SYNTHESIS OF SOME 1,4-OXAZEPANES FUSED WITH 1,6-ANHYDRO-β-D-HEXOPYRANOSES. 3,11,13-TRIOXA-7-AZATRICYCLO[8.2.1.$0^{2,8}$]-TRIDECANE DERIVATIVES

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The other authors (T. T., T. T., M. B. and I. C.) wish to dedicate this paper to Professor Miloslav Černý on the occasion of his 75th birthday.

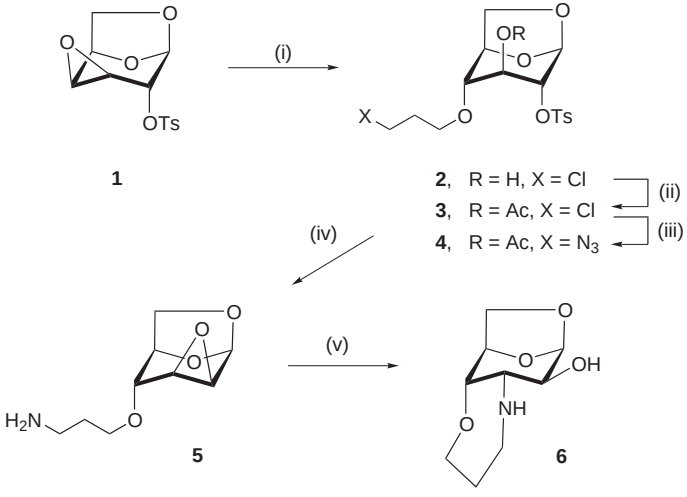
Some 1,4-oxazepanes based on 1,6-anhydro-β-D-hexopyranoses were prepared from 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose (**1**). Cleavage of its oxirane ring with 3-chloropropanol gave 1,6-anhydro-4-*O*-(3-chloropropyl)-2-*O*-tosyl-β-D-glucopyranose (**2**), which was converted in three steps into 4-*O*-(3-aminopropyl)-1,6:2,3-dianhydro-β-D-mannopyranose (**5**). The latter compound underwent intramolecular cyclization to afford 3-amino-1,6-anhydro-3-deoxy-3-*N*,4-*O*-(propane-1,3-diyl)-β-D-altropyranose (**6**) that gave the corresponding quaternary ammonium salt **10** by *N*-methylation. Acid cleavage of the 1,6-anhydro bond in **7** gave the D-altrose derivative 3-acetamido-3-deoxy-3-*N*,4-*O*-(propane-1,3-diyl)-β-D-altropyranose (**11**).

Keywords: Carbohydrates; Heterocycles; 1,6-Anhydrosugars; 1,4-Oxazepanes; Amino sugars; Oxiranes; Epoxides; Cyclizations; X-ray diffraction; NMR spectroscopy.

Nitrogen-containing heterocyclic compounds fused with the pyran ring of carbohydrates in non-anomeric position have been studied to a limited extent, irrespective of their potential biological activity[1,2]. In connection with our previous paper on 1,6-anhydro-β-D-hexopyranoses fused with morpholine[3], we focused herein on the synthesis of analogous heterocycles based on 1,4-oxazepane ring.

1,6:3,4-Dianhydro-2-*O*-tosyl-β-D-galactopyranose[4] (**1**), which is readily accessible from 1,6-anhydro-β-D-glucopyranose in two simple steps, was

a suitable starting compound in the synthesis of compound **6** (Scheme 1). The oxirane ring of **1** was cleaved with 3-chloropropanol under catalysis with boron trifluoride in refluxing dichloromethane to give 3-chloropropyl derivative **2** in 92% yield. This reaction proceeds with high regioselectivity under similar conditions as with other nucleophiles[5,6]. After acetylation of **2** and subsequent treatment of the resulting acetate **3** with sodium azide in *N*,*N*-dimethylformamide, 3-azidopropyl derivative **4** was formed. The latter was reduced with hydrogen over palladium catalyst and the amino derivative thus obtained was converted into epoxide **5** by the action of methanolic sodium methoxide at room temperature. Base-catalyzed (DBU) intramolecular opening of the epoxide ring in **5** by the amino group resulted in the formation of 3-amino-1,6-anhydro-3-deoxy-3-*N*,4-*O*-(propane-1,3-diyl)-β-D-altropyranose (**6**) in 72% yield. In spite of the fact that this five-step synthesis of **6** was not optimized it was effected in overall 48% yield.



