SYNTHESIS OF TRICYCLES BASED ON 1,6-ANHYDRO-β-D-HEXOPYRANOSES FUSED WITH MORPHOLINE. 3,10,12-TRIOXA-6-AZATRICYCLO[7.2.1.$0^{2,7}$]DODECANES

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Dedicated to the memory of Professor Jaroslav Staněk.

The key step of the synthetic route was opening of the oxirane ring in 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose (**1**) with 2-chloroethanol to give 1,6-anhydro-4-*O*-(2-chloroethyl)-2-*O*-tosyl-β-D-glucopyranose (**2**), which was converted in four steps into 4-*O*-(2-aminoethyl)-1,6:2,3-dianhydro-β-D-mannopyranose (**6**). The latter compound underwent intramolecular cyclisation to afford the fused morpholine derivative 3-amino-1,6-anhydro-3-deoxy-3-*N*,4-*O*-ethylene-β-D-altropyranose (**7**) which gave the corresponding quaternary ammonium salt **11** by *N*-methylation. Acid cleavage of the 1,6-anhydro bond in **7** gave 3-acetamido-3-deoxy-3-*N*,4-*O*-ethylene-D-altropyranose (**9**).

Keywords: Carbohydrates; Heterocycles; 1,6-Anhydrosugars; Morpholines; Amino sugars; Oxiranes; Epoxides; Cyclizations; X-ray diffraction; Conformation analysis.

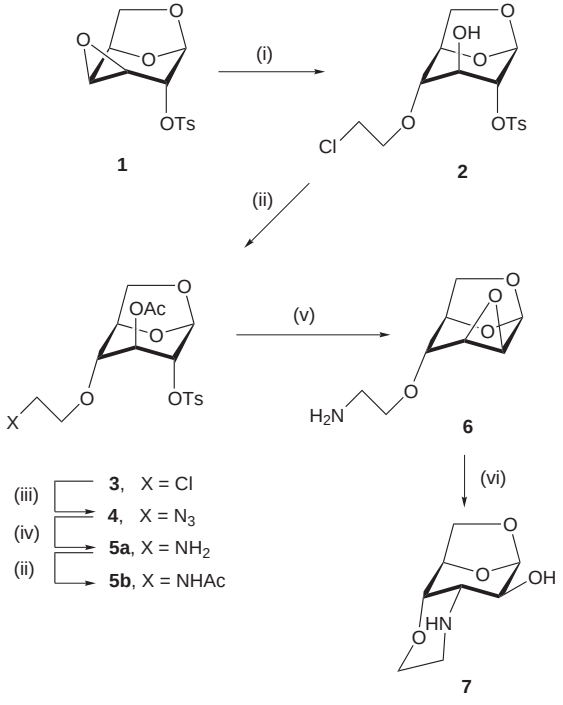
Morpholine derivatives are widely used as pharmaceuticals with a broad spectrum of biological effects. In these compounds, morpholine ring is frequently present as a *N*-substituted terminal group[1]. On the other hand, *C*-substituted morpholines also exhibit biological activity as follows from recent studies[2], for example, on hypocholesteromic and hypolipidemic activity[3].

A search for new biologically active compounds promted us to explore this field. Common requirements for chiral purity of new compounds turned our attention to the use of carbohydrates, particularly 1,6-anhydro-

pyranoses, as starting materials. Being chiral, they are used to advantage in stereoselective syntheses of natural compounds[4], their analogs[5,6], and polymers[7].

In this paper, we describe the synthesis of the amino sugars **7**–**11** containing the morpholine ring, fused with a carbohydrate skeleton. For their synthesis, we used reactions of dianhydro sugars[8] (sugar epoxides). Opening of the oxirane ring in these rigid systems proceeds *trans*-diaxially, affording enantiomerically and diastereomerically pure compounds.

As a starting compound for the synthesis (Scheme 1) of morpholine sugar derivatives we chose 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose (**1**), readily accessible in two steps from 1,6-anhydro-β-D-glucopyranose[9]. Its oxirane ring was cleaved with 2-chloroethanol under catalysis with boron trifluoride in refluxing dichloromethane to give the chloroethyl derivative **2** in 87% yield. The reaction proceeded with high regioselectivity, as with other nucleophiles[8,10]. After acetylation of **2**, the chlorine atom in **3** was re-

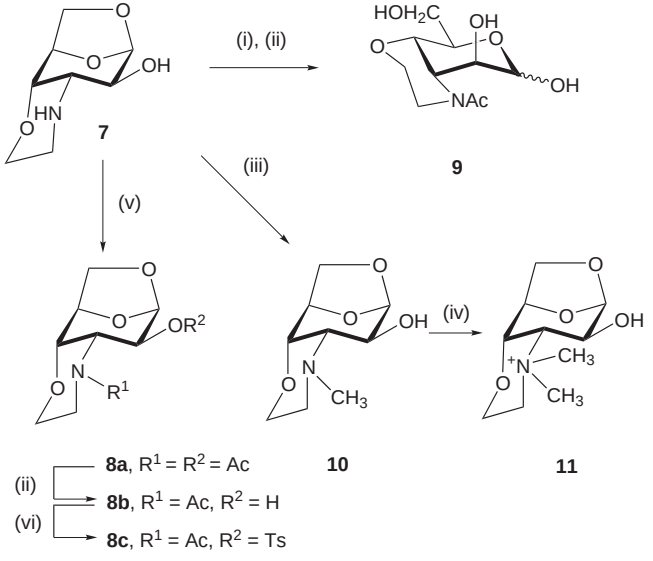


(i) $ClCH_2CH_2OH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 40 °C; (ii) Ac_2O, pyridine, r.t.; (iii) NaN_3, DMF, 90 °C; (iv) H_2, Pd/C, EtOH, r.t.; (v) MeONa, MeOH, r.t.; (vi) DBU, BuOH, 120 °C

