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The synthesis of derivatives of 2,4-diamino-2,4,6-trideoxy-D-*gulo*- and L-*altro*-hexopyranoses

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Abstract

Syntheses of two derivatives of two 2,4-diamino-2,4,6-trideoxyhexoses having the D-*gulo* (**16**) and L-*altro* (**29**) configuration have been described. Derivative **16** was obtained by two routes starting from benzyl 2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside. Derivative **29** was obtained from 3,4-di-*O*-acetyl-L-rhamnal in a 10-step reaction sequence.

Keywords: 2,4-Diamino-2,4,6-trideoxy-D-gulopyranose; 2,4-Diamino-2,4,6-trideoxy-L-altropyranose

1. Introduction

2,4-Diamino-2,4,6-trideoxyhexoses occur in Nature as components of bacterial polysaccharides. Most of them belong to the D configurational series, for example, 2,4-diamino-2,4,6-trideoxy-D-glucose, isolated from *Bacillus subtilis* polysaccharide [1], or its D-*galacto* stereoisomer, a component of polysaccharide antigens of *Streptococcus pneumoniae* [2] and *Shigella sonnei* [3]. On the other hand, 2,4-diamino-2,4,6-trideoxyhexoses of D-*gulo* (**1**) and L-*altro* (**2**) configuration can be recognized as the C-4–C-9 fragment of the structure of 5,7-diamino-3,5,7,9-tetradeoxy-D-*glycero*-L-*galacto*- and L-*glycero*-L-*manno*-nonulosonic acid, respectively, recently identified as constituents of O-antigenic lipopolysaccharides (LPS) of Gram-negative bacteria *Pseudomonas aeruginosa* [4], *Shigella boydii* [5], and *Vibrio cholerae* [6]. We thought that sugars **1** and **2** could be used for the synthesis (or biosynthesis) of the above-mentioned

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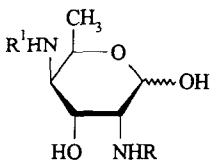
nonulosonic acids, and also as model compounds for structural investigations of bacterial polysaccharides.



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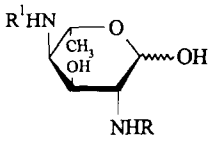

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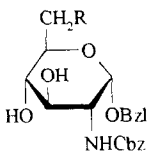
2. Results and discussion

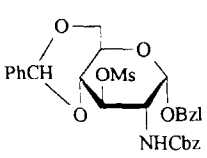
Although many syntheses of 2,4-diamino-2,4,6-trideoxyhexoses have been described in the literature [7] no synthetic approach to the D-*gulo* stereoisomer **1** has been reported so far. In our synthesis D-glucosamine served as the substrate.

In the first step benzyl 2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (**3**) [8] was converted into the 6-bromo-6-deoxy derivative (**4**) in high yield, via the Appel reaction with carbon tetrabromide–triphenylphosphine [9]. Alternatively, 4-*O*-benzoyl-3-*O*-mesyl-**4** (**7**) could be prepared by the *N*-bromosuccinimide (NBS) cleavage [10] of the 4,6-*O*-benzylidene ring in **6** [11]. Reduction of **4** with tributyltin hydride led to **5** (89%) which was next treated with 1-(2,4,6-triisopropylbenzenesulfonyl)imidazole (TPSI) [9] to afford the required epoxide **10** in low yield (13%). In the second route, reduction of the bromine atom in **7** with tributyltin hydride gave 6-deoxy derivative **8** (84%). However, attempts to transform **8** into the epoxide **10** via the standard procedure (sodium hydride or potassium carbonate) were unsuccessful. Therefore, a two-step procedure had to be employed. In the first step, the benzoyl residue at O-4 was removed by treatment with potassium carbonate, and in the second, treatment of the liberated alcohol **9** with sodium hydride furnished the epoxide **10** in 53% yield.

A better method of preparation of **10** was found in the epoxidation of the olefin **11** [12]. Reaction with 3-chloroperoxybenzoic acid furnished epoxide **10** as a single product in a quantitative yield. Full stereoselectivity in the oxirane ring formation on the side of the vicinal 2-amido group has also been noted [13] during the reaction of ethyl 2,3,4-trideoxy-2-trichloroacetamido-α-D-*threo*-hex-3-enopyranoside with 3-chloroperoxybenzoic acid, leading to the corresponding epoxide of D-*talo* configuration. This is another example of the steering effect of the 2-amido group (via a hydrogen bond between the NH group and one of the oxygen atoms of the peroxy acid) similar to that of the hydroxyl group in allylic-type alcohols [14].



3 R = OH
4 R = Br
5 R = H



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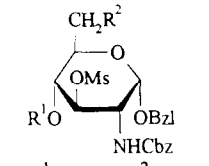
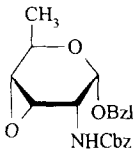


7 R^1 = Bz, R^2 = Br
8 R^1 = Bz, R^2 = H
9 R^1 = R^2 = H



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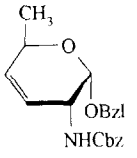

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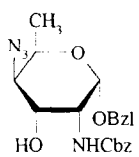
Nucleophilic *trans*-diaxial cleavage of the oxirane ring in **10**, using sodium azide/ammonium chloride, led to the 4-azido derivative **12** (70%) as the main product, accompanied by its 3-azido regioisomer **13** (13%). The azido group in both sugars underwent smooth reduction with sodium borohydride/nickel(II) chloride [15] to afford, after acetylation, the α-D-*gulo* derivative **14** and its α-D-*gluco* isomer **15**. Catalytic hydrogenation of **14** in ethanol in the presence of acetic anhydride gave 2,4-di-acetamido-3-*O*-acetyl-2,4,6-trideoxy-D-gulopyranose (**16**).



