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Synthesis and Molecular Structure of Methyl 4-*O*-methyl-α-D-glucopyranuronate

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Abstract: A method for the preparation of methyl 4-*O*-methyl-α-D-glucopyranuronate and its single crystal X-ray structure determination are reported. The molecule adopts an almost ideal $^4C_1$ ($^OC_3$) conformation.

Keywords: Glucuronate, X-ray crystal structure, conformation.

Introduction

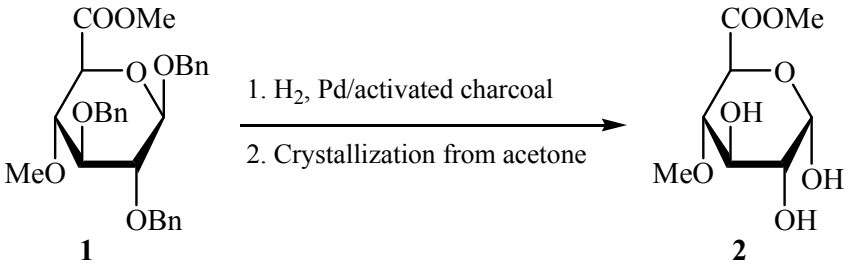
(4-*O*-Methylglucurono)xylans are important constituents of cell-wall polysaccharides of woods and other plants. These biopolymers are composed mainly of (1→4)-β-linked D-xylopyranoses, some of which are randomly branched at position O-2 with 4-*O*-methyl-α-D-glucopyranosyluronic acid. In this respect, methyl (benzyl 2,3-di-*O*-benzyl-4-*O*-methyl-β-D-glucopyranosid)uronate (**1**) and methyl 4-*O*-methyl-α-D-glucopyranuronate (**2**) represent very useful compounds in the synthesis and structural studies of model aldobiouronic acids (needed in studies related to chemical processing of wood) that reflect these structural features [1–4]. Regarding the preparation of **2**, there are two methods described in the literature. The first is based on the conversion of 4-*O*-methyl-D-glucuronic acid to the corresponding methyl ester by refluxing in absolute methanol in the presence of Dowex-50 X-8 (H^+) resin for 20 h [5]. The product was used in the next reaction step without isolation and neither experimental nor structural description data were given. The second method involves the deacetylation of methyl 1,1,2,3,5-penta-*O*-acetyl-4-*O*-methyl-*aldehydo*-D-glucuronate affording methyl 4-*O*-methyl-

D-glucopyranuronate as an unseparable mixture of α- and β-anomers and, therefore, only uncomplete ^{1}H-NMR data, $[\alpha]_D$ and R_f values were given for this mixture [6]. Pure α-anomer was incompletely characterized (^{1}H-NMR, $[\alpha]_D$, R_f) only as a corresponding 1,2,3-tri-*O*-acetyl derivative [6]. We now report an alternative method for the preparation and isolation of a single anomer – methyl 4-*O*-methyl-α-D-glucopyranuronate (**2**) as well as its relevant structural and spectral characteristics, including X-ray crystallography data.

Results and Discussion

According to published results [7], acetolysis of (**1**) led to the formation of both α- and β-1-*O*-acetates. On the other hand, acid hydrolysis of benzyl 2,3-di-*O*-benzyl-4-*O*-methyl-β-D-glucopyranosiduronic acid produced the 1-*O*-deprotected derivative which, without isolation, was treated with diazomethane to give the corresponding methyl glucopyranuronate as a single α-anomer [7]. It is evident that anomerization must occur during both mentioned reactions. In our hands, conventional debenzylation (hydrogenation, Pd/C) of the known **1** [7] afforded an about 2:1 mixture (by NMR) of α- and β-anomers of methyl 4-*O*-methyl-D-glucopyranuronate, from which the title α-anomer **2** was isolated by the slow crystallization using acetone as a solvent (Scheme 1).

Scheme 1



1 **2**

The relevant coupling constant $J_{1,2}$ = 3.6 Hz in the ^{1}H-NMR as well as the signal at 93.2 ppm in the ^{13}C-NMR spectrum, respectively, are indicative of an α-configuration at the anomeric position in **2**. This structural arrangement was unambiguously confirmed by X-ray crystalography. A perspective view and the numbering scheme adopted for the molecule of **2** is depicted in Figure 1. The selected bond lengths and bond angles are listed in Table 1. A list of selected torsion angles is given in Table 2. The hydrogen bond geometry is shown in Table 3. The relevant crystallographic and structure refinement data for glucopyranuronate **2** are given in Table 4. Atomic coordinates and displacement parameters have been deposited with CCDC as supplementary information [8].