SCHEME 1

placed by the azide group. This substitution was carried out in *N*,*N*-dimethylformamide with sodium azide in almost 90% yield, giving the azidoethyl derivative **4**, which was then hydrogenated over palladium catalyst in almost quantitative yield. Treatment of the resulting amine **5a** with methanolic sodium methoxide at room temperature afforded the amino epoxide **6**. Base-catalysed intramolecular opening of the epoxide ring by the amino group in compound **6** resulted in the formation of 3-amino-1,6-anhydro-3-deoxy-3-*N*,4-*O*-ethylene-β-D-altropyranose (**7**). Whereas nucleophilic bases (NaOH, *t*-BuOK) caused partial solvolysis of the oxirane ring (*cf.* ref.[11]), using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a non-nucleophilic base circumvented these difficulties to give **7** in 85% yield. *N*,*O*-Diacetate **8a** was prepared for X-ray analysis (Fig. 1) by acetylation of **7** in a mixture of acetic anhydride and sodium acetate.

Hydrolysis of the 1,6-anhydro bond in tricyclic compound **7** with aqueous hydrochloric acid failed because the equilibrium between compound **7** and the corresponding reducing sugar is completely shifted to **7**. This was verified by conversion of pure compounds **8a** and **9** into **7** in a hot aqueous 15% solution of HCl and demonstrated by TLC. Nevertheless, acetolysis in the mixture of trifluoroacetic acid and acetic anhydride at room temperature followed by Zemplén deacetylation gave the reducing sugar **9** (Scheme 2).



(i) CF_3COOH, Ac_2O, r.t.; (ii) MeONa, MeOH, r.t.; (iii) CH_2O, HCOOH, 80 °C; (iv) MeI, THF, r.t.; (v) Ac_2O, AcONa, 70 °C; (vi) TsCl, pyridine, r.t.

SCHEME 2

Quaternary ammonium salt **11** was prepared as a potential acetylcholine esterase inhibitor. Direct *N*-methylation of amine **7** with methyl iodide in the presence of $KHCO_3$ was complicated by isolation of the ammonium salt from the reaction mixture. That is why we decided to prepare **11** by partial *N*-methylation of amino compound **7** using the Eschweiler–Clark procedure, followed by *N*-methylation of the resulting *N*-methyl derivative **10** with methyl iodide in tetrahydrofuran at room temperature.

NMR AND X-RAY DISCUSSION

The structure of compounds **2**, **4**, **5b**, **6**, **7**, **8a**, **8b**, **8c**, **10**, **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 with D-*gluco* configuration **2**, **4**, **5** (mainly of proton H-1) were identified with selective homodecoupling experiments. In compound **2**, the higher observed values of coupling constants $J(2,3)$ = 3.7 Hz and $J(3,4)$ = 4.0 Hz (in comparison with typical lower values $J(2,3) \approx 1.8$ Hz and $J(3,4) \approx 1.8$ Hz found in **4**, **5b**) can be explained either by flattening of the pyranose ring, and/or a certain amount of the boat form in chair-boat equilibrium of compound **2**.

The presence of the oxirane ring in D-*manno*-compound **6** manifests itself by upfield shifts of protons and carbon atoms in positions 2 and 3 (δ(H) 3.46 and 3.19; δ(C) 54.35 and 47.66) and a characteristic *J*-value of *cis*-oxirane protons ($J(2,3)$ = 3.8 Hz). Also other proton coupling constants ($J(1,2)$ = 3.2; $J(3,4) < 0.5$, $J(4,5)$ = 1.1 Hz) are in agreement with the D-*manno* configuration.

The D-*altro* configuration of tricyclic compounds **7**, **8a**, **8b**, **8c**, **10**, **11** was proved by a large value of $J(2,3) \approx 9$ Hz (indicating a *trans*-diaxial arrangement of H-2, H-3) and low $J(3,4) \approx 4$ 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 46–60 in compounds **7**, **8a**, **8b**) also leads to an increase in both of the above mentioned vicinal couplings of H-3. The D-*altro* configuration of compound **7** is further supported by a high negative value of optical rotation ($[\alpha]_D$ –140.5). The morpholine ring fused in position 3,4 adopts a chair conformation as it is indicated by vicinal couplings in the O-CH_2-CH_2-N fragment (see Table II) and a long-range coupling (*ca* 1 Hz) of protons in the approximate byplanar four-bond fragment H(eq)-C-N-C(3)-H. The partial double-bond character of the tertiary amide bond in *N*-acetyl derivatives **8a**, **8b** and **8c** leads to the existence of two iso-