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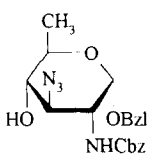

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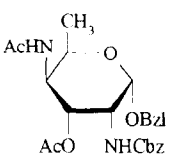

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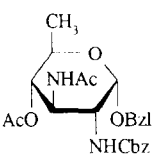

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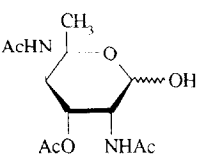
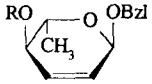


16

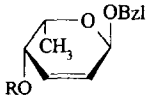
Little information is available in the literature on the synthesis of the L-*altro* isomer **2**. Sharon and co-workers [16] have reported the conversion of methyl 2-*O*-acetyl-3,4-di-*O*-methanesulfonyl-α-L-fucopyranoside into methyl 2,4-diacetamido-2,4,6-trideoxy-α-L-altropyranoside by a reaction sequence involving formation of the 2,3-epoxide, displacement of the 4-*O*-mesyl group by the azide ion, nucleophilic cleavage of oxirane ring with sodium azide, followed by reduction of both azide groups and acetylation. The compound thus obtained was isolated in ca. 10% yield as a crude product contaminated with a non-separable impurity. Another product isolated in this preparation was methyl 2,4-diacetamido-2,4,6-trideoxy-α-L-idopyranoside, formation of which was supposed [16] to originate from an intermediate 3,4-epoxide formed during the azidolysis of methyl 2,3-anhydro-6-deoxy-4-*O*-methanesulfonyl-α-L-gulopyranoside.

Our synthesis of the L-*altro* isomer **2** started from 3,4-di-*O*-acetyl-L-rhamnal which was converted into benzyl 4-*O*-acetyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside **17** [17] by Ferrier [18] rearrangement. The next step based on the Overman sigmatropic rearrangement of 4-trichloroacetimidates of alkyl hex-2-enopyranosides to alkyl 2-deoxy-2-trichloroacetamido-hex-3-enopyranosides [19], with retention of the configuration of the allylic substituents. Before that, the configuration of 4-OH group in **18** had to be inverted. To this end, alcohol **18**, obtained by deacetylation of **17** with potassium carbonate in methanol, was treated with *p*-nitrobenzoic acid/diethyl azodicarboxylate/triphenylphosphine [20] to give **19**. Removal of the ester group as above afforded alcohol **20**, which was converted into trichloroacetimidate **21** by

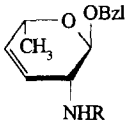
treatment with trichloroacetonitrile/sodium hydride in dichloromethane solution. Sigmatropic rearrangement [19] of **21** (1,2-dichlorobenzene, 160°C) led to **22** (68%).



17 R = Ac
18 R = H



19 R = p-NO_2-C_6H_4-CO
20 R = H
21 R = -$C(CCl_3)$=NH

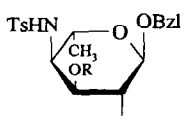


22 R = $COCCl_3$
23 R = H
24 R = $COCH_3$

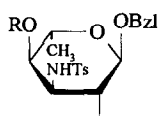
Addition of 3-OH and 4-NHR groups to the double bond in **22** *trans* to the allylic substituent should be possible in one step by the Sharpless [21] oxyamination procedure. This assumption was based on the previous results [21,22] of oxyamination of an analogue of **22** possessing a hydroxyl group in the allylic position. However, oxyamination of **22** led to a small amount of product from which the desired substance could not be isolated. Evidently, replacement of the 2-OH group by the 2-$NHCOCCl_3$ substituent caused a distinctly reduced susceptibility of the substrate towards the oxyamination reagent. This result confirmed the earlier observations on the suppressing influence of an electronegative substituent on the oxyamination reaction [21,22]. Therefore the trichloroacetyl residue was removed with sodium hydroxide in ethanol [23] to yield the free amine **23** and, after acetylation to **24**, the product was treated with the chloramine T/osmium tetraoxide reagent using the modified phase-transfer procedure [24]. Under these conditions the desired oxyamination product **25** was formed in 39% yield accompanied by its regioisomer **26** (23%). A small amount (4%) of 3,4-dihydroxylated products was also isolated; these were not investigated further.

The structures of **25** and **26** were readily deduced from the ^1H NMR data. In particular, the chemical shifts and coupling constants observed for H-4 (δ 3.38, $J_{4,5}$ 9.6 Hz) and H-3 (δ 4.43, $J_{3,4}$ 3.4 Hz) in **27** (acetylated **25**), as well as those for H-3 (δ 3.93, $J_{3,4}$ 3.3 Hz) and H-4 (δ 4.58, $J_{4,5}$ 10.0 Hz) in the regioisomer **28** confirmed their structure.

