NEW HETEROCYCLIC DERIVATIVES OF 2-AMINO-1,6-ANHYDRO-2-DEOXY-β-D-GLUCOPYRANOSE CONTAINING 1,4-OXAZEPANE OR AZEPANE RING

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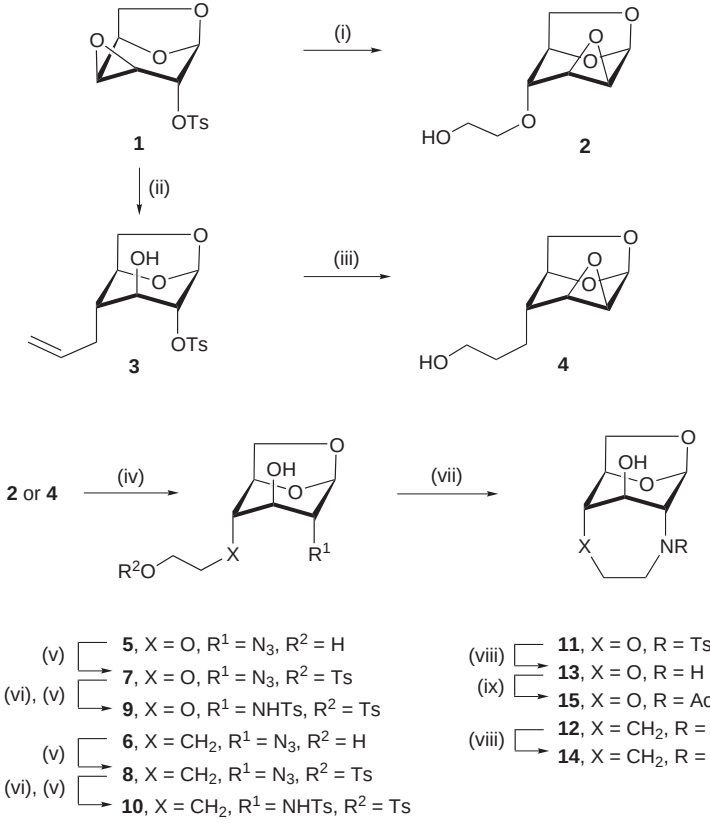
Two heterocyclic derivatives of D-glucosamine, 2-amino-1,6-anhydro-2-deoxy-2-*N*,4-*O*-(ethane-1,2-diyl)-β-D-glucopyranose (**13**) and 2-amino-1,6-anhydro-2,4-dideoxy-2-*N*,4-(propane-1,3-diyl)-β-D-glucopyranose (**14**) were prepared from 1,6-anhydro-β-D-glucopyranose (levoglucosan) in ten steps via O-4 or C-4 substituted 1,6:2,3-dianhydro-β-D-mannopyranose derivatives **2** and **4**. Selective oxirane-ring cleavage with sodium azide at C-2 followed by tosylation afforded 2-azido-2-deoxy derivatives **7** and **8** of D-*gluco* configuration. These were reduced to amines and, after tosylation, azepane and oxazepane *N*-tosyl derivatives **11** and **12** were formed by intramolecular substitution. Their detosylation afforded the target D-glucosamine derivatives **13** and **14**.

Keywords: Carbohydrates; Aminosugars; Oxazepanes; Azepanes; Heterocycles; 1,6-Anhydrosugars; 2-Amino-2-deoxy-D-glucose; Oxiranes; Epoxides; Cyclizations; X-ray diffraction; NMR spectroscopy; Conformation analysis.

Many glycoconjugates of biological importance and some naturally occurring aminoglycoside antibiotics contain 2-amino-2-deoxy-D-glucose. A number of its derivatives were synthesized in recent decades[1]. These compounds are effective as potential inhibitors of carbohydrate-processing enzymes or can interfere with biosynthesis of glycoconjugates. Lately, it was shown that glycosylated glucosamine derivatives could interact with ribosomal RNA of bacteria in analogy to aminoglycoside antibiotics[2]. In connection with our previous papers[3], we report herein a synthesis of two derivatives of 2-amino-1,6-anhydro-2-deoxy-β-D-glucopyranose **13** and **14**

which involve 1,4-oxazepane and azepane ring, respectively, annelated at C-2 and C-4 position of the pyranose ring.

As starting compounds in the parallel synthesis of target compounds **13** and **14** we used a pair of epoxides **2** [4] and **4** (Scheme 1), accessible from 1,6-anhydro-β-D-glucopyranose[5] via 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galacto-pyranose[6] (**1**) in four steps. Acid-catalyzed reaction of the tosyl epoxide **1** with ethane-1,2-diol and subsequent alkalization of the reaction mixture gave the epoxide **2** in 73% yield. Treatment of **1** with allylmagnesium chloride gave the known allyl derivative[7] **3**. Hydroboration of the terminal dou-



(i) ethylene glycol, $BF_3{\cdot}Et_2O$, DME, 100 °C; then NaOMe, MeOH, $CHCl_3$, r.t.; (ii) $CH_2{=}CHCH_2MgCl$, CuI, THF, r.t.; (iii) $BH_3{\cdot}THF$, then NaOH, H_2O_2; (iv) NaN_3, NH_4Cl, $CH_3OCH_2CH_2OH$, H_2O, 115 °C; (v) TsCl, pyridine, r.t.; (vi) H_2, Pd/C, EtOH, AcOH, r.t.; (vii) K_2CO_3, DMF, 60 °C; (viii) sodium naphthalenide, DME, –10 °C; (ix) TFA, Ac_2O, r.t

