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Efficient synthesis of multifunctional furanoid *C*-glycoamino acid precursors

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Abstract—Ready access to constrained, multifunctionalized, hydrolytically stable amino acids has been established by the synthesis of their direct precursors using 2,5-anhydro-3-azido-3-deoxy-D-altrose (a 'formyl azido-*C*-glycofuranoside'), or its readily available, stable synthetic equivalent [(1*R*) and (1*S*)-2,5-anhydro-3-azido-4,6-*O*-benzylidene-3-deoxy-1-fluoro-1-*O*-methyl-D-altritol], as novel molecular scaffolds.

1. Introduction

The structural control of molecular assemblies using peptide chains, which possess stereogenic centers and hydrogen bonding sites, is considered to be a useful approach to artificial highly-ordered systems.[1] Protein secondary structure such as α-helices, β-sheets, and β-turns are important in inducing the three-dimensional structure and biological activity of proteins. Relatively short oligomers of β- and γ-amino acids, especially those of conformationally restricted systems, have been shown to adopt ordered secondary structures.[2,3] In particular, Fleet et al.[4,5] have reported a number of peptidomimetics and unnatural biopolymers adopting interesting secondary structures because of the carbohydrate-derived tetrahydrofuran systems they contain. On their hand, the Seebach's[6,7] and Gellman's[8–11] groups have found that β-peptides are able to adopt defined three-dimensional structures similar to those of natural peptides. The unnatural β-peptide backbone is resistant to proteolysis,[2] in contrast to α-amino acid backbone.

On the other hand, template-assembled multivalent peptides have found wide applications in recent years. This kind of molecules, in which several copies of a certain peptide are attached to a cyclic core, has been developed for two applications: as novel artificial proteins to study the factors governing protein folding and stability,[12] and as chemically defined immunogens for vaccine development.[13,14] Enhanced activities of peptide inhibitors were also obtained through multivalent peptide assembly.[15–20] Several types of cyclic molecules (cyclic peptides, calix[4]arenes, cholic acid, and carbohydrates, among others)[21–24] have been used as templates for multivalent assembly, and it seems to be that the topology of multivalent peptides can be controlled by the defined spatial orientation of the functionalities on the rigid scaffold core.[25]

On the basis of our previous experience with formyl nitro- and azido-*C*-glycofuranosides,[26–28] we recently started a project based on exploiting the potential of these readily available compounds for the synthesis of hydrolytically stable glycoamino acids (GAAs). GAAs,[29–31] which are carbohydrates bearing both an amino group and a carboxyl group, are ideal building blocks[32] to generate peptidomimetics because of their rigidity and multifunctionality. These compounds may be (a) inserted in appropriate sites of small peptides, providing the specific three-dimensional structures required for bonding to their receptors,[33,34] (b) connected, furnishing peptide-bond linked carbohydrates[35] (carbopeptoids), or (c) exploited as templates for multivalent peptide assembly. We now propose the use of formyl azido-*C*-glycofuranosides **I**, readily available from their synthetic equivalents **II** (Fig. 1), as molecular scaffolds

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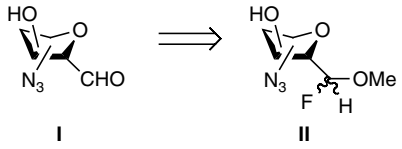


Figure 1. 'Formyl azido-*C*-glycofuranoside' scaffolds.

for *C*-glycoamino acids or precursors, that is, compounds **1**–**4** (Fig. 2), which are rigid and multifunctionalized compounds that may serve as differently shaped (*AB*, *A-spacer-B*, AB_2, and A_2B) templates for attaching peptides.

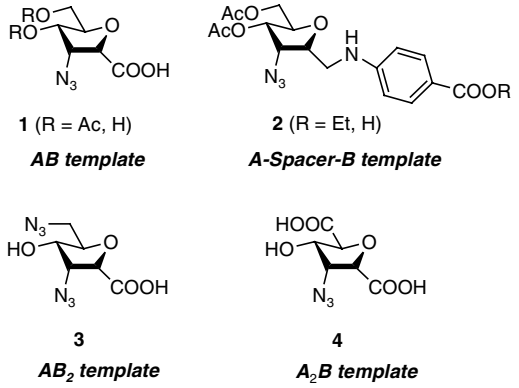
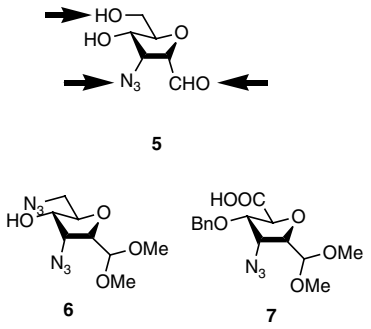


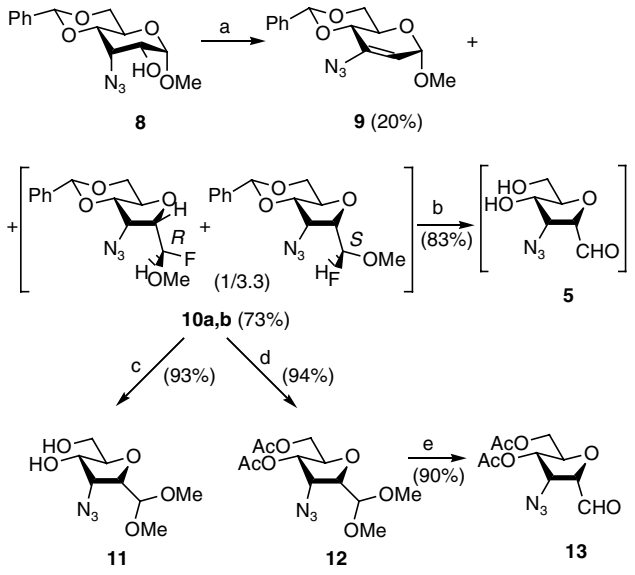
Figure 2. Azido-*C*-glycocarboxylic acids.

We describe herein the synthesis of one member of series **I**, the 2,5-anhydro-3-azido-3-deoxy-D-altrose **5**, and the high-yielding preparation of 4,6-di-*O*-acetyl-2,5-anhydro-3-azido-D-altronic acid **1** (R = Ac)[36] and 4,6-di-*O*-acetyl-2,5-anhydro-1-arylamino-3-azido-1,3-dideoxy-D-altritol **2** (R = Et). The precursors **6** and **7** of compounds **3** and **4** have also been successfully obtained. Compound **5** provides three points of diversification, indicated by bold arrows in the formula, with orthogonal chemical reactivity.



2. Results and discussion

The known[37] methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-allopyranoside **8**, treated with diethylaminosulfur trifluoride (DAST) in refluxing acetonitrile for 12 min, gave a mixture of the 2-enopyranoside **9** (20%) and a 1:3.3 mixture (73%) of the ring contracted, rearranged (1*R*)- and (1*S*)-2,5-anhydro-1-fluoro-1-*O*-methyl-D-altritol derivatives **10a** and **10b** (Scheme 1). Separation of these epimers was achieved by column chromatography. This reaction is a new example of the DAST-mediated rearrangement previously observed in other equatorial-2-OH glycopyranosides.[26] The H(1)/F coupling constant values observed for **10a** and **10b** (J = 68 Hz for **10a**, and J = 63 Hz for **10b**) are in the range observed[38] for ring-contracted products (J = 63–68 Hz). Assignment of configuration to these epimers was made on the basis of the H(2)/F coupling constant value (J = 11.5 Hz for **10a**, J = 3.1 Hz for **10b**, suggesting[39] the H(2)/F *gauche* relationship in both cases, as an *anti* one would lead to a J value of ~20 Hz), and the C(2)/F coupling constant value, lower for **10a** (J = 11.5 Hz) than for **10b** (J = 32.7 Hz), in agreement[39] with the F/ring O *gauche* and *anti* relationships, respectively. This stereochemical difference has no effect in the subsequent synthetic transformations to which the diastereomeric **10a**/**10b** mixture was subjected, leading to products that lack stereogenic character at C(1).

