SYNTHESIS OF 1,6-ANHYDRO-β-D-HEXOPYRANOSES FUSED TO THE PIPERIDINE RING

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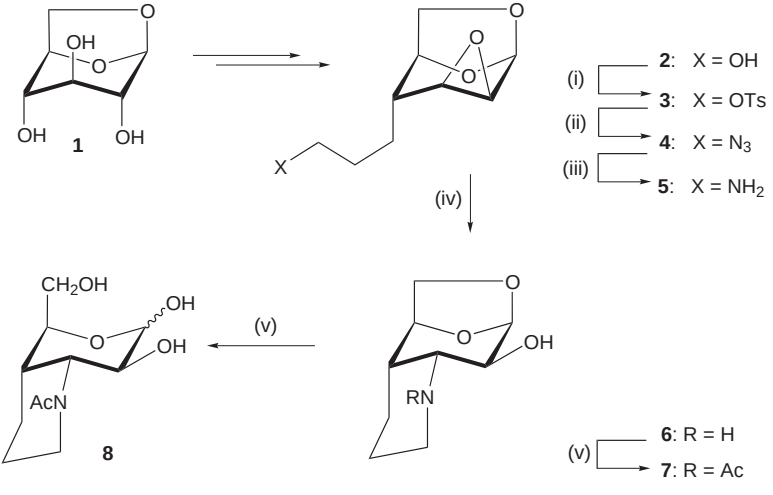
Two piperidine derivatives (**6** and **17**) containing fused 1,6-anhydro-β-D-hexopyranose moiety were prepared from 1,6-anhydro-β-D-glucopyranose (**1**). The first synthetic route led via the known 1,6:2,3-dianhydro-4-deoxy-4-(3-hydroxypropyl)-β-D-mannopyranose (**2**) obtained in four steps from **1**. Its hydroxyl group was converted into amino group via tosylate and azide. The corresponding amino epoxide **5** readily rearranged into 3-amino-1,6-anhydro-3,4-dideoxy-3-*N*,4-*C*-(propane-1,3-diyl)-β-D-altropyranose (**6**). The second route used the known 1,6-anhydro-2,4-di-*O*-tosyl-β-D-*ribo*-hexopyranos-3-ulose (**9**) as an intermediate. Addition of allylmagnesium chloride to ketose **9** afforded 3-*C*-allyl-1,6-anhydro-2,4-di-*O*-tosyl-β-D-allopyranose (**10**). Hydroboration of its double bond followed by transformation of the resulting primary hydroxyl group into tosylamido group gave tritosyl derivative **15**. Intramolecular replacement of the tosyloxy group in position 4 by tosylamido group gave tosylated piperidine derivative **16**. Detosylation of **16** afforded the target 4-amino-1,6-anhydro-3,4-dideoxy-3-*C*,4-*N*-(propane-1,3-diyl)-β-D-gulopyranose (**17**).

Keywords: Carbohydrates; Heterocycles; 1,6-Anhydrosugars; Piperidines; Oxiranes; Alkaloids; Cyclizations; X-ray diffraction; NMR spectroscopy; Conformation analysis.

Piperidine-based compounds[1] still attract attention because of their biological significance. The piperidine ring is one of the most common heterocyclic motives in the structure of alkaloids and synthetic pharmaceuticals. Piperidine alkaloids are based on substituted piperidine ring, often bearing alkyl chain (functionalized or not), hydroxyl group, or another ring. Sugar-derived alkaloids, possessing glycosidase-inhibiting activities, usually include in their skeleton a highly functionalised piperidine ring. Analogous derivatives with morpholine or 1,4-oxazepane ring we described recently[2,3].

In the present paper, we report on the synthesis of two nitrogen carbohydrate derivatives based on piperidine fused to the pyran ring of 1,6-anhydro-β-D-hexopyranose in positions 3 and 4. For their preparation were used two synthetic routes, both starting from 1,6-anhydro-β-D-glucopyranose (**1**) (levoglucosan)[4].

The first route uses the known 1,6:2,3-dianhydro-4-deoxy-4-(3-hydroxypropyl)-β-D-mannopyranose[5] (**2**) which was prepared from **1** via 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose[6] and 4-allyl-1,6-anhydro-4-deoxy-2-*O*-tosyl-β-D-glucopyranose[7] in four steps. The hydroxyl group of **2** was tosylated and the resulting tosyloxy group in **3** was replaced by azido group in the reaction of **3** with sodium azide in 83% yield. Catalytic hydrogenation of the azido derivative **4** gave the corresponding amine **5** which readily rearranged into the piperidine derivative **6** in refluxing methanol. Thus, the conversion **4** → **5** → **6** was performed to advantage in one-step procedure giving 3-amino-1,6-anhydro-3,4-dideoxy-3-*N*,4-*C*-(propane-1,3-diyl)-β-D-altropyranose (**6**) in 64% yield. Acetolysis of **6** followed by Zemplén deacetylation afforded a mixture of the corresponding reducing sugar **8** containing two major isomers of the α-anomer and two minor isomers of the β-anomer (see NMR discussion), and *N*-acetylated starting material **7** in the 1:2 ratio (Scheme 1).



SCHEME 1

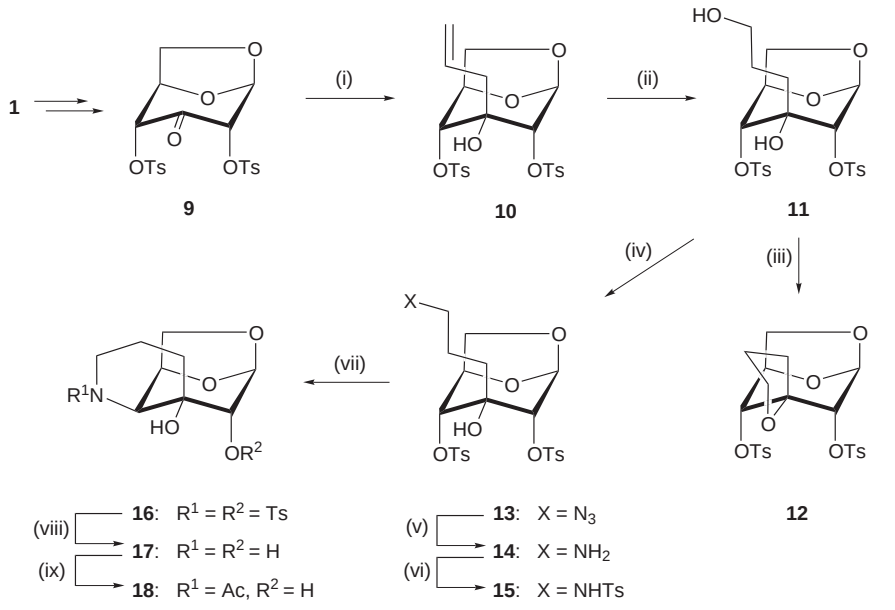
(i) TsCl, py, r.t. (84%); (ii) NaN_3, DMF, 60 °C (83%); (iii) H_2, Pd/C, MeOH, r.t.; (iv) MeOH, 65 °C (64%); (v) TFA, Ac_2O, r.t., then MeONa, MeOH, r.t. (70%)