SCHEME 1

ble bond in **3** with gaseous diborane followed by conventional work-up of the reaction mixture with H_2O_2 and NaOH, resulted in formation of epoxide **4** in 87% yield. Cleavage of the oxirane ring in epoxides **3** and **4** with sodium azide afforded azido derivatives **5** and **6** in 73 and 68% yield, respectively. The primary hydroxy group in both azido derivatives was selectively tosylated to obtain tosylates **7** and **8**. The azido group in **7** and **8** was reduced with hydrogen in the presence of 10% Pd on activated carbon. The corresponding amines thus obtained proved to be instable after standing at room temperature for several hours. Consequently, they were directly tosylated without purification to give tosyl amides **9** and **10**. Formation of the seven-membered ring in **11** and **12** was effected by the modified Richman–Atkins procedure[8] in 85 and 82% yields on heating tosyl derivatives **9** and **10** with a mixture of potassium carbonate in dimethylformamide at 60 °C. The target compounds **13** and **14** were obtained in 69 and 73% yield by detosylation with sodium naphthalenide in 1,2-dimethoxyethane. Attempted acid hydrolysis as well as acetolysis of the 1,6-anhydride bond in **13** failed and *N*-acetyl derivative **15** was isolated as a sole product. This may be accounted for by the fact that the pyranoid ring in **13** adopts a less common $^1C_4$ conformation and should also adopt this conformation, due to limited flexibility of the bicyclic pyranoid–oxazepane skeleton, if the 1,6-anhydride bond is interrupted. As a result, a strong tendency to regenerate the 1,6-anhydride bond in the equilibrium mixture may be expected. An analogy of this situation was described for acid equilibration of some free hexoses partially adopting $^1C_4$ conformation[9].

NMR AND X-RAY DISCUSSION

The structure of compounds **2**, **4**–**15** was determined by ^{1}H and ^{13}C NMR spectroscopy. Structural assignment of protons and carbon atoms was achieved using correlated homonuclear 2D-COSY and heteronuclear ^{1}H, ^{13}C 2D-HSQC spectra. The long-range couplings, typical of compounds with D-*gluco* configuration, were identified by selective decoupling experiments in 1D ^{1}H NMR spectra. The 2,3-epoxy group in compounds **2** and **4** manifests itself by upfield shifts of carbon atoms C-2 and C-3 (δ 50–54) and characteristic vicinal coupling $J(2,3) \approx 4$ Hz. The NMR data of compounds **5**–**15** are summarized in Tables I–III. The *gluco* configuration of compounds **5**–**15** and preferred $^1C_4$ conformation of their pyranose ring is documented by low values of vicinal couplings $J(2,3)$ and $J(3,4)$. Slightly higher values of $J(2,3)$ and $J(3,4)$ in **6**, **8**, **10** (see Table II) indicate a certain amount of $B_{3,O}$ boat form in a chair–boat equilibrium due to the steric interactions be-

TABLE I
^{1}H NMR chemical shifts (in ppm, δ-scale) of compounds **5**–**15**

Comp.	Solvent	H-1	H-2	H-3	H-4	H-5	H-6en	H-6ex	Other protons
5	$CDCl_3$	5.48 bt	3.22 dm	3.91 tt	3.37 ddt	4.67 dm	4.03 bdd	3.77 ddd	O-$(CH_2)_2$OH: 3.69–3.81 m (4 H)
6	$CDCl_3$	5.46 t	3.47 m	3.65 m	~1.69 m	4.43 bd	4.09 dd	3.78 dd	$(CH_2)_3$OH: 1.75 m (1 H), 1.65 m (1 H), 1.73 m (2 H), 3.71 m (2 H)
7	$CDCl_3$	5.43 bt	3.18 dm	3.81 tt	3.34 ddt	4.56 dm	3.98 bdd	3.72 ddd	O-$(CH_2)_2$-O: 3.85 m (2 H), 4.22 t (2 H); OTs: 2.45 bs (3 H), 7.80 m (2 H), 7.36 m (2 H)
8	$CDCl_3$	5.44 t	3.46 m	3.58 m	1.63 m	4.34 bd	4.09 dd	3.76 dd	$(CH_2)_3$O: 1.63 m (2 H), 1.70–1.85 m (2 H), 4.07 t (2 H); OTs: 2.46 bs (3 H), 7.79 m (2 H), 7.36 m (2 H)
9	$CDCl_3$	5.22 t	3.36 dm	3.56 p	3.31 m	4.51 m	4.11 dd	3.70 dd	O-$(CH_2)_2$-O: 3.75 m (2 H), 3.68 m (2 H); OTs: 2.46 bs (3 H), 7.84 m (2 H), 7.39 m (2 H); NTs: 2.42 bs (3 H), 7.77 m (2 H), 7.31 m (2 H); NH: 5.24 d
10	$CDCl_3$	5.05 t	3.24 dm	3.55 bs	1.60 m	4.28 bd	4.09 dd	3.70 dd	$(CH_2)_3$-O: 1.61 m, 1.52 m, 1.76 m, 1.66 m, 4.04 m (2 H); OTs: 2.46 bs (3 H), 7.81 m (2 H), 7.38 m (2 H); NTs: 2.43 bs (3 H), 7.75 m (2 H), 7.32 m (2 H); NH: 4.95 d
11	$CDCl_3$	5.63 t	3.96 m	3.87 p	3.77 m	4.63 m	4.23 dd	3.73 dd	OH: 3.18 bd; O-$(CH_2)_2$-N: 4.60 ddd, 3.83 ddd, 3.96 ddt, 3.39 ddd; NTs: 2.44 bs (3 H), 7.70 m (2 H), 7.34 m (2 H)
12	$CDCl_3$	5.65 m	3.86 dm	3.62 dm	2.02 m	4.40 dm	4.20 dd	3.72 dd	$(CH_2)_3$-N: 1.57 m, 1.82 m, 1.74 m, 2.41 m, 2.90 ddd, 3.91 m; NTs: 2.43 bs (3 H), 7.69 m (2 H), 7.32 m (2 H)
13	$CDCl_3$ + CD_3OD (5:1)	5.44 bt	3.06 m	4.23 p	3.88 bq	4.49 m	4.29 dd	3.69 dd	O-$(CH_2)_2$-N: 4.15 ddd, 3.92 ddd, 3.57 ddd, 3.00 ddd
14	$CDCl_3$+DMSO-d_6 (1:1)	5.24 m	2.96 m	3.97 p	2.03 m	4.27 dm	4.35 dd	3.60 dd	$(CH_2)_3$-N: 1.77 m, 1.66 m, 2.01 m, 1.62 m, 3.14 ddd, 2.90 ddd
(*Z*)-**15**[a]	$CDCl_3$	5.73 bt	4.47 um	4.19 dp	3.83 m	4.71 m	4.26 dd	3.74 dd	O-$(CH_2)_2$-N: 4.70 ddd, 3.87 ddd, 3.81 ddd, 3.71 ddd; OH: 3.37 d; NAc: 2.15 s
(*E*)-**15**[b]	$CDCl_3$	5.57 bt	3.95 m	4.31 dp	3.88 m	4.71 m	4.29 dd	3.77 dd	O-$(CH_2)_2$-N: 4.49 ddd, 3.87 ddd, 4.48 ddd, 3.70 ddd; OH: 3.23 d; NAc: 2.21 s