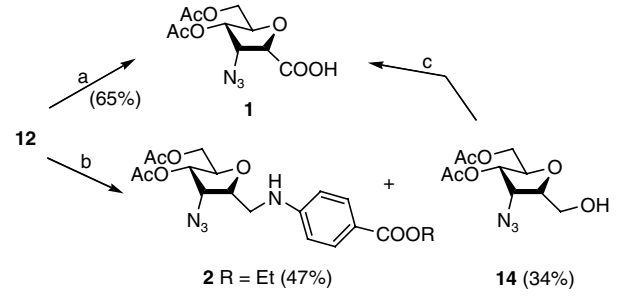


Scheme 1. Reagents and conditions: (a) DAST, MeCN, reflux (12 min). (b) PTSA, acetone, rt (1 h). (c) MeOH, PTSA, rt (1 h). (d) i. MeOH, PTSA, rt (1 h); ii. Ac_2O, Py, 0 °C. (e) 9:1 TFA/H_2O, rt (1 h).

When the **10a**,**b** mixture was treated in acetone with *p*-toluenesulfonic acid (PTSA) at room temperature for 1 h, usual work-up led to the crude *aldehydo*-sugar **5** in 83% yield, pure enough to be used for further transformation, but unstable to be purified by column chromatography. Crude product **5** showed in its ^{1}H NMR spectrum a signal at δ 9.51 ppm, assigned to the formyl proton. The same **10a**,**b** mixture was transformed, by the action of PTSA and methanol, into the 4,6-*O*-deprotected dimethyl acetal **11** in high yield (93%), the structure of which being deduced from its high-resolution mass spectrum and the appearance of signals for two methyl groups in its ^{1}H and ^{13}C NMR spectra. When the foregoing reaction was performed without purifying the product, and this was subjected to standard acetylation

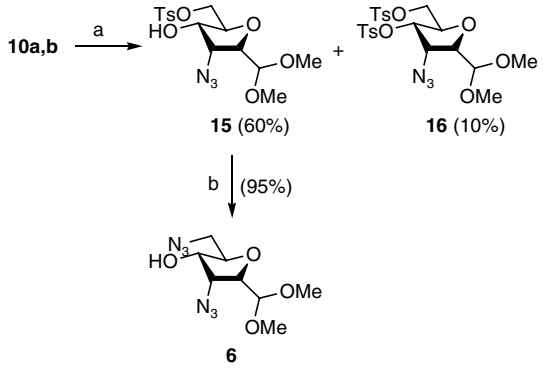
conditions, the 4,6-di-*O*-acetyl derivative **12** (94% after column chromatography) was obtained, thus corroborating the presence of two hydroxyl groups in **11** and, hence, in **5**. Treatment of **12** with 9:1 trifluoroacetic acid/water afforded 90% of crude **13**, a sample of which was purified by column chromatography and showed in its ^{1}H NMR spectrum the formyl proton signal as a doublet (J 1.5 Hz) at δ 9.63 ppm, as well as the two acetyl proton singlets at δ 2.17 and 2.11 ppm, and in its ^{13}C NMR spectrum, three carbonyl carbon signals (δ 199.2 ppm for the aldehydic one; 170.6 and 170.3 ppm for the two ester carbonyl carbons).

Scheme 2 shows the synthesis of *AB* and *A-spacer-B* templates. Hydrolysis of **12** with 9:1 trifluoroacetic acid (TFA)/water, followed by oxidation with aqueous sodium dichromate/sulfuric acid (Jones' reagent), gave the 4,6-di-*O*-acetyl-β-azido acid **1** in 65% yield (Scheme 2). Reductive amination of **13** was achieved starting from **12** as above and treating crude **13** with ethyl *p*-aminobenzoate and sodium triacetoxy-borohydride, to give 4,6-di-*O*-acetyl-2,5-anhydro-3-azido-1,3-dideoxy-1-[(4-ethoxycarbonylphenyl)amino]-D-altritol (**2**, R = Et, 47% after column chromatography) accompanied by 34% of the primary alcohol **14**. Last product may be useful for obtaining an additional amount of **1** by oxidation with Jones' reagent. Compound **1** showed in the ^{13}C NMR spectrum three carbonyl carbon signals, among them that of highest δ value (172.0 ppm) being assigned to the carboxyl carbon. The ^{1}H NMR spectrum of compound **2** showed two doublets at δ 7.78 and 6.71 ppm, each for two aromatic protons, two signals for the two C(1) diastereotopic protons at δ 3.57 and 3.40 ppm, and a broad signal at $\delta \sim 5.6$ ppm assigned to the amine proton, as well as the typical quartet/triplet signal tandem for the *O*-ethyl protons of an ester; corresponding signals in the ^{13}C NMR spectrum and the high-resolution mass spectrum corroborated the proposed structure. Compound **14** had NMR spectra showing a broad OH-proton signal at $\delta \sim 1.95$ ppm and signals for the two C(1) protons (doublet at δ 3.82 ppm) and for the C(1) nucleus (δ 62.0 ppm), but lacking any signal assignable to aromatics.



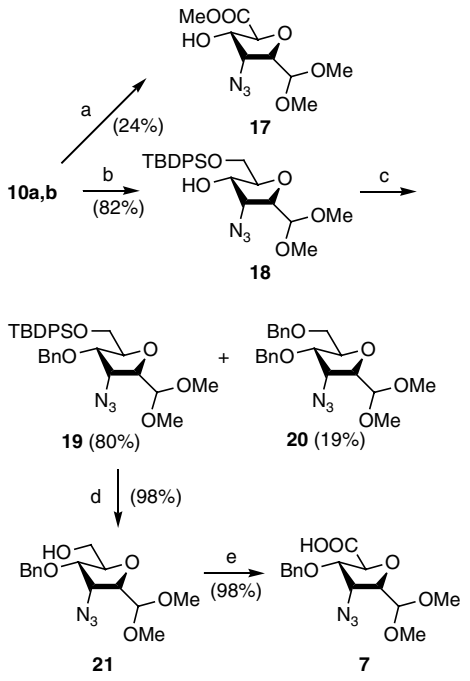
Scheme 2. Synthesis of *AB* and *A-spacer-B* templates. Reagents and conditions: (a) i. 9:1 TFA/H_2O, rt (1 h); ii. Jones' reagent, −30 °C→rt (1 h). (b) i. 9:1 TFA/H_2O, rt (1 h); ii. 4-H_2N–C_6H_4–CO_2Et, $NaBH(OAc)_3$, DCE, rt (18 h). (c) Jones' reagent, −30 °C→rt (1 h).