The second synthetic route (Scheme 2) leading to the piperidine derivative **17** uses as a starting compound 1,6-anhydro-2,4-di-*O*-tosyl-β-D-*ribo*-hexopyranos-3-ulose (**9**) easily accessible by oxidation of 1,6-anhydro-2,4-di-*O*-tosyl-β-D-glucopyranose with chromium trioxide in acetic acid[8]. As expected, stereoselective addition of allylmagnesium chloride to the carbonyl group of ketose **9** gave 3-*C*-allyl-1,6-anhydro-2,4-di-*O*-tosyl-β-D-allopyranose (**10**) (64%) in agreement with analogous reactions[9] of **9** with methylmagnesium iodide or phenylmagnesium chloride (for comparison, see ref.[8]). Hydroboration of the double bond in **10** afforded the diol **11** (in 77% yield). In an effort to prepare compound **14** via azide **13**, we intended to use a similar reaction sequence including reactions **2** → **3** → **4** → **5** as shown in Scheme 1. Surprisingly, the only product of the tosylation step performed with tosyl chloride in pyridine at room temperature was the oxolane spiro compound **12**. This outcome may be accounted for by expected preferential tosylation of the primary hydroxyl group followed by rapid intramolecular replacement of the leaving tosyloxy group by suitably oriented tertiary hydroxyl group at C-3. (For analogous reactions, see the formation of spirocyclic oxolane derivatives of substituted cyclohexanes[10].) A significant role in this reaction might play a favorable entropic factor generally forcing intramolecular cyclizations that result in the formation of relatively stable five-membered rings. In connection with the smooth formation of the oxolane ring mentioned above, it is worth noting that the tertiary hydroxyl group of **11** resists acetylation with acetic anhydride in pyridine solution under usual reaction conditions (for relevant literature, see ref.[9]).

In order to obtain azide **13**, compound **11** was treated with hydrogen azide under Mitsunobu reaction conditions[11]. The obtained azido derivative **13** was reduced to give the corresponding amine **14** which was converted to the tosyl derivative **15**. Intramolecular substitution of the tosyloxy group at C-4 by the tosylamido group in **15** proceeded with high regioselectivity giving the piperidine derivative **16** in 69% yield. Such a reaction course is in agreement with the regioselective reaction of 1,6-anhydro-2,4-di-*O*-tosyl-β-D-glucopyranose in alkaline solution yielding 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose (for a detailed discussion, see ref.[12]). Detosylation performed with sodium amalgam in boiling methanol afforded the target 4-amino-1,6-anhydro-4-deoxy-3-*C*,4-*N*-(propane-1,3-diyl)-β-D-gulopyranose (**17**) in 65% yield.

An attempt at acetolysis of **17** under the conditions used for acetolysis of compound **6** failed, and *N*-acetylated starting compound **18** was isolated as

a sole product in 71% yield. On the other hand, preliminary experiments on hydrolysis of **17** using 6 M hydrochloric acid at 100 °C were successful.



SCHEME 2

(i) H_2C=CH–CH_2MgCl, THF, 0 °C (64%); (ii) BH_3, THF, r.t., then H_2O_2, NaOH (77%); (iii) TsCl, py, r.t. (79%); (iv) HN_3, Ph_3P, iPrOOCN=NCOOiPr, THF, r.t. (95%); (v) H_2, Pd/C, EtOH, r.t. (73%); (vi) TsCl, Et_3N, CH_2Cl_2, r.t. (71%); (vii) K_2CO_3, DMF, 110 °C (69%); (viii) Na-Hg, Na_2HPO_4, MeOH, 65 °C (65%); (ix) TFA, Ac_2O, r.t., then MeONa, MeOH, r.t. (71%)

NMR DISCUSSION

The structure of compounds **3**–**8** and **10**–**18** was determined by ^{1}H and ^{13}C NMR spectroscopy. Structural assignment of protons and carbon atoms was achieved using correlated homonuclear 2D-COSY, 2D-ROESY and heteronuclear ^{1}H,^{13}C-2D-HSQC spectra; NMR parameters are summarized in Tables I–III. The presence of 2,3-epoxy group in compounds **3**–**5** is manifested 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 presence of substituents $-(CH_2)_3X$ at C-4 is well documented in ^{1}H and ^{13}C NMR spectra. The fusion of the piperidine ring at C-3 and C-4 in compounds **6**–**8** is proved by the observed upfield shifts of these carbon atoms (C-3 to δ ≈ 50–56; C-4 to δ ≈ 35–40). The partial double-bond character of the tertiary amide bond in *N*-acetyl derivative **7** leads to the existence of two isomers observed in the NMR