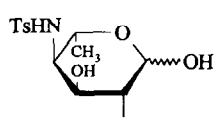
Reductive debenzylation of **25** yielded 2-acetamido-2,4,6-trideoxy-4-*p*-toluenesulfonamido-α,β-L-altropyranose (**29**). Thus, both 2,4-diamino-2,4,6-trideoxyhexoses have been obtained in a form suitable for further reactions, e.g., for chain elongation.



25 R = H
27 R = Ac



26 R = H
28 R = Ac



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3. Experimental

General methods.—The solvents were purified and dried according to literature methods. TLC was performed on Silica Gel HF-254 and column chromatography on

Silica Gel 230–400 mesh (Merck). ^{1}H NMR spectra were recorded with a Bruker AM-500 (500 MHz) or Varian AC-200 (200 MHz) spectrometer in C_6D_6, Me_2SO-d_6, and $CDCl_3$ with Me_4Si as internal standard. High-resolution mass spectra (HR-MS) were measured with an AMD-604 mass spectrometer. IR spectra were recorded on a Perkin–Elmer 1640 FT-IR spectrophotometer. Optical rotations were measured with a JASCO DIP-360 automatic polarimeter.

Benzyl 2-benzyloxycarbonylamino-6-bromo-2,6-dideoxy-α-D-glucopyranoside (**4**).—To a solution of **3** [8] (2.06 g, 5.1 mmol) in pyridine (50 mL) were added triphenylphosphine (5.40 g) and CBr_4 (3.40 g) at −5°C. The mixture was stirred for 2 h at 60–65°C, whereupon MeOH (40 mL) was added. After evaporation to dryness, the residue was purified by column chromatography (20:1 $CHCl_3$–MeOH) to yield **4** (1.31 g, 55%); mp 185–186°C; ^{1}H NMR (Me_2SO-d_6), δ 5.01 (s, 2 H, Cbz), 4.81 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.70 and 4.45 (ABq, 2 H, J 12.0 Hz, PhCH_2), 3.75 (d, 1 H, $J_{NH,2}$ 8.8 Hz, NH), 3.52–3.65 (m, 4 H, H-3,4,6a,6b), 3.45 (m, 1 H, H-2), 3.15 (m, 1 H, H-5). Anal. Calcd for $C_{21}H_{24}BrNO_6$: C, 54.09; H, 5.19; Br, 17.13; N, 3.00. Found: C, 53.96; H, 5.00; Br, 17.03; N, 3.07.

Benzyl 2-benzyloxycarbonylamino-2,6-dideoxy-α-D-glucopyranoside (**5**).—To a solution of **4** (0.73 g, 1.56 mmol) in toluene (10 mL) were added tributyltin hydride (0.5 g, 1.72 mmol) and α,α′-azobisisobutyronitrile (AIBN, 10 mg). The mixture was refluxed for 1.5 h, then the solvent was evaporated to dryness. The residue was crystallized from EtOH to afford **5** (0.54 g, 89%); mp 161–162°C; $[\alpha]_D^{20}$ +136.3° (*c* 1.0, pyridine); ^{1}H NMR (Me_2SO-d_6), δ 5.02 (s, 2 H, Cbz), 4.74 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1), 4.63 and 4.44 (ABq, 2 H, J 12.6 Hz, PhCH_2), 3.44 (m, 1 H, H-2), 3.45–3.55 (m, 2 H, H-3,4), 2.91 (m, 1 H, H-5), 1.16 (d, 3 H, $J_{6,5}$ 6.2 Hz, CH_3). HR-MS/EI: $C_{21}H_{26}NO_6$ $(M+H)^+$. Calcd: 388.1760. Found: 388.1757.

Benzyl 4-O-benzoyl-2-benzyloxycarbonylamino-6-bromo-2,6-dideoxy-3-O-methanesulfonyl-α-D-glucopyranoside (**7**).—To a solution of **6** [10] (8.0 g, 14 mmol) and NBS (5.0 g, 28 mmol) in CCl_4 (300 mL, freshly filtered through a short column filled with neutral aluminum oxide) were added $BaCO_3$ (7.0 g) and freshly distilled 1,1,2,2-tetrachloroethane (20 mL). The mixture was refluxed for 2 h, then filtered through a Celite pad, and the filtrate was concentrated to dryness. Column chromatography (95:5 toluene–EtOAc) of the residue gave 3.72 g (41%) of **7**; mp 136–139°C; $[\alpha]_D^{22}$ −13.1° (*c* 1.8, $CHCl_3$); ^{1}H NMR (C_6D_6), δ 5.08 and 4.92 (2 t, 2 H, $J_{3,2} = J_{4,5} = J_{3,4} = 10$ Hz, H-3,4), 4.98 (d, 1 H, $J_{NH,2}$ 9.8 Hz, NH), 4.81 and 4.65 (ABq, 2 H, J 12.4 Hz, Cbz), 4.44 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.21 and 3.90 (ABq, 2 H, J 11.8 Hz, PhCH_2), 3.76 (m, 1 H, H-2), 4.05 (m, 1 H, H-5), 2.93 (dd, 1 H, $J_{6a,5}$ 2.5, $J_{6a,6b}$ 11.2 Hz, H-6a), 2.85 (dd, 1 H, $J_{6b,5}$ 8.1 Hz, H-6b), 1.81 (s, 3 H, Ms). HR-MS/EI: $C_{29}H_{30}BrNO_9S$ $(M)^+$. Calcd: 647.0825. Found: 647.0827.