mers observed in their NMR spectra. They could be assigned (*Z*)- and (*E*)-isomer 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) of the corresponding protons in calculated energy minimized structures. In all cases, the population of (*Z*)-isomer prevails (55% in **8a**, 69% in **8b** and 61% in **8c**) in agreement with the lower energy calculated for (*Z*)-isomer using the MM+ method (HYPERCHEM program). It is interesting that also X-ray analysis of diacetate **8a** showed the presence of (*E*)- and (*Z*)-isomers in the 1:1 ratio (see Figs 1a and 1b). Bond distances and angles are unexceptional, witnessing electron delocalisation in N–C=O moiety (N–C_{Ac} being 0.1 Å shorter than the remaining two N–C bonds – see Table I) as well as a great similarity of two isomers. With the exception of orientation of *N*-acetyl moiety (torsion angles C*7–N*6–C*61–O*62 are 9.4(2) and –174.1(2)° for (*Z*)- and (*E*)-form, respectively) they differ slightly in orientation of the second acetyl plane, because of steric requirements of the methyl group of the (*E*)-isomer (dihedral angles between least-squares planes defined by C*61, N*6, O*62, C*63 and C*82, O*81, O*83, C*84 are 36.2(1) and 49.8(1)° for (*Z*)- (* = 1) and (*E*)-isomer (* = 2), respectively).

NMR spectra of compound **9** showed the presence of four species in solution obviously due to the equilibrium population of α- and β-anomers, each of them existing as a mixture of (*E*)- and (*Z*)-isomers of the tertiary acetamide grouping. This is supported by the signals of anomeric protons – *e.g.*, in compound **9**, two signals at δ 5.07 and 5.03 show large $J(1,2)$ = 6.5 and 7.4 Hz in accordance with a *trans*-diaxial orientation of H-1, H-2 in α-anomers and two additional signals at δ 5.35 and 5.33 with a small $J(1,2)$ = 3.6 Hz indicating *gauche*-orientation of H-1, H-2 in β-anomers. Complete structure assignment of all protons or carbons in **9** is extremely difficult.

In conclusion, new enantiomerically pure morpholine derivatives **7**–**11** were prepared using regio- and stereoselective reactions of dianhydro sugars obtained from 1,6-anhydro-β-D-glucopyranose. The synthetic route de-

TABLE I
Selected bond lengths (in Å) for (*Z*)- and (*E*)-isomers of **8a**

N16–C15	1.463(2)	N26–C25	1.463(2)
N16–C161	1.359(2)	N26–C261	1.368(2)
N16–C17	1.464(2)	N26–C27	1.464(2)
C161–O162	1.232(2)	C261–O262	1.230(2)