[a] 82%; [b] 18%.

TABLE II
^{1}H NMR coupling constants (J, Hz) of compounds **5**–**15**

Comp.	Solvent	1,2	2,3	3,4	4,5	5,6en	5,6ex	6en,6ex	1,3	1,4	2,4	2,5	3,5
5[a]	$CDCl_3$	1.3	3.7	3.7	1.4	1.0	5.4	7.5	1.1	0.6	0.7	0.5	1.2
6	$CDCl_3$	1.5	2.8	2.9	[b]	0.8	5.1	7.0	1.3	[b]	0.7	~0.5	[b]
7[c]	$CDCl_3$	1.3	3.4	3.6	1.5	1.0	5.4	7.5	1.2	0.6	0.7	0.5	1.3
8	$CDCl_3$	1.5	[b]	[b]	[b]	0.9	5.3	7.2	1.5	[b]	0.8	[b]	[b]
9[d]	$CDCl_3$	2.2	1.8	1.7	2.0	0.8	5.3	7.8	1.7	0.7	1.2	0.7	1.7
10[e]	$CDCl_3$	1.7	1.8	[b]	[b]	0.7	5.0	7.2	1.6	[b]	[b]	0.7	[b]
11[f]	$CDCl_3$	2.3	1.7	1.5	2.1	0.8	5.2	7.8	1.9	0.7	1.5	0.7	1.7
12[g]	$CDCl_3$	~2.0	~1.4	~1.4	~1.2	0.5	4.8	7.3	~1.7	~0.8	[b]	[b]	~1.4
13[h]	$CDCl_3$+CD_3OD (5:1)	2.2	1.2	2.0	2.0	0.8	5.4	7.4	2.0	≤0.3	1.0	0.8	2.0
14	$CDCl_3$+DMSO-d_6 (1:1)	2.2	1.4	1.5	[b]	0.8	5.2	6.6	1.6	0.8	2.0	[b]	1.5
(*Z*)-**15**[i,j]	$CDCl_3$	1.6	1.7	1.7	[b]	0.6	5.2	7.6	2.0	[b]	[b]	[b]	1.6
(*E*)-**15**[i,k]	$CDCl_3$	~2.0	1.7	1.7	[b]	0.6	5.2	7.7	~2.0	[b]	[b]	[b]	1.6

[a] J(1,6ex) = 0.6, J(1,6en) ≤ 0.3; [b] J-value could not be determined; [c] J(1,6ex) = 0.5, J(1,6en) ≤ 0.3; [d] J(2,NH) = 10.6; [e] J(2,NH) = 9.1; [f] J(3,OH) = 8.5; [g] J(3,OH) = 9.1; [h] J(1,5) ≤ 0.3, J(1,6ex) ≤ 0.3, J(1,6en) ≤ 0.3; [i] J(3,OH) = 8.7; [j] 82%; [k] 18%.