Due to absence of such protecting groups which could impose some conformational rigidity on molecule of **2**, it is not surprising that the values of the relevant torsion angles O5–C1–C2–C3 = 60.05(13)°, C1–C2–C3–C4 = – 57.05(14)°, C2–C3–C4–C5 = 52.98(16)°, C3–C4–C5–O5 = – 52.65(17)°, C4–C5–O5–C1 = 58.02(16)°, C5–O5–C1–C2 = – 61.29(14)°, as well as puckering parameters [9] Q = 0.576(1) Å, Φ = 94.4(17)°, Θ = 4.9(2)° indicate an almost ideal $^4C_1$ ($^OC_3$) conformation for the six-membered (O5–C1–C2–C3–C4–C5) pyranose ring .

Figure 1. Atomic numbering scheme and atomic displacement ellipsoid plot at 30% probability level for compound **2**.

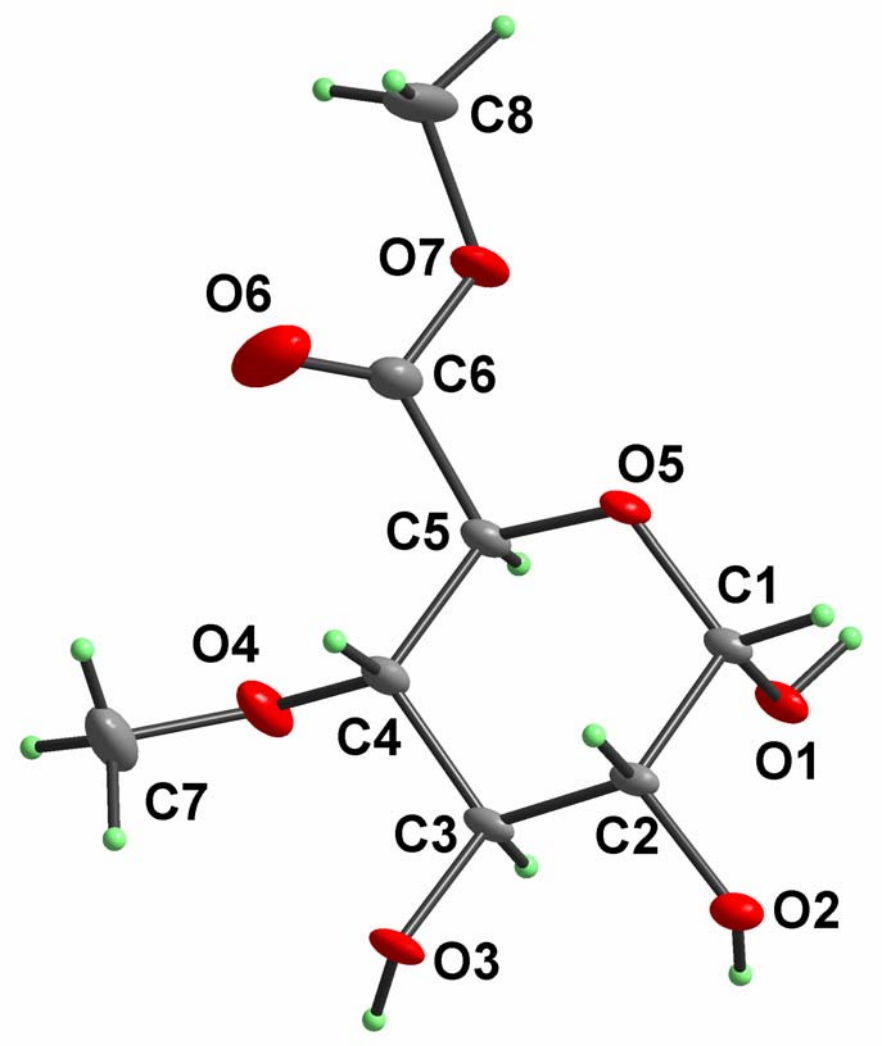


Table 1. Selected bond lengths [Å] and bond angles [º] for compound **2**[a]