The synthesis of an AB_2 template precursor is summarized in Scheme 3. When crude **11**, obtained from **10a**,**b** as indicated above, was made to react with tosyl chloride in pyridine at −25 °C, the 6-*O*-tosyl **15** and the 4,6-di-*O*-tosyl **16** derivatives were obtained in 60% and 10% yields, respectively. The latter is the 4,6-di-*O*-tosyl derivative, as evidenced by the MS and NMR spectra (four doublets, each for two protons, at δ 7.59, 7.52, 7.41, and 7.32 ppm), while the unique tosyl group of the former is located at *O*-6, giving rise to a broadening of the C(4)H signal by the additional coupling with the hydroxyl proton, and to the expected shift of this signal to lower δ value (4.36 ppm) in comparison with that of **16** (4.94 ppm). Compound **15**, treated with sodium azide in dimethylformamide at 110 °C for 3 h, led to the 3,6-diazido compound **6** (95% yield after column chromatography), whose structure was confirmed by its high-resolution MS and the absence of aromatic signals in its NMR spectra; **6** is a precursor of 2,5-anhydro-3,6-diazido-3,6-dideoxy-D-altronic acid **4**.



Scheme 3. Synthesis of an AB_2 template precursor. Reagents and conditions: (a) i. MeOH, PTSA, rt (1 h); ii. TsCl, Py, −25 °C (2.5 h). (b) NaN_3, DMF, 110 °C (3 h).

The A_2B template precursor **7** was prepared as shown in Scheme 4. In order to make possible the selective oxidation of the primary alcohol at C-6, a 1:3.3 mixture of **10a**,**b** was first transformed into **11** as seen above and, without further purification, treated with the 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO)/KBr/NaClO system in ethyl acetate, and aqueous $NaClO_2$ as the terminal oxidant,[40] to give, after methylation with trimethylsilyl-diazomethane, the desired methyl uronate **17** in poor yield (24%); its spectral data (mainly MS and NMR) corroborated this structure: the novel methyl ester function gave rise to a singlet at δ 3.78 ppm for the three methyl protons, as well as an ester carbonyl signal at 171.6 ppm and an additional methyl carbon signal at 52.6 ppm. Alternatively, crude **11** was treated with *tert*-butyl-diphenyl-chlorosilane to obtain the 6-*O tert*-butyl-diphenylsilyl derivative **18** in good yield, high-resolution MS of which evidenced the presence of a unique *tert*-butyl-diphenylsilyl (TBDPS) protecting group and one free-remaining OH group in the molecule, corroborated by its NMR spectra. Conventional benzylation of **18** with benzyl chloride/potassium hydroxide in toluene afforded, after column chromatography, 80% of the expected 2,5-anhydro-3-azido-4-*O*-benzyl-6-*O*-(*tert*-butyl-diphenylsilyl)-3-deoxy D-altrose dimethyl acetal **19** and 19% of the 4,6-di-*O*-benzyl derivative **20**. High-resolution mass spectrum (HRMS) of **19** and the appearance,



Scheme 4. Synthesis of an A_2B template precursor. Reagents and conditions: (a) i. MeOH, PTSA, rt (1 h); ii. TEMPO/KBr/NaClO; iii. $NaClO_2$; iv. $TMSCHN_2$/hexane. (b) i. MeOH, PTSA, rt (1 h); ii. TBDPSCl, DCM/Py, DMAP, rt (15 h). (c) BnCl, KOH, toluene, 90 °C (45 min). (d) TBAF/THF 1 M, THF, rt (3 h). (e) TCCA/TEMPO, NaBr, acetone, aq $NaHCO_3$, rt (45 min).

in its NMR spectra, of two doublets (J_{gem} = 12.0) at δ 4.81 and 4.65, each for one proton, assigned to the benzyl methylenic protons, and the corresponding methylenic carbon signal at δ 73.3 ppm, confirmed that **19** was the 4-*O*-benzyl derivative. The side product **20** had HRMS and NMR spectra congruent with the absence of any TBDPS group and the presence of two benzyl groups in the molecule. Pure **19** was 6-*O*-deprotected by the action of tetrabutylammonium fluoride, affording compound **21** in almost quantitative yield. The spectral properties of **21** were in agreement with the expected loss of the TBDPS group (HRMS *m*/*z* values corresponding to the molecular formula, NMR signals for only one phenyl group). Finally, oxidation of **21** with trichloroisocyanuric acid, promoted by the TEMPO radical, led to 2,5-anhydro-3-azido-4-*O*-benzyl-3-deoxy-D-altruronic acid dimethylacetal **7** in 98% yield. Again, the HRMS and the NMR spectra corroborated the structure of the product; thus, the carboxylic group gave rise to the appearance of a ^{13}C signal at δ 175.4 ppm, while the remaining 4-*O*-benzyl group originated aromatic signals and two doublets, at δ 4.77 and 4.71 ppm (*J* 11.7 Hz), for the methylene diastereotopic protons, as expected.

3. Conclusion

In summary, a DAST-promoted rearrangement observed in a hexose-derived azido-2-equatorial-hydroxy glycopyranoside, involving ring contraction under remarkably mild conditions, leads to a new class of molecular scaffolds with a 2,5-anhydro-sugar framework. Their potential for both structural and functional diversification has been demonstrated by the synthesis of various unusual *C*-glycoamino acid precursors that may act as key structure-inducing templates in generating folded, hydrolytically stable peptidomimetics.

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures. TLC was performed on silica gel plates (DC-Alufolien F_{254}, E. Merck); detection of compounds was accomplished with UV light (254 nm) and by charring with H_2SO_4 or an anisaldehyde reagent. Preparative column chromatography was carried out using silica gel (E. Merck, 0.063–0.200 mm or 0.040–0.063 mm). Melting points were recorded on a Gallenkamp MFB-595 apparatus and are uncorrected. A Perkin–Elmer 241 MC polarimeter was used for the measurement of optical rotations. Infrared spectra were obtained for films on a FTIR Bomem Michelson MB-120 spectrophotometer. ^1H NMR spectra (300 or 500 MHz) and ^{13}C NMR spectra (75.4 or 125.7 MHz) were recorded with a Bruker AMX-300 or a Bruker AMX-500 spectrometer, using the solvent peak as internal reference; chemical shifts (δ) are expressed in parts per million from TMS; coupling constants (*J*), in hertz. Assignments were confirmed by decoupling, homonuclear 2D COSY correlated spectra, and heteronuclear 2D correlated (HETCOR) spectra. HRCIMS (150 eV) experiments were performed with a Micromass AutoSpecQ instrument with a resolution of 10,000 (5% valley definition), and HRFABMS was performed on a VG AutoSpec spectrometer (Fisons Instruments) (30 keV).

4.2. Preparation of (1*R*)- and (1*S*)-2,5-anhydro-3-azido-4,6-*O*-benzylidene-3-deoxy-1-fluoro-1-*O*-methyl-D-altritols, 10a and 10b

To a solution of methyl 3-azido-4,6-*O*-benzylidene-3-deoxy-α-D-allopyranoside[37] (103.7 mg, 0.338 mmol) in acetonitrile (6.2 mL), cooled at 0 °C, DAST (223 μL, 1.69 mmol) was added dropwise. The mixture was refluxed for 12 min and then the solvent was evaporated under vacuum. The residue was treated with dichloromethane and poured into a cold, saturated aqueous sodium hydrogen carbonate solution (50 mL). The phases were separated and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The ^1H NMR spectrum of the crude product showed the presence of a 1:3.3 **10a**/**10b** diastereomeric mixture. Column chromatography (10:1→6:1 gradient, hexane/ethyl acetate) gave pure 2-enopyranoside **9** (19.6 mg, 20%) as a white crystalline product, **10a** (18.9 mg, 18%) as an amorphous solid, and **10b** (57.6 mg, 55%) as white crystalline compound.

Methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside, 9. Mp 112–114 °C; R_f 0.47 (4:1 hexane/ethyl acetate); $[\alpha]_D^{23} = +7.90$ (*c* 0.83, ace-

tone); IR ν_{max} 2116 (N_3) and 1651 cm^{-1} (C=C); ^1H NMR (500 MHz, CD_3COCD_3) δ 7.51–7.34 (m, 5H, Ph), 5.77 (s, 1H, C*H*–Ph), 5.31 (dd, 1H, $J_{1,2}$ = 3.0, $J_{2,5}$ = 2.0, H-2), 5.03 (dd, 1H, $J_{1,5}$ = 1.0, H-1), 4.58–4.55 (m, 1H, H-5), 4.29 (dd, 1H, $J_{6,6'}$ = 8.7, $J_{5,6}$ = 3.2, H-6), 3.96–3.89 (m, 2H, H-4 and H-6′), and 3.39 (s, 3H, OMe); ^{13}C NMR (125.7 MHz, CD_3COCD_3) δ 138.8 (C-3), 138.5–127.0 (Ph), 111.9 (C-2), 102.6 (*C*H–Ph), 97.3 (C-1), 75.8 (C-5), 69.5 (C-6), 65.0 (C-4), and 55.8 (OMe); FABHRMS: *m/z* 312.0955 (calcd for $C_{14}H_{15}N_3O_4$+Na^+: 312.0960).

Compound **10a**: R_f 0.42 (4:1 hexane/ethyl acetate); $[\alpha]_D^{25} = -72.0$ (*c* 0.60, acetone); IR ν_{max} 2108 (N_3), 982 cm^{-1} (CF); ^1H NMR (500 MHz, CD_3COCD_3) δ 7.52–7.37 (m, 5H, Ph), 5.69 (s, 1H, C*H*–Ph), 5.28 (dd, 1H, $^2J_{1,F}$ = 68.0, $J_{1,2}$ = 7.2, H-1), 4.66 (dd, 1H, $J_{2,3} = J_{3,4}$ = 4.6, H-3), 4.47 (dd, 1H, $J_{6,6'}$ = 8.6, $J_{5,6}$ = 3.5, H-6), 4.22 (ddd, 1H, $^3J_{2,F}$ = 11.5, H-2), 3.96 (dd, 1H, $J_{4,5}$ = 9.2, H-4), 3.88–3.84 (m, 2H, H-5 and H-6′), and 3.61 (d, 3H, $^4J_{OMe,F}$ = 1.2, O*Me*); ^{13}C NMR (125.7 MHz, CD_3COCD_3) δ 138.4–127.3 (m, Ph), 112.4 (d, $^1J_{1,F}$ = 220.0, C-1), 102.8 (*C*H–Ph), 81.9 (C-4), 80.1 (d, $^2J_{2,F}$ = 23.9, C-2), 71.8 (C-6), 71.0 (C-5), 62.1 (d, $^3J_{3,F}$ = 6.3, C-3), and 57.4 (OMe); CIHRMS: *m/z* 310.1208 (calcd for $C_{14}H_{17}FN_3O_4$+H^+: 310.1203).

Compound **10b**: R_f 0.40 (4:1 hexane/ethyl acetate); mp 132–136 °C; $[\alpha]_D^{24} = -61.0$ (*c* 0.75, acetone); IR ν_{max} 2108 (N_3), 949 cm^{-1} (CF); ^1H NMR (500 MHz, CD_3COCD_3) 7.52–7.36 (m, 5H, Ph), 5.69 (s, 1H, C*H*–Ph), 5.36 (dd, 1H, $^2J_{1,F}$ = 62.6, $J_{1,2}$ = 7.0, H-1), 4.70 (dd, 1H, $J_{2,3} = J_{3,4}$ = 4.3, H-3), 4.46 (dd, 1H, $J_{6,6'}$ = 8.6, $J_{5,6}$ = 3.5, H-6), 4.24 (ddd, 1H, $^3J_{2,F}$ = 3.1, H-2), 3.98 (dd, 1H, $J_{4,5}$ = 9.3, H-4), 3.86–3.82 (m, 2H, H-5 and H-6′), and 3.58 (d, 3H, $^4J_{OMe,F}$ = 1.5, O*Me*); ^{13}C NMR (125.7 MHz, CD_3COCD_3) δ 138.4–127.3 (m, Ph), 111.9 (d, $^1J_{1,F}$ = 215.0, C-1), 102.8 (*C*H–Ph), 82.0 (C-4), 79.5 (d, $^2J_{2,F}$ = 32.7, C-2), 71.8 (C-6), 71.1 (C-5), 61.7 (C-3), 57.4 (OMe); CIHRMS: *m/z* 310.1204 (calcd for $C_{14}H_{17}FN_3O_4$+H^+: 310.1203).

4.3. Preparation of 2,5-anhydro-3-azido-3-deoxy-D-altrose, 5

To a solution of 50 mg (0.162 mmol) of the diastereomeric mixture **10a**,**b** in acetone (1.5 mL), *p*-toluenesulfonic acid (12 mg, 0.064 mmol) was added. The solution was allowed to stand at room temperature for 1 h and then neutralized with triethylamine. The mixture was evaporated under vacuum to give a residue, extraction of which with dichloromethane gave 25 mg (83%) of chromatographically homogeneous crude **5**, pure enough to be used for further transformation, but unstable to be purified by column chromatography.

4.4. Preparation of 2,5-anhydro-3-azido-3-deoxy-D-altrose dimethyl acetal, 11

To a solution of 50 mg (0.162 mmol) of the diastereomeric mixture **10a**,**b** in methanol (1.5 mL), *p*-toluenesulfonic acid (6 mg, 0.032 mmol) was added. The mixture was stirred at room temperature for 1 h and then neutralized with triethylamine. The organic solvent was evaporated under vacuum and the residue purified by column chromatography (10:1 dichloromethane/methanol) to give pure **11** (35 mg, 93%) as an oil; R_f 0.51 (10:1 dichloromethane/methanol); $[\alpha]_D^{25} = +58.5$ (*c* 0.46, dichloromethane); IR ν_{max} 2102 cm^{-1} (N_3); ^1H NMR (500 MHz, $CDCl_3$) δ 4.54 (d, 1H, $J_{1,2}$ = 7.0, H-1), 4.38 (br dd, 1H, $J_{3,4} = J_{4,5}$ = 6.3, H-4), 4.16 (dd, 1H, $J_{2,3}$ = 4.3, H-3), 4.11 (dd, 1H, H-2), 3.86 (dd, 1H, $J_{6,6'}$ = 12.5, $J_{5,6}$ = 2.8, H-6), 3.79 (ddd, 1H, $J_{5,6'}$ = 3.3, H-5), 3.66 (dd, 1H, H-6′), 3.49 and 3.48 (each s, each 3H, 2O*Me*), and 2.66 (br s, 1H, HO-4); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 103.8 (C-1), 82.5 (C-5), 78.7 (C-2), 71.9 (C-4), 66.0 (C-3), 61.7 (C-6), and 55.4 and 54.6 (2O*Me*); FABHRMS: *m/z* 256.0922 (calcd for $C_8H_{15}N_3O_5$+Na^+: 256.0910).