TABLE III
^{13}C NMR chemical shifts (in ppm, δ-scale) of compounds **5**–**15**

Comp.	Solvent	C-1	C-2	C-3	C-4	C-5	C-6	Other carbons
5	$CDCl_3$	101.07	62.70	70.33	80.05	74.81	66.19	O-$(CH_2)_2$OH: 61.92, 71.27
6	$CDCl_3$	100.61	63.87	71.00	44.31	75.01	68.59	$(CH_2)_3$OH: 30.14, 27.56, 62.56
7	$CDCl_3$	101.09	62.67	70.48	80.52	74.74	66.20	O-$(CH_2)_2$-O: 67.74, 69.28; OTs: 145.13, 133.72, 129.92(2), 127.92(2), 21.64
8	$CDCl_3$	100.50	63.46	70.81	43.82	74.74	68.39	$(CH_2)_3$O: 26.71, 27.08, 70.04; OTs: 144.92, 132.92, 129.89(2), 127.88(2), 21.63
9	$CDCl_3$	101.31	54.55	69.48	78.40	73.68	65.52	O-$(CH_2)_2$-O: 67.27, 68.93; OTs: 145.13, 132.92, 130.01(2), 127.94(2), 21.62; NTs: 143.71, 137.99, 129.90(2), 126.96(2), 21.49
10	$CDCl_3$	101.00	56.27	71.62	44.04	74.76	68.46	$(CH_2)_3$-O: 26.93, 27.58, 69.95; OTs: 144.09, 132.83, 130.02(2), 127.90(2), 21.65; NTs: 144.04, 137.08, 129.97(2), 126.97(2), 21.54
11	$CDCl_3$	101.96	57.36	67.35	74.34	76.58	65.72	O-$(CH_2)_2$-N: 66.81, 49.33; NTs: 143.94, 135.73, 130.04(2), 126.92(2), 21.45
12	$CDCl_3$	102.71	58.27	68.14	42.01	77.14	68.12	$(CH_2)_3$-N: 30.57, 26.37, 46.46; NTs: 143.54, 135.81, 129.90(2), 126.96(2), 21.50
13	$CDCl_3$+CD_3OD (5:1)	103.39	57.25	67.96	75.17	76.43	64.94	O-$(CH_2)_2$-N: 69.42, 48.00
14	$CDCl_3$+DMSO-d_6 (1:1)	103.58	57.91	68.11	41.51	77.08	66.75	$(CH_2)_3$N: 28.81, 29.15, 45.08
(*Z*)-**15**[a]	$CDCl_3$	99.59	56.44	68.17	74.38	77.36	65.95	O-$(CH_2)_2$-N: 66.94, 50.11; NAc[b]: 22.62
(*E*)-**15**	$CDCl_3$	100.96	59.02	68.20	74.26	77.36	65.83	O-$(CH_2)_2$-N: 66.90, 45.54; NAc[c]

[a] 82%; [b] carbonyl signal could not be detected; [c] both signals could not be detected.

tween the substituent at C-2 and alkyl chain at C-4 (for detailed discussion of this phenomenon, see lit.[10]). The presence of all substituents as well as an additional seven-membered ring in **11–15** is clearly proved by corresponding signals in ^{1}H and ^{13}C NMR spectra. The partial double-bond character of tertiary amide bond in *N*-acetyl derivatives **15** leads to the existence of two isomers observed in their NMR spectra. These isomers could be identified as *Z*- and *E*-isomers on the basis of the observed NOE contacts between methyl protons of *N*-acetyl group and the protons of N-CH_2 group (in *Z*-isomer; 82%) and/or H-2 proton (in *E*-isomer; 18%).

The crystal structure of compound **11** is shown in Fig. 1. The five-membered ring adopts envelope form E^{O2}, the six-membered ring a flattened chair form $^{C3}C_{O2}$ and the seven-membered ring exists in a slightly distorted chair conformation $^{C4,O4}C_{N1}$. The aromatic ring of tosyl group is folded over bottom face of the seven-membered ring. The selected torsion angles are given in Table IV.

The conformation of compound **11** in solution is very close to that found in crystal as it is evidenced by vicinal interproton coupling constants when compared with torsion angles of corresponding hydrogen atoms in crystal (see Table IV).

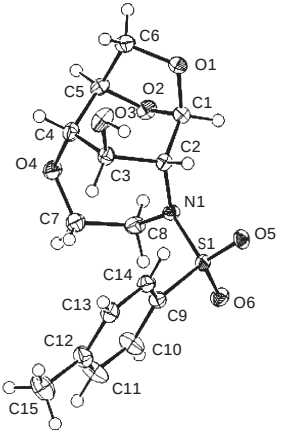


FIG. 1
View of the molecule of **11** with atom numbering scheme. The displacement ellipsoids are drawn on 50% probability level (PLATON)[13]

TABLE IV
Selected torsion angles (in °) found in crystal structure of compound **11** and vicinal coupling constants of corresponding hydrogen atoms in solution (in parentheses)

Five-membered ring		Six-membered ring		Seven-membered ring	
O1–C1–O2–C5	–46	C1–C2–C3–C4	39	C2–N1–C8–C7	–52
C1–O2–C5–C6	44	C2–C3–C4–C5	–41	N1–C8–C7–O4	78
O2–C5–C6–O1	–28	C3–C4–C5–O2	62	C8–C7–O4–C4	–61
C5–C6–O1–C1	1	C4–C5–O2–C1	–76	C7–O4–C4–C3	–12
C6–O1–C1–O2	27	C5–O2–C1–C2	74	O4–C4–C3–C2	81
		O2–C1–C2–C3	–58	C4–C3–C2–N1	–84
				C3–C2–N1–C8	53
H5–C5–C6–H6en	95 (0.8)	H1–C1–C2–H2	62 (2.3)	H3–C3–C4–H4	80 (1.5)
H5–C5–C6–H6ex	–26 (5.2)	H2–C2–C3–H3	–82 (1.7)	H4–C4–C5–H5	–59 (2.1)
		H3–C3–C4–H4	80 (1.5)	H7A–C7–C8–H8A	78 (1.2)
		H4–C4–C5–H5	–59 (2.1)	H7A–C7–C8–H8B	–38 (6.4)
				H7B–C7–C8–H8A	–166 (8.9)
				H7B–C7–C8–H8B	78 (1.2)