Bond	Distance	Bond angle	Angle
O1–C1	1.3922(17)	C1–O5–C5	113.76(10)
O2–C2	1.4251(15)	O1–C1–O5	111.61(12)
O3–C3	1.4315(14)	O1–C1–C2	108.61(10)
O3–C8	1.4211(15)	O5–C1–C2	108.69(11)
O4–C4	1.4198(19)	O2–C2–C1	110.58(11)
O4–C7	1.421(3)	O2–C2–C3	113.74(10)
O5–C1	1.4361(16)	C1–C2–C3	109.73(10)
O5–C5	1.4396(18)	O3–C3–C2	110.36(11)
O6–C6	1.189(3)	O3–C3–C4	109.98(11)
O7–C6	1.332(2)	C2–C3–C4	109.51(10)
O7–C8	1.453(3)	O4–C4–C5	106.10(12)

Table 1. Cont.

C1–C2	1.5251(17)	O4–C4–C3	110.30(12)
C2–C3	1.5267(19)	C5–C4–C3	110.65(12)
C3–C4	1.5263(19)	O5–C5–C6	103.62(12)
C4–C5	1.5284(18)	C6–C5–C4	111.59(13)
C5–C5	1.528(2)	O6–C6–O7	125.27(17)
C7–C8	1.5315(19)	O7–C6–C5	109.43(16)

[a] Standard deviations in parentheses.

Table 2. Selected bond lengths [Å] and bond angles [º] for compound **2**[a]

Torsion angle	Angle	Torsion angle	Angle
C5–O5–C1–O1	58.47(15)	O5–C1–C2–C3	60.05(13)
C5–O5–C1–C2	–61.29(14)	O2–C2–C3–O3	57.30(14)
O1–C1–C2–O2	64.70(14)	C3–C4–C5–O5	–52.65(17)
O5–C1–C2–O2	–173.69(11)	C3–C4–C5–C6	–167.86(14)
C1–O5–C5–C6	178.06(13)	C4–C5–C6–O7	–173.33(15)
O2–C2–C3–C4	178.51(11)	C1–C2–C3–C4	–57.05(14)
C1–C2–C3–O3	–178.26(11)	O3–C3–C4–O4	–68.49(16)
C1–O5–C5–C4	58.02(16)	C2–C3–C4–C5	52.98(16)
O3–C3–C4–C5	174.43(11)	O4–C4–C5–C6	72.50(18)
C2–C3–C4–O4	170.07(11)	O5–C5–C6–O7	66.8(2)
O4–C4–C5–O5	–172.30(14)	O5–C5–C6–O6	–110.3(3)

[a] Standard deviations in parentheses.

Table 3. Hydrogen bond geometry in compound **2**[a]

