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Note

Synthesis, crystal structure, and high-resolution NMR spectroscopy of methyl 3-azido-2,3-dideoxy-4,6-di-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexopyranoside

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Abstract—Synthesis of methyl 3-azido-2,3-dideoxy-4,6-di-*O*-*p*-tolylsulfonyl- and -6-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexopyranosides is presented. High-resolution ^{1}H and ^{13}C NMR spectral data for both compounds and their precursors, and the single-crystal X-ray diffraction analysis for methyl 3-azido-2,3-dideoxy-4,6-di-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexopyranoside are reported. The influence of the *O*-protective group on the chemical shift of adjacent atoms in the ^{1}H and ^{13}C NMR spectra is discussed.
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Keywords: Methyl 3-azido-2,3-dideoxy-α-D-*xylo*-hexopyranoside, tosylated; X-ray diffraction, single crystal; *O*-Protection, influence on chemical shift

Although the hydroxyl group is poor leaving group in nucleophilic substitution reactions, it is often convenient to replace the OH group, particularly in carbohydrate chemistry. The OH group is frequently converted to a reactive ester, most commonly a *p*-toluenesulfonic ester, to make the nucleophilic substitution possible. Due to our interest in obtaining methyl 3-azido-2,3,6-trideoxy-hex-5-eno-pyranosides, we synthesized 3-azido-2,3-dideoxy-4,6-di-*O*-*p*-tolylsulfonyl- (**7**) and -6-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexopyranosides (**8**).

As previously reported, addition of hydrazoic acid to the α,β-unsaturated aldehyde derived from tri-*O*-acetyl-D-galactal (**1**), followed by methyl glycosidation, led to a mixture of 3-azido-2,3-dideoxy glycosides.[1] Column chromatography of this mixture gave in turn: methyl 4,6-di-*O*-acetyl-3-azido-2,3-dideoxy-α-D-*lyxo*- (**2**), -β-D-*xylo*- (**3**), -α-D-*xylo*- (**4**), -β-D-*lyxo*-hexopyranosides (**5**). Deacetylation of methyl 4,6-di-*O*-acetyl-3-azido-2,3-dideoxy-α-D-*xylo*-hexopyranoside (**4**) with a 0.1 M solution of sodium methoxide in absolute methanol yielded methyl 3-azido-2,3-dideoxy-α-D-*xylo*-hexopyranoside (**6**). Tosylation of **6** with *p*-toluenesulfonyl chloride in pyridine at room temperature provided a mixture of methyl 3-azido-2,3-dideoxy-4,6-di-*O*-*p*-tolylsulfonyl- (**7**) and -6-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexopyranosides (**8**), which were separated by column chromatography (Scheme 1).

Compounds synthesized in the sequence of reactions of **4** → **6** → **7** and **8** differ solely in the type of OH group protection: 4-OAc and 6-OAc (**4**), 4-OH and 6-OH (**6**), 4-OTs and 6-OTs (**7**), 4-OH and 6-OTs (**8**). The presence of the above-mentioned protective groups in **4**, **6**, **7**, and **8**, respectively, was confirmed by IR (Table 1) and by ^{1}H (Table 2) and ^{13}C NMR spectroscopy (Table 4). All these compounds have the same α-D-*xylo* configuration and also the same $^{4}C_{1}$ conformation in $CDCl_3$ solution, which is demonstrated by respective coupling constants (Table 3). As was reported earlier, the lack of coupling between the equatorial H-1 and H-2 protons is characteristic for 2-deoxy-α-D-glycosides with the $^{4}C_{1}$ conformation.[1,2] Additionally, the $J_{4,5}$ coupling constant in a range of 0–2 Hz is diagnostic for a compound having

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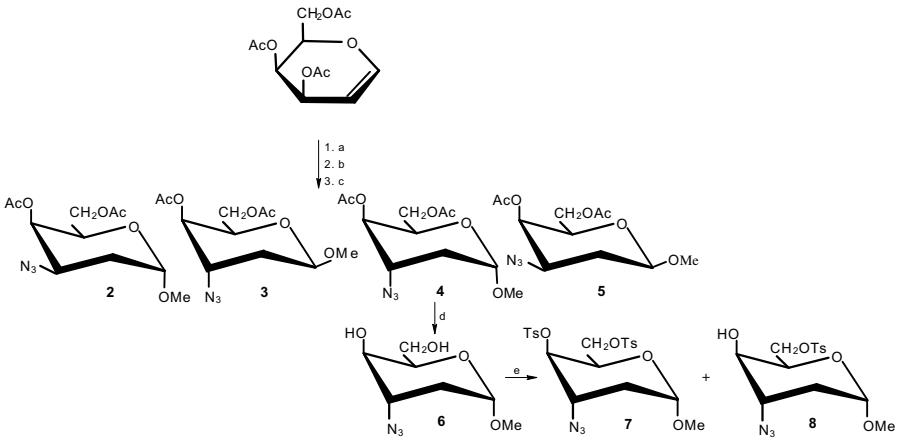