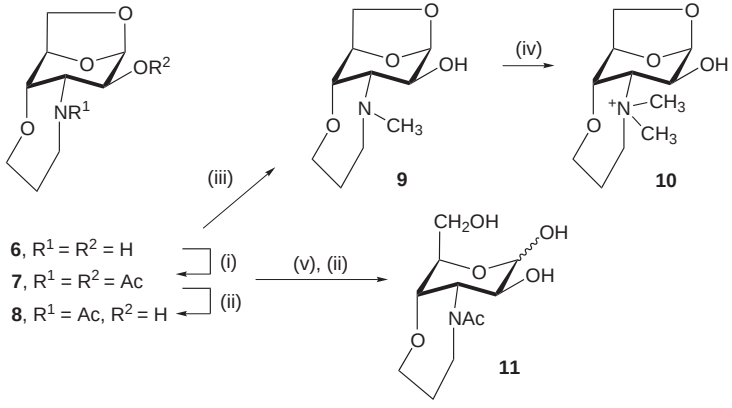
(i) $Cl(CH_2)_3OH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 40 °C; (ii) Ac_2O, pyridine, r.t.; (iii) NaN_3, DMF, 90 °C; (iv) H_2, Pd/C, EtOH, r.t., then MeONa, MeOH, r.t.; (v) DBU, BuOH, 120 °C

SCHEME 1

Acid hydrolysis of the 1,6-anhydride bond in compound **6** with aqueous hydrochloric acid failed because the chemical equilibrium between the compound **6** and the corresponding reducing sugar is completely shifted to **6**. Such a tendency to form the 1,6-anhydride bond is typical of hexoses of *altro*, *gulo*, and *ido* configuration[7]. Nevertheless, acetolysis of **7** in a mixture of trifluoroacetic acid and acetic anhydride at room temperature and subsequent Zemplén deacetylation gave the expected *N*-acetylated reducing

sugar **11** (Scheme 2) as a mixture of four compounds, namely (*Z*)- and (*E*)-isomers, and α and β anomers identified by NMR data (Tables I–III).

Quaternary ammonium salt **10** was prepared by a two-step procedure involving the Eschweiler–Clarke methylation followed by *N*-methylation of the intermediate **9** with methyl iodide in tetrahydrofuran at room temperature. The resulting ammonium salt **10** did not show any activity at muscarinic M3 receptors.



(i) Ac_2O, py, r.t.; (ii) MeONa, MeOH, r.t.; (iii) CH_2O, HCOOH, 80 °C; (iv) MeI, THF, r.t.; (v) CF_3COOH, Ac_2O, r.t.

SCHEME 2

NMR DISCUSSION

The structure of compounds **2**–**11** was determined by ^1H and ^{13}C NMR spectroscopy. Structural assignment of protons and carbon atoms was achieved using correlated homonuclear 2D-COSY and heteronuclear ^1H, ^{13}C-2D-HMQC spectra. The long-range couplings, typical of compounds **2**–**4** with D-*gluco* configuration, were identified with selective decoupling experiments in 1D ^1H NMR spectra. In compound **2** the higher observed values of coupling constants $J(2,3) = 3.3$ and $J(3,4) = 3.5$ Hz (compared with typical lower values $J(2,3) \approx 1.8$, $J(3,4) \approx 1.8$ Hz found in **3** and **4**) can be explained either by flattening of the pyranoid ring, and/or a certain amount of a $B_{3,O}$ boat form in a chair-boat equilibrium of compound **2**.

The presence of oxirane ring in D-*manno*-derivative **5** is manifested by upfield shifts of protons and carbon atoms in positions 2 and 3 (δ(H) 3.42 and 3.14; δ(C) 54.31 and 47.55) and characteristic *J*-value of *cis*-oxirane protons ($J(2,3) = 3.8$ Hz). Also other proton coupling constants ($J(1,2) = 3.2$; $J(3,4) \approx J(4,5) = 1.5$ Hz) are in agreement with the D-*manno* configuration.