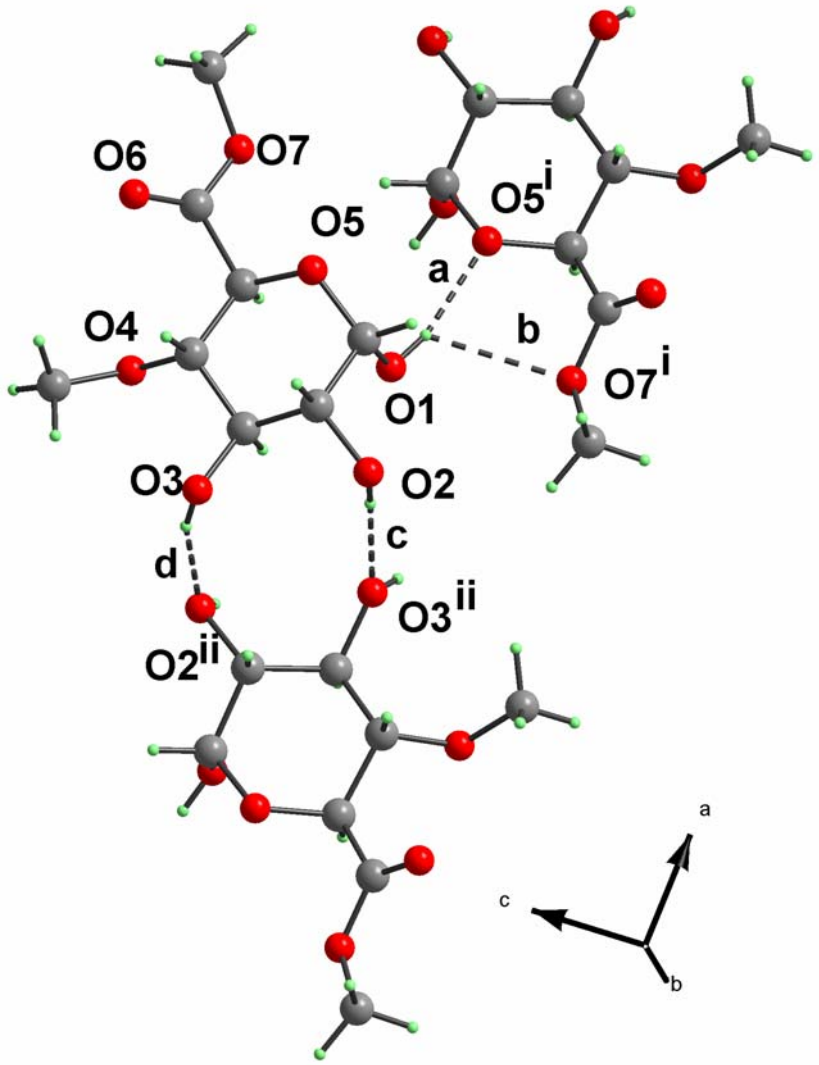
Notation	X–H···Y	Symmetry code	X–H (Å)	H···Y (Å)	X···Y (Å)	X–H···Y (°)
a	O1–H1···O5^{i}	–x+2, y+1/2, –z+1	0.84	2.00	2.8219(13)	166.9
b	O1–H1···O7^{i}	–x+2, y+1/2, –z+1	0.84	2.55	3.0637(18)	120.3
c	O2–H2···O3^{ii}	–x+1, y+1/2, –z+1	0.84	1.94	2.7724(15)	168.8
d	O3–H3···O2^{ii}	–x+1, y+1/2, –z+1	0.84	1.88	2.6845(15)	159.6
e	C2–H2A···O1^{iii}	x, y–1, z	1.00	2.43	3.2272(17)	136.4
f	C8–H8A···O6^{iv}	–x+2, y+1/2, –z+2	0.98	2.41	3.313(4)	152.4

[a] Standard deviations in parentheses.

Analysis of the molecular packing in the unit cell revealed six principal hydrogen bonds (Table 3 and Figure 2). The first-level descriptors based on the graph-set theory [10] include chain C1,1(4), formed by hydrogen bonds [a] and [e], chain C1,1(7) (bonds [b]) and chain C1,1(5) formed by bonds [c], [d] and [f]). On the second-level of graph-set theory, the most interesting features are rings

R2,2(10) and R2,1(5) formed by hydrogen bonds [c], [d] and [a], [b], respectively. Assignment of the H-bond descriptors, based on the graph-set theory [10] was obtained using the program PLUTO [11]. For convenience, the X*a*,*d*(*n*) notation has also been adopted in this paper, in which (X) is the pattern descriptor, (*a*) is number of acceptors, (*d*) is number of donors and (*n*) is the number of atoms comprising the pattern.

Figure 2. Hydrogen bonding pattern in compound **2**. For notation and symmetry codes see Table 3.



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Experimental

General

^{1}H- and ^{13}C-NMR spectra (in D_2O, internal standard TSP-d_4) were recorded on a Bruker Avance DPX 300 instrument (equipped with gradient-enhanced spectroscopy kit GRASP for generation of Z gradient up to 50 Gauss/cm) operating at working frequencies of 300.13 and 75.46 MHz, respectively. For the assignments of signals, 1D NOESY and C–H heterocorrelated experiments were used. Specific rotations were determined on a Perkin–Elmer 241 polarimeter (25 °C, 10 cm cell). Microanalyses were performed on a Fisons EA 1108 analyser. Melting points were determined with a Boetius PHMK 05 microscope. All reactions were monitored by TLC on Silica Gel 60 plates (E. Merck). Visualisation was effected by spraying the plates with 5% (v/v) solution of H_2SO_4 in ethanol followed by heating at approx. 200 °C.

X-ray techniques

X-ray quality crystals of the title compound **2** were obtained by slow crystallization from dilute acetone solution. Crystal and experimental data are summarized in Table 4. Preliminary orientation matrix was obtained from the first frames using Siemens SMART software [12]. Final cell parameters were obtained by refinement of 6468 reflections using Siemens SAINT software [12]. The data were empirically corrected for absorption and other effects using the SADABS program [13] based on the method of Blessing [14]. The structure was solved by direct methods and refined by full-matrix least-squares on all F^2 data using Bruker SHELXTL [15]. The non-H atoms were refined anisotropically. Hydrogen atoms were constrained to the ideal geometry using an appropriate riding model. Molecular graphics were obtained using the program DIAMOND [16].