Scheme 1. Reagents and conditions: (a) Hg^{2+}, H_3O^+, dioxane; (b) NaN_3, CH_3COOH; (c) MsCl, MeOH, s-collidine; (d) MeONa, MeOH; (e) TsCl, pyridine.

Table 1. Stretching frequencies (cm^{-1}) of some important groups in IR spectra of **4** and **6**–**8**

	OH	N_3	C=O	C_6H_4	CO–O	O=S=O
4	—	2111	1747	—	1231	—
6	3419	2101	—	—	—	—
7	—	2114	—	1598	—	1191 1178
8	3472	2108	—	1598	—	1190 1176

Table 3. The ^1H–^1H coupling constants (Hz) for compounds **4** and **6**–**8**

	$J_{1,2a}$	$J_{1,2e}$	$J_{2a,2e}$	$J_{2a,3}$	$J_{2e,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
4	3.6	—	15.2	4.8	3.2	3.2	1.6	6.4	6.0	11.6
6	4.4	—	14.8	4.4	2.8	3.2	1.2	3.6	3.6	11.6
7	4.4	—	15.2	4.4	3.2	3.6	0.8	7.2	4.8	10.8
8	4.4	—	15.2	4.4	4.8	3.6	1.2	6.8	5.6	10.4

an anti-periplanar relationship of the H-4 proton and ring oxygen atom in hexopyranoses of the D series.[1,2] The differences in the 4- and 6-OH group protection of the **4** and **6**–**8** glycosides are illustrated by the chemical shifts of H-4 and H-6 protons as well as those of the C-3, C-4, and C-6 carbons in their NMR spectra. The most evident difference is the change of the chemical shift of the H-4 proton with change of the 4-OH group protection. A comparison of respective substituents shows that their deshielding influence on the H-4 proton decreases as follows: –OAc (δ 4.73, **4**), –OTs (δ 4.18, **7**), –OH (δ 3.72, **6** or 3.55, **8**). Inversely in its ^{13}C NMR spectrum (Table 4), both the C-4 and C-6 carbons are the most deshielding, while the *p*-tolylsulfonyl substituent protects respective OH groups ($\Delta\delta \sim 4$ ppm). The change of OAc into an OH group does not significantly alter the position of the C-4 and C-6 carbon signals. However, it seems that the 4-OH group has a deshielding influence on the C-3 carbon. The signal of the C-3 carbon appears at ~57 ppm when the 4-OH group is not protected (**6** and **8**) and at ~54 ppm, when 4-OH group is protected by an acetyl (**4**) or a *p*-tolylsulfonyl group (**7**).

Most important is that the X-ray structural analysis of crystalline **7** fully confirmed the relative configuration and conformation obtained from analysis of the NMR spectra.

1. Experimental

1.1. General methods

Melting points are uncorrected. Optical rotations were determined at room temperature with a Hilger-Watt

Table 2. Chemical shifts (ppm) in the ^1H NMR spectra ($CDCl_3$) of **4** and **6**–**8**

	H-1	H-2_a	H-2_e	H-3	H-4	H-5	H-6	H-6′	OCH_3	OAc	OTs	
											C_6H_4	CH_3
4	4.81 (d)	2.15 (dt)	1.93 (dq)	3.88 (q)	4.73 (d)	4.34 (td)	4.15 (dd)	4.11 (dd)	3.40 (s)	2.08 (s) 2.13 (s)	—	—
6	4.81 (d)	2.28 (dt)	1.87 (dm)	3.81 (q)	3.72 (bd)	4.00 (td)	3.96 (dd)	3.91 (dd)	3.37 (s)	—	—	—
7	4.67 (d)	2.14 (dt)	1.86 (dm)	3.93 (q)	4.18 (d)	4.22 (ddd)	3.92 (dd)	3.73 (dd)	3.27 (s)	—	7.77 (d) 7.73 (d) 7.38 (d) 7.35 (d)	2.48 (s) 2.46 (s)
8	4.72 (d)	2.17 (dt)	1.87 (dm)	3.81 (q)	3.55 (b)	4.24 (td)	4.12 (dd)	4.19 (dd)	3.33 (s)	—	7.81 (d) 7.36 (d)	2.46 (s)