TABLE I

^{1}H NMR chemical shifts of compounds **2–9**, **11** in $CDCl_3$ and **10** in D_2O

Compound	H-1	H-2	H-3	H-4	H-5	H-6en	H-6ex	O-CH_2-	-CH_2-	-CH_2-X	OR; NR
2[a]	5.33 t	4.20 dm	3.91 m	3.25 m	4.60 dq	3.95 dd	3.70 dd	3.70 t (2H)	2.03 m (2H)	3.65 m (2H)	2.55 d (OH)
3[b]	5.41 bt	4.29 m	4.91 m	3.15 m	4.59 m	3.90 dd	3.75 ddd	3.74 m 3.66 m	2.00 m (2H)	3.61 m (2H)	2.05 s (OAc)
4[c]	5.38 t	4.29 m	4.92 m	3.15 m	4.60 m	3.91 dd	3.76 ddd	3.69 dt 3.61 dt	1.83 m (2H)	3.41 dt 3.35 dt	2.06 s (OAc)
5	5.68 dd	3.42 ddd	3.14 ddd	3.55 m	4.49 dm	3.64 dd	3.67 dd	3.76 dt (2H)	1.94 m (2H)	3.01 bt (2H)	6.08 b (NH_2)
6	5.41 d	3.63 dd	2.99 dd	3.58 dd	4.64 ddd	3.71 dd	3.81 dd	4.19 ddd 3.53 ddd	1.90 m 1.81 m	3.13 m 2.76 ddd	2.47 bs (OH+NH)
(*Z*)-**7** (76%)	5.49 d	5.20 dd	5.24 ddd	3.56 dd	4.64 ddd	3.93 dd	3.85 dd	4.24 ddd 3.46 ddd	2.08 m 1.89 m	3.65 ddd 3.57 m	2.14 s (NAc) 2.05 s (OAc)
(*E*)-**7** (24%)	5.54 d	5.26 dd	4.08 bdd	3.58 dd	4.68 ddd	3.81 dd	3.89 dd	4.22 ddd 3.46 ddd	2.04 m 1.97 m	4.20 m 3.14 ddd	2.18 s (NAc) 2.08 s (OAc)
(*Z*)-**8** (77%)	5.49 d	3.86 dd	4.95 dd	3.51 dd	4.60 ddd	3.91 dd	3.83 dd	4.19 ddd 3.49 ddd	2.08 m 1.91 m	3.69 ddd 3.57 ddd	2.19 s (NAc) OH: [d]
(*E*)-**8** (23%)	5.54 d	4.04 dd	3.89	3.52	4.64 ddd	3.77 dd	3.88 dd	4.20 ddd 3.44 ddd	~2.05 m ~1.93 m	4.24 m 3.12 ddd	2.22 s (NAc) OH: [d]
9	5.50 d	3.88 dd	2.68 dd	3.71 dd	4.62 ddd	3.70 dd	3.79 dd	4.11 ddd 3.58 ddd	2.10 m 1.80 m	3.27 ddd 2.78 m	2.61 s (NMe) OH:[d]
10	5.49 d	4.31 dd	3.80 m	4.38 dd	4.84 ddd	3.91 dd	3.82 dd	4.15 ddt 3.80 ddd	2.64 m 2.00 dm	4.32 ddd 3.56 dm	3.81 s 3.48 s (2×NME)
β-(*Z*)-**11** (41%)	5.34 d	4.11 dd	5.20 dd	3.63	4.00	*d*	*d*	*d*	*d*	*d*	2.21 s (NAc)
α-(*Z*)-**11** (32%)	5.08 d	3.95 dd	4.92 dd	3.61	3.98	*d*	*d*	*d*	*d*	*d*	2.20 s (NAc)
β-(*E*)-**11** (15%)	5.38 d	4.23 dd	4.39 bdd	3.68	4.03	*d*	*d*	*d*	*d*	*d*	2.20 s (NAc)
α-(*E*)-**11** (12%)	5.09 d	4.09 dd	3.69	3.67	3.98	*d*	*d*	*d*	*d*	*d*	2.21 s (NAc)

Additional protons: [a] OTs: 2.46 bs (3 H), 7.83 m (2 H), 7.36 m (2 H). [b] OTs: 2.45 bs (3 H), 7.83 m (2 H), 7.35 m (2 H). [c] OTs: 2.46 bs (3 H), 7.83 m (2 H), 7.36 m (2 H). [d] The position of signals could not be accurately determined.

TABLE II
^{1}H NMR coupling constants of compounds **2**–**9**, **11** in $CDCl_3$ and **10** in D_2O