4.5. Preparation of 4,6-di-*O*-acetyl-2,5-anhydro-3-azido-3-deoxy-D-altrose dimethyl acetal, 12

To a solution of 50 mg (0.162 mmol) of the diastereomeric mixture **10a**,**b** in methanol (1.5 mL), *p*-toluenesulfonic acid (6 mg, 0.032 mmol) was added. The mixture was stirred at room temperature for 1 h, then neutralized with triethylamine, and concentrated. The residue, without purification, was dissolved in anhydrous pyridine (1 mL), cooled at 0 °C and treated with acetic anhydride (1 mL). The reaction mixture was stirred at room temperature for 20 h and then evaporated under vacuum. Purification of the residue by column chromatography (2:1 ether/hexane) gave pure **12** (48.2 mg, 94%) as an oil; R_f 0.57 (1:1 hexane/ethyl acetate); $[\alpha]_D^{24} = +57.5$ (*c* 0.52, dichloromethane); IR ν_{max} 2108 (N_3), 1746 (C=O), 1229 (C–O), 1121 cm^{-1} (C–O–C); ^1H NMR (500 MHz, $CDCl_3$) δ 5.14 (dd, 1H, $J_{4,5}$ = 8.5, $J_{3,4}$ = 5.0, H-4), 4.55 (d, 1H, $J_{1,2}$ = 7.5, H-1), 4.40 (dd, 1H, $J_{2,3}$ = 4.7, H-3), 4.30 (dd, 1H, $J_{6,6'}$ = 12.0, $J_{5,6}$ = 3.0, H-6), 4.25 (ddd, 1H, $J_{5,6'}$ = 4.0 Hz, H-5), 4.11 (dd, 1H, H-6′), 4.10 (dd, 1H, H-2), 3.46 and 3.44 (each s, each 3H, 2O*Me*), and 2.16 and 2.07 (each s, each 3H, 2CO*Me*); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.9 and 170.5 (2C=O), 103.1 (C-1), 78.8 (C-2), 77.1 (C-5), 73.8 (C-4), 63.5 (C-3), 63.2 (C-6), 55.7 and 54.0 (2O*Me*), and 21.0 and 20.6 (2CO*Me*); FABHRMS: *m/z* 340.1136 (calcd for $C_{12}H_{19}N_3O_7$+Na^+: 340.1121).

4.6. Preparation of 4,6-di-*O*-acetyl-2,5-anhydro-3-azido-3-deoxy-D-altrose, 13

Dimethylacetal **12** (111 mg, 0.299 mmol) was dissolved in a 9:1 trifluoroacetic acid/water mixture (3.1 mL) and the solution was allowed to stand at room temperature for 1 h. The reaction mixture was poured into an ice-water mixture (100 mL) and extracted with dichloromethane (4 × 20 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate, brine, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded crude **13** (85.5 mg, 90%) as a chromatographically homogeneous oil, pure enough for further transformations without purification. An analytical sample of **13** was obtained after column chromatography (4:1 hexane/ethyl acetate)

of the crude product; R_f 0.37 (4:1 hexane/ethyl acetate); $[\alpha]_D^{26} = +40.9$ (*c* 0.49, dichloromethane); IR ν_{max} 2114 (N_3), 1742 (C=O), 1233 and 1125 cm^{-1} (C–O); ^1H NMR (500 MHz, $CDCl_3$) δ 9.63 (d, 1H, $J_{CHO,2} = 1.5$, C*H*O), 4.31 (dd, 1H, $J_{3,4} = 5.0$, $J_{4,5} = 7.0$, H-4), 4.69 (dd, 1H, $J_{2,3} = 5.0$, H-3), 4.46 (dd, 1H, H-2), 4.45 (m, 1H, H-5), 4.39 (dd, 1H, $J_{5,6} = 3.2$, $J_{6,6'} = 12.2$ Hz, H-6), 4.15 (dd, 1H, $J_{5,6'} = 4.2$, H-6′), and 2.17 and 2.11 (each s, each 3H, 2CO*Me*); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 199.2 (*C*HO), 170.6 and 170.3 (2*C*OMe), 82.7 (C-2), 78.8 (C-5), 73.8 (C-4), 63.3 (C-3), 63.1 (C-6), and 20.9 and 20.5 (2CO*Me*); CIHRMS: *m*/*z* 272.0892 (calcd for $C_{10}H_{13}N_3O_6+H^+$: 272.0883).

4.7. Preparation of 4,6-di-*O*-acetyl-2,5-anhydro-3-azido-3-deoxy-D-altronic acid, 1

Compound **12** (111 mg, 0.299 mmol) was dissolved in a 9:1 trifluoroacetic acid/water mixture (3.1 mL) and the solution was allowed to stand at room temperature for 1 h. The reaction mixture was poured into ice-water (100 mL) and extracted with dichloromethane (4 × 20 mL). The combined organic layers were successively washed with saturated sodium hydrogen carbonate and brine, then dried (Na_2SO_4), and concentrated. The residue (crude **13**) was dissolved in ether (2.3 mL) and cooled at −30 °C. This solution was treated with aqueous sodium dichromate/sulfuric acid (Jones' reagent, 3.6 mL, 2.35 mmol) and the temperature was allowed to rise the ambient. The organic solvent was evaporated under reduced pressure and the residue was filtered through a silica gel path by using ether (100 mL) and then ethyl acetate (150 mL) as eluents, to give pure **1** (44 mg, 65%); R_f 0.37 (4:1 ether/acetone); $[\alpha]_D^{26} = +40.2$ (*c* 0.50, dichloromethane); IR ν_{max} 3300 (OH), 2120 (N_3), 1746 (C=O), 1231 and 1119 cm^{-1} (C–O); ^1H NMR (500 MHz, $CDCl_3$) 5.19 (dd, 1H, $J_{3,4} = 5.0$, $J_{4,5} = 8.0$, H-4), 4.77 (d, 1H, $J_{2,3} = 4.5$, H-2), 4.69 (dd, 1H, H-3), 4.45 (ddd, 1H, $J_{5,6} = 2.8$, $J_{5,6'} = 4.0$, H-5), 4.39 (dd, 1H, $J_{6,6'} = 12.5$, H-6), 4.15 (dd, 1H, H-6′), and 2.18 and 2.10 (each s, each 3H, 2CO*Me*); ^{13}C NMR (125.7 MHz) δ 172.0 (*C*OOH), 170.7 and 170.4 (2*C* OMe), 78.3 and 78.2 (C-2 and C-5), 73.2 (C-4), 62.8 and 62.7 (C-3 and C-6), and 20.9 and 20.4 (2CO*Me*); CIHRMS: *m*/*z* 288.0836 (calcd for $C_{10}H_{13}N_3O_7+H^+$: 288.0832).

4.8. Preparation of 4,6-di-*O*-acetyl-2,5-anhydro-3-azido-1,3-dideoxy-1-(4-ethoxycarbonyl-phenylamino)-D-altritol, 2, and 4,6-di-*O*-acetyl-2,5-anhydro-3-azido-3-deoxy-D-altritol, 14

Compound **12** (100 mg, 0.315 mmol) was dissolved in a 9:1 trifluoroacetic acid/water mixture (2.7 mL) and the solution was allowed to stand at room temperature for 1 h. The reaction mixture was poured into ice-water (100 mL) and extracted with dichloromethane (4 × 20 mL). The combined organic layers were successively washed with saturated sodium hydrogen carbonate and brine, then dried (Na_2SO_4), and concentrated. The residue (crude **13**) was dissolved in 1,2-dichloroethane (3.1 mL) and treated with ethyl 4-aminobenzoate (72.1 mg, 0.437 mmol) and sodium triacetoxyborohydride (93.0 mg, 0.441 mmol). The reaction mixture was stirred at room temperature until total consumption (18 h) of **13**. The mixture was then diluted with saturated aqueous sodium hydrogen carbonate (25 mL) and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography (1:1 ether/hexane) of the residue afforded pure 4,6-di-*O*-acetyl-2,5-anhydro-3-azido-1,3-dideoxy-1-(4-ethoxycarbonyl-phenylamino)-D-altritol (**2**, 62.5 mg, 47%) and 4,6-di-*O*-acetyl-2,5-anhydro-3-azido-3-deoxy-D-altritol (**14**, 32.5 mg, 34%).