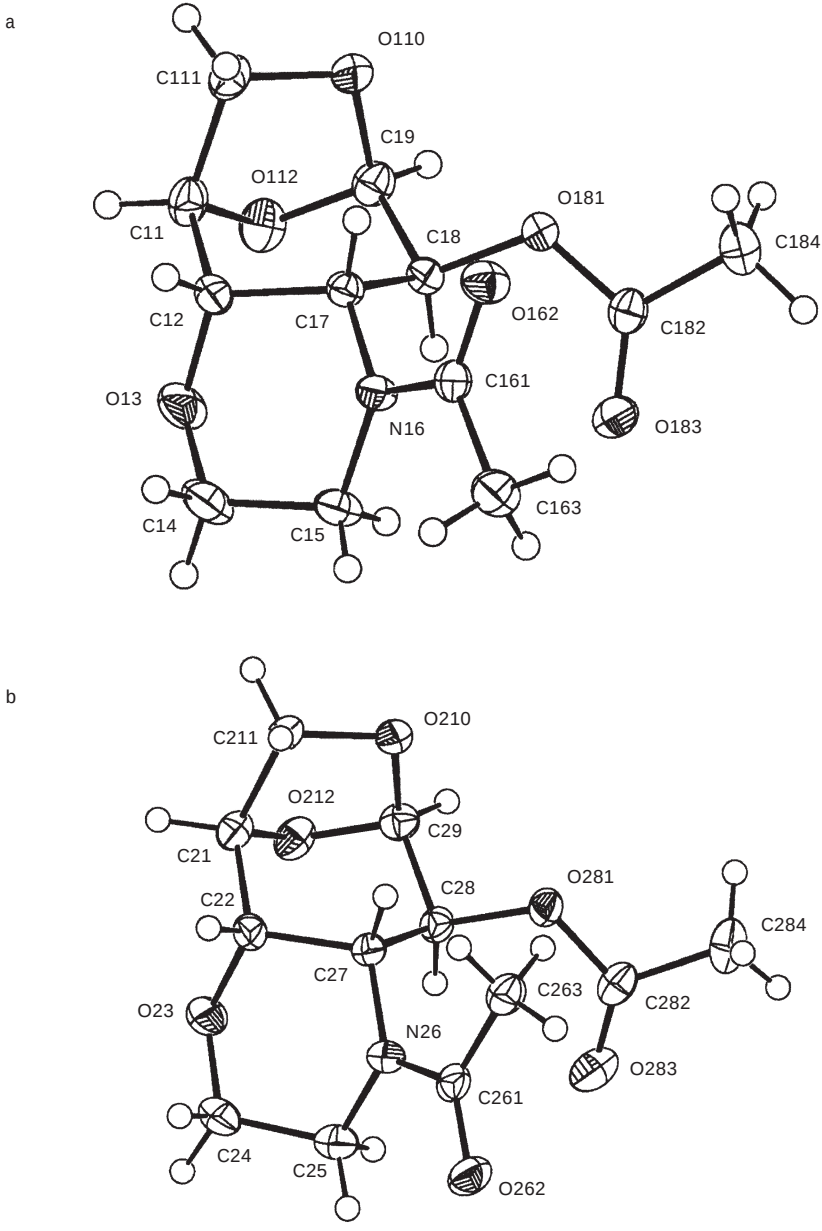


FIG. 1

View of (*Z*)-isomer (a) and (*E*)-isomer (b) of **8a**. The thermal ellipsoids are drawn on 50% probability level (PLATON [12])

scribed here allows an easy access to some other chiral heterocycles of potential biological activity.

EXPERIMENTAL

Melting points were determined with a Boetius 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, ^{13}C at 125.7 MHz) in $CDCl_3$ or D_2O. Chemical shifts (in ppm, δ-scale) were referenced to tetramethylsilane as internal standard; coupling constants (*J*) are given in Hz. 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 by 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.

1,6-Anhydro-4-*O*-(2-chloroethyl)-2-*O*-tosyl-β-D-glucopyranose (**2**)

To a solution of the tosylepoxide **1** (2.0 g, 6.7 mmol) in anhydrous dichloromethane (20 ml) boron trifluoride etherate (1.0 ml, 7.9 mmol) and 2-chloroethanol (2.2 ml, 33 mmol) were added. The mixture was refluxed for 4 h. The reaction course was monitored by TLC (ethyl acetate–toluene 1:2). The dichloromethane 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 2-chloroethanol were evaporated to obtain 2.2 g (87%) of **2**, m.p. 67–68 °C (ethanol–ether–light petroleum), $[\alpha]_D$ –39.0 (*c* 0.25, $CHCl_3$). For ^{1}H and ^{13}C NMR data, see Tables II–IV. For $C_{15}H_{19}ClO_7S$ (378.8) calculated: 47.57% C, 5.06% H, 8.46% S; found: 47.68% C, 5.16% H, 8.58% S.

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

Chloroethyl derivative **2** (1.4 g, 3.7 mmol) was dissolved in anhydrous pyridine (4.0 ml), the solution was cooled to 0 °C and acetic anhydride (1.1 ml, 9.0 mmol) was added dropwise. The solution was stirred at room temperature overnight and then poured into ice-water (30 ml) while stirring. The resulting precipitate was filtered off, washed with water (30 ml) and dried to give 1.5 g (98%) of **3**, m.p. 111–112 °C (acetone–ether–light petroleum), $[\alpha]_D$ –24.8 (*c* 0.20, $CHCl_3$). For $C_{17}H_{21}ClO_8S$ (420.9) calculated: 48.52% C, 5.03% H, 7.62% S; found: 48.37% C, 5.13% H, 7.41% S.

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

Compound **3** (1.4 g, 3.7 mmol) and sodium azide (470 mg, 6.8 mmol) were dissolved in anhydrous *N*,*N*-dimethylformamide (5.0 ml) and the mixture was heated to 90 °C for 3 h under argon atmosphere, while stirring. After evaporation of *N*,*N*-dimethylformamide, water (30 ml) was added to the residue. The insoluble product was filtered off and recrystallized from acetone–ether–light petroleum affording 1.2 g (89%) of azide derivative **4**, m.p.

TABLE II

^{1}H NMR chemical shifts (in ppm, δ-scale) of compounds **2**, **4**–**8**, **10** (in $CDCl_3$) and **11** (in D_2O)