								O-CH_aH_b-CH_cH_d-CH_eH_f-X				
Comp.	*J*(1,2)	*J*(2,3)	*J*(3,4)	*J*(4,5)	*J*(5,6n)	*J*(5,6x)	*J*(6n,6x)	*J*(a,b) *J*(c,d) *J*(e,f)	*J*(a,c) *J*(a,d)	*J*(b,c) *J*(b,d)	*J*(c,e) *J*(c,f)	*J*(d,e) *J*(d,f)
2[a]	1.3	3.3	3.5	1.5	1.0	5.4	7.5	[e]	[e]	[e]	[e]	[e]
3[b]	1.7	1.8	1.8	1.8	1.1	5.7	7.6	[e]	[e]	[e]	[e]	[e]
4[c]	2.0	1.5	1.8	1.8	1.1	5.7	7.6	9.4 [e] 12.3	5.9 5.9	5.8 5.8	6.7 6.7	6.1 6.1
5[d]	3.2	3.8	1.5	1.5	2.2	6.4	7.2	[e]	[e]	[e]	[e]	[e]
6	2.0	9.0	4.8	2.3	1.1	5.7	7.8	12.6 14.6 14.4	6.7 2.8	10.5 4.8	3.6 9.0	6.2 3.1
(*Z*)-**7** 76%	1.9	10.2	4.2	2.2	1.1	5.6	8.0	12.8 13.9 15.9	8.4 2.0	10.4 6.5	5.5 1.9	11.7 6.5
(*E*)-**7** 24%	1.9	9.8	4.4	2.2	1.1	5.4	8.2	12.6 [e] 14.1	8.6 1.9	9.4 7.2	5.8 2.2	11.5 5.1
(*Z*)-**8** 77%	2.0	10.0	4.2	2.3	1.0	5.6	8.1	12.7 14.0 15.6	8.3 2.8	9.6 6.5	2.3 5.3	6.2 11.4
(*E*)-**8** 23%	2.0	9.2	[e]	2.2	1.0	5.5	8.2	12.7 [e] 13.7	8.6 2.6	9.8 6.9	2.0 5.8	5.1 11.4
9	1.8	9.7	3.6	2.5	1.0	5.5	7.8	12.6 14.6 14.7	4.4 8.7	7.3 7.8	11.3 4.7	4.1 3.5
10	2.1	10.2	4.7	2.6	1.1	5.6	8.7	12.6 16.6 14.5	6.9 1.1	7.8 4.2	13.2 2.0	4.0 3.0
β-(*Z*)-**11** 41%	3.8	11.2	2.8	[e]	[e]	[e]	[e]	[e]	[e]	[e]	[e]	[e]
α-(*Z*)-**11** 32%	6.1	11.5	4.3	[e]	[e]	[e]	[e]	[e]	[e]	[e]	[e]	[e]
β-(*E*)-**11** 15%	3.8	10.3	2.7	[e]	[e]	[e]	[e]	[e]	[e]	[e]	[e]	[e]
α-(*E*)-**11** 12%	5.5	[e]	[e]	[e]	[e]	[e]	[e]	[e]	[e]	[e]	[e]	[e]

Additional coupling constants: [a] *J*(1,3) = 1.1, *J*(1,4) = 0.4, *J*(1,6x) ≤ 0.3, *J*(2,4) = 0.7, *J*(3,OH) = 5.4, *J*(3,5) = 1.1. [b] *J*(1,3) = 1.4, *J*(1,4) = 0.7, *J*(1,6x) = 0.4, *J*(2,4) = 1.0, *J*(2,5) = 0.5, *J*(3,5) = 1.8. [c] *J*(1,3) = 1.4, *J*(1,4) = 0.6, *J*(1,6x) = 0.4, *J*(2,4) = 1.1, *J*(2,5) = 0.6, *J*(3,5) = 1.9. [d] *J*(1,3) = 0.6, *J*(2,4) = 0.8. [e] The *J*-value could not be determined.

The D-*altro* configuration of tricyclic compounds **6**–**10**, which is in agreement with high negative values of their optical rotations[3,5a] was proved by a high value of $J(2,3)$ = 9.0–10.2 Hz (indicating a *trans*-diaxial arrangement of H-2, H-3) and a low value of $J(3,4)$ = 3.6-4.8 Hz of *gauche*-oriented H-3 and H-4. The presence of nitrogen substituent instead of oxygen in position 3 (evidenced by upfield shifts of carbon C-3 to δ 50–64 in compounds **6**–**9**) also leads to an increase in both of the above mentioned vicinal couplings of proton H-3. The seven-membered 1,4-oxazepane ring fused in positions

TABLE III
^{13}C NMR chemical shifts of compounds **2**–**9**, **11** in $CDCl_3$ and **10** in D_2O