Compound **2**: R_f 0.39 (10:1 ether/hexane); $[\alpha]_D^{26} = -6.8$ (*c* 0.42, dichloromethane); IR ν_{max} 3376 (NH), 2110 (N_3), 1746 and 1699 (C=O), 1279, 1231, 1177, and 1113 cm^{-1} (C–O); ^1H NMR (300 MHz, CD_3COCD_3) δ 7.78 (d, 2H, $J_{2',3'} = 8.7$, aromatic H-3′), 6.71 (d, 2H, aromatic H-2′), 5.81 (br dd, 1H, $J_{1a,NH} \approx J_{1b,NH} = 5.6$, N*H*), 5.38 (dd, 1H, $J_{4,5} = 6.7$, $J_{3,4} = 5.2$, H-4), 4.61 (dd, 1H, $J_{2,3} = 4.4$, H-3), 4.43 (td, 1H, $J_{1a,2} = J_{1b,2} = 6.6$, H-2), 4.28–4.21 (m, 2H, H-5 and H-6), 4.25 (q, 2H, $J = 7.1$, CH_3CH_2O), 4.13 (dd, 1H, $J_{6,6'} = 12.5$, $J_{5,6'} = 6.2$, H-6′), 3.57 (ddd, 1H, $J_{1a,1b} = 13.4$, H-1a), 3.40 (ddd, 1H, H-1b), 2.13 and 2.00 (2s, each 3H, 2CO*Me*), and 1.31 (t, 3H, CH_3CH_2O); ^{13}C NMR (75.4 MHz, CD_3COCD_3) δ 170.8 and 170.7 (2*C*OMe), 166.8 (Ar*C*OOEt), 153.3–112.2 (Ph), 78.4 (C-2 and C-5), 75.8 (C-4), 64.5 (C-6), 64.0 (C-3), 60.4 (CH_3CH_2O), 43.9 (C-1), 20.6 and 20.3 (2CO*Me*), and 14.7 (CH_3CH_2O); CIHRMS: *m*/*z* 420.1644 (calcd for $C_{19}H_{24}N_4O_7$: 420.1645).

Compound **14**: R_f 0.40 (1:4 hexane/ethyl acetate); $[\alpha]_D^{26} = +19.4$ (*c* 0.72, dichloromethane); IR ν_{max} 3306 (OH), 2108 (N_3), 1227 and 1119 cm^{-1} (C–O); ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (dd, 1H, $J_{4,5} = 7.3$, $J_{3,4} = 5.2$, H-4), 4.41 (dd, 1H, $J_{2,3} = 4.8$, H-3), 4.32 (dd, 1H, $J_{6,6'} = 11.7$, $J_{5,6} = 3.0$, H-6), 4.30–4.21 (m, 2H, H-2 and H-5), 4.11 (dd, 1H, $J_{5,6'} = 4.2$, H-6′), 3.82 (d, 2H, $J_{1 \text{ and } 1',2} = 6.0$, H-1 and H-1′), 2.19 and 2.12 (each s, each 3H, 2CO*Me*), and 1.95 (br s, 1H, OH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.8 and 170.5 (2*C*OMe), 79.7 and 77.3 (C-5 and C-2), 74.3 (C-4), 63.6 (C-6), 62.5 (C-3), 62.0 (C-1), and 20.9 and 20.5 (2CO*Me*); CIHRMS: *m*/*z* 274.1026 (calcd for $C_{10}H_{15}N_3O_6+H^+$: 274.1039).

4.9. Preparation of 2,5-anhydro-3-azido-3-deoxy-6-*O*-(4-toluenesulfonyl)-D-altrose dimethyl acetal, 15, and 2,5-anhydro-3-azido-3-deoxy-4,6-di-*O*-(4-toluenesulfonyl)-D-altrose dimethyl acetal, 16

To a solution of 61.3 mg (0.198 mmol) of the diastereomeric mixture **10a**,**b** in methanol (1.8 mL), *p*-toluenesulfonic acid (7.3 mg, 0.037 mmol) was added. The mixture was stirred at room temperature for 1 h, then neutralized with triethylamine, and concentrated. The residue, without purification, was dissolved in anhydrous pyridine (1 mL), cooled at −25 °C, and treated with a solution of tosyl chloride (115 mg, 0.603 mmol) in anhydrous pyridine (1 mL) at 0 °C. The reaction mixture was stirred at −25 °C for 2.5 h, then diluted with

water (1 mL), the temperature was allowed to rise the ambient, and the reaction mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography of the residue (4:1 2:1 gradient, hexane/ethyl acetate) gave pure 2,5-anhydro-3-azido-3-deoxy-4,6-di-*O*-(4-toluenesulfonyl)-D-altrose dimethyl acetal (**16**, 10.5 mg, 10%) and 2,5-anhydro-3-azido-3-deoxy-6-*O*-(4-toluenesulfonyl)-D-altrose dimethyl acetal (**15**, 46 mg, 60%), both as oils.

Compound **15**: R_f 0.50 (1:1 hexane/ethyl acetate); $[\alpha]_D^{25} = +36.8$ (*c* 0.83, dichloromethane); IR ν_{max} 3308 (OH), 2112 (N_3), 1360 and 1177 (SO_2), 1119 cm^{-1} (C–O–C); ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 and 7.34 (each d, each 2H, $J \approx 8.5$, aromatic protons), 4.49 (d, 1H, $J_{1,2} = 6.5$, H-1), 4.36 (br dd, 1H, $J_{3,4} \approx J_{4,5} = 6.0$, H-4), 4.20 (dd, 1H, $J_{6,6'} = 11.0$, $J_{5,6} = 3.0$, H-6), 4.15 (dd, 1H, $J_{5,6'} = 3.0$, H-6′), 4.14 (dd, 1H, $J_{2,3} = 4.0$ Hz, H-3), 4.09 (dd, 1H, H-2), 3.90 (ddd, 1H, H-5), 3.45 and 3.40 (each s, each 3H, 2OMe), and 2.45 (s, 3H, Ar*Me*); ^{13}C NMR (125.7 MHz) δ 145.1–128.0 (Ph), 103.1 (C-1), 80.2 (C-5), 78.5 (C-2), 72.2 (C-4), 68.8 (C-6), 65.4 (C-3), 55.3 and 53.6 (2OMe), and 21.8 (Ar*Me*); FABHRMS: *m*/*z* 410.0984 (calcd for $C_{15}H_{21}N_3O_7S$+Na^+: 410.0998).

Compound **16**: R_f 0.60 (1:1 hexane/ethyl acetate); $[\alpha]_D^{24} = +52.0$ (*c* 0.52, dichloromethane); IR ν_{max} 2114 (N_3), 1362 and 1177 (SO_2), 1121 cm^{-1} (C–O–C); ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 and 7.52 (each d, each 2H, $J \approx 9$, aromatic protons), 7.41 and 7.32 (each d, each 2H, aromatic protons), 4.94 (dd, 1H, $J_{4,5} = 8.0$, $J_{3,4} = 5.0$, H-4), 4.47 (d, 1H, $J_{1,2} = 7.5$, H-1), 4.15 (dd, 1H, $J_{2,3} = 3.7$, H-3), 4.09 (m, 2H, H-5 and H-6), 3.98 (dd, 1H, H-2), 3.86 (d, 1H, $J_{6,6'} = 10.5$ Hz, H-6′), 3.40 and 3.31 (each s, each 3H, 2OMe), 2.48 and 2.44 (each s, each 3H, 2 Ar*Me*); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 146.3–128.1 (2Ph), 102.5 (C-1), 78.4 (C-2), 76.7 (C-5), 76.4 (C-4), 67.4 (C-6), 63.5 (C-3), 55.3 and 53.0 (OMe), and 21.9 and 21.8 (2 Ar*Me*); FABHRMS: *m*/*z* 564.1071 (calcd for $C_{22}H_{27}N_3O_9S_2$+Na^+: 564.1086).