TABLE I
^{1}H NMR chemical shifts of compounds **3–8** and **10–18**

Compound	Solvent	H-1	H-2	H-3	H-4	H-5	H-6en	H-6ex	Other protons
3	$CDCl_3$	5.65 dq	3.34 ddd	2.86 ddd	1.89 bt	4.15 m	3.71 m	3.71 m	O-$(CH_2)_3$: 4.08 t (2 H), 1.84 m (2 H), 1.64 m (2 H); OTs: 2.46 bs (3 H), 7.80 m (2 H), 7.36 m (2 H)
4	$CDCl_3$	5.68 dq	3.38 ddd	2.94 ddd	1.97 m	4.23 m	3.76 m	3.76 m	N-$(CH_2)_3$: 3.36 m (2 H), 1.78 m (2 H), 1.69 m (2 H)
5	$CDCl_3$	5.67 dq	3.37 ddd	2.95 ddd	1.95 m	4.25 m	3.74 m	3.74 m	N-$(CH_2)_3$: 2.76 m (2 H), 1.63 m (4 H)
6	$CDCl_3$	5.40 d	3.82 dd	2.98 dd	1.86 m	4.27 m	3.83 m	3.83 m	N-$(CH_2)_3$: 2.80 dt (1 H), 2.68 dt (1 H), 1.69 m (3 H), 1.48 m (1 H)
(*Z*)-7 74%	$CDCl_3$	5.41 d	3.77 dd	4.95 bdd	1.82 m	4.32 bd	3.97 dd	3.87 dd	N-$(CH_2)_3$: 3.75 m (1 H), 3.16 dt (1 H), 1.81 m (1 H), 1.78 m (1 H), 1.73 m (1 H), 1.49 m (1 H); NAc: 2.17 s
(*E*)-7 26%	$CDCl_3$	5.46 d	3.93 dd	4.04 bdd	1.88 m	4.35 dt	3.94 dd	3.91 dd	N-$(CH_2)_3$: 4.60 m (1 H), 2.56 dt (1 H), 1.70–1.80 m (4 H); NAc: 2.24 s
α**(*Z*)-8**[a] 49%	D_2O	4.97 d	3.92 dd	4.83 bdd	1.89 m	3.80 ddd	3.99 dd	3.74 dd	N-$(CH_2)_3$: 3.85 m, 3.27 m, 1.88 m (2 H), 1.70 m, 1.58 m; NAc: 2.19 s
α**(*E*)-8**[a] 38%	D_2O	5.01 d	3.98 dd	4.10 dd	2.08 m	3.78 ddd	3.98 dd	3.74 dd	N-$(CH_2)_3$: 4.41 m, 2.78 m, 1.83 m, 1.70 m, 1.85 m, 1.47 m; NAc: 2.20 s
10	$CDCl_3$	5.43 d	4.19 d	–	4.40 bd	4.70 bdd	3.77 dd	3.68 dd	2 × OTs: 2.46 bs (3 H), 2.47 bs (3 H), 7.79 m (2 H), 7.78 m (2 H), 7.36 m (2 H), 7.34 m (2 H); OH: 2.72 t; CH_2–CH=CH_2: 2.36 m (1 H), 2.33 m (1 H), 5.46 dddd (1 H), 5.03 dq (1 H), 5.06 ddt (1 H)
11	$CDCl_3$	5.39 d	4.23 dt	–	4.44 dt	4.67 m	3.83 dd	3.66 ddd	2 × OTs: 2.46 bs (3 H), 2.45 bs (3 H), 7.80 m (2 H), 7.79 m (2 H), 7.36 m (2 H), 7.35 m (2 H); OH: 1.35 t; O-$(CH_2)_3$: 3.52 m (2 H), 1.75 m, 1.69 m, 1.46 m (2 H)

TABLE I
(*Continued*)

Compound	Solvent	H-1	H-2	H-3	H-4	H-5	H-6en	H-6ex	Other protons
12	$CDCl_3$	5.47 d	4.14 dd	–	4.37 dt	4.72 m	3.83 dd	3.70 ddd	2 × OTs: 2.45 bs (3 H), 2.44 bs (3 H), 7.77 m (2 H), 7.75 m (2 H), 7.30 m (2 H), 7.29 m (2 H); O-$(CH_2)_3$: 3.30 m, 3.19 m, 2.22 m, 1.79 m, 1.78 m, 1.71 m
13	$CDCl_3$	5.40 d	4.17 d	–	4.35 d	4.68 bdd	3.80 dd	3.68 dd	2 × OTs: 2.47 bs (3 H), 2.46 bs (3 H), 7.80 m (2 H), 7.79 m (2 H), 7.37 m (2 H), 7.35 m (2 H); N-$(CH_2)_3$: 3.19 m, 3.13 m, 1.65 m (2 H), 1.43 m (2 H)
14	$CDCl_3$	5.38 d	4.23 d	–	4.42 bd	4.66 m	3.80 dd	3.65 dd	2 × OTs: 2.46 bs (3 H), 2.45 bs (3 H), 7.81 m (2 H), 7.79 m (2 H), 7.34 m (2 H), 7.33 m (2 H); N-$(CH_2)_3$: 2.58 m (2 H), 1.70 m, 1.64 m, 1.36 m (2 H)
15	$CDCl_3$	5.34 d	4.15 d	–	4.34 d	4.61 dd	3.78 dd	3.63 dd	2 × OTs + NTs: 2.47 bs (3 H), 2.46 bs (3 H), 2.44 bs (3 H), 7.79 m (2 H), 7.77 m (2 H), 7.71 m (2 H), 7.36 m (2 H), 7.34 m (2 H), 7.32 m (2 H); N-$(CH_2)_3$: 2.81 m (2 H), 1.65 m, 1.58 m, 1.43 m (2 H); NH: 4.47 t
16	$CDCl_3$	5.29 d	4.24 d	–	4.07 bd	4.60 t	4.13 d	3.74 ddd	OTs + NTs: 2.46 bs (3 H), 2.42 bs (3 H), 7.82 m (2 H), 7.76 m (2 H), 7.37 m (2 H), 7.28 m (2 H); N-$(CH_2)_3$: 3.75 m, 3.20 ddd, 1.68 m, 1.41 m, 1.88 m, 1.59 m
17	$CDCl_3$	5.49 d	3.36 d	–	3.06 dm	4.43 t	4.28 d	3.75 ddd	N-$(CH_2)_3$: 2.85 dd (2 H), 1.84 m, 1.51 m, 2.00 ddd, 1.61 m
(*Z*)-18 80%	$CDCl_3$	5.54 d	3.42 d	–	4.80 bd	4.50 t	4.08 d	3.73 ddd	N-$(CH_2)_3$: 3.82 m, 3.27 dt, 2.08 m, 1.64 dm, 1.94 dt, 1.70 dm; NAc: 2.16 s
(*E*)-18 20%	$CDCl_3$	5.57 d	3.51 d	–	4.01 bd	4.33 t	4.23 d	3.78 ddd	N-$(CH_2)_3$: 4.70 m, 2.73 dt, 1.87 m, 1.62 dm, 2.00 dt, 1.70 m; NAc: 2.21 s

[a] The presence of two additional isomers – β-(*Z*) and β-(*E*) – was detected in a low amount (ca. 7 and 6%) not allowing their complete characterization with NMR data.