Compound	C-1	C-2	C-3	C-4	C-5	C-6	Other carbons
2	99.83	78.86	70.06	79.60	74.97	66.34	O-CH_2-CH_2-CH_2-Cl: 66.08, 32.52, 41.70 OTs: 145.38, 133.01, 130.01(2), 127.98(2), 21.68
3	99.20	74.40	68.91	76.25	74.39	65.40	O-CH_2-CH_2-CH_2-Cl: 66.08, 32.54, 41.59 OAc: 168.98, 20.82 OTs: 145.27, 133.35, 129.92(2), 128.00(2), 21.64
4	99.06	74.21	68.74	76.00	74.19	65.32	O-CH_2-CH_2-CH_2-N: 66.30, 29.10, 48.09 OAc: 169.03, 20.85 OTs: 145.33, 133.26, 129.94(2), 127.97(2), 21.66
5	97.56	54.31	47.55	74.90	71.30	65.75	O-CH_2-CH_2-CH_2-N: 67.56, 29.51, 37.77
6	101.80	71.70	58.88	81.54	77.17	66.19	O-CH_2-CH_2-CH_2-N: 72.03, 34.33, 41.93
(*Z*)-**7** 76%	99.90	68.83	50.88	82.81	76.84	66.21	O-CH_2-CH_2-CH_2-N: 68.91, 28.80, 40.69 NAc: 171.44, 21.27 OAc: 170.63, 20.87
(*E*)-**7** 24%	99.64	69.20	56.09	83.72	76.84	66.45	O-CH_2-CH_2-CH_2-N: 69.76, 27.61, 37.61 NAc: 171.44, 21.27 OAc: 170.63, 20.87
(*Z*)-**8** 77%	102.23	68.50	53.87	82.15	76.72	66.10	O-CH_2-CH_2-CH_2-N: 68.51, 28.99, 40.43 NAc: [a], 21.40
(*E*)-**8** 23%	102.00	67.99	59.60	83.59	76.78	66.30	O-CH_2-CH_2-CH_2-N: 69.57, 27.60, 37.32 NAc: [a], 21.95
9	101.72	68.72	64.31	79.64	77.66	66.33	O-CH_2-CH_2-CH_2-N: 69.18, 26.65, 45.31 NMe: 42.07
10	104.26	70.76	75.82	80.53	79.69	68.37	O-CH_2-CH_2-CH_2-N: 73.83, 28.93, 68.19 NMe_2: 63.63, 51.32
β-(*Z*)-**11** 41%	93.22	64.83	51.67	80.19	79.23	68.56	O-CH_2-CH_2-CH_2-N: 66.46, 29.01, 40.83 NAc: 173.44, 21.68
α-(*Z*)-**11** 32%	96.67	67.77	54.39	79.57	75.17	67.82	O-CH_2-CH_2-CH_2-N: 63.66, 28.81, 40.40 NAc: 173.42, 21.18
β-(*E*)-**11** 15%	92.50	64.46	56.70	81.14	79.50	69.18	O-CH_2-CH_2-CH_2-N: 61.74, 28.19, 36.76 NAc: 173.16, 21.71
α-(*E*)-**11** 12%	97.29	67.70	59.65	80.31	74.58	68.44	O-CH_2-CH_2-CH_2-N: 64.25, 27.73, 37.21 OAc: 173.20, 21.89

[a] The position of signals could not be accurately determined.

C-3–C-4 adopts a chair $^{7}C_{3,4}$-type conformation (slightly influenced by substitution at nitrogen atom) as it is indicated by vicinal couplings in the O–CH_2–CH_2–CH_2–N fragment (Table II).

The partial double-bond character of tertiary amide bond in *N*-acetyl derivatives **7** and **8** 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 equatorial hydrogen of N–CH_2 group (in (*Z*)-isomer) and/or H-3 proton (in (*E*)-isomer), in accordance with a short distance (ca. 2.5 Å) between the corresponding protons in calculated energy-minimized structures. In all cases, the population of the (*Z*)-isomer significantly prevails (76% in **7** and 77% in **8**; determined from the intensities of H-1 signals).

Cleavage of the 1,6-anhydride bond in **7** leads to the observation of an equilibrium mixture of four shapes of **11** due to the presence of α and β anomers, each as (*Z*)- and (*E*)-isomers at the tertiary amide bond. Isomers are present in the ratio β-(*Z*):α-(*Z*):β-(*E*):α-(*E*) = 41:32:15:12 (determined from the heights of doublet lines of H-1 only, since partial overlap of two H-1 doublets at 5.08 and 5.09 did not allow their separate integration). The detailed NMR analysis combining homonuclear and heteronuclear correlated 2D-NMR spectra resulted in a nearly complete structure assignment of signals in all the four isomers (Tables I and III). The different *J*(1,2) couplings were used to distinguish α anomers (*J*(1,2) ≈ 6 Hz) and β anomers (*J*(1,2) = 3.8 Hz) while (*E*)/(*Z*)-isomers were distinguished in 2D-ROESY spectra similarly as described above for compounds **7** and **8**. It is interesting that the pyran ring in all the four isomers of bicyclic compound **11** adopts the $^{1}C_4$ conformation (the observed *J*(2,3) = 10–11.5 Hz indicate diaxial orientation of H-2 and H-3 protons) similarly to those in the tricyclic compounds **6**–**10**.