Table 4. Chemical shifts (ppm) in the ^{13}C NMR spectra ($CDCl_3$) of **4** and **6–8**

	C-1	C-2	C-3	C-4	C-5	C-6	OCH_3	OAc		OTs	
								C=O	CH_3	C_6H_4	CH_3
4	96.97	28.16	54.56	67.60	63.39	63.12	55.65	170.52 169.93	21.16 21.09	—	—
6	97.79	27.36	57.32	69.28	64.96		55.67	—	—	—	—
7	96.69	27.33	54.83	73.49	63.27	68.43	55.83	—	—	130.38 129.97 128.02 127.95	22.11 22.02
8	97.25	27.52	57.26	66.43	64.31	69.02	55.79	—	—	130.03 128.08	22.01

polarimeter in 1-dm tubes at the D line of sodium for solutions in $CHCl_3$. The IR spectra were recorded as Nujol mulls with a Bruker IFS 66 spectrophotometer. The ^1H and ^{13}C NMR spectra ($CDCl_3$, internal Me_4Si) were measured with a Varian Mercury 400 (400.49/100.70 MHz) instrument. Elemental analyses were conducted with a Carlo Erba EA1108 elemental analyzer. TLC was performed on the E. Merck Kieselgel 60 F-254 plates using the following eluent systems (v/v): A, 4:1 petroleum ether–AcOEt; B, 4:1 Et_2O–AcOEt; C, 1:4 petroleum ether–AcOEt; D, 2:1 toluene–AcOEt. Column chromatography was performed on MN Kieselgel 60 (<0.08 mm).

Table 5. Crystal data and structure refinement for **7**

Empirical formula	$C_{21}H_{25}N_3O_8N_2$
Formula weight	511.56
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	
a (Å)	6.0130(10)
b (Å)	14.121(3)
c (Å)	28.399(6)
V (Å^3)	2411.3(8)
Z	4
D_{calcd} (Mg m^{-3})	1.409
Absorption coefficient (mm^{-1})	0.272
$F(000)$	1027
Crystal size (mm)	$0.4 \times 0.3 \times 0.3$
Θ range for data collection (°)	4.06–50.00
Limiting indices	$0 \leqslant h \leqslant 7$, $-16 \leqslant k \leqslant 0$, $-33 \leqslant l \leqslant 0$
Reflections collected/unique	2472/2472 (R_{int} = 0.0)
Completeness 2Θ = 50.00° (%)	99.9
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2472/0/308
Goodness-of-fit on F^2	0.947
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0375 wR_2 = 0.0641
R indices (all data)	R_1 = 0.1414 wR_2 = 0.0909
Absolute structure parameter	−0.02(14)
Extinction coefficient	0.0016(3)
Largest diff. peak and hole (eÅ^{-3})	0.195 and −0.237

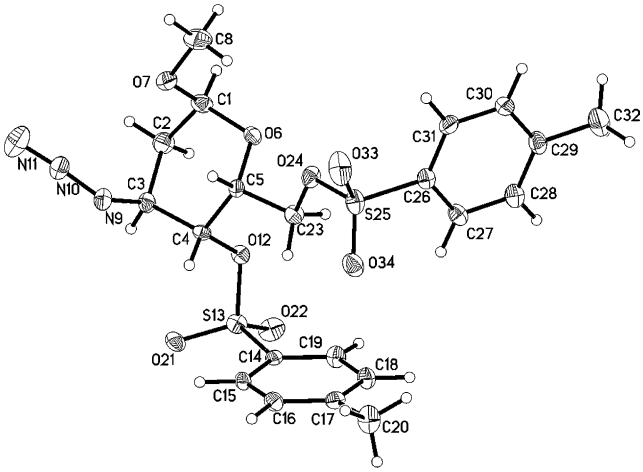

Figure 1. Structure of **7** showing 50% probability displacement for ellipsoids.