4.10. Preparation of 2,5-anhydro-3,6-diazido-3,6-dideoxy-D-altrose dimethyl acetal, 6

To a solution of 44 mg (0.114 mmol) of **15** in *N*,*N*-dimethylformamide (1 mL), sodium azide (32 mg, 0.492 mmol) was added. The mixture was heated at 110 °C under reflux for 3 h. After evaporation of the solvent, the residue was extracted with ethyl acetate (30 mL). The extract was washed with water (3 × 20 mL), dried (Na_2SO_4), and concentrated, and the residue was purified by column chromatography (2:1 hexane/ethyl acetate) to give **6** (27.8 mg, 95%) as an amorphous solid; R_f 0.53 (1:3 hexane/ethyl acetate); $[\alpha]_D^{22} = +117.4$ (*c* 0.74, dichloromethane); IR ν_{max} 2106 (N_3), 1120 cm^{-1} (C–O–C); ^1H NMR (500 MHz, $CDCl_3$) δ 4.56 (d, 1H, $J_{1,2} = 6.5$, H-1), 4.31 (br m, 1H, H-4), 4.18 (m, 2H, H-2 and H-3), 3.89 (ddd, 1H, $J_{4,5} = 7.5$, $J_{5,6} \approx J_{5,6'} = 3.5$, H-5), 3.65 (dd, 1H, $J_{6,6'} = 13.5$, H-6), 3.47 and 3.43 (each s, each 3H, 2OMe), 3.29 (dd, 1H, H-6′), and 2.59 (br s, 1H, OH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 103.0 (C-1), 81.5 (C-5), 78.2 (C-2), 72.7 (C-4), 65.9 (C-3), 55.2 and 53.1 (2OMe), and 51.6 (C-6); FABHRMS: *m*/*z* 281.0970 (calcd for $C_8H_{14}N_6O_4$+Na^+: 281.0974).

4.11. Preparation of methyl 2,5-anhydro-3-azido-3-deoxy-D-altruronate dimethyl acetal, 17

To a solution of 61 mg (0.197 mmol) of the diastereomeric mixture **10a**,**b** in methanol (1.8 mL), *p*-toluenesulfonic acid (15 mg, 0.08 mmol) was added. The mixture was stirred at room temperature for 1 h, then neutralized with triethylamine, and concentrated. The residue, without purification, was dissolved in ethyl acetate (300 μL). To this solution, 39 μL of 0.5 M KBr and 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO, 0.6 mg, 0.004 mmol) were added. The mixture was cooled at 5 °C, treated with a 10% aqueous sodium hypochlorite (800 μL, 1.04 mmol) dropwise, and stirred at room temperature for 30 min. Then, 25% aqueous sodium chlorite (1.1 mL) was added. After 30 min at room temperature, the organic phase was separated, and the remaining aqueous phase was extracted with ethyl acetate (2 × 15 mL). The aqueous layer was acidified with 1 M HCl and then extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in 1:1 methanol/acetonitrile (1mL) and treated with 400 μL of 2 M trimethylsilyl-diazomethane in hexane. After 2 h at room temperature, the solvents were evaporated under reduced pressure and the residue was purified by column chromatography (40:1 dichloromethane/methanol) to give pure **17** (12 mg, 24%) as an oil; R_f 0.51 (10:1 dichloromethane/methanol); $[\alpha]_D^{20} = +19.7$ (*c* 0.68, dichloromethane); IR ν_{max} 3325 (OH), 2110 (N_3), 1732 (C=O), and 1202 and 1119 cm^{-1} (C–O–C); ^1H NMR (500 MHz, $CDCl_3$) δ 4.55 (d, 1H, $J_{1,2} = 6.0$, H-1), 4.50 (dd, 1H, $J_{3,4} = J_{4,5} = 5.5$, H-4), 4.34 (d, 1H, H-5), 4.31 (dd, 1H, $J_{2,3} = 5.5$, H-2), 4.23 (dd, 1H, H-3), 3.78 (s, 3H, COOMe), and 3.49 and 3.48 (each s, each 3H, two acetal OMe); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.6 (*C*OOMe), 103.0 (C-1), 81.6 (C-5), 79.2 (C-2), 75.4 (C-4), 64.4 (C-3), 55.5 and 54.3 (two acetal O*Me*), and 52.6 (COO*Me*); CIHRMS: *m*/*z* 262.1037 (calcd for $C_9H_{15}N_3O_6$+H^+: 262.1039).

4.12. Preparation of 2,5-anhydro-3-azido-6-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-D-altrose dimethyl acetal, 18

p-Toluenesulfonic acid (11.4 mg, 0.058 mmol) was added to solution of the diastereomeric mixture **10a**,**b** (96 mg, 0.311 mmol) in methanol (2.8 mL). The mixture was stirred at room temperature for 1 h, then neutralized with triethylamine, and concentrated. The residue, without purification, was dissolved in anhydrous dichloromethane (1 mL) under argon atmosphere, and anhydrous pyridine (100 μL) and 4-(dimethylamino)pyridine (4 mg) were added to that solution. The mixture was cooled at 0 °C and treated with *tert*-butyl-diphenyl-chlorosilane (248 μL, 0.944 mmol). The reaction mixture was stirred at room temperature for

15 h, then neutralized with 1 M HCl, dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography of the residue (5:1 hexane/ethyl acetate) gave pure **18** (120.4 mg, 82%) as an oil; R_f 0.43 (2:1 hexane/ethyl acetate); $[\alpha]_D^{25} = +33.3$ (*c* 0.63, dichloromethane); IR ν_{max} 3295 (OH), 2108 (N_3), 1115 and 1055 (C–O–C), 706 cm^{-1} (CSi); ^1H NMR (300 MHz, $CDCl_3$) 7.69–7.38 (m, 10H, 2Ph), 4.55 (d, 1H, $J_{1,2} = 6.6$, H-1), 4.55 (m, 1H, H-4), 4.20 (dd, 1H, $J_{2,3} \approx J_{3,4} = 4.8$, H-3), 4.18 (dd, 1H, H-2), 3.83 (m, 3H, H-5, H-6, and H-6′), 3.49 and 3.46 (each s, each 3H, 2OMe), and 1.06 (s, 9H, CMe_3); (300 MHz, CD_3COCD_3): δ 7.76–7.40 (m, 10H, 2Ph), 4.77 (m, 2H, H-4 and OH), 4.49 (d, 1H, $J_{1,2} = 7.2$, H-1), 4.15 (dd, 1H, $J_{2,3} \approx J_{3,4} = 3.8$, H-3), 4.10 (dd, 1H, H-2), 3.90 (m, 2H, H-5, H-6), 3.78 (dd, 1H, $J_{6,6'} = 11.7$, $J_{5,6'} = 3.9$, H-6′), 3.41 and 3.40 (each s, each 3H, 2OMe), 1.03 (s, 9H, CMe_3); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 135.8–127.9 (m, 2Ph), 103.5 (C-1), 83.1 (C-5), 78.8 (C-2), 73.0 (C-4), 66.1 (C-3), 63.8 (C-6), 55.3 and 53.7 (2OMe), 27.0 (C*Me*$_3$), and 19.4 (*C*Me_3); (75.4 MHz, CD_3COCD_3) δ 136.5–128.6 (m, 2Ph), 104.5 (C-1), 83.0 (C-5), 79.3 (C-2), 73.3 (C-4), 67.2 (C-3), 64.4 (C-6), 55.1 and 53.7 (2OMe), 27.1 (C*Me*$_3$), and 19.8 (*C*Me_3); FABHRMS: *m*/*z* 494.2101 (calcd for $C_{24}H_{33}N_3O_5Si+Na^+$: 494.2087).