TABLE II
^{1}H NMR coupling constants of compounds **3**–**8** and **10**–**18**

Compound	Solvent	1,2	2,3	3,4	4,5	5,6en	5,6ex	6en,6ex
3[a]	$CDCl_3$	3.2	3.9	0.4	≈0.8	[b]	[b]	[b]
4[a]	$CDCl_3$	3.2	3.9	0.5	≈0.8	[b]	[b]	[b]
5[a]	$CDCl_3$	3.2	3.9	0.5	≈0.8	[b]	[b]	[b]
6	$CDCl_3$	1.8	9.3	5.8	[b]	[b]	[b]	[b]
(*Z*)-7 74%	$CDCl_3$	1.8	10.0	5.3	≈1.5	0.9	5.2	7.5
(*E*)-7 26%	$CDCl_3$	1.8	9.3	5.5	1.8	0.9	5.0	7.5
α-**(*Z*)-8** 49%	D_2O	7.5	11.2	4.8	[b]	4.7	5.0	12.0
α-**(*E*)-8** 38%	D_2O	7.4	10.7	5.6	[b]	4.3	4.7	12.0
10	$CDCl_3$	2.1	–	–	2.1	1.0	5.4	8.6
11[c]	$CDCl_3$	2.1	–	–	2.1	0.8	5.4	8.6
12[d]	$CDCl_3$	2.3	–	–	2.3	0.9	5.5	8.5
13[e]	$CDCl_3$	2.1	–	–	2.1	0.8	5.3	8.6
14	$CDCl_3$	2.0	–	–	2.1	0.8	5.3	8.5
15	$CDCl_3$	2.1	–	–	2.1	0.8	5.4	8.8
16	$CDCl_3$	2.0	–	–	4.4	0	4.6	8.6
17[f]	$CDCl_3$	1.8	–	–	4.7	0	4.7	8.2
(*Z*)-18[g] 80%	$CDCl_3$	2.1	–	–	4.2	0	4.6	8.3
(*E*)-18[h] 20%	$CDCl_3$	2.1	–	–	4.0	0	4.7	8.5

[a] $J(1,4) \approx 0.5$, $J(2,4) = 0.6$, $J(3,5) = 1.4$, $J(1,6ex) \approx J(1,6en) \approx 0.5$; [b] *J* value could not be determined; [c] $J(1,6ex) = 0.4$, $J(2,4) = 0.6$, $J(2,5) = 0.5$; [d] $J(1,4) = 0.5$, $J(2,4) = 1.0$, $J(1,6ex) = 0.3$, $J(2,5) = 0.3$; [e] $J(1,5) = 0.5$; [f] $J(4,6ex) = 1.2$; [g] $J(4,6ex) = 1.3$; [h] $J(4,6ex) = 1.1$.

TABLE III
^{13}C NMR chemical shifts of compounds **3–8** and **10–18**

Compound	Solvent	C-1	C-2	C-3	C-4	C-5	C-6	Other carbons
3	$CDCl_3$	97.97	53.80	50.37	38.89	71.44	68.54	O-$(CH_2)_3$: 69.93, 26.55, 26.92; OTs: 144.90, 133.01, 129.88(2), 127.87(2), 21.61
4	$CDCl_3$	99.02	53.85	50.52	39.22	71.55	68.58	N-$(CH_2)_3$: 51.34, 26.25, 28.16
5	$CDCl_3$	98.07	53.85	50.72	39.50	71.64	68.60	N-$(CH_2)_3$: 42.13, 31.30, 28.24
6	$CDCl_3$	102.51	66.81	54.15	39.99	77.82	68.32	N-$(CH_2)_3$: 40.12, 25.98, 24.62
(*Z*)-7 74%	$CDCl_3$	102.62	69.07	49.76	39.76	76.86	68.23	N-$(CH_2)_3$: 36.84, 24.60, 24.57; NAc: 170.93, 21.97
(*E*)-7 26%	$CDCl_3$	102.67	67.32	55.59	40.37	[a]	68.36	N-$(CH_2)_3$: 42.59, 25.21, 24.36; NAc: 172.31, 21.98
α-**(*Z*)-8** 49%	D_2O	93.59	67.14	50.46	35.19	78.27	60.16	N-$(CH_2)_3$: 41.74, 24.71, 24.61; NAc: 173.52, 21.04
α-**(*E*)-8** 38%	D_2O	93.76	67.30	56.34	35.56	77.98	60.62	N-$(CH_2)_3$: 36.77, 24.85, 23.69; NAc: 173.70, 20.90
10	$CDCl_3$	99.68	77.55	67.49	78.36	74.82	64.77	2 × OTs: 145.36, 145.28, 133.22, 133.13, 129.94(2), 129.93(2), 128.05(2), 127.98(2), 21.68(2); CH_2-CH=CH_2: 43.87, 132.20, 119.88
11	$CDCl_3$	99.78	77.86	67.88	79.14	74.92	65.03	2 × OTs: 145.39, 145.33, 133.44, 133.42, 130.01(2), 129.99(2), 127.94(2), 127.90(2), 21.68, 21.67; O-$(CH_2)_3$: 62.22, 26.33, 25.60
12	$CDCl_3$	100.26	77.72	77.00	80.44	75.38	64.89	2 × OTs: 144.28, 144.22, 134.51, 134.48, 129.41(2), 129.36(2), 127.92(2), 127.90(2), 21.62(2); O-$(CH_2)_3$: 67.61, 26.25, 38.41

TABLE III
(*Continued*)

Compound	Solvent	C-1	C-2	C-3	C-4	C-5	C-6	Other carbons
13	$CDCl_3$	99.67	77.40	67.61	79.02	74.81	64.99	2 × OTs: 145.54, 145.48, 133.07, 133.03, 130.04(2), 130.02(2), 127.96(2), 127.91(2), 21.70, 21.69; N-$(CH_2)_3$: 51.13, 36.24, 22.73
14	$CDCl_3$	99.82	78.00	67.63	79.24	74.94	65.11	2 × OTs: 145.23, 145.18, 133.41, 133.39, 129.92(2), 129.91(2), 127.94(2), 127.93(2), 21.69, 21.68; N-$(CH_2)_3$: 41.08, 29.96, 37.08
15	$CDCl_3$	99.62	77.42	67.69	78.97	74.49	65.01	2 × OTs + NTs: 145.59, 145.53, 143.56, 136.67, 133.11, 133.09, 130.11(2), 130.06(2), 129.79(2), 127.91(2), 127.89(2), 127.06(2), 21.73, 21.71, 21.53; N-$(CH_2)_3$: 42.81, 23.33, 35.82
16	$CDCl_3$	99.79	80.86	66.94	58.49	75.70	66.16	OTs + NTs: 145.60, 143.56, 136.84, 133.07, 130.11(2), 129.62(2), 127.89(2), 127.26(2), 21.73, 21.56; N-$(CH_2)_3$: 41.89, 18.60, 32.38
17	$CDCl_3$	102.53	73.98	67.41	58.20	76.34	66.06	N-$(CH_2)_3$: 41.82, 21.91, 32.37
(*Z*)-18 80%	$CDCl_3$	102.12	74.24	65.70	55.39	72.44	67.74	N-$(CH_2)_3$: 43.69, 19.89, 32.10; NAc: 171.69, 22.45
(*E*)-18 20%	$CDCl_3$	102.30	73.62	65.88	60.00	74.40	68.30	N-$(CH_2)_3$: 37.96, 19.41, 32.53; NAc: 171.51, 21.58