EXPERIMENTAL

The melting points were determined with a Boëtius micro melting-point apparatus and are uncorrected. Optical rotations were measured with a polarimeter Autopol III (Rudolph Research, Flanders (NJ)) at 23–25 °C, $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. NMR spectra were measured on a Varian UNITY-500 and/or a Bruker Avance-500 apparatus (^{1}H at 500 MHz, ^{13}C at 125.7 MHz). Chemical shifts (in ppm, δ-scale) were referenced to tetramethylsilane (in ^{1}H NMR spectra) and/or to the signal of solvent (δ($CDCl_3$) 77.0 in ^{13}C NMR spectra); coupling constants (*J*) are given in Hz. For ^{1}H and ^{13}C NMR data see Tables I–III. ESI MS were measured on an Esquire 3000 apparatus (Bruker). Thin-layer chromatography (TLC) was performed on DC Alufolien plates (Merck, type 5554) coated with Kieselgel 60 F_{254}; detection was performed with 3% ethanolic solution of anisaldehyde acidified with concentrated sulfuric acid, and heating. For preparative column chromatography, silica gel Kieselgel 60 (Merck) was used. Solutions were dried with anhydrous calcium chloride and were evaporated under reduced pressure at temperatures below 40 °C. Analytical samples were dried over phosphorus pentoxide at room temperature under reduced pressure.

1,6:2,3-Dianhydro-4-*O*-(2-hydroxyethyl)-β-D-mannopyranose (**2**)

Modified procedure[4] for preparation of **2**: A mixture of 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose (**1**; 10.0 g, 33.6 mmol), dry 1,2-dimethoxyethane (25 ml), ethylene glycol (25 ml) and $BF_3{\cdot}Et_2O$ (1.0 ml) was heated to 100 °C under argon atmosphere. TLC (toluene–ethyl acetate, 4:1) showed complete conversion after 1 h. 1,2-Dimethoxyethane was evaporated and water (25 ml) was added. The mixture was set aside at 0 °C overnight. Precipitated crystals were filtered off, washed with water and dried; yield 11.0 g (91%) of crude 1,6-anhydro-4-*O*-(2-hydroxyethyl)-2-*O*-tosyl-β-D-glucopyranose[4]. This was dissolved in a mixture of chloroform–methanol (1:1, 50 ml) and cooled to 0 °C. A solution of NaOMe in MeOH (1 mol l^{-1}, 35 ml, 35 mmol) was added, resulting mixture was stirred for 1 h and then neutralized with acetic acid. Solvents were evaporated to dryness and the residue was extracted with dichloromethane (50 ml). Salts were filtered off and washed with dichloromethane. The dichloromethane solution was evaporated and the residue was crystallized from ethanol–ether–light petroleum. Yield 4.6 g (73% overall) of **2**, m.p. 92–95 °C; lit.[4] gives m.p. 93–95 °C. ^{1}H NMR ($CDCl_3$): 5.72 d, 1 H, *J*(1,2) = 3.1 (H-1); 4.54 ddd, 1 H, *J*(5,4) = 1.1, *J*(5,6en) = 2.1, *J*(5,6ex) = 6.6 (H-5); 3.80 m, 4 H (O-CH_2-CH_2-O); 3.75 dd, 1 H, *J*(6ex,6en) = 7.3, *J*(6ex,5) = 6.6 (H-6ex); 3.72 dd, 1 H, *J*(6en,6ex) = 7.3, *J*(6en,5) = 2.1 (H-6en); 3.65 dd, 1 H, *J*(4,3) = 0.7, *J*(4,5) = 1.1 (H-4); 3.47 dd, 1 H, *J*(2,1) = 3.1, *J*(2,3) = 3.8 (H-2); 3.20 dd, 1 H, *J*(3,2) = 3.8, *J*(3,4) = 0.7 (H-3).

1,6:2,3-Dianhydro-4-deoxy-4-(3-hydroxypropyl)-β-D-mannopyranose (**4**)

A mixture of $BF_3{\cdot}Et_2O$ (10 ml) and bis(2-methoxyethyl) ether (10 ml) was added dropwise under nitrogen to a stirred suspension of sodium borohydride (4 g) in bis(2-methoxyethyl) ether (20 ml), and the resulting stream of diborane was passed through a stirred solution of **3**[7] (6.3 g, 18 mmol) in dry THF (20 ml) at room temperature. After 1 h, the reaction was quenched cautiously with aqueous 3 M NaOH (20 ml) and subsequently 30% H_2O_2 (20 ml) was added. The mixture was stirred at room temperature overnight. The water layer was saturated with Na_2SO_4 and the organic phase was separated. The aqueous layer was extracted twice more with $CHCl_3$ (2 × 30 ml). Combined organic phases were washed with a saturated solution of Na_2SO_3 (30 ml), dried and evaporated giving 3.0 g (87%) of syrupy compound **4**; $[\alpha]_D$ –19 (*c* 0.75, $CHCl_3$). ESI MS, *m/z* (%): for $C_9H_{14}O_4$ calculated 186.1; found 209.0 (100) $[M + Na]^+$. ^{1}H NMR ($CDCl_3$ + C_6D_6, 3:1): 5.60 dm, 1 H, *J*(1,2) = 3.1, *J*(1,4) = 1.0, *J*(1,6en) = 0.5, *J*(1,6ex) = 0.5 (H-1); 4.12 m, 1 H, *J*(5,3) = 0.8, *J*(5,4) = 1.2, *J*(5,6en) = 2.2, *J*(5,6ex) = 6.0 (H-5); 3.68 ddd, 1 H, *J*(6en,6ex) = 6.8, *J*(6en,5) = 2.2, *J*(6en,1) = 0.5 (H-6en); 3.66 ddd, 1 H, *J*(6ex,6en) = 6.8, *J*(6ex,5) = 6.0, *J*(6ex,1) = 0.5 (H-6ex); 3.58 t, 2 H, ^3J = 6.2 (C**H**$_2$-OH); 3.25 ddd, 1 H, *J*(2,1) = 3.1, *J*(2,3) = 4.0, *J*(2,4) = 0.7 (H-2); 2.85 ddd, 1 H, *J*(3,2) = 4.0, *J*(3,4) = 0.3, *J*(3,5) = 0.8 (H-3); 1.83 m, 1 H, *J*(4,1) = 1.0, *J*(4,2) = 0.7, *J*(4,3) = 0.3, *J*(4,5) = 1.2, *J*(4,CH_2) = 7.0 (H-4); 1.50–1.70 m, 4 H (CH_2-CH_2). ^{13}C NMR ($CDCl_3$): 98.02 (C-1); 71.63 (C-5); 68.62 (C-6); 62.59 (CH_2OH); 53.86 (C-2); 50.71 (C-3); 39.36 (C-4); 30.19 and 27.18 (CH_2-CH_2).