Benzyl 4-O-benzoyl-2-benzyloxycarbonylamino-2,6-dideoxy-3-O-methanesulfonyl-α-D-glucopyranoside (**8**).—To a solution of **7** (2.6 g, 4.0 mmol) in benzene (30 mL) was added tributyltin hydride (1.28 g, 4.4 mmol) followed by AIBN (10 mg). The mixture was refluxed for 3 h and then concentrated to dryness. Column chromatography (95:5 toluene–EtOAc) of the residue yielded **8** (1.91 g, 84%); mp 118–119°C; $[\alpha]_D^{25}$ +52.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ 5.22 (d, 1 H, $J_{NH,2}$ 10 Hz, NH), 5.12 and 5.05 (ABq, 2 H, J 12.2 Hz, Cbz), 5.16 and 5.00 (2 t, 2 H, $J_{3,2} = J_{3,4} = J_{4,5} = 10$ Hz, H-3,4),

4.97 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 4.70 and 4.53 (ABq, 2 H, J 11.8 Hz, PhCH_2), 4.19 (m, 1 H, H-2), 3.98 (dq, 1 H, H-5), 2.66 (s, 3 H, Ms), 1.22 (d, 3 H, $J_{6,5}$ 6.3 Hz, CH_3). HR-MS/EI: $C_{29}H_{31}NO_9S$ $(M)^+$. Calcd: 569.1719. Found: 569.1714.

Benzyl 3,4-anhydro-2-benzyloxycarbonylamino-2,6-dideoxy-α-D-allopyranoside (**10**). —Method a (*from* **5**). To a cooled solution of **5** (0.5 g, 1.30 mmol) in HMPA (4.4 mL) was added NaH (0.125 g) and the mixture was stirred for 0.5 h at room temperature. After cooling to −30°C, THF (2.2 mL) and a solution of TPSI (0.48 g) in THF (1.5 mL) were added, and stirring was continued at −30°C for 1 h, then at −5°C for 3 h. The mixture was diluted with water (10 mL) and extracted with ether (5 × 10 mL). The combined organic layer was washed with water (10 mL), dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified by column chromatography (17:1 toluene–EtOAc) to yield **10** (60 mg, 13%).

Method b (*from* **8**). To a solution of **8** (1.14 g, 2.0 mmol) in MeOH (30 mL) was added K_2CO_3 (1 g) and the mixture was stirred at room temperature for 4 h. The solid was filtered off and the filtrate was concentrated to dryness. To the residue were added THF (40 mL) and NaH (100 mg, 4.0 mmol), and the mixture was stirred overnight. Then, water (0.1 mL) was slowly added and the solvents were evaporated. Column chromatography (9:1 benzene–EtOAc) of the residue yielded **10** (390 mg, 53%).

Method c (*from* **11**). A mixture of **11** [12] [1] (2.81 g, 8.0 mmol) and 3-chloroperoxybenzoic acid (2.80 g, 16.0 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 12 h, filtered through a Celite pad, and concentrated to dryness. Column chromatography (9:1 toluene–EtOAc) of the residue gave 2.92 g (quantitatively) of **10**; mp 84–86°C; $[\alpha]_D^{23}$ +27.7° (*c* 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ 5.39 (d, 1 H, $J_{NH,2}$ 9.4 Hz, NH), 5.11 (s, 2 H, Cbz), 4.81 (d, 1 H, $J_{1,2}$ 5.3 Hz, H-1), 4.70 and 4.44 (ABq, 2 H, J 12.2 Hz, PhCH_2), 4.24 (m, 1 H, $J_{2,3}$ 2.6 Hz, H-2), 4.13 (q, 1 H, $J_{5,6}$ 6.9 Hz, H-5), 3.39 (m, 1 H, $J_{3,4}$ 4.4 Hz, H-3), 3.16 (d, 1 H, H-4), 1.35 (d, 3 H, CH_3). HR-MS/LSIMS: $C_{21}H_{24}NO_5$ $(M + H)^+$. Calcd: 370.1654. Found: 370.1656.

Benzyl 4-azido-2-benzyloxycarbonylamino-2,4,6-trideoxy-α-D-gulopyranoside (**12**) and *benzyl 3-azido-2-benzyloxycarbonylamino-2,3,6-trideoxy-α-D-glucopyranoside* (**13**). —To a solution of **10** (370 mg, 1.0 mmol) in EtOH (30 mL) and water (10 mL) were added NaN_3 (700 mg) and NH_4Cl (900 mg). The mixture was refluxed for 22 h. Then, the solvents were evaporated and water (10 mL) was added to the residue. Product was extracted with $CHCl_3$ (5 × 10 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to dryness. Column chromatography (9:1 toluene–EtOAc) of the residue yielded **12** (290 mg, 70%) and **13** (56 mg, 13%).

