11)	O1–C1–C2–C3	– 72.74(11)
O5–C1–C2–O2	– 71.41(12)	O1–C1–C2–O2	164.93(8)
O5–C1–O1–C11	78.15(12)	C2–C1–O1–C11	–157.90(9)
C2–C1–O5–C5	– 58.25(12)	O1–C1–O5–C5	62.99(13)
C1–C2–C3–C4	– 49.71(11)	O2–C2–C3–C4	70.49(12)
C1–C2–C3–O3	–170.21(8)	O2–C2–C3–O3	– 50.01(12)
C2–C3–C4–C5	53.61(12)	O3–C3–C4–C5	176.74(8)
C2–C3–C4–O4	175.75(8)	O3–C3–C4–O4	– 61.12(12)
C3–C4–C5–O5	– 57.78(10)	O4–C4–C5–O5	– 177.39(7)
C3–C4–C5–C51	–175.84(8)	O4–C4–C5–C51	64.55(10)
C4–C5–O5–C1	60.79(11)	C51–C5–O5–C1	178.85(8)
C4–C5–C51–O52	89.04(13)	O5–C5–C51–O52	– 29.35(13)
C4–C5–C51–O53	– 86.63(13)	O5–C5–C51–O53	154.98(9)

Coordination of Na^+ ion

Bond	Distance (Å)	Bond angle	Angle (°)	Bond angle	Angle (°)
Na1–O3′	2.3641(18)	O3′–Na1–O4′	69.69(6)	O4′–Na1–O5	103.87(7)
Na1–O4′	2.4439(20)	O3′–Na1–O5	89.04(8)	O4′–Na1–O52	98.39(8)
Na1–O5	2.5105(20)	O3′–Na1–O52	150.38(4)	O4′–Na1–O53″	84.18(5)
Na1–O52	2.2638(18)	O3′–Na1–O53″	126.85(7)	O4′–Na1–W1	158.93(4)
Na1–O53″	2.5540(24)	O3′–Na1–W1	91.29(7)	O52–Na1–O53″	76.30(5)
Na1–W1	2.3017(21)	O5–Na1–O52	66.97(6)	O52–Na1–W1	102.67(8)
		O5–Na1–O53″	143.11(5)	O53–Na1–W1	101.23(5)
		O5–Na1–W1	84.12(6)		

Symmetry of O3′ and O4′ atoms is $1 + x, y, z$ and of O53″ atom is $1/2 + x, 1/2–y, 1–z$.

[a] The standard uncertainties are shown in parentheses.

nation geometry of sodium ion is shown in Figure 3. Incidentally, analogous atoms of the three sugar and one water molecules coordinate the Na^+ ion in the structure of sodium D-glucuronate,[18] but in the latter structure the coordination is much more distorted from the octahedral geometry. The intermolecular hydrogen bonds and coordination of Na^+ by three sugar molecules create three-dimensional network of strong interactions extending throughout the whole crystal.

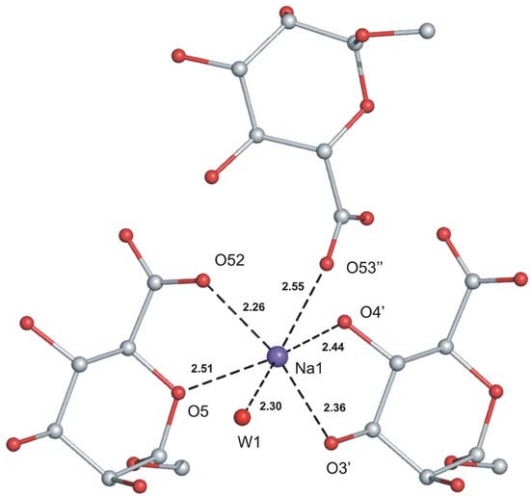

Figure 3 Coordination of the Na^+ ion. Distances to neighboring atoms are given in Å. O3′ and O4′ atoms belong to molecule transformed by 1 + *x*, *y*, *z* and O53″ atom to molecule transformed by 1/2 + *x*, 1/2–*y*, 1–*z* from the original position.