General Procedure for Preparation of Compounds **5** and **6**

A mixture of 1,6:2,3-dianhydro-4-*O*-(2-hydroxyethyl)-β-D-mannopyranose (**2**; 1.9 g, 10 mmol) or 1,6:2,3-dianhydro-4-deoxy-4-(3-hydroxypropyl)-β-D-mannopyranose (**4**; 1.9 g, 10 mmol), sodium azide (3.3 g, 50 mmol), ammonium chloride (4.0 g, 74 mmol), 2-methoxyethanol (50 ml) and water (15 ml) was heated to 115 °C for 28 h. The reaction course was monitored

by TLC in chloroform–methanol (10:1). After cooling, the reaction mixture was evaporated to dryness and the solid residue was extracted with chloroform (20 ml). The insoluble salts were filtered off and washed with chloroform (10 ml). Combined chloroform solutions were evaporated and the residue was chromatographed on a silica gel column (80 g) in chloroform–methanol (10:1) to give the syrupy product.

1,6-Anhydro-2-azido-2-deoxy-4-O-(2-hydroxyethyl)-β-D-*glucopyranose* (**5**). Yield 1.7 g (73%), $[\alpha]_D$ –10 (*c* 0.60, $CHCl_3$). ESI MS, *m/z* (%): for $C_8H_{13}N_3O_5$ calculated 231.1; found 254.0 (100) $[M + Na]^+$, 318.3 (23).

1,6-Anhydro-2-azido-2,4-dideoxy-4-(3-hydroxypropyl)-β-D-*glucopyranose* (**6**). Yield 1.6 g (68%), $[\alpha]_D$ –18 (*c* 0.42, $CHCl_3$). ESI MS, *m/z* (%): for $C_9H_{15}N_3O_4$ calculated 229.1; found 252.2 (100) $[M + Na]^+$.

General Procedure for Preparation of Compounds **7** and **8**

A solution of compound **5** or **6** (1.5 g, 6.5 mmol) in dry pyridine (10 ml) was cooled to 0 °C and tosyl chloride (1.8 g, 9.4 mmol) in pyridine (10 ml) was added. The mixture was stirred at room temperature for 2 h and then was poured into ice–water (50 ml). The solution was extracted with chloroform (3 × 20 ml). Combined organic phases were dried and evaporated. The syrupy residue was purified on a silica gel column (100 g) with toluene–acetone (10:1).

1,6-Anhydro-2-azido-2-deoxy-4-O-[2-(tosyloxy)ethyl]-β-D-*glucopyranose* (**7**). Yield 2.0 g (80%) of slowly crystallizing syrup, m.p. 50–52 °C (ether–light petroleum), $[\alpha]_D$ –9 (*c* 0.66, $CHCl_3$). For $C_{15}H_{19}N_3O_7S$ (385.4) calculated: 46.75% C, 4.97% H, 10.90% N, 8.32% S; found: 46.86% C, 4.90% H, 10.64% N, 8.25% S.

1,6-Anhydro-2-azido-2,4-dideoxy-4-[3-(tosyloxy)propyl]-β-D-*glucopyranose* (**8**). Yield 2.0 g (80%) of a syrup which contained a small amount of ditosylate as indicated by NMR spectrum, $[\alpha]_D$ –16 (*c* 0.34, $CHCl_3$). ESI MS, *m/z* (%): for $C_{16}H_{21}N_3O_6S$ calculated 383.1; found 301.2 (74), 406.1 (100) $[M + Na]^+$. This product was used without further purification.

General Procedure for Preparation of Compounds **9** and **10**

Azido compound **7** or **8** (1.8 g, 4.7 mmol) was hydrogenated in a mixture of ethanol (45 ml) and acetic acid (1 ml) over palladium on activated carbon (200 mg, 5%) for 24 h. The catalyst was filtered off and solvents were evaporated. The crude product was purified on a silica gel column (30 g). Nonpolar impurities were eluted with ethyl acetate and the product with a mixture of ethyl acetate–methanol–20% ammonia in methanol (30:2:1). Fractions containing the corresponding amine were evaporated, several times codistilled with toluene (20 ml) and tosylated in the mixture of pyridine (10 ml) and tosyl chloride (0.8 g, 4.6 mmol) at 0 °C. After 1 h the reaction mixture was poured into ice–water (50 ml) and extracted with chloroform (3 × 20 ml). Combined chloroform extracts were dried, evaporated and the residue was chromatographed on a silica gel column (40 g) in toluene–acetone (10:1).