12: $[\alpha]_D^{27}$ +84.6° (*c* 1.4, $CHCl_3$); IR (film): 2100 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ 5.40 (d, 1 H, $J_{NH,2}$ 9.0 Hz, NH), 5.10 (s, 2 H, Cbz), 4.98 (d, 1 H, $J_{1,2}$ 2.7 Hz, H-1), 4.68 and 4.50 (ABq, 2 H, J 11.7 Hz, PhCH_2), 4.23 (dq, 1 H, $J_{5,6}$ 6.4, $J_{5,4}$ 1.5 Hz, H-5), 4.10 (m, 1 H, H-2), 4.01 (m, 1 H, H-3), 3.54 (dd, 1 H, $J_{4,3}$ 3.3 Hz, H-4), 1.29 (d, 3 H, CH_3). HR-MS/EI: $C_{21}H_{25}N_4O_5$ $(M + H)^+$. Calcd: 413.1825. Found: 413.1825.

[1] In the synthesis of **11** separation of the mixture of benzyl 2-benzyloxycarbonylamino-2,3,4,6-tetradeoxy-6-iodo-α-D-*erythro*-hex-3-enopyranoside and benzyl 2-benzyloxycarbonylamino-2,3,4,6-tetradeoxy-3(4),6-diiodo-α-D-*erythro*-hex-3-enopyranoside obtained as described in [12] is not necessary. The proportion of products was measured by ^{1}H NMR and tributyltin hydride was used in a 10 mol% excess for 1 equiv of iodine.

13: mp 119–121°C; $[\alpha]_D^{27}$ +72.3° (*c* 0.7, $CHCl_3$); IR (oil): 2120 cm^{-1}; ^1H NMR ($CDCl_3$), δ 5.15 and 5.10 (ABq, 2 H, *J* 12.0 Hz, Cbz), 5.09 (d, 1 H, $J_{NH,2}$ 10.4 Hz, NH), 4.83 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.69 and 4.47 (ABq, 2 H, *J* 11.6 Hz, PhCH_2), 3.94 (m, 1 H, $J_{2,3}$ 10.5 Hz, H-2), 3.74 (dq, 1 H, $J_{5,4}$ 9.9, $J_{5,6}$ 6.2 Hz, H-5), 3.53 and 3.21 (2 t, 2 H, H-3,4), 1.28 (d, 3 H, CH_3). HR-MS/EI: $C_{21}H_{25}N_4O_5$ $(M+H)^+$. Calcd: 413.1825. Found: 413.1829.

*Benzyl 4-acetamido-3-*O*-acetyl-2-benzyloxycarbonylamino-2,4,6-trideoxy-α-*D*-gulopyranoside* (**14**).—To a solution of **12** (210 mg, 0.5 mmol) in EtOH (40 mL) were added $NaBH_4$ (80 mg) and a 0.16 M solution of $NiCl_2$ in EtOH (0.1 mL). The mixture was stirred for 45 min at room temperature, and AcOH was slowly added to give a neutral solution. The solvents were evaporated. To the residue were added Ac_2O (10 mL) and anhydrous NaOAc (500 mg). The mixture was refluxed for 10 min, the solvents were evaporated, and water (10 mL) was added to the residue. Product was extracted with $CHCl_3$ (5 × 10 mL). Combined organic extracts were washed with water (10 mL), dried ($MgSO_4$), and concentrated to dryness. Column chromatography (9:1 benzene–2-propanol) of the residue gave **14** (230 mg, 98%); $[\alpha]_D^{27}$ +74.8° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$), δ 5.92 and 5.18 (2 d, 2 H, *J* 8.7 and 9.6 Hz, N*H*Ac, N*H*Cbz), 5.15 (t, 1 H, $J_{3,2} = J_{3,4} = 3.6$ Hz, H-3), 5.09 and 5.05 (ABq, 2 H, *J* 12.1 Hz, Cbz), 4.87 (d, 1 H, $J_{1,2}$ 4.3 Hz, H-1), 4.74 and 4.48 (ABq, 2 H, *J* 12.0 Hz, PhCH_2), 4.38 (dq, 1 H, $J_{5,4}$ 1.1, $J_{5,6}$ 6.6 Hz, H-5), 4.11 (m, 2 H, H-2,4), 2.09 and 2.06 (2 s, 6 H, 2 × OAc), 1.07 (d, 3 H, CH_3). HR-MS/EI: $C_{25}H_{30}N_2O_7$ $(M)^+$. Calcd: 470.2053. Found: 470.2057.

*Benzyl 3-acetamido-4-*O*-acetyl-2-benzyloxycarbonylamino-2,3,6-trideoxy-α-*D*-glucopyranoside* (**15**).—Compound **13** (0.46 g, 1.11 mmol) was converted into **15** according to the procedure described for **14**, using $NaBH_4$ (0.2 g) and $NiCl_2$ (0.2 mL of 0.16 M solution in EtOH) to give 440 mg (85%); mp 225–227°C; $[\alpha]_D^{20}$ +96.2° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$), δ 5.68 and 5.21 (2 d, 2 H, 2 × NH), 5.10 and 5.01 (ABq, 2 H, *J* 12.4 Hz, Cbz), 4.88 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.71 and 4.51 (ABq, 2 H, *J* 11.8 Hz, PhCH_2), 4.56 (t, 1 H, $J_{4,3} = J_{4,5} = 10.0$ Hz, H-4), 4.39 (m, 1 H, H-3), 3.94 (m, 1 H, H-5), 3.82 (m, 1 H, $J_{2,NH}$ 9.7, $J_{2,3}$ 11.4 Hz, H-2), 2.04 and 1.77 (2 s, 6 H, NH*Ac*, OAc), 1.14 (d, 3 H, $J_{6,5}$ 6.2 Hz, CH_3). HR-MS/EI: $C_{25}H_{30}N_2O_7$ $(M)^+$. Calcd: 470.2053. Found: 470.2052.