Comp.	H-1	H-2	H-3	H-4	H-5	H-6en	H-6ex	OCH_2	CH_2N	OAc (NAc)	OTos
2[a]	5.31 t	4.21 dm	3.93 m	3.34 dd	4.63 dq	3.93 dd	3.70 dd	–	–	–	2.46 bs (3 H) 7.83 m (2 H) 7.36 m (2 H)
4	5.37 bt	4.31 m	4.95 m	3.26 m	4.65 m	3.91 dd	3.76 ddd	3.84 ddd 3.71 ddd	3.46 ddd 3.32 ddd	2.07 s	2.45 bs (3 H) 7.83 m (2 H) 7.35 m (2 H)
5b[b]	5.32 t	4.24 q	4.92 p	3.19 m	4.61 dm	3.92 dd	3.76 dd	3.69 m 3.67 m	3.51 dddd 3.41 dddd	2.06 s (2.01 s)	2.46 bs (3 H) 7.81 m (2 H) 7.37 m (2 H)
6[c]	5.72 d	3.46 bt	3.19 dd	3.60 b	4.53 dm	3.70 dd	3.74 dd	3.71 t (2 H)	2.95 t (2 H)	–	–
7	5.45 d	4.02 dd	2.92 dd	3.71 dd	4.55 ddd	3.78 dd	3.81 dd	3.95 bdd 3.68 dt	3.11 ddd 2.72 ddd	–	–
(*Z*)-**8a**	5.44 d	5.24 dd	4.93 ddd	3.57 bdd	4.62 ddd	3.96 dd	3.88 dd	4.03 ddd 3.56 ddd	3.66 ddd 3.47 dm	2.04 s (2.04 s)	–
(*E*)-**8a**	5.52 d	5.26 dd	3.98 bdd	3.65 dd	4.66 dt	3.90 m	3.90 m	4.03 ddd 3.52 ddd	4.42 ddt 2.98 ddd	2.09 s (2.19 s)	–
(*Z*)-**8b**[d]	5.44 d	3.92 ddd	4.65 bdd	3.56 dd	4.60 dt	3.87 m	3.87 m	4.03 m 3.58 m	3.56 m (2 H)	(2.16 s)	–
(*E*)-**8b**	5.48 d	4.08 ddd	3.77 bdd	3.61 dd	4.62 ddd	3.86 dd	3.90 dd	4.02 ddd 3.51 m	4.40 dm 2.95 ddd	(2.23 s)	–
(*Z*)-**8c**	5.61 d	4.63 dd	3.92 dd	3.58 dd	4.60 ddd	3.88 m	3.88 m	3.89 m 3.42 m	4.13 dm 2.18 ddd	(2.09 s)	2.46 bs (3 H) 7.72 m (2 H) 7.36 m (2 H)
(*E*)-**8c**	5.39 d	4.84 dd	5.05 bdd	3.59 dd	4.57 ddd	3.92 dd	3.83 dd	3.99 ddd 3.53 dt	3.41 m (2 H)	(2.05 s)	2.44 bs (3 H) 7.78 m (2 H) 7.34 m (2 H)
10[e]	5.38 d	4.08 dd	2.66 bdd	3.70 dd	4.56 ddd	3.74 dd	3.81 dd	3.86 ddd 3.76 ddd	2.94 ddd 2.47 ddd	–	–
11[f]	5.49 d	4.34 dd	3.52 ddd	4.45 dd	4.88 ddd	3.97 dd	3.86 dd	4.24 ddd 4.13 bdd	3.85 m 3.43 dm	–	–

Additional signals: [a] 2.73 d (OH); 3.85 m ($O\text{-}CH_2$); 3.63 m (CH_2Cl). [b] 6.15 b (NH). [c] 1.85 b (NH_2). [d] 3.16 d (2-OH). [e] 2.63 s ($N\text{-}CH_3$). [f] 3.42 s and 3.33 s ($N(CH_3)_2$). Ratio of (*Z*)- and (*E*)-isomers: 55% (*Z*)-**8a**, 45% (*E*)-**8a**, 69% (*Z*)-**8b**, 31% (*E*)-**8b**, 61% (*Z*)-**8c**, 39% (*E*)-**8c**.

TABLE III

^{1}H NMR coupling constants (*J*, Hz) of compounds **2**, **4**–**8**, **10** (in $CDCl_3$) and **11** (in D_2O)

Comp.	*J*(1,2)	*J*(2,3)	*J*(3,4)	*J*(4,5)	*J*(5,6n)	*J*(5,6x)	*J*(6n,6x)	O-CHaHb-CHcHd-N					
								J(a,b)	*J*(a,c)	*J*(a,d)	*J*(b,c)	*J*(b,d)	*J*(c,d)
2[a]	1.3	3.7	4.0	1.4	1.0	5.4	7.4	–	–	–	–	–	–
4[b]	1.7	1.8	1.8	1.8	1.1	5.7	7.6	10.5	3.6	5.5	7.5	3.4	13.3
5b[c]	1.7	1.7	1.7	1.5	1.0	5.7	7.7	*	3.4	6.2	6.9	4.0	14.4
6[d]	3.2	3.8	≤0.5	1.1	2.0	6.5	7.1	*	5.2	5.2	5.2	5.2	*
7	1.8	9.3	3.8	2.4	1.3	5.2	7.9	11.4	3.4	1.2	12.0	2.4	12.9
(*Z*)-**8a**	1.7	9.7	3.9	2.4	1.0	5.5	8.0	11.4	3.2	1.4	12.2	2.4	13.7
(*E*)-**8a**	1.6	9.7	3.9	2.3	*	*	*	11.5	3.0	1.4	12.3	2.8	14.3
(*Z*)-**8b**[e]	1.8	9.6	4.2	2.3	*	*	*	*	*	*	*	*	*
(*E*)-**8b**[f]	1.8	8.9	3.9	2.3	1.1	5.3	8.1	11.7	1.1	3.6	12.3	2.7	14.0
(*Z*)-**8c**[g]	1.6	9.5	3.8	2.3	*	*	*	*	1.1	3.6	12.2	2.8	14.3
(*E*)-**8c**	1.8	9.7	3.9	2.4	0.8	5.4	8.1	11.5	1.4	3.0	11.1	4.0	*
10[h]	2.0	8.8	3.7	2.4	1.0	5.4	7.9	11.3	3.6	1.3	11.8	2.6	12.8
11[i]	2.2	9.3	3.4	2.8	1.1	5.6	8.7	13.8	12.2	2.3	4.1	1.3	13.7