Table 3 Hydrogen Bonds[a]

D–H	d(D.A.) (Å)	< DHA (°)	A	Symmetry of A
O2–HO2	2.786	162.3	O53	[–x, ½ + y, 3/2–z]
O3–HO3	2.663	164.1	O4	[–x, ½ + y, 3/2–z]
O4–HO4	2.586	173.1	O53	[–1/2 + x, ½–y, 1–z]
W1–HW1	2.894	125.6	O1	[1/2 – x,1–y, –1/2 + z]
W1–HW2	2.761	157.0	O2	[x, y, z]

[a] d(D.A.) is the donor–acceptor distance and < DHA is the donor–hydrogen–acceptor angle.

Methyl α-D-mannopyranoside (**1**) was purchased from Sigma Chemical Co. and used as supplied. Optical rotations were measured at r.t. for solution in H_2O with a digital Jasco automatic polarimeter, Model P-2000. Melting points were measured on a Kofler hot stage. TLC was performed on silica gel 60 coated glass slides. Visualization of spots was effected by charring with 5% H_2SO_4 in EtOH. NMR spectra were recorded at 600 MHz (^{1}H) and 150 MHz (^{13}C) with a Bruker Avance spectrometer. Assignments of NMR signals were made by homonuclear and heteronuclear 2-dimensional correlation spectroscopy, run with the software supplied with the spectrometers. HPLC was performed with Agilent 1100 Series Chromatography System, using a 4.6 × 250 mm SunFire column packed with C-18 silica gel, particle size, 5 µm (Waters). A mobile phase of 100% H_2O (1 mL/min) was used. Compounds were detected at 200 nm. Conversion of crude **2** to the corresponding methyl ester was performed as described[13] except that Na_2CO_3 was used as the base. Unless stated otherwise, solutions were concentrated (rotary evaporator) at 40 °C/2 kPa. Combustion analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

X-ray Crystal Structure Analysis

A single crystal of **3** was glued at the tip of the thin glass capillary, mounted at the goniometer head and placed in the stream of 100 K N_2 gas at the goniostat of the NE-CAT beam line 24-ID-C at the Advanced Photon Source, Argonne, USA. The data collection parameters are presented in Table 1. Diffraction images were integrated, reflection intensities scaled and merged with program *HKL*2000.[22] Pairs of reflections related by center of symmetry (Friedel mates) were kept separate to utilize the potential anomalous diffraction signal contained in the data. The structure was solved using program SHELXD and refined by full-matrix least-squares technique using SHELXL.[23] All non-hydrogen atoms were refined anisotropically and all hydrogen atoms, identified in the difference electron density map, were refined isotropically as riding on their parent atoms. The Flack parameter[24] refined to 0.096(59), confirmed the chirality of the molecule on the basis of weak, but significant amount of anomalous signal in diffraction data, despite using short X-ray wavelength at which the anomalous correction of sodium is f′(Na) = 0.019.[25]

Sodium (Methyl α-D-Mannopyranosid)uronate Monohydrate (3)

TEMPO (48 mg, 0.31 mmol, 0.02 equiv) and 0.5 M KBr (3.09 mL, 1.54 mmol, 0.1 equiv) were added to a solution of methyl α-D-mannopyranoside (**1**; 3.0 g, 15.4 mmol, 1.0 equiv) in H_2O (20 mL) contained in a 200 mL two-necked round-bottomed flask equipped with a thermometer. While the temperature of the yellow solution formed was kept between 0–3 °C (ice-salt bath), an aq solution of NaOCl (made from commercial, household bleach containing 6.15% of NaOCl, 57 mL, 46.3 mmol, 3.0 equiv) was added during 30 min, dropwise with stirring. The stirring of the clear solution was continued at 0–3 °C for 1 h, when pH was adjusted to 10 by the addition of aq 1 N NaOH (~20 mL). Additional amount of NaOCl solution was added (19 mL, 15.4 mmol, 1.0 equiv), and the mixture was stirred for 3 h. TLC (R_f = 0.5, CH_2Cl_2–MeOH, 1:1) showed that all the starting material was consumed and that a slower moving product was formed. The pH of the solution was adjusted to 5.0 with aq 1 N HCl (~3.5 mL, portionwise) and then brought to pH 7.0 by the addition of solid $NaHCO_3$ (~1.5 g). After washing with CH_2Cl_2 (150 mL) to remove TEMPO, the aqueous phase was concentrated. The residual H_2O was removed by co-evaporation with absolute EtOH (3 × 200 mL) and drying at r.t. and <133 Pa overnight. MeOH (150 mL) was added and the mixture was stirred for 20 min, filtered, and the solids were washed with MeOH until no desired product could be detected (TLC, eluent: same as above) in the filtrate (~6 times). The filtrates were combined and concentrated to give 6.3 g of solid crude product. Pure **3** (colorless crystals, 2.25 g, 59%, Figure 1, E) was obtained by crystallization from H_2O and drying at 60 °C and <133 Pa overnight. For crystallization, the crude product (6.3 g) was dissolved in warm (~60 °C) H_2O (30 mL) and the solution was concentrated slowly at 60 °C/13 kPa. Shortly after the first crystals appeared, the flask was removed from the evaporator, and crystallization was completed at r.t. with occasional manual stirring. After ~30 min, the crystals were filtered, washed with cold (~0 to +5 °C) 20% H_2O in MeOH (3 × 2 mL) and sucked dry; mp 267–269 °C (dec.); $[\alpha]_D$ +48.5 (*c* 1, H_2O).