[a] The signal could not be detected.

spectra. They 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; 74%) and/or H-3 proton (in (*E*)-isomer; 24%). The additional NOE contacts between H-2 and two axial protons of piperidine ring, observed in both isomers, confirm the orientation of piperidine ring (see Figs 1a and 1b). The opening of the 1,6-anhydride ring and the presence of *N*-acetyl group leads to the observation of four stereoisomers (ratio 49:38:7:6) in the NMR spectrum of compound **8** in D_2O solution. Two major α-anomers have an axial anomeric proton C(1)–H (as indicated by a large value of $J(1,2) \approx 7.5$ Hz) and (*Z*)- and (*E*)-configuration, respectively, as follows from the NOE contacts of *N*-acetyl group. Minor β-anomers contain equatorial proton C(1)–H (small $J(1,2) \approx 3.5$ Hz) and (*Z*)- and (*E*)-configuration, respectively. It is of interest that the pyran ring in both major isomers adopts $^1C_4$ conformation (the observed $J(2,3) \approx 11$ Hz indicates diaxial orientation of H-2 and H-3). The NMR parameters of mi-

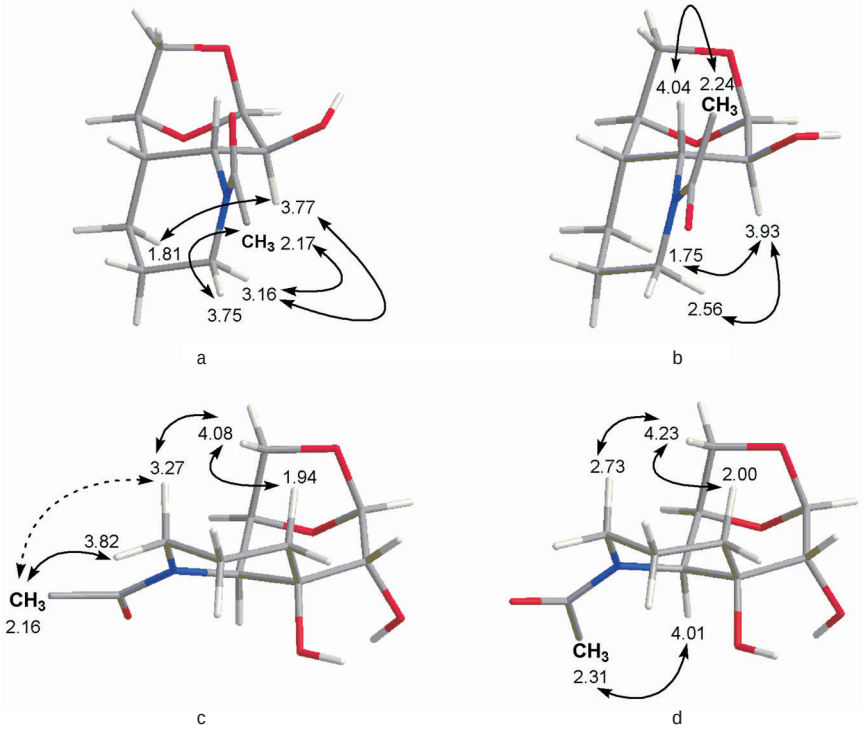


FIG. 1

The selected NOE contacts (indicated with arrows) observed in *N*-acetyl derivatives **7** and **18**: a **7** (*Z*)-isomer; b **7** (*E*)-isomer; c **18** (*Z*)-isomer; d **18** (*E*)-isomer

nor β-anomers are not given in Tables I–III since their low population (ca. 7 and 6%) does not allow extracting complete data sets.

The presence of the quaternary carbon atom C-3 in compounds **10**–**18** follows from ^{13}C NMR spectra (a weak signal with positive amplitude in APT spectrum) and from the absence of H-3 signal in ^{1}H NMR spectrum. The presence of OH group at position C-3 is indicated by chemical shifts of carbon C-3 (δ ≈ 65.7–67.9). The three-carbon substiuent at C-3 and the tosyl groups at C-2 and C-4 are manifested by characteristic signals in ^{1}H and ^{13}C NMR spectra. Oxolane ring closure leading to the spiro compound **12** is indicated by dramatic downfield shift of C-3 (δ 77.00 in **12** versus 67.88 in **11**) together with nonequivalence of six $–(CH_2)_3–O–C(3)$ protons in **12**. The observed NOE contacts of the protons of $–C(3)–CH_2–$ group in the oxolane ring with H-6en of the 1,6-anhydride bond and with protons H-2 and H-4 of pyranose ring (Fig. 2) clearly demonstrate the configuration of the $–(CH_2)_3–O–$ group at C-3 as well as the $^{1}C_4$ conformation of the pyranose ring. Those NOE contacts could not be observed in case of the inverted configuration at C-3 and/or presence of the $B_{3,O}$ conformation of the pyranose ring. The piperidine ring in compounds **16**–**18** leads to an upfield shift of C-4 (to δ ≈ 55–60) as the result of the replacement of oxygen with nitrogen substituent that is also responsible for an increase of proton coupling *J*(4,5) from ≈2 Hz in **10**–**15** to ≈4 Hz in **16**–**18**. The *N*-acetyl derivative **18** exists in solution again as a mixture of (*Z*)- and (*E*)-isomer in the ratio 80:20 determined from the NOE contacts of *N*-acetyl group. The additional NOE contacts between H-6en and two axial protons of piperidine ring, observed in both isomers, confirm the orientation of the piperidine ring (see Figs 1c and 1d). The observed decrease in vicinal couplings *J*(6en,5) and *J*(6ex,5) (from ca. 0.8 and 5.4 Hz in **10**–**15** to about 0 and 4.5 Hz in **16**–**18**)

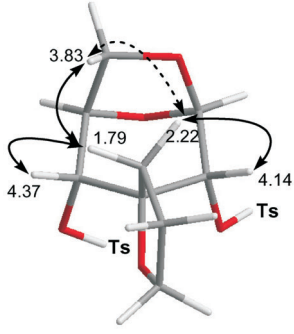


FIG. 2
The observed NOE contacts (indicated with arrows) proving the structure of compound **12**

results probably from the steric interaction between the piperidine ring and 1,6-anhydride bond in **16**–**18**.