*2,4-Diacetamido-3-*O*-acetyl-2,4,6-trideoxy-*D*-gulopyranose* (**16**).—To a solution of **14** (500 mg, 1.1 mmol) in EtOH (20 mL) were added Ac_2O (340 mg, 3.3 mmol) and 10% Pd–C (1 g). The suspension was hydrogenolyzed for 20 h. The mixture was filtered through a Celite pad and solvents were evaporated to afford **16** (305 mg, quantitatively) as a mixture of α,β-anomers [$\beta:\alpha > 30:1$ (from ^1H NMR)]; $[\alpha]_D^{20}$ −66.5° (*c* 0.19, MeOH; after 2 h); ^1H NMR (Me_2SO-d_6), δ (for β-anomer) 8.05 (d, 1 H, $J_{NH,4}$ 9.1 Hz, NH), 7.72 (d, 1 H, $J_{NH,2}$ 8.0 Hz, NH), 6.74 (d, 1 H, $J_{OH,1}$ 5.1 Hz, OH), 4.85 (m, 1 H, $J_{3,4}$ 3.2 Hz, H-3), 4.76 (dd, 1 H, $J_{1,2}$ 8.7 Hz, H-1), 3.98 (dq, 1 H, $J_{5,4}$ 2.0, $J_{5,6}$ 6.3 Hz, H-5), 3.92 (m, 1 H, $J_{2,3}$ 3.3 Hz, H-2), 3.76 (m, 1 H, H-4), 2.07, 1.92, and 1.76 (3 s, 9 H, 3 × Ac), 1.03 (d, 3 H, CH_3). HR-MS/LSIMS: $C_{12}H_{20}N_2NaO_6$ $(M+Na)^+$. Calcd: 311.1219. Found: 311.1215.

*Benzyl 2,3,6-trideoxy-α-*L*-threo-hex-2-enopyranoside* (**18**).—This compound was prepared from **17** [17] (6 g, 22.3 mmol) according to the known procedure [17].

Colourless crystals (4.8 g, 80%); mp 61°C; $[\alpha]_D^{22}$ +103.0° (*c* 1.0, $CHCl_3$); lit. [16]: mp 62°C; $[\alpha]_D^{20}$ +102.6° (*c* 1.0, $CHCl_3$).

*Benzyl 2,3,6-trideoxy-4-*O*-trichloroacetimidoyl-α-*L*-*threo*-hex-2-enopyranoside* (**21**). —To a well-stirred solution of **20** [17] (4 g, 18.2 mmol) in dry CH_2Cl_2 (100 mL) was slowly added NaH (4.75 mmol) at room temperature under Ar. After 5 min the mixture was cooled (0°C), whereupon a solution of trichloroacetonitrile (2.4 mL, 24 mmol) in dry CH_2Cl_2 (17 mL) was added dropwise. The mixture was stirred at 0°C until TLC (7:3 hexane–acetone) showed disappearance of the substrate. After filtration through a Celite pad, the filtrate was concentrated to dryness to give **21** (6.4 g, quantitatively). This product was used in the next reaction step without further purification.

A sample of **21** was chromatographed on a silica gel column (49:1 hexane–acetone) to afford an oil; $[\alpha]_D^{21}$ −75.1° (*c* 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ 6.19 (ddd, 1 H, $J_{3,2}$ 9.9, $J_{3,4}$ 5.5, $J_{3,5}$ 0.9 Hz, H-3), 5.90 (ddd, 1 H, $J_{2,1}$ 3.1, $J_{2,4}$ 0.5 Hz, H-2), 5.06 (d, 1 H, H-1), 4.77 and 4.61 (ABq, 2 H, *J* 11.8 Hz, PhCH_2), 4.17 (ddq, 1 H, $J_{5,4}$ 2.2, $J_{5,6}$ 6.6 Hz, H-5), 3.61–3.58 (m, 1 H, H-4), 1.26 (d, 3 H, CH_3). Anal. Calcd for $C_{15}H_{16}Cl_3NO_3$: C, 49.41; H, 4.42; N, 3.84. Found: C, 49.04; H, 4.22; N, 3.54.