The presence of *N*-methyl signals (^{1}H: δ 2.61 s (3 H) and ^{13}C: δ 42.07 in *N*-methyl derivative **9**; ^{1}H: δ 3.48 s (3 H), δ 3.81 s (3 H) and ^{13}C: δ 51.32, 63.63 in *N*,*N*-dimethylammonium derivative **10**) and dramatic downfield shifts of carbon signals C-3 and N–CH_2 in **10** confirm the structure of compounds **9** and **10**.

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 apparatus (^{1}H at 500 MHz, ^{13}C at 125.7 MHz) in $CDCl_3$ or D_2O. Chemical shifts (in ppm, δ-scale) were referenced to tetramethylsilane as in-

ternal standard; coupling constants (*J*) are given in Hz. ESI MS were measured on Esquire 3000 (Bruker) instrument. 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 then 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-Anhydro-4-*O*-(3-chloropropyl)-2-*O*-tosyl-β-D-glucopyranose (**2**)

To a solution of tosyl epoxide[4] **1** (2.0 g, 6.7 mmol) in anhydrous dichloromethane (20 ml) boron trifluoride etherate (1.0 ml, 7.9 mmol) and 3-chloropropanol (2.8 ml, 34.5 mmol) were added. The mixture was refluxed for 4 h. The reaction course was monitored by TLC (ethyl acetate–toluene 1:2). The solution was washed with a saturated solution of sodium hydrogencarbonate (2 × 20 ml) and with water (20 ml). Combined organic extracts were dried, dichloromethane and 3-chloropropanol were evaporated to obtain 2.4 g (92%) of **2**, m.p. 74–76 °C (ether–light petroleum), $[\alpha]_D$ –35 (*c* 0.19, $CHCl_3$). For $C_{16}H_{21}ClO_7S$ (392.8) calculated: 48.92% C, 5.39% H, 9.02% Cl, 8.16% S; found: 49.00% C, 5.47% H, 9.01% Cl, 8.05% S.

3-*O*-Acetyl-1,6-anhydro-4-*O*-(3-chloropropyl)-2-*O*-tosyl-β-D-glucopyranose (**3**)

To a solution of chloropropyl derivative **2** (1.9 g, 4.8 mmol) in anhydrous pyridine (4.0 ml), acetic anhydride (1.4 ml, 11.0 mmol) was added dropwise at 0 °C. The solution was stirred at room temperature overnight and then poured into ice-water (30 ml) while stirring. The resulting precipitate was filtered off after 20 min, washed with water (30 ml) and dried to give 2.0 g (96%) of **3**, m.p. 64–66 °C (ether–light petroleum), $[\alpha]_D$ –29 (*c* 0.17, $CHCl_3$). For $C_{18}H_{23}ClO_8S$ (434.8) calculated: 49.71% C, 5.33% H, 8.15% Cl, 7.37% S; found: 49.59% C, 5.46% H, 8.02% Cl, 7.43% S.

3-*O*-Acetyl-1,6-anhydro-4-*O*-(3-azidopropyl)-2-*O*-tosyl-β-D-glucopyranose (**4**)

Compound **3** (2.0 g, 4.6 mmol) and sodium azide (600 mg, 9.2 mmol) were dissolved in anhydrous *N*,*N*-dimethylformamide (7.0 ml) and the mixture was heated to 90 °C for 3 h under argon atmosphere, while stirring. After evaporation of *N*,*N*-dimethylformamide, water (40 ml) was added to the residue. The insoluble product was filtered off and crystallized from ether–light petroleum to afford 1.8 g (86%) of **4**, m.p. 69–70 °C (ether–light petroleum), $[\alpha]_D$ –31 (*c* 0.19, $CHCl_3$). For $C_{18}H_{23}N_3O_8S$ (455.4) calculated: 48.97% C, 5.25% H, 9.52% N, 7.26% S; found: 48.93% C, 5.18% H, 9.26% N, 7.15% S.