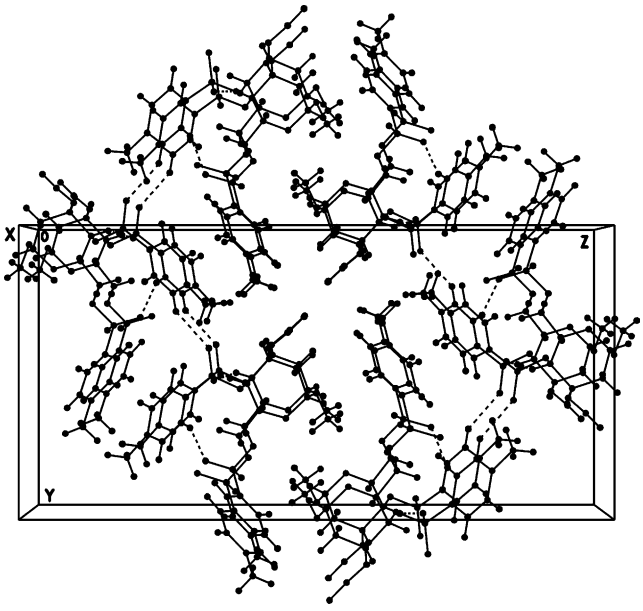

Figure 2. Molecular packing of **7** (view along x-axis).

Table 6. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **7** U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor

Atom	*x*	*y*	*z*	U_{eq}
C-1	−2727(12)	775(4)	150(2)	64(2)
C-2	−1696(11)	−133(4)	314(2)	71(2)
C-3	−2543(7)	−486(3)	782(1)	57(1)
C-4	−2618(7)	330(3)	1145(1)	43(1)
C-5	−3669(10)	1195(3)	937(2)	45(1)
O-6	−2615(6)	1478(2)	508(2)	54(1)
O-7	−4876(8)	590(3)	9(2)	77(1)
C-8	−5985(13)	1400(5)	−183(2)	102(3)
N-9	−4809(10)	−860(4)	782(1)	78(2)
N-10	−5315(11)	−1389(4)	467(2)	86(2)
N-11	−5984(15)	−1894(5)	203(3)	146(3)
O-12	−349(6)	552(2)	1282(1)	50(1)
S-13	523(2)	132(1)	1763(1)	55(1)
C-14	−811(9)	821(4)	2181(1)	44(1)
C-15	−2739(10)	515(4)	2396(2)	52(2)
C-16	−3869(10)	1116(4)	2686(2)	58(2)
C-17	−3149(10)	2016(4)	2775(2)	55(2)
C-18	−1171(10)	2311(4)	2568(2)	63(2)
C-19	−36(9)	1722(4)	2273(2)	58(2)
C-20	−4499(11)	2702(4)	3073(2)	88(2)
O-21	−235(7)	−822(2)	1804(1)	65(1)
O-22	2842(6)	342(2)	1761(2)	76(1)
C-23	−3587(9)	2033(3)	1266(2)	54(2)
O-24	−5257(7)	2681(2)	1101(1)	64(1)
S-25	−6203(3)	3451(1)	1446(1)	66(1)
C-26	−4568(10)	4450(4)	1338(2)	54(2)
C-27	−2625(10)	4567(4)	1585(2)	59(2)
C-28	−1327(10)	5361(4)	1495(2)	65(2)
C-29	−1917(12)	6006(4)	1167(2)	67(2)
C-30	−3899(14)	5878(4)	915(2)	74(2)
C-31	−5216(11)	5098(4)	1005(2)	66(2)
C-32	−508(13)	6869(4)	1068(2)	100(3)
O-33	−8368(7)	3634(3)	1269(2)	105(2)
O-34	−5887(9)	3164(3)	1915(1)	82(2)
H-1A	−1910	1000	−118	77
H-2B	−1752	−611	73	85
H-2A	−162	18	369	85
H-3A	−1575	−974	897	68
H-4A	−3457	136	1416	51
H-5A	−5209	1068	873	54
H-8A	−6283	1846	64	153
H-8B	−5056	1690	−417	153
H-8C	−7361	1206	−325	153
H-15A	−3313	−109	2338	63
H-16A	−5186	891	2841	70
H-18A	−652	2942	2630	75
H-19A	1356	1930	2144	70
H-20A	−4100	2630	3398	132
H-20B	−4194	3340	2974	132
H-20C	−6054	2571	3034	132
H-23A	−2153	2331	1254	65
H-23B	−3902	1834	1582	65
H-27A	−2161	4095	1808	70
H-28A	63	5438	1657	77
H-30A	−4303	6342	684	89
H-31A	−6528	5007	817	80
H-32A	−892	7123	765	150
H-32B	−772	7338	1306	150
H-32C	1035	6694	1070	150