*Benzyl 2,3,4,6-tetradeoxy-2-trichloroacetamido-α-*L*-*threo*-hex-3-enopyranoside* (**22**). —A solution of crude **21** (6 g, 16.4 mmol) in 1,2-dichlorobenzene (200 mL) was heated at 160°C for 5 h. The solution was concentrated to dryness and the residue was purified on a silica gel column (49:1 hexane–acetone) to yield **22** (4.1 g, 68%) as an oil; $[\alpha]_D^{20}$ −183.9° (*c* 2.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ 6.61 (d, 1 H, $J_{NH,2}$ 7.3 Hz, NH), 5.79 (ddd, 1 H, $J_{3,2}$ 4.3, $J_{3,4}$ 10.2, $J_{3,5}$ 1.3 Hz, H-3), 4.93 (s, 1 H, H-1), 4.79 and 4.65 (ABq, 2 H, *J* 11.8 Hz, PhCH_2), 4.35 (ddq, 1 H, $J_{5,4}$ 1.9, $J_{5,6}$ 6.9 Hz, H-5), 4.31 (ddd, 1 H, $J_{2,1}$ 1.2 Hz, H-2), 3.97 (d, 1 H, H-4), 1.30 (d, 3 H, CH_3). Anal. Calcd for $C_{15}H_{16}Cl_3NO_3$: C, 49.41; H, 4.42; Cl, 29.17; N, 3.84. Found: C, 49.04; H, 4.22; Cl, 29.50; N, 3.39.

*Benzyl 2-amino-2,3,4,6-tetradeoxy-α-*L*-*threo*-hex-3-enopyranoside* (**23**).—To a solution of **22** (4.58 g, 12.56 mmol) in EtOH (100 mL) was added NaOH (1 M solution in EtOH, 50 mL) and the mixture was heated at 80°C for 2 h. After evaporation of EtOH the residue was extracted with hot $CHCl_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was purified on a silica gel column (19:1 $CHCl_3$–MeOH) to yield **23** (2.29 g, 83%) as an amorphous powder; $[\alpha]_D^{22}$ −267.8° (*c* 2.1, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 70.89; H, 7.69; N, 6.13.

*Benzyl 2-acetamido-2,3,4,6-tetradeoxy-α-*L*-*threo*-hex-3-enopyranoside* (**24**).—Compound **23** (2.19 g, 10 mmol) was treated with Ac_2O (3 mL) in pyridine (6 mL) to yield, after concentration to dryness, **24** (2.61 g, quantitatively). Crystallization from acetone gave a product with mp 129–130°C; $[\alpha]_D^{20}$ −208° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ 5.86 (dt, 1 H, $J_{4,3}$ 10.3, $J_{4,5}$ 1.9 Hz, H-4), 5.72 (m, 1 H, $J_{3,2}$ 5.2, $J_{3,5}$ 1.3 Hz, H-3), 5.52 (d, 1 H, $J_{NH,2}$ 8.2 Hz, NH), 4.86 (d, 1 H, $J_{1,2}$ 1.2 Hz, H-1), 4.76 and 4.62 (ABq, 2 H, *J* 12.0 Hz, PhCH_2), 4.36 (ddd, 1 H, H-2), 4.31 (ddq, 1 H, $J_{5,6}$ 6.8 Hz, H-5), 1.98 (s, 3 H, NAc), 1.27 (d, 3 H, CH_3). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.52; H, 6.94; N, 4.99.

*Benzyl 2-acetamido-2,4,6-trideoxy-4-*p*-*toluenesulfonamido-α-*L*-*altropyranoside* (**25**) and *benzyl 2-acetamido-2,3,6-trideoxy-3-*p*-*toluenesulfonamido-α-*L*-*altropyranoside* (**26**).—To a mixture of chloramine T (3.28 g, 11.64 mmol), OsO_4 (18 mg), and

triethylbenzylammonium chloride (TEBA, 110 mg) in water (35 mL) and *tert*-butyl alcohol (3.5 mL) was added a solution of **24** (1.63 g, 6.23 mmol) in $CHCl_3$ (35 mL). The mixture was heated at 60–70°C for 72 h. The cooled mixture was filtered through a Celite pad and extracted with $CHCl_3$. The organic layer was stirred overnight with satd aq $NaHSO_3$. The organic layer was separated, washed with aq 1% NaOH, then with brine, dried ($MgSO_4$), and concentrated to dryness to give a mixture of regioisomers **25** and **26** (TLC, 9:1 $CHCl_3$–MeOH, 3:2 hexane–acetone). These compounds were separated by flash chromatography (7:3 hexane–acetone) to afford **25** (1.9 g, 39%) as a first fraction, then **26** (0.64 g, 23%), and a mixture of dihydroxylated products (74 mg, 4%) which were not separated further.

25: mp 194°C; $[\alpha]_D^{20}$ −76.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ 5.33 (d, 1 H, $J_{NH,2}$ 8.5 Hz, N*H*Ac), 5.19 (d, 1 H, $J_{NH,4}$ 9.2 Hz, N*H*Ts), 4.69 (d, 1 H, $J_{1,2}$ 1.3 Hz, H-1), 4.68 and 4.51 (ABq, 2 H, *J* 11.7 Hz, PhCH_2), 4.19 (ddd, 1 H, $J_{2,3}$ 2.8 Hz, H-2), 3.80 (dq, 1 H, $J_{5,4}$ 10.4, $J_{5,6}$ 6.3 Hz, H-5), 3.49 (d, 1 H, $J_{OH,3}$ 10.0 Hz, 3-OH), 3.12–3.07 (m, 2 H, $J_{3,4}$ 3.2 Hz, H-3,4), 2.42 (s, 3 H, CH_3C$_6$H$_4$), 1.94 (s, 3 H, NAc), 1.35 (d, 1 H, CH_3). HR-MS/EI: $C_{22}H_{29}N_2O_6S$ $(M + H)^+$. Calcd: 449.1746. Found: 449.1746.