4-*O*-(3-Aminopropyl)-1,6:2,3-dianhydro-β-D-mannopyranose (**5**)

Azide derivative **4** (1.8 g, 4.0 mmol) was hydrogenated in ethanol (60 ml) over Pd/C (90 mg, 5%) at atmospheric pressure for 24 h. The catalyst was removed by filtration, washed with ethanol and the combined filtrates were evaporated. The residue was dissolved in water (15 ml), and neutralized with 10% hydrochloric acid to pH ≈ 6. The aqueous solution was extracted with dichloromethane (2 × 10 ml) and organic extracts were washed with water

(5 ml) again. Combined aqueous phases were evaporated and codistilled with toluene (3 × 10 ml). The residue was dissolved, while stirring, in 0.5 M methanolic sodium methoxide (20 ml) and the solution was set aside at room temperature overnight. Then the mixture was neutralized with acetic acid (0.34 ml, 6.0 mmol) to pH ≈ 8. After evaporation of the solvent, dichloromethane (10 ml) was added. Insoluble salts were filtered off and washed with dichloromethane (2 ml). The filtrate was concentrated and purified on a short silica gel column (15 g) in ethyl acetate–methanol–ammonia (40:10:1) to obtain 680 mg (84%) of syrupy **5**, $[\alpha]_D$ –33 (*c* 0.22, $CHCl_3$).

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

A solution of aminoepoxide **5** (680 mg, 3.4 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.6 ml, 4.0 mmol) in butan-1-ol (20 ml) was refluxed for 8 h. The solvent was evaporated and the residue chromatographed on a silica gel column (30 g) in ethyl acetate–methanol–ammonia (50:10:1) to give 490 mg (72%) of compound **6**, m.p. 175–177 °C (ethanol–ether), $[\alpha]_D$ –139 (*c* 0.18, MeOH). For $C_9H_{15}NO_4$ (201.2) calculated: 53.72% C, 7.51% H, 6.96% N; found: 53.57% C, 7.51% H, 6.58% N.

Crystal Structure Analysis of Compound **6**

$C_9H_{15}NO_4$, M = 201.22, orthorhombic, $P2_12_12_1$ (No. 19), a = 5.2480(1) Å, b = 10.8820(2) Å, c = 15.6700(5) Å, V = 894.89(4) Å^3, Z = 4, D_x = 1.494 Mg m^{-3}. A colorless crystal of dimensions 0.5 × 0.3 × 0.25 mm was mounted on glass capillary with epoxy glue and measured at Nonius KappaCCD diffractometer by monochromatized MoKα radiation (λ = 0.71073 Å) at 150(2) K. An absorption was neglected (μ = 0.117 mm^{-1}); a total of 10 129 measured reflections in the range h = –6 to 6, k = –14 to 13, l = –20 to 20 (θ_{max} = 27.5°), from which 2044 were unique (R_{int} = 0.024) and 1979 observed according to the $I > 2\sigma(I)$ criterion. Cell parameters from 5994 reflections (θ = 1–27.5°). The structure was solved by direct methods (SIR92 [9], Altomare, 1994) and refined by full-matrix least squares based on F^2 (SHELXL97 [10]). The hydrogen atoms were found on difference Fourier map and refined isotropically. The refinement converged (Δ/σ_{max} = 0.000) to R = 0.026 for observed reflections and wR = 0.067, GOF = 1.065 for 187 parameters and all 2044 reflections. The final difference map displayed no peaks of chemical significance ($\Delta\rho_{max}$ = 0.219, $\Delta\rho_{min}$ –0.168 e Å^{-3}). The absolute structure was assigned by reference to the known chiral centre. (Flack parameter = –0.2(8) (Fig. 1).) CCDC 237036 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-2-*O*-acetyl-1,6-anhydro-3-deoxy-3-*N*,4-*O*-(propane-1,3-diyl)-β-D-altropyranose (**7**) and 3-Acetamido-1,6-anhydro-3-deoxy-3-*N*,4-*O*-(propane-1,3-diyl)-β-D-altropyranose (**8**)

Amino derivative **6** (140 mg, 0.70 mmol) was dissolved in anhydrous pyridine (1 ml) and acetic anhydride (0.25 ml, 2.6 mmol) was added dropwise. The solution was stirred at room temperature overnight and then poured into ice-water (5 ml) while stirring. After decomposition of acetic anhydride, the mixture was extracted with chloroform (3 × 5 ml). Combined organic layers were dried, evaporated and codistilled with toluene (3 × 5 ml) to give syrupy **7** (180 mg, 91%), which was dissolved in 0.1 M sodium methanolate (3 ml). The solution

was stirred at room temperature for 1 h. The mixture was then neutralized with Dowex 50 (H^+), the resin was filtered off, washed with methanol and the combined filtrates were evaporated to give 135 mg (80%) of the crystalline compound **8**, m.p. 194–196 °C (acetone–ether–light petroleum), $[\alpha]_D$ –103 (*c* 0.26, $CHCl_3$). For $C_{11}H_{17}NO_5$ calculated: 243.1. ESI MS, *m/z*: 244.0 $[M + H]^+$, 266.0 $[M + Na]^+$, 282.2 $[M + K]^+$, 304.3.