1,6-Anhydro-2-deoxy-2-(tosylamino)-4-O-[2-(tosyloxy)ethyl]-β-D-*glucopyranose* (**9**). Yield 1.2 g (50%), m.p. 139–140 °C (ethanol), $[\alpha]_D$ –32 (*c* 0.63, $CHCl_3$). For $C_{22}H_{27}NO_9S_2$ (513.6) calculated: 51.45% C, 5.30% H, 2.73% N, 12.49% S; found: 51.13% C, 5.23% H, 2.56% N, 12.24% S.

1,6-Anhydro-2,4-dideoxy-2-(tosylamino)-4-[3-(tosyloxy)propyl]-β-D-*glucopyranose* (**10**). Yield 1.0 (42%) of syrup, $[\alpha]_D$ –44 (*c* 0.67, $CHCl_3$). ESI MS, *m/z* (%): for $C_{23}H_{29}NO_8S_2$ calculated 511.1; found 534.1 (100) $[M + Na]^+$, 550.1 (95) $[M + K]^+$.

General Procedure for Preparation of Compounds **11** and **12**

A mixture of ditosyl derivative **9** or **10** (900 mg, 1.8 mmol) and K_2CO_3 (750 mg, 5.4 mmol) in DMF (22 ml) was heated at 60 °C for 3 h. DMF was evaporated at 40 °C and the residue was partitioned between chloroform (10 ml) and water (10 ml). The water phase was extracted with chloroform again (2 × 5 ml). Combined chloroform extracts were dried and evaporated. The crude product was crystallized from ethanol–ether–light petroleum (compound **11**) or toluene (compound **12**). The mother liquor was evaporated and the residue was chromatographed on a silica gel column in toluene–acetone (10:1).

1,6-Anhydro-2-deoxy-2-N,4-O-(ethane-1,2-diyl)-2-(tosylamino)-β-*D-glucopyranose* (**11**). Yield 490 mg (82%), m.p. 159–161 °C (ethanol–ether–light petroleum), $[\alpha]_D$ +34 (*c* 0.70, $CHCl_3$). For $C_{15}H_{19}NO_6S$ (341.4) calculated: 52.77% C, 5.61% H, 4.10% N, 9.39% S; found: 52.52% C, 5.65% H, 4.10% N, 9.06% S.

1,6-Anhydro-2,4-dideoxy-2-N,4-(propane-1,3-diyl)-2-(tosylamino)-β-*D-glucopyranose* (**12**). Yield 510 mg (85%), m.p. 108–109 °C (toluene), $[\alpha]_D$ +29 (*c* 0.63, $CHCl_3$). For $C_{16}H_{21}NO_5S$ (339.4) calculated: 56.62% C, 6.24% H, 4.13% N, 9.45% S; found: 56.71% C, 6.33% H, 3.90% N, 9.43% S.

General Procedure for Preparation of Compounds **13** and **14**

A mixture of sodium (230 mg, 10 mmol) and naphthalene (650 mg, 5.0 mmol) in dimethoxyethane (10 ml) was stirred under argon atmosphere at room temperature for 2 h. Thus prepared solution of sodium naphthalenide was added dropwise at –10 °C to a stirred solution of tosylamide **11** or **12** (400 mg, 1.2 mmol) in 1,2-dimethoxyethane (4 ml) until it became dark. After 10 min, the reaction was quenched with water (0.1 ml) and evaporated to dryness. Naphthalene was removed by dissolution in light petroleum (10 ml) and the product was extracted from the residue with hot ethanol (10 ml). Salts were filtered off and the filtrate was evaporated. The residue was purified on a silica gel column (10 g) in ethyl acetate–methanol–20% ammonia in methanol (15:3:1).

2-Amino-1,6-anhydro-2-deoxy-2-N,4-O-(ethane-1,2-diyl)-β-*D-glucopyranose* (**13**). Yield 160 mg (73%), m.p. 210–213 °C (ethanol–ether, decomp.), $[\alpha]_D$ –72 (*c* 0.50, MeOH). For $C_8H_{13}NO_4$ (187.2) calculated: 51.33% C, 7.00% H, 7.48% N; found: 51.09% C, 7.03% H, 7.56% N.

2-Amino-1,6-anhydro-2,4-dideoxy-2-N,4-(propane-1,3-diyl)-β-*D-glucopyranose* (**14**). Yield 150 mg (69%), m.p. 196–197 °C (ethanol), $[\alpha]_D$ –60 (*c* 0.66, MeOH). For $C_9H_{15}NO_3$ (185.2) calculated: 58.36% C, 8.16% H, 7.56% N; found: 58.11% C, 8.15% H, 7.29% N.

Attempted Acid Hydrolysis of the 1,6-Anhydride Bond in Compound **13**

Compound **13** (15 mg) was heated to 100 °C in aqueous hydrochloric acid (6 mol l^{-1}, 0.3 ml) in a sealed tube for 3 h. ^{1}H NMR spectrum as well as TLC (butanol–pyridine–water, 3:2:1) of the evaporated reaction mixture showed only the presence of the starting compound.