26: mp 76–78°C; $[\alpha]_D^{20}$ −48.6° (*c* 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ 6.08 (d, 1 H, $J_{NH,3}$ 9.4 Hz, N*H*Ts), 5.53 (d, 1 H, $J_{NH,2}$ 7.5 Hz, N*H*Ac), 4.53 (d, 1 H, $J_{1,2}$ 1.3 Hz, H-1), 4.71 and 4.46 (ABq, 2 H, *J* 11.9 Hz, PhCH_2), 3.81 (dt, 1 H, $J_{3,4}$ 4.3 Hz, H-3), 3.76 (ddd, 1 H, H-2), 3.74 (dq, 1 H, $J_{5,4}$ 9.5, $J_{5,6}$ 6.2 Hz, H-5), 3.38 (ddd, 1 H, $J_{4,OH}$ 8.9 Hz, H-4), 2.74 (d, 1 H, 4-OH), 2.45 (s, 3 H, CH_3C$_6$H$_4$), 1.91 (s, 3 H, NAc), 1.32 (d, 3 H, CH_3). HR-MS/EI: $C_{22}H_{29}N_2O_6S$ $(M + H)^+$. Calcd: 449.1746. Found: 449.1746.

*Benzyl 2-acetamido-3-*O*-acetyl-2,4,6-trideoxy-4-*p*-toluenesulfonamido-α-*L*-altropyranoside* (**27**).—Compound **27** was prepared by acetylation of **25** (448 mg, 1 mmol) with Ac_2O (2 mL) in pyridine (4 mL). Concentration of the reaction mixture to dryness followed by purification of the residue on a silica gel column (7:3 hexane–acetone) gave **27** (449 mg, 90%); mp 103°C; $[\alpha]_D^{20}$ −94.6° (*c* 0.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ 5.71 (d, 1 H, $J_{NH,2}$ 8.6 Hz, N*H*Ac), 5.08 (d, 1 H, $J_{NH,4}$ 9.9 Hz, N*H*Ts), 4.63 (d, 1 H, $J_{1,2}$ 1.4 Hz, H-1), 4.62 and 4.42 (ABq, 2 H, *J* 11.8 Hz, PhCH_2), 4.43 (dd, 1 H, $J_{3,2}$ 4.1, $J_{3,4}$ 3.4 Hz, H-3), 4.27 (ddd, 1 H, H-2), 3.98 (dq, 1 H, $J_{5,4}$ 9.6, $J_{5,6}$ 6.4 Hz, H-5), 3.38 (ddd, 1 H, H-4), 2.43 (s, 3 H, CH_3C$_6$H$_4$), 1.96 (s, 3 H, OAc), 1.91 (s, 3 H, NAc), 1.25 (d, 3 H, CH_3). HR-MS/EI: $C_{24}H_{31}N_2O_7S$ $(M + H)^+$. Calcd: 491.1852. Found: 491.1847.

*Benzyl 2-acetamido-4-*O*-acetyl-2,3,6-trideoxy-3-*p*-toluenesulfonamido-α-*L*-altropyranoside* (**28**).—Prepared from **26** (448 mg, 1 mmol) as described for **27**; mp 155°C; $[\alpha]_D^{20}$ −71.0° (*c* 1.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ 5.94 (d, 1 H, $J_{NH,3}$ 9.5 Hz, N*H*Ts), 5.72 (d, 1 H, $J_{NH,2}$ 8.5 Hz, N*H*Ac), 4.61–4.58 (m, 2 H, $J_{1,2}$ 1.4, $J_{4,5}$ 10.0 Hz, H-1,4), 4.71 and 4.50 (ABq, 2 H, *J* 12.0 Hz, PhCH_2), 4.06 (dq, 1 H, $J_{5,6}$ 6.2 Hz, H-5), 3.93 (dt, 1 H, $J_{3,2} = J_{3,4} = 3.3$ Hz, H-3), 3.84 (ddd, 1 H, H-2), 2.42 (s, 3 H, CH_3C$_6$H$_4$), 2.12 (s, 3 H, OAc), 1.94 (s, 3 H, NAc), 1.21 (s, 3 H, CH_3). HR-MS/EI: $C_{24}H_{31}N_2O_7S$ $(M + H)^+$. Calcd: 491.1852. Found: 491.1847.

*2-Acetamido-2,4,6-trideoxy-4-*p*-toluenesulfonamido-*L*-altropyranose* (**29**).—A solution of **25** (224 mg, 0.5 mmol) in EtOH (20 mL) was hydrogenolyzed in the presence of

10% Pd–C (80 mg) overnight. The solution was filtered through Celite and concentrated to dryness to afford **29** (156 mg, 87%); mp 166°C; $[\alpha]_D^{20}$ −42.2° (*c* 0.8, MeOH; after 2 h). HR-MS/EI: $C_{15}H_{23}N_2O_6S$ $(M + H)^+$. Calcd: 359.1277. Found: 359.1275.

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