Table 4. Crystallographic and experimental data for compound **2**[a]

Empirical formula	$C_8H_{14}O_7$
Formula weight	222.19
Temperature, T (K)	183(2)
Wavelength, λ (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1$
Unit-cell dimensions (Å)	a = 10.4000(2)
	b = 4.6969(1)
	c = 10.6190(2)
Unit-cell volume, V (Å^3)	518.510(18)
Formula per unit cell, Z	2
D_{calcd} (g/cm^3)	1.423
Absorption coefficient, μ (mm^{-1})	0.127
F(000)	236
Crystal size (mm)	1.00 × 0.22 × 0.16

Table 4. Cont.

Diffractometer	Siemens SMART CCD
θ Range (°)	1.92–33.08
Index ranges	$-15 \le h \le 15$
	$-7 \le k \le 7$
	$-16 \le l \le 16$
Reflections	8554
Independent reflections	3690 (R_{int} = 0.0328)
Completeness to θ = 33.08 (%)	96.4
Absorption correction	SADABS
Max. and min. transmission	0.9800 and 0.8838
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3690 / 1 / 155
Goodness-of-fit on F^2	1.095
Final R indices [$I>2\sigma(I)$]	R_1 = 0.0550, wR_2 = 0.1488
R indices (all data)	R_1 = 0.0610, wR_2 = 0.1548
Largest difference peak and hole (e/Å^3)	0.343 and –0.238

[a] Standard deviations in parentheses.

Syntheses

Methyl (benzyl 2,3-di-*O*-benzyl-4-*O*-methyl-β-D-glucopyranosid)uronate (**1**) was prepared from the known benzyl 2,3-di-*O*-benzyl-β-D-glucopyranoside [17] according to the published five-step synthetic method [7].

Methyl 4-O-*methyl-α-D-glucopyranuronate* (**2**).

A mixture of methyl (benzyl 2,3-di-*O*-benzyl-4-*O*-methyl-β-D-glucopyranosid)uronate (**1**) (4.0 g, 8.1 mmol) and 10 % Pd on activated charcoal (0.5 g) in acetone–methanol (1:4, v/v, 200 mL) was stirred under a hydrogen atmosphere (normal pressure) at room temperature. After 2 h, when the debenzylation was complete, the product (R_f = 0.49, chloroform–methanol 5:1; ref. [6] gives R_f = 0.38 in the same solvent) was isolated in the usual manner (filtering off the catalyst, evaporation of the solvent on a vacuum evaporator) affording a mixture of α- and β-anomers (in the ratio of about 2:1) of methyl 4-*O*-methyl-D-glucopyranuronate (1.75 g, 97 %). From this mixture, the pure α-anomer **2** (1.1 g, 61 %) crystallized slowly from acetone at room temperature. Recrystallization from acetone (with seeding) provided the analytical sample of the title compound **2** as colourless crystals, m.p. 130–131 °C; $[\alpha]_D$ + 100° (*c* 1, MeOH), $[\alpha]_D$ + 79° (*c* 1, H_2O) {ref. [6] gives $[\alpha]_D$ + 47.5° (*c* 0.6, 1:1 H_2O–EtOH) for a mixture of α- and β-anomers}; ^{1}H-NMR: δ 5.25 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1), 4.39 (d, 1 H, $J_{4,5}$ = 9.6 Hz, H-5), 3.84 (s, 3 H, $COOCH_3$), 3.81 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.6 Hz, H-3), 3.59 (dd, 1 H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 3.48 (s, 3 H, OCH_3), 3.35 (t, 1 H, $J_{3,4} = J_{4,5}$ = 9.6 Hz, H-4); ^{13}C-NMR: δ 172.9

(COOCH$_3$), 93.2 (C-1), 82.2 (C-4), 72.8 (C-3), 71.9 (C-2), 70.0 (C-5), 60.8 (OCH$_3$), 54.2 (COOCH$_3$). Anal. Calcd for $C_8H_{14}O_7$ (222.19): C, 43.24; H, 6.35. Found: C, 43.09; H, 6.40.

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Sample Availability: Samples of methyl 4-*O*-methyl-α-D-glucopyranuronate may be obtained from the authors.