Table 7. Selected bond lengths (Å), valence angles (°), and torsion angles (°) for **7**

Bond lengths	
C-1–O-7	1.378(7)
C-1–O-6	1.423(7)
C-1–C-2	1.499(7)
C-2–C-3	1.509(6)
C-3–N-9	1.461(7)
C-3–C-4	1.547(6)
C-4–O-12	1.452(5)
C-4–C-5	1.497(6)
C-5–O-6	1.429(6)
C-5–C-23	1.509(6)
O-7–C-8	1.431(7)
N-9–N-10	1.205(7)
N-10–N-11	1.111(7)
Valence angles	
O-7–C-1–O-6	112.6(5)
O-7–C-1–C-2	108.4(6)
O-6–C-1–C-2	110.8(5)
C-1–C-2–C-3	114.6(4)
N-9–C-3–C-2	115.8(4)
N-9–C-3–C-4	104.0(3)
C-2–C-3–C-4	110.6(2)
O-12–C-4–C-5	109.0(4)
O-12–C-4–C-3	108.1(2)
C-5–C-4–C-3	110.8(2)
O-6–C-5–C-4	112.2(4)
O-6–C-5–C-23	107.1(4)
C-4–C-5–C-23	112.4(4)
C-1–O-6–C-5	113.1(4)
C-1–O-7–C-8	113.4(5)
N-10–N-9–C-3	117.4(6)
N-11–N-10–N-9	172.5(9)
Torsion angles	
O-7–C-1–C-2–C-3	−72.8(6)
O-6–C-1–C-2–C-3	51.2(7)
C-1–C-2–C-3–N-9	71.7(6)
C-1–C-2–C-3–C-4	−46.2(6)
N-9–C-3–C-4–O-12	162.3(4)
C-2–C-3–C-4–O-12	−72.8(4)
N-9–C-3–C-4–C-5	−78.3(4)
C-2–C-3–C-4–C-5	46.6(4)
O-12–C-4–C-5–O-6	64.8(5)
C-3–C-4–C-5–O-6	−54.1(4)
O-12–C-4–C-5–C-23	−56.0(5)
C-3–C-4–C-5–C-23	−174.9(3)
O-7–C-1–O-6–C-5	64.0(6)
C-2–C-1–O-6–C-5	−57.6(7)
C-4–C-5–O-6–C-1	60.9(6)
C-23–C-5–O-6–C-1	−175.4(5)
O-6–C-1–O-7–C-8	60.7(6)
C-2–C-1–O-7–C-8	−176.4(5)
C-2–C-3–N-9–N-10	45.1(6)
C-4–C-3–N-9–N-10	166.6(4)
C-3–N-9–N-10–N-11	170.9(6)
H-1A–C-1–C-2–H-2A	55.5
H-1A–C-1–C-2–H-2B	−60.9
H-2A–C-2–C-3–H-3A	−51.9
H-2B–C-2–C-3–H-3A	64.9
H-3A–C-3–C-4–H-4A	−72.4
H-4A–C-4–C-5–H-5A	−54.5
H-5A–C-5–C-23–H-23A	−159.5
H-5A–C-5–C-23–H-23B	79.1

Table 8. Short contacts for **7**

D–H	*d*(D–H)	*d*(H···A)	<DHA	*d*(D···A)	A	Symm. op.
C-4–H-4A	0.96	2.45	140	3.242(5)	O22	[1 − *x*, *y*, *z*]
C-19–H-19A	0.96	2.49	153	3.377(7)	O34	[1 + *x*, *y*, *z*]

1.2. Methyl 4,6-di-*O*-acetyl-3-azido-2,3-dideoxy-α-D-*lyxo*-(2), -β-D-*xylo*- (3), -α-D-*xylo*- (4), and -β-D-*lyxo*-hexopyranosides (5)

These were synthesized as previously reported.[1]

1.3. Methyl 3-azido-2,3-dideoxy-α-D-*xylo*-hexopyranoside (6)

A mixture of **4** (2.84 g, 8.1 mM) and 0.1 M NaOMe in abs MeOH (35 mL) was stirred for 0.5 h at rt. The end of deacetylation was verified by TLC (solvent A). The solution was then neutralized with Dowex-50W × 8 (H^+) ion-exchange resin and filtered, and the filtrate was evaporated to give **6** (99%, solid); R_f 0.39 (solvent B).