*Conformation of Compound **6** in Crystal*

The crystal structure of compound **6** is shown in Fig. 3. The five-membered ring adopts the envelope conformation E^{O2}, the pyranose ring has a flattened chair conformation $^{C3}C_{O2}$ and the piperidine ring exists in the chair conformation $^{N1}C_{C9}$. The selected torsion angles are given in Table IV.

TABLE IV
Selected torsion angles (in °) found in crystal structure of compound **6**

Dioxolane ring		Pyranose ring		Piperidine ring	
O1–C1–O2–C5	–43.8	C1–C2–C3–C4	47.7	C3–N1–C7–C8	–59.6
C1–O2–C5–C6	44.9	C2–C3–C4–C5	–46.2	N1–C7–C8–C9	59.8
O2–C5–C6–O1	–30.6	C3–C4–C5–O2	60.4	C7–C8–C9–C4	–57.2
C5–C6–O1–C1	4.9	C4–C5–O2–C1	–74.4	C8–C9–C4–C3	51.8
C6–O1–C1–O2	23.7	C5–O2–C1–C2	76.2	C9–C4–C3–N1	–49.5
		O2–C1–C2–C3	–64.6	C4–C3–N1–C7	54.3

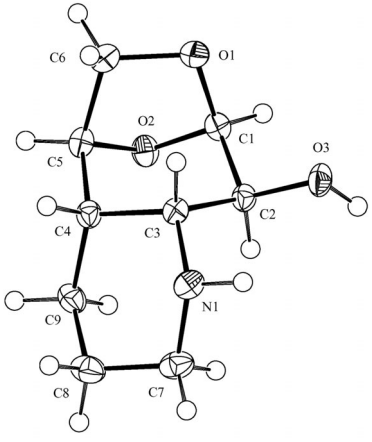


FIG. 3
A view on the molecule of **6** with atom numbering scheme. The displacement ellipsoids are drawn on 50% probability level (PLATON [17])

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 Varian UNITY-500 and/or 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 solvent signal (δ($CDCl_3$) 77.0 in ^{13}C NMR spectra); coupling constants (*J*) are given in Hz. 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. For ^{1}H and ^{13}C NMR data see Tables I–III.

1,6:2,3-Dianhydro-4-deoxy-4-[3-(tosyloxy)propyl]-β-D-mannopyranose (**3**)

A solution of 1,6:2,3-dianhydro-4-deoxy-4-(3-hydroxypropyl)-β-D-mannopyranose[5] (**2**) (2.2 g, 12 mmol) in dry pyridine (20 ml) was cooled to 0 °C and tosyl chloride (4.5 g, 24 mmol) in pyridine (20 ml) was added. The mixture was stirred at room temperature for 2 h and then poured into ice-water (100 ml). The emulsion was extracted with dichloromethane (3 × 30 ml). Combined organic phases were dried and evaporated. Yield 3.4 g (84%) of slowly crystallizing syrup **3**, m.p. 81–83 °C (ether–light petroleum), $[\alpha]_D$ –18 (*c* 0.7, $CHCl_3$). For $C_{16}H_{20}O_6S$ (340.4) calculated: 56.46% C, 5.92% H, 9.42% S; found: 56.57% C, 6.02% H, 9.37% S.

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

A mixture of tosylate **3** (3.1 g, 9.1 mmol) and sodium azide (1.2 g, 18 mmol) in anhydrous *N*,*N*-dimethylformamide (15 ml) was heated to 60 °C under argon atmosphere, while stirring. The reaction was monitored by TLC (toluene–ethyl acetate 3:1; complete conversion was observed after ca. 2 h). After cooling down, *N*,*N*-dimethylformamide was evaporated and the residue was extracted with ether (30 ml). Insoluble salts were filtered off, washed with ether (10 ml) and the filtrate was evaporated. The crude product was partially purified on a silica gel column (70 g) in toluene–ethyl acetate (4:1); yield 1.6 g (83%) of the syrupy azide derivative **4**, $[\alpha]_D$ –15 (*c* 0.6, $CHCl_3$). For $C_9H_{13}N_3O_3$ calculated 211.1. ESI MS, *m/z* (%): 234.0 (100) $[M + Na]^+$, 279.0 (46), 345.3 (91), 363.1 (30) [M of **3** + $Na]^+$.

3-Amino-1,6-anhydro-3,4-dideoxy-3-*N*,4-*C*-(propane-1,3-diyl)-β-D-altropyranose (**6**)

Azide **4** (1.5 g, 7.1 mmol) was hydrogenated in methanol (20 ml) over 5% palladium on activated carbon (100 mg) at atmospheric pressure for 8 h. The catalyst was filtered off and the filtrate containing 4-(3-aminopropyl)-1,6:2,3-dianhydro-4-deoxy-β-D-mannopyranose (**5**) was refluxed for 4 h. The solvent was evaporated and the crude product was purified on a short silica gel column (15 g). Nonpolar impurities were eluted with ethyl acetate–methanol (10:1) and the product **6** was eluted with ethyl acetate–methanol–20% ammonia in metha-

nol (15:3:1). It was crystallized from ethanol–ether, yield 840 mg (64%) of **6**, m.p. 160–162 °C, $[\alpha]_D$ –178 (*c* 0.6, MeOH). For $C_9H_{15}NO_3$ (185.2) calculated: 58.36% C, 8.16% H, 7.56% N; found: 58.37% C, 8.26% H, 7.38% N.