* *J*-Value could not be determined. Additional coupling constants: [a] *J*(1,3) = 1.1; *J*(1,4) < 0.5; *J*(1,6n) ≤ 0.3; *J*(1,6x) < 0.5; *J*(2,4) = 0.7; *J*(3,OH) = 5.1; *J*(3,5) = 1.1. [b] *J*(1,3) = 1.4; *J*(1,4) = 0.7; *J*(1,6n) ≤ 0.2; *J*(1,6x) = 0.5; *J*(2,4) = 1.0; *J*(2,5) = 0.5; *J*(3,5) = 1.7; *J*(NH,Hc) = 5.1; *J*(NH,Hd) = 5.1. [c] *J*(1,3) = 1.4; *J*(1,4) ≤ 0.5; *J*(1,6n) ≤ 0.2; *J*(1,6x) ≤ 0.2; *J*(2,4) ≈ 1.5; *J*(3,5) = 1.6. [d] *J*(3,5) = 1.7; *J*(2,4) = 0.6. [e] *J*(2,OH) = 7.6. [f] *J*(2,OH) = 6.8; *J*(3,Hc) = 1.1. [g] *J*((3,Hc) = 1.1. [h] *J*(3,Hd) = 0.7. [i] *J*(3,Hd) = 1.3; *J*(NMe,Hd) = 0.8. Ratio of (*Z*)- and (*E*)-isomers: 55% (*Z*)-**8a**, 45% (*E*)-**8a**, 69% (*Z*)-**8b**, 31% (*E*)-**8b**, 61% (*Z*)-**8c**, 39% (*E*)-**8c**.

TABLE IV
^{13}C NMR data (in ppm, δ-scale) of compounds **2**, **4**–**8**, **10** (in $CDCl_3$) and **11** (in D_2O)

Comp.	C-1	C-2	C-3	C-4	C-5	C-6	Other carbons
2	99.98	79.46	70.39	80.51	75.26	66.60	OCH_2CH_2Cl: 70.39, 42.96 OTos: 145.44, 132.94, 130.02(2), 127.97(2), 21.68
4	99.02	74.14	68.50	76.47	74.21	65.31	OCH_2CH_2N: 68.57, 50.63 OAc: 169.11, 20.85 OTos: 145.33, 133.24, 129.93(2), 127.97(2), 21.66
5b	98.84	74.22	68.84	75.57	74.04	65.23	OCH_2CH_2N: 68.73, 39.20 NAc: 169.06, 23.15 OAc: 169.06, 20.82 OTos: 145.54, 132.98, 130.05(2), 127.90(2), 21.67
6	97.59	54.35	47.66	75.05	71.44	65.78	OCH_2CH_2N: 72.67, 41.90
7	102.04	67.31	53.04	74.19	76.05	65.79	OCH_2CH_2N: 67.53, 39.44
(*Z*)-**8a**	100.22	69.13	47.11	74.48	75.66	65.85	OCH_2CH_2N: 66.60, 42.14 NAc: 171.06, 21.58 OAc: 169.54, 21.04
(*E*)-**8a**	99.64	69.78	51.93	74.48	75.62	66.07	OCH_2CH_2N: 66.94, 36.64 NAc: 171.06, 20.90 OAc: 170.04, 20.75
(*Z*)-**8b**	102.08	69.96	49.84	74.62	75.41	65.80	OCH_2CH_2N: 66.46, 42.25 NAc: 171.06, 21.56
(*E*)-**8b**	102.14	68.42	55.19	74.30	75.61	65.90	OCH_2CH_2N: 66.88, 36.86 NAc: 171.06, 21.56
(*Z*)-**8c**	99.91	75.20	51.94	74.82	75.51	66.13	OCH_2CH_2N: 66.88, 35.88 NAc: 169.23, 21.65 OTos: 145.64, 133.31, 130.21(2), 128.03(2), 21.65
(*E*)-**8c**	99.96	75.56	46.11	74.79	75.56	65.94	OCH_2CH_2N: 66.70, 41.85 OAc: 169.23, 21.14 OTos: 145.06, 132.16, 129.85(2), 127.91(2), 21.69
10	102.00	66.95	59.95	73.12	75.93	65.51	OCH_2CH_2N: 65.47, 47.68 NMe: 44.34
11	104.02	68.80	70.91	72.30	78.44	67.43	OCH_2CH_2N: 63.38, 60.28 NMe_2: 59.12, 53.58

Ratio of (*Z*)- and (*E*)-isomers: 55% (*Z*)-**8a**, 45% (*E*)-**8a**, 69% (*Z*)-**8b**, 31% (*E*)-**8b**, 61% (*Z*)-**8c**, 39% (*E*)-**8c**.

103–104 °C, $[\alpha]_D$ –30.2 (*c* 0.24, $CHCl_3$). For ^1H and ^{13}C NMR data, see Tables II–IV. For $C_{17}H_{21}N_3O_8S$ (427.4) calculated: 47.77% C, 4.95% H, 9.83% N, 7.50% S; found: 47.91% C, 5.13% H, 9.61% N, 7.27% S.