1.4. Methyl 3-azido-2,3-dideoxy-4,6-di-*O*-*p*-tolylsulfonyl-(7) and 6-*O*-*p*-*tolylsulfonyl*-α-D-*xylo*-hexopyranosides (8)

To a solution of **6** (1.39 g, 6.84 mM) in CH_2Cl_2 (50 mL), dry pyridine (2.8 mL) and *p*-toluenesulfonyl chloride (2.61 g, 13.7 mM) were added. The mixture was stirred at rt for 24 h. The end of the reaction was determined by TLC (solvent C). The mixture was then diluted with Et_2O (50 mL), and the precipitated salts were filtered off. The filtrate was concentrated and diluted with $CHCl_3$. The organic solution was washed with satd $NaHCO_3$ and water and dried over Na_2SO_4. Concentration under reduced pressure led to the crude product, which was chromatographed (solvent D) to give first **7** (44%, mp 138–140 °C); $[\alpha]_D^{20}$ +58 (*c* 1, $CHCl_3$); R_f 0.81 (solvent D). Anal. Calcd for $C_{21}H_{25}N_3O_8S_2$: C, 49.31; H, 4.93; N, 8.21; S, 12.54. Found: C, 49.68; H, 4.95; N, 8.10; S, 12.50.

Eluted second was **8** (36%, syrup); $[\alpha]_D^{20}$ +102 (*c* 1, $CHCl_3$); R_f 0.44 (solvent D). Anal. Calcd for $C_{14}H_{19}N_3O_6S$: C, 47.05; H, 5.36; N, 11.76; S, 8.97. Found: C, 47.38; H, 5.13; N, 11.52; S, 8.70.

1.5. Description of the crystal structure

The crystal structure of **7** was solved by the SHELXS program and refined by SHELXL-97.[3,4] A summary of crystallographic data, data collection and structure refinement is presented in Table 5. A view of **7** and its molecular packing in the crystal are presented in Figures 1 and 2, respectively.[5,6] The coordinates of atoms and their isotropic temperature factors are presented in Table 6. A selection of important geometric parameters of **7** is tabulated in Table 7, and short contacts are summarized in Table 8.

In the crystal, **7** adopts a $^4C_1$ chair conformation with puckering parameters $Q = 0.512(4)$ and $\Theta = 6.8(4)°$.[7,8] The values of bond lengths and angles determined in this work for **7** agree well with the expected ones.[9,10] All H atoms were placed geometrically and refined using a riding model with C–H = 0.96 Å and $U_{iso}(H) = 1.2\ U_{eq}(C)$ (C–H = 0.96 Å and $U_{iso}(H) = 1.5\ U_{eq}(C)$ in the case of the methyl H atoms).

Supplementary data

Full crystallographic details, excluding structure features, have been deposited (deposition no. CCDC 247410) with the Cambridge Crystallographic Data Centre. These data may be obtained, on request, from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (tel.: +44 1223 336408; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or <www:http://www.ccdc.cam.ac.uk>).

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References

1. Liberek, B.; Dąbrowska, A.; Frankowski, R.; Matuszewska, M.; Smiatacz, Z. *Carbohydr. Res.* **2002**, *337*, 1803–1820.
2. Liberek, B.; Sikorski, A.; Melcer, A.; Konitz, A. *Carbohydr. Res.* **2003**, *338*, 795–799.
3. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467–473.
4. Sheldrick, G. M. SHELXL-97; *Program for the Refinement of Crystal Structures*; University of Goetingen: Goetingen, 1997.
5. Johnson, C. K. ORTEP II; *Report ORNL*-5138; Oak Ridge National Laboratory: Oak Ridge, TN, 1976.
6. Motherwell, S.; Clegg, S. PLUTO-78; *Program for Drawing Crystal and Molecular Structure*; University of Cambridge: Cambridge, 1978.
7. Nardelli, M. *Comput. Chem.* **1983**, *7*, 95–97.
8. Nardelli, M. *J. Appl. Crystallogr.* **1995**, *28*, 659.
9. Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1–19.
10. Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.