1,6-Anhydro-3-deoxy-3-(methylamino)-3-*N*,4-*O*-(propane-1,3-diyl)-β-D-altropyranose (**9**)

Compound **6** (400 mg, 2.0 mmol) was dissolved in 85% formic acid (0.15 ml, 3.3 mmol) and a solution of 35% aqueous formaldehyde (0.23 ml, 3.1 mmol) was added. The mixture was heated to 80 °C overnight. After cooling to room temperature, the solution was acidified with 6 M hydrochloric acid (0.5 ml) and extracted with chloroform (2 × 1 ml). Evaporation of combined organic layers afforded 8 mg of a syrup. Aqueous layer was alkalinized with a 20% water solution of NaOH and set aside at room temperature for 30 min. The reaction mixture was then extracted with chloroform (6 × 1 ml). The combined chloroform extracts were dried and evaporated to give 350 mg (82%) of syrupy **9**, $[\alpha]_D$ –136 (*c* 0.27, $CHCl_3$). For $C_{10}H_{17}NO_4$ calculated: 215.1. EI MS, *m/z* (rel.%): 215 (45) $[M^+]$, 184 (15), 113 (20), 84 (100), 42 (35). ESI MS, *m/z*: 216.1 $[M + H]^+$, 238.1 $[M + Na]^+$.

1,6-Anhydro-3-deoxy-3-(dimethylammonio)-3-*N*,4-*O*-(propane-1,3-diyl)- β-D-altropyranose Iodide (**10**)

The crude product **9** (350 mg, 1.6 mmol) was dissolved in tetrahydrofuran (3 ml), methyl iodide (350 µl, 5.6 mmol) was added and the mixture was kept at room temperature for 24 h. The precipitated product was filtered off and washed with tetrahydrofuran (2 ml) to give 510 mg (88%) of **10**, m.p. 277–279 °C (decomp., ethanol), $[\alpha]_D$ –113 (*c* 0.23, MeOH). For $C_{11}H_{20}INO_4$ (355.2) calculated: 36.99% C, 5.64% H, 35.53% I, 3.92% N; found: 37.00% C, 5.86% H, 35.58% I, 3.65% N.

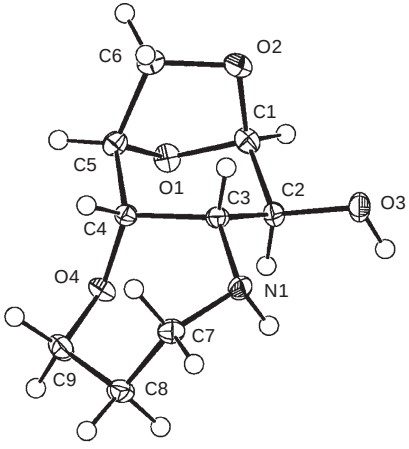


FIG. 1
View of compound **6**. Thermal ellipsoids are drawn on the 50% probability level (PLATON [8])

3-Acetamido-3-deoxy-3-*N*,4-*O*-(propane-1,3-diyl)-β-D-altropyranose (**11**)

The compound **7** (800 mg, 2.8 mmol) was dissolved in acetic anhydride (5.0 ml) while cooling to 0 °C, and trifluoroacetic acid (0.5 ml, 6.5 mmol) was added. The mixture was stirred for 2 days. Solvents were evaporated and the residue was separated between a saturated solution of sodium hydrogencarbonate (10 ml) and chloroform (10 ml). The aqueous layer was then extracted with chloroform (2 × 10 ml). The combined organic layers were dried and evaporated. The crude product thus obtained was deacetylated in a solution of 0.1 M methanolic sodium methanolate (10 ml) at room temperature for 2 h. 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 (20 g) in ethyl acetate–methanol (6:1) to give 410 mg (56%) of the syrupy **11**, $[\alpha]_D$ +27 (*c* 0.29, MeOH). For $C_{11}H_{19}NO_6$ calculated 261.1. ESI MS, *m/z*: 284.1 $[M + Na]^+$.

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