3-*O*-Acetyl-4-*O*-(2-aminoethyl)-1,6-anhydro-2-*O*-tosyl-β-D-glucopyranose (**5a**) and 4-*O*-(2-Acetamidoethyl)-3-*O*-acetyl-1,6-anhydro-2-*O*-tosyl-β-D-glucopyranose (**5b**)

Azide derivative **4** (1.2 g, 3.1 mmol) was hydrogenated in ethanol (50 ml) over Pd/C (60 mg, 5%) at atmospheric pressure for 24 h. The catalyst was removed by filtration, washed with ethanol, and 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) to give 1.3 g of syrupy **5a** which was used without further purification.

To a solution of amine derivative **5a** (100 mg, 0.25 mmol) in anhydrous pyridine (1.0 ml) cooled to 0 °C, acetic anhydride (66 µl, 0.70 mmol) was added while stirring. The mixture was set aside at room temperature overnight. Then ice-water (8.0 ml) was added, and the solution was extracted with dichloromethane (3 × 4 ml). Combined organic phases were dried and evaporated. Chromatography of the residue on a silica gel column (5 g) in methanol–chloroform (1:20) afforded 88 mg (79%) of syrup **5b**, $[\alpha]_D$ –38.0 (*c* 0.28, $CHCl_3$). For ^1H and ^{13}C NMR data, see Tables II–IV.

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

Compound **5a** (1.2 g, 2.6 mmol) was dissolved, while stirring, in 0.5 M methanolic sodium methoxide (11 ml) and the solution was set aside at room temperature overnight. Then the mixture was neutralized with acetic acid to pH ≈ 7. After evaporation of the solvent, methanol was replaced with dichloromethane (5 ml). Insoluble salts were filtered off and washed with dichloromethane (1 ml). The filtrate was concentrated and purified on a short silica gel column (12 g) in ethyl acetate–methanol (3:1) to obtain 460 mg (94%) of syrup **6**, $[\alpha]_D$ –31.5 (*c* 0.25, $CHCl_3$). For ^1H and ^{13}C NMR data, see Tables II–IV.

3-Amino-1,6-anhydro-3-deoxy-3-*N*,4-*O*-ethylene-β-D-altropyranose (**7**)

A solution of aminoepoxide **6** (460 mg, 2.4 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-en (0.4 ml, 2.7 mmol) in butan-1-ol (14 ml) was refluxed for 2 h. The solvent was evaporated and residue was chromatographed on a silica gel column (25 g) in methanol–ethyl acetate (1:3) to give 390 mg (85%) of syrupy compound **7**, $[\alpha]_D$ –140.5 (*c* 0.16, MeOH). For ^1H and ^{13}C NMR data, see Tables II–IV. EI HRMS, *m/z*: calculated for $C_8H_{13}NO_4$ 187.084458; found 187.085928 (M^+).

3-Acetamido-2-*O*-acetyl-1,6-anhydro-3-deoxy-3-*N*,4-*O*-ethylene-β-D-altropyranose (**8a**)

Amine derivative **7** (280 mg, 1.4 mmol) was dissolved in a suspension of anhydrous sodium acetate (400 mg, 4.9 mmol) in acetic anhydride (1.0 ml). The mixture was heated to 70 °C for 30 min, then cooled down and a saturated solution of sodium hydrogencarbonate (10 ml) was added in several portions. After decomposition of acetic anhydride, the mixture was extracted with dichloromethane (3 × 5 ml). Combined organic layers were dried and evapo-

rated to give 390 mg (96%) of crystalline **8a**, m.p. 142–144 °C (ethanol–ether–light petroleum), $[\alpha]_D$ –23 (*c* 0.18, $CHCl_3$). For ^1H and ^{13}C NMR data, see Tables II–IV. For $C_{12}H_{17}NO_6$ (271.3) calculated: 53.13% C, 6.32% H, 5.16% N; found: 53.13% C, 6.49% H, 5.05% N.

Crystal Structure Analysis of Compound **8a**

A colourless crystal of dimensions 0.4 × 0.28 × 0.25 mm is triclinic, space group *P*1, $C_{12}H_{17}NO_6$, M = 271.27, a = 8.2590(3) Å, b = 8.3350(2) Å, c = 10.6890(4) Å, α = 69.189(2)°, β = 70.444(2)°, γ = 72.717(2)°, V = 634.74(4) Å^3, Z = 2, D_x = 1.419 Mg m^{-3}.

All data were collected on a Nonius KappaCCD diffractometer using monochromatized MoKα radiation (λ = 0.71073 Å) at 150(2) K. An absorption was neglected (μ = 0.114 mm^{-1}); a total of 8298 measured reflections in the range h = –10 to 10, k = –9 to 10, l = –13 to 11 (θ_{max} = 27.5°), from which 4446 were unique (R_{int} = 0.033) and 4228 observed according to the $I > 2\sigma(I)$ criterion. Cell parameters from 5074 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 were found on difference Fourier map and refined isotropically except those of methyl, which were recalculated into idealised positions and fixed during refinement (riding model) with assigned temperature factors H_{iso}(H) = 1.5 U_{eq} (pivot atom). The refinement converged (Δ/σ_{max} = 0.001) to R = 0.029 for observed reflections and *wR* = 0.068, *GOF* = 1.064 for 435 parameters and all 4443 reflections. The final difference map displayed no peaks of chemical significance ($\Delta\rho_{max}$ = 0.156, $\Delta\rho_{min}$ = –0.202 e Å^{-3}). The absolute structure was assigned by reference to the known chiral centre. (Flack parameter = 0.4(5).) CCDC 200816 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-deoxy-3-*N*,4-*O*-ethylene-β-D-altropyranose (**8b**)