Attempted Acetolysis of the 1,6-Anhydride Bond in Compound **13**

2-Acetamido-1,6-anhydro-2-deoxy-2-N,4-O-(ethane-1,2-diyl)-β-*D-glucopyranose* (**15**). Compound **13** (50 mg, 0.27 mmol) was dissolved in acetic anhydride (0.5 ml) while cooling to 0 °C, and trifluoroacetic acid (50 µl, 0.7 mmol) was added. The mixture was kept at room temperature under stirring for 2 days. Solvents were evaporated at 30 °C. The syrupy material thus ob-

tained was deacetylated with 0.1 M methanolic sodium methanolate (2 ml) at room temperature for 1 h. TLC (chloroform–methanol, 5:1) showed the presence of single product. The mixture was then neutralized with Dowex 50 (H^+), the resin was filtered off, washed with methanol and the combined filtrates were evaporated. The residue was chromatographed on a silica gel column (2 g). Compound **15** was eluted with ethyl acetate. Addition of methanol to the eluent did not afford any more polar compounds. Yield 45 mg (74%) of acetate **15**, m.p. 223–225 °C (ethanol–ether). ESI MS, *m/z* (%): for $C_{10}H_{15}NO_5$ calculated 229.1; found 230.0 (13) $[M + H]^+$, 252.0 (100) $[M + Na]^+$, 276.2 (16), 481.1 (100) $[2 M + Na]^+$.

Crystal Structure Analysis of Compound **11**

$C_{15}H_{19}NO_6S$, M = 341.37, orthorhombic, $P2_12_12_1$ (No. 19), a = 6.2580(2) Å, b = 11.9860(3) Å, c = 20.1180(5) Å, V = 1509.02(7) Å^3, Z = 4, D_x = 1.503 Mg m^{-3}. A colorless crystal of dimensions 0.5 × 0.18 × 0.17 mm was mounted on glass capillary with epoxy glue and measured with a Nonius KappaCCD diffractometer using monochromatized MoKα radiation (λ = 0.71073 Å) at 150(2) K. Absorption was neglected (μ = 0.247 mm^{-1}); a total of 10 002 measured reflections in the range h = –8 to 8, k = –15 to 15, l = –25 to 25 (θ_{max}= 27.5°), from which 3456 were unique (R_{int} = 0.030) and 3201 observed according to the $I > 2\sigma(I)$ criterion. Cell parameters from 1968 reflections (θ = 1–27.5°). The structure was solved by direct methods (SIR92, Altomare, 1994)[11] and refined by full-matrix least squares based on F^2 (SHELXL97)[12]. The hydrogen atoms on carbons were found on difference Fourier map, recalculated into idealized positions and fixed during refinement (riding model) with assigned temperature factors $H_{iso}(H)$ = 1.2 U_{eq} (pivot atom) or $H_{iso}(H)$ = 1.5 U_{eq} (pivot atom) for methyl group. The hydrogen atom of hydroxy group was found on difference Fourier map and refined isotropically. The refinement converged (Δ/σ_{max} = 0.000) to R = 0.034 for observed reflections and wR = 0.082, GOF = 1.074 for 213 parameters and all 3456 reflections. The final difference map displayed no peaks of chemical significance ($\Delta\rho_{max}$ = 0.191, $\Delta\rho_{min}$ = –0.347 e Å^{-3}). The absolute structure was assigned by reference to the known chiral centre (Flack parameter = –0.04(7)). CCDC 256863 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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REFERENCES

1. Sharma M., Korytnyk W.: *Carbohydr. Res.* **1980**, *79*, 39.
2. Rosenbohm C., Berghe D. V., Vlietinck A., Wengel J.: *Tetrahedron* **2001**, *57*, 6277.
3. a) Trtek T., Černý M., Trnka T., Buděšínský M., Císařová I.: *Collect. Czech. Chem. Commun.* **2003**, *68*, 1295; b) Trtek T., Černý M., Trnka T., Buděšínský M., Císařová I.: *Collect. Czech. Chem. Commun.* **2004**, *69*, 1818.

4. Jindřich J., Černý M., Trnka T., Buděšínský M.: *Collect. Czech. Chem. Commun.* **1991**, *56*, 2950.
5. Černý M., Trnka T., Redlich H.: *Carbohydr. Res.* **1988**, *174*, 349.
6. Černý M., Gut V., Pacák J.: *Collect. Czech. Chem. Commun.* **1961**, *26*, 2542.
7. a) Kelly A. G., Roberts J. S.: *J. Chem. Soc., Chem. Commun.* **1980**, 228; b) Kalè V. N., Clive D. L. J.: *J. Org. Chem.* **1984**, *49*, 1554.
8. Richman J. E., Atkins T. J.: *J. Am. Chem. Soc.* **1974**, *96*, 2268.
9. a) Angyal S. J., Dawes K.: *Aust. J. Chem.* **1968**, *21*, 2747; b) Černý M., Staněk J., Jr.: *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23.
10. Grindley T. B., Cude A., Kralovic J., Thangarasa R. in: *Levoglucosenone and Levoglucosans, Frontiers in Biomedicine and Biotechnology* (Z. J. Witzak, Ed.), Vol. 2, p. 147. ATL Press, Mount Prospect (IL) 1994.
11. Altomare A., Cascarano G., Giacovazzo C., Guagliardi A., Burla M. C., Polidori G., Camalli M.: *J. Appl. Crystallogr.* **1994**, *27*, 435.
12. Sheldrick G. M.: *SHELXL97, Program for Structure Determination*. University of Göttingen, Göttingen 1997.
13. Spek A. L.: *PLATON, A Multipurpose Crystallographic Tool*. Utrecht University, Utrecht 2001.