Crystal data for **6**: $C_9H_{15}NO_3$, M = 185.22, orthorhombic, $P2_12_12_1$ (No. 19), a = 8.1500(2) Å, b = 8.4880(2) Å, c = 12.8770(4) Å, V = 890.79(4) Å^3, Z = 4, D_x = 1.381 Mg m^{-3}. A yellow crystal of dimensions 0.6 × 0.45 × 0.22 mm was mounted on glass capillary with epoxy glue and measured at Nonius KappaCCD diffractometer using monochromatized MoKα radiation (λ = 0.71073 Å) at 150(2) K. An absorption was neglected (μ = 0.103 mm^{-1}); a total of 11 508 measured reflections in the range h = –10 to 10, k = –10 to 11, l = –16 to 16 (θ_{max} = 27.5°), from which 2042 were unique (R_{int} = 0.026) and 1961 observed according to the $I > 2\sigma(I)$ criterion. Cell parameters from 1210 reflections (θ = 1–27.5°). The structure was solved by direct methods (SIR92 [13], Altomare, 1994) and refined by full-matrix least squares based on F^2 (SHELXL97 [14]). The hydrogen atoms on carbons were found on difference Fourier map, were recalculated into idealised positions and fixed during refinement (riding model) with assigned temperature factors H_{iso}(H) = 1.2U_{eq}(pivot atom). The hydrogen atom on N and O were found on difference Fourier map and refined isotropically. The refinement converged (Δ/σ_{max} = 0.000) to R = 0.029 for observed reflections and wR = 0.078, GOF = 1.061 for 126 parameters and all 2042 reflections. The final difference map displayed no peaks of chemical significance ($\Delta\rho_{max}$ = 0.223 e Å^{-3}, $\Delta\rho_{min}$ –0.173 e Å^{-3}). The absolute structure was assigned by reference to known chiral centre. (Flack parameter is –0.2(9).) CCDC 268301 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).

3-Acetamido-1,6-anhydro-3,4-dideoxy-3-*N*,4-*C*-(propane-1,3-diyl)-β-D-altropyranose (**7**) and 3-Acetamido-3,4-dideoxy-3-*N*,4-*C*-(propane-1,3-diyl)-D-altropyranose (**8**)

Compound **6** (80 mg, 0.40 mmol) was dissolved in acetic anhydride (1.0 ml), while cooling to 0 °C, and trifluoroacetic acid (100 μl, 1.3 mmol) was added. The mixture was kept at room temperature under stirring for 2 days. Solvents were evaporated at 30 °C. Syrupy material obtained was deacetylated in a solution of 0.2 M methanolic sodium methanolate (2 ml) at room temperature for 1 h. TLC (ethyl acetate-methanol 10:1) showed the presence of two products. The mixture was then neutralized with Dowex 50 (H^+), the resin was filtered off, washed with methanol and combined filtrates were evaporated. The residue was chromatographed on a silica gel column (5 g). Compound **7** was eluted with ethyl acetate and compound **8** was eluted with ethyl acetate–methanol (6:1).

Compound **7**: Yield 45 mg (46%) of crystals, m.p. 190–191 °C (ethanol–ether), $[\alpha]_D$ –49 (*c* 0.2, $CHCl_3$). For $C_{11}H_{17}NO_4$ (227.3) calculated: 58.14% C, 7.54% H, 6.16% N; found: 58.08% C, 7.55% H, 5.91% N.

Compound **8**: Yield 25 mg (24%) of the syrup. For $C_{11}H_{19}NO_5$ calculated 245.1. ESI MS, *m/z* (%): 250.0 (20), 268.1 (100) $[M + Na]^+$.

3-*C*-Allyl-1,6-anhydro-2,4-di-*O*-tosyl-β-D-allopyranose (**10**)

A solution of 1,6-anhydro-2,4-di-*O*-tosyl-β-D-*ribo*-hexopyranos-3-ulose (**9**)[8] (4.0 g, 8.6 mmol) in dry THF (20 ml) was slowly added, while stirring and cooling (–10 °C) to a solution of allylmagnesium chloride in THF (10 ml, 2 mol/l, 20 mmol). After 1 h, the reaction mixture

was warmed to room temperature and stirred for additional 1 h. The reaction was quenched carefully with 10% HCl (10 ml) under cooling (0 °C). The mixture was separated between ether (40 ml) and water (40 ml). The water phase was extracted with ether (40 ml) again. Combined ether extracts were dried and evaporated. The crude product was crystallized from ether–light petroleum, yield 2.8 g (64%) of the allyl derivative **10**, m.p. 127–128 °C, $[\alpha]_D$ –51 (*c* 0.7, $CHCl_3$). For $C_{23}H_{26}O_9S_2$ (510.6) calculated: 54.10% C, 5.13% H, 12.56% S; found: 54.22% C, 5.18% H, 12.42% S.

1,6-Anhydro-3-(3-hydroxypropyl)-2,4-di-*O*-tosyl-β-D-allopyranose (**11**)

A mixture of $BF_3{\cdot}Et_2O$ (2.6 ml) and bis(2-methoxyethyl) ether (5 ml) was added dropwise under argon atmosphere during ca. 20 min to a stirred suspension of sodium borohydride (1.1 g) in bis-(2-methoxyethyl) ether (5 ml). The resulting stream of diborane[15] was passed through a stirred solution of **10** (2.5 g, 4.9 mmol) in dry THF (20 ml). After complete addition of the $BF_3{\cdot}Et_2O$ solution, the reaction mixture was stirred for 1 h. The reaction was quenched cautiously under cooling (0 °C) with aqueous 3 M NaOH (55 ml) and subsequentially with 30% H_2O_2 (55 ml). The mixture was stirred at room temperature for 1 h and then extracted with chloroform (2 × 30 ml). Combined organic phases were washed with saturated solution of Na_2SO_3 (50 ml), water (50 ml), and then were dried and evaporated. The residue was crystallized from ethanol affording 2.0 g (77%) of diol **11**, m.p. 152–154 °C, $[\alpha]_D$ –33 (*c* 0.7, $CHCl_3$). For $C_{23}H_{28}O_{10}S_2$ (528.6) calculated: 52.26% C, 5.34% H, 12.13% S; found: 51.87% C, 5.28% H, 11.96% S.

1,6-Anhydro-3-*C*,3-*O*-(propane-1,3-diyl)-2,4-di-*O*-tosyl-β-D-allopyranose (**12**)

A solution of the compound **11** (1.0 g, 1.9 mmol) in dry pyridine (5 ml) was cooled to 0 °C and tosyl chloride (760 mg, 4.0 mmol) in pyridine (5 ml) was added. The mixture was stirred at room temperature for 2 h and then was poured into ice-water (50 ml). The solid material precipitated overnight was washed with water, dried and crystallized from acetone, yield 760 mg (79%) of **12**, m.p. 196–199 °C (acetone), $[\alpha]_D$ –30 (*c* 0.8, CH_3CN). For $C_{23}H_{26}O_9S_2$ (510.6) calculated: 54.10% C, 5.13% H, 12.56% S; found: 54.11% C, 5.11% H, 12.27% S. ESI MS, *m/z* (%): 533.2 (100) $[M + Na]^+$, 549.1 (69) $[M + K]^+$.