A solution of diacetate **8a** (300 mg, 1.31 mmol) in 0.1 M sodium methanolate (6 ml) 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 250 mg (98%) of crystalline **8b**, m.p. 195–197 °C (ethanol–ether), $[\alpha]_D$ –38.8 (*c* 0.20, $CHCl_3$). For ^1H and ^{13}C NMR data, see Tables II–IV. For $C_{10}H_{15}NO_5$ (229.2) calculated: 52.40% C, 6.60% H, 6.11% N; found: 52.11% C, 6.78% H, 6.15% N.

3-Acetamido-1,6-anhydro-3-deoxy-3-*N*,4-*O*-ethylene-2-*O*-tosyl-β-D-altropyranose (**8c**)

Compound **8b** (180 mg, 0.79 mmol) was dissolved in anhydrous pyridine (2.0 ml) and tosyl chloride (225 mg, 1.18 mmol) was added while stirring. The reaction mixture was set aside at room temperature overnight and then poured into water (15 ml). Crystalline tosylate was filtered off, washed with water (10 ml) and dried to give 255 mg (85%) of **8c**, m.p. 183–185 °C (acetone–ether–light petroleum), $[\alpha]_D$ –36.6 (*c* 0.34, $CHCl_3$). For ^1H and ^{13}C NMR data, see Tables II–IV. For $C_{17}H_{21}NO_7S$ (383.4) calculated: 53.25% C, 5.52% H, 3.65% N, 8.36% S; found: 53.63% C, 5.73% H, 3.77% N, 8.40% S.

3-Acetamido-3-deoxy-3-*N*,4-*O*-ethylene-D-altropyranose (**9**)

To a solution of diacetate **8a** (100 mg, 0.37 mmol) in acetic anhydride (3.3 ml) was added trifluoroacetic acid (0.33 ml, 4.3 mmol) and the mixture was stirred overnight. The solvents were removed *in vacuo* and the residue was separated between a saturated solution of sodium hydrogencarbonate (2 ml) and chloroform (2 ml). The aqueous layer was then extracted by means of chloroform (2 × 2 ml). Combined organic layers were dried and evaporated. The crude product thus obtained was deacetylated in a solution of 0.1 M methanolic sodium methanolate (2.5 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 (3 g) in ethyl acetate–methanol (4:1) to give 55 mg (60%) of **9**, $[\alpha]_D$ +26.3 (*c* 0.24, MeOH). FAB MS, *m/z*: calculated for $C_8H_{16}NO_6$ 247.2; found 270.1 $[M + Na]^+$.

1,6-Anhydro-3-deoxy-3-*N*,4-*O*-ethylene-3-methylamino-β-D-altropyranose (**10**)

Compound **7** (380 mg, 2.0 mmol) was dissolved in 85% formic acid (0.15 ml, 3.3 mmol) and a solution of 35% formaldehyde (0.23 ml, 3.1 mmol) was added. The mixture was heated to 80 °C overnight. After cooling down, the solution was acidified with 6 M hydrochloric acid (0.5 ml) and extracted with chloroform (2 × 1 ml). Evaporation of combined extracts afforded 5 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). Combined chloroform extracts were dried and evaporated to give 280 mg (68%) of **10**, m.p. 113–115 °C (ethyl acetate–ether–light petroleum), $[\alpha]_D$ −140.9 (*c* 0.26, $CHCl_3$). For ^1H and ^{13}C NMR data, see Tables II–IV. For $C_9H_{15}NO_4$ (201.2) calculated: 53.72% C, 7.51% H, 6.96% N; found: 53.37% C, 7.74% H, 6.76% N.

1,6-Anhydro-3-deoxy-3-O,4-*N*-ethylene-3-(*N*,*N*-dimethylammonio)-β-D-altropyranose Iodide (Alternative Name (1*R*,2*S*,7*S*,8*S*,9*R*)-8-Hydroxy-6,6-dimethyl-3,10,12-trioxa-6-azoniatricyclo[7.2.1.$0^{2,7}$]dodecane Iodide) (**11**)

The crude product of *N*-methylation **10** (280 mg, 1.4 mmol) was dissolved in tetrahydrofuran (3 ml), methyl iodide (300 µl, 4.8 mmol) was added and the mixture was kept at room temperature for 24 h. Precipitated product was filtered off and washed with tetrahydrofuran (2 ml) to give 440 mg (92%) of **11**, m.p. 276–277 °C (decomp., ethanol), $[\alpha]_D$ −74.4 (*c* 0.17, MeOH). For ^1H and ^{13}C NMR data, see Tables II–IV. For $C_{10}H_{18}INO_4$ (343.2) calculated: 35.00% C, 5.29% H, 4.08% N; found: 34.74% C, 5.38% H, 3.83% N.

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