Anal. Calcd for $C_7H_{11}NaO_7 \cdot H_2O$: C, 33.88; H, 5.28. Found: C, 33.77; H, 5.25.

For recrystallization to obtain the analytical sample (Figure 1, G), the amounts of H_2O and 80% MeOH for washing were adjusted accordingly.

^{1}H NMR (600 MHz, D_2O): δ = 4.79 (d, *J* = 2.0 Hz, 1 H, H-1), 3.90 (dd, *J* = 2.0, 3.0 Hz, 1 H, H-2), 3.87 (d, *J* = 9.0 Hz, 1 H, H-5), 3.80

(dd, J = 9.0, 9.3 Hz, 1 H, H-4), 3.77 (dd, J = 3.0, 9.3 Hz, 1 H, H-3), 3.41 (s, 3 H, 1-OCH_3).

^{13}C NMR (150 MHz, D_2O): δ = 177.5 (C-6), 101.6 (C-1), 73.6 (C-5), 71.0 (C-3), 70.5 (C-2), 69.5 (C-4), 55.6 (1-OCH_3).

HRMS-ESI: m/z $[M + H]^+$ calcd for $C_7H_{12}NaO_7$: 231.0475; found: 231.0477.

Anal. Calcd for $C_7H_{11}NaO_7 \cdot H_2O$: C, 33.88; H, 5.28. Found: C, 34.01; H, 5.12.

Crystallization in the same manner of the material which remained in the mother liquor gave a second crop of crystals (1.0 g), which showed the presence of small amount of salts (HPLC profile not shown in Figure 1). Recrystallization from H_2O gave, after drying, additional pure **3** (Figure 1, F, 0.38 g, 10%; total yield ~70%).

Anal. Calcd for $C_7H_{11}NaO_7 \cdot H_2O$: C, 33.88; H, 5.28. Found: C, 34.04; H, 5.32.

Variable amount of methyl (methyl α-D-mannopyranosid)uronate (**4**), corresponding to 5–10% of the desired product of oxidation, was obtained as a syrup by methylation (with MeI and Na_2CO_3 in DMF) of the material from the combined mother liquors.

^{1}H NMR (600 MHz, D_2O): δ = 4.83 (d, J = 2.3 Hz, 1 H, H-1), 4.20 (d, J = 9.3 Hz, 1 H, H-5), 3.94 (dd, J = 2.3, 3.0 Hz, 1 H, H-2), 3.90 (t, J = 9.3 Hz, 1 H, H-4), 3.82 (s, 3 H, 6-OCH_3), 3.81 (dd, J = 3.0, 9.3 Hz, 1 H, H-3), 3.43 (s, 3 H, 1-OCH_3).

^{13}C NMR (150 MHz, D_2O): δ = 172.3 (C-6), 102.0 (C-1), 72.4 (C-5), 70.7 (C-3), 70.0 (C-2), 68.7 (C-4), 56.0 (1-OCH_3), 53.6 (6-OCH_3).

HRMS-ESI: m/z $[M + Na]^+$ calcd for $C_8H_{14}NaO_7$: 245.0637; found: 245.0633.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(25) The structural data have been deposited at the Cambridge Crystallographic Data Centre with the ID code CCDC 964974. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or by writing to the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk.