1,6-Anhydro-3-*C*-(3-azidopropyl)-2,4-di-*O*-tosyl-β-D-allopyranose (**13**)

Compound **11** (2.0 g, 3.8 mmol) and triphenylphosphine (1.2 g, 4.6 mmol) were dissolved in THF (12 ml). To this solution were added subsequently under cooling (0 °C): a) a dried benzene solution of HN_3 (4.5 ml), which was prepared[16] from a mixture of NaN_3 (1.0 g), water (1 ml), benzene (6 ml) and concentrated sulfuric acid (0.4 ml) under cooling (0 °C); b) diisopropyl diazenedicarboxylate (0.94 ml, 4.6 mmol). The reaction mixture was stirred at room temperature for 1 h, then evaporated and the residue was chromatographed on a silica gel column (100 g) in toluene–acetone (10:1). Yield 2.0 g (95%) of azide derivative **13**, m.p. 129–130 °C (acetone–ether–light petroleum), $[\alpha]_D$ –30 (*c* 0.6, $CHCl_3$). For $C_{23}H_{27}O_9N_3S_2$ (553.6) calculated: 49.90% C, 4.92% H, 7.59% N, 11.58% S; found: 49.64% C, 4.90% H, 7.44% N, 11.64% S.

3-*C*-(3-Aminopropyl)-1,6-anhydro-2,4-di-*O*-tosyl-β-D-allopyranose (**14**)

Azido compound **13** (2.0 g, 3.6 mmol) was hydrogenated in a mixture of chloroform (10 ml), methanol (30 ml), acetic acid (1 ml) and palladium on activated carbon (10%, 100 mg) for 48 h. The catalyst was filtered off and solvents were evaporated. The crude product was purified on a short silica gel column (50 g) in chloroform–methanol–20% ammonia in methanol (20:3:1). Yield 1.4 g (73%) of a syrupy amine **14**, $[\alpha]_D$ –29 (*c* 0.7, $CHCl_3$). For $C_{23}H_{29}O_9NS_2$ calculated 527.1. ESI MS, *m/z* (%): 528.1 (100) $[M + H]^+$, 550.1 (70) $[M + Na]^+$.

1,6-Anhydro-2,4-di-*O*-tosyl-3-*C*-[3-(tosylamino)propyl]-β-D-allopyranose (**15**)

To a solution of amine **14** (3.5 g, 6.6 mmol) in dry dichloromethane (20 ml) and triethylamine (2.5 ml) was added tosyl chloride (2.5 g, 13 mmol) in dichloromethane (20 ml) under cooling (0 °C). The mixture was stirred at 0 °C for 1 h and then poured into ice-water (40 ml). Dichloromethane layer was separated and the water phase was extracted with dichloromethane (20 ml) again. Combined dichloromethane solutions were dried and evaporated. The residue was chromatographed on a silica gel column (150 g) in toluene–acetone (10:1 → 4:1), yield 3.2 g of tosylamide **15** (71%), m.p. 165–167 °C (ethanol), $[\alpha]_D$ –21 (*c* 0.7, $CHCl_3$). For $C_{30}H_{35}NO_{11}S_3$ (681.8) calculated: 52.85% C, 5.17% H, 2.05% N, 14.11% S; found: 52.59% C, 5.14% H, 1.90% N, 13.77% S.

1,6-Anhydro-4-deoxy-3-*C*,4-*N*-(propane-1,3-diyl)-2-*O*-tosyl-4-(tosylamino)-β-D-gulopyranose (**16**)

A mixture of tritosyl derivative **15** (2.9 g, 4.3 mmol) and K_2CO_3 (1.8 g, 13 mmol) in DMF (50 ml) was heated under argon atmosphere to 110 °C for 10 h, until the conversion was nearly complete (TLC, toluene–acetone 10:1). DMF was evaporated at 40 °C and the residue was portitioned between water (30 ml) and dichloromethane (30 ml). The water phase was extracted with dichloromethane (20 ml) again. Combined dichloromethane extracts were dried and evaporated. The syrup thus obtained was chomatographed on a silica gel column (110 g) in toluene–acetone (20:1 → 10:1). Yield 1.5 g (69%) of the syrupy tosyl amide **16**, $[\alpha]_D$ +61 (*c* 0.7, $CHCl_3$). For $C_{23}H_{27}NO_8S_2$ calculated 509.1. ESI MS, *m/z* (%): 532.3 (100) $[M + Na]^+$.

4-Amino-1,6-anhydro-4-deoxy-3-*C*,4-*N*-(propane-1,3-diyl)-β-D-gulopyranose (**17**)

To a mixture of the sulfonamide **16** (900 mg, 1.8 mmol) and Na_2HPO_4 (1.3 g, 9.1 mmol) in dry methanol (30 ml) was added 3% sodium amalgam (6.7 g, 8.7 mmol Na) at room temperature. The mixture was heated to reflux and stirred under argon atmosphere. The same amounts of amalgam and Na_2HPO_4 were added after 6 h and the mixture was refluxed for another 6 h. The reaction was allowed to reach room temperature, the amalgam was separated and the methanolic suspension was filtered through celite. The filtrate was evaporated and the residue was chromatographed on a silica gel column (12 g) in chloroform–methanol–20% ammonia in methanol (20:1:1). Yield 230 mg (65%) of **17**, m.p. 183–184 °C (ethanol–ether), $[\alpha]_D$ –14 (*c* 0.7, MeOH). For $C_9H_{15}NO_4$ (201.2) calculated: 53.72% C, 7.51% H, 6.96% N; found: 53.47% C, 7.48% H, 6.70% N.

Attempt at Acetolysis of the 1,6-Anhydride Bond in **17**:
4-Acetamido-1,6-anhydro-4-deoxy-3-*C*,4-*N*-(propane-1,3-diyl)-β-D-gulopyranose (**18**)

Compound **17** (50 mg, 0.25 mmol) was dissolved in a mixture of acetic anhydride (0.5 ml) and acetic acid (50 μl), 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 obtained was deacetylated in a solution of 0.2 M methanolic sodium methanolate (2 ml) at room temperature for 1 h. TLC (chloroform–methanol 5:1) showed the presence of a single product. The mixture was then neutralized with Dowex 50 (H^+), the resin filtered off, washed with methanol and the combined filtrates were evaporated. The residue was chromatographed on a silica gel column (3 g) in ethyl acetate–methanol (10:1). Yield 43 mg (71%) of syrupy acetamide **18**, $[\alpha]_D$ +56 (*c* 0.5, $CHCl_3$). For $C_{11}H_{17}NO_5$ calculated 243.1. ESI MS, *m/z* (%): 266.0 (100) $[M + Na]^+$.

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