4.13. Preparation of 2,5-anhydro-3-azido-4-*O*-benzyl-6-*O*-(*tert*-butyl-diphenylsilyl)-3-deoxy-D-altrose dimethyl acetal, 19, and 2,5-anhydro-3-azido-4,6-di-*O*-benzyl-3-deoxy-D-altrose dimethyl acetal, 20

To a solution of **18** (87.8 mg, 0.186 mmol) in dry toluene (1.5 mL) powdered potassium hydroxide (100 mg, 1.79 mmol) was added. The mixture was stirred at room temperature for 30 min, and then a solution of benzyl chloride (350 μL, 3.06 mmol) in anhydrous toluene (200 μL) was added. The reaction mixture was heated at 90 °C for 45 min and then diluted with water (1 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography of the residue (10:1→4:1 gradient, hexane/ethyl acetate) gave pure 2,5-anhydro-3-azido-4-*O*-benzyl-6-*O*-(*tert*-butyl-diphenylsilyl)-3-deoxy-D-altrose dimethyl acetal **19** (83.6 mg, 80%) and 2,5-anhydro-3-azido-4,6-di-*O*-benzyl-3-deoxy-D-altrose dimethyl acetal **20** (14.5 mg, 19%), both as oils.

Compound **19**: R_f 0.59 (4:1 hexane/ethyl acetate); $[\alpha]_D^{26} = +21.8$ (*c* 0.64, dichloromethane); IR ν_{max} 2106 (N_3), 1113 and 1069 (C–O–C), 702 cm^{-1} (CSi); ^1H NMR (300 MHz, CD_3COCD_3) δ 7.81–7.32 (m, 15H, 3 Ph), 4.81 and 4.65 (each d, each 1H, $J_{gem} = 12.0$, CH_2Ph), 4.64 (dd, 1H, $J_{4,5} = 8.1$, $J_{3,4} = 4.5$, H-4), 4.53 (d, 1H, $J_{1,2} = 7.5$, H-1), 4.40 (dd, 1H, $J_{2,3} = 3.0$, H-3), 4.12 (dd, 1H, H-2), 4.01 (ddd, 1H, $J_{5,6} = J_{5,6'} = 2.7$, H-5), 3.81 (dd, 1H, $J_{6,6'} = 11.1$, H-6), 3.73 (dd, 1H, H6), 3.42 and 3.42 (each s, each 3H, 2OMe), and 1.00 (s, 9H, CMe_3); ^{13}C NMR (75.4 MHz, CD_3COCD_3) δ 139.0–128.3 (3Ph), 104.4 (C-1), 81.7 (C-5), 80.1 (C-2), 80.0 (C-4), 73.3 (*C*H_2Ph), 64.3 (C-6), 64.0 (C-3), 55.1 and 53.8 (2OMe), 27.2 (C*Me*$_3$), and 19.7 (*C*Me_3); FABHRMS: *m*/*z* 584.2551 (calcd for $C_{31}H_{39}N_3O_5Si+Na^+$: 584.2557).

Compound **20**: R_f 0.54 (2:1 hexane/ethyl acetate); $[\alpha]_D^{28} = +61.4$ (*c* 0.69, dichloromethane); IR ν_{max} 2106 (N_3), 1119 and 1067 cm^{-1} (C–O–C); ^1H NMR (500 MHz, CD_3COCD_3) δ 7.45–7.31 (m, 10H, 2Ph), 4.76 and 4.63 (each d, each 1H, $J_{gem} = 12.0$, CH_2Ph), 4.55 and 4.50 (each d, each 1H, $J_{gem} = 12.0$, CH_2Ph), 4.48 (d, 1H, $J_{1,2} = 8.0$, H-1), 4.43 (dd, 1H, $J_{4,5} = 8.0$, $J_{3,4} = 4.5$, H-4), 4.30 (dd, 1H, $J_{2,3} = 4.0$, H-3), 4.03–4.01 (m, 2H, H-2 and H-5), 3.66 (dd, 1H, $J_{5,6} = 3.0$, $J_{6,6'} = 11.0$, H-6), 3.55 (dd, 1H, $J_{5,6'} = 4.0$, H-6′), and 3.40 and 3.36 (each s, each 3H, 2OMe); ^{13}C NMR (125.7 MHz, CD_3COCD_3) δ 139.6–128.2 (m, 2Ph), 104.3 (C-1), 81.0 (C-4), 80.7 and 79.6 (C-5 and C-2), 73.7 and 73.3 (2*C*H_2Ph), 70.0 (C-6), 64.0 (C-3), and 55.1 and 53.7 (2OMe); FABHRMS: *m*/*z* 436.1851 (calcd for $C_{22}H_{27}N_3O_5+Na^+$: 436.1848).

4.14. Preparation of 2,5-anhydro-3-azido-4-*O*-benzyl-3-deoxy-D-altrose dimethyl acetal, 21

A solution of **19** (71.8 mg, 0.128 mmol) in dry tetrahydrofuran (THF, 5.8 mL) at 0 °C was treated with 256 μL (256 mmol) of 1 M tetrabutylammonium fluoride (TBAF)/THF solution. The mixture was stirred until TLC indicated total consumption of the starting material (3 h), then concentrated under reduced pressure. Column chromatography of the residue (1:3 hexane/ethyl acetate) gave pure **21** (40.6 mg, 98%). R_f 0.41 (1:5 hexane/ethyl acetate); $[\alpha]_D^{26} = +60.2$ (*c* 0.62, dichloromethane); IR ν_{max} 3474 (OH), 2105 (N_3), 1109 and 1063 cm^{-1} (C–O–C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.32 (m, 5H, Ph), 4.70 and 4.61 (each d, each 1H, $J_{gem} = 11.7$, CH_2Ph), 4.54 (d, 1H, $J_{1,2} = 7.5$, H-1), 4.27 (dd, 1H, $J_{4,5} = 8.7$, $J_{3,4} = 4.5$, H-4), 4.06 (dd, 1H, $J_{2,3} = 4.1$, H-3), 4.02 (ddd, 1H, $J_{5,6} = 2.7$, $J_{5,6'} = 4.0$, H-5), 3.96 (dd, 1H, H-2), 3.88 (dd, 1H, $J_{6,6'} = 12.4$, H-6), 3.57 (dd, 1H, H-6′), and 3.47 and 3.45 (each s, each 3H, 2OMe); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.2–128.1 (m, Ph), 103.7 (C-1), 80.5 (C-5), 79.1 (C-2), 78.8 (C-4), 73.4 (*C*H_2Ph), 63.1 (C-3), 61.5 (C-6), and 55.7 and 54.5 (2OMe); FABHRMS: *m*/*z* 346.1376 (calcd for $C_{15}H_{21}N_3O_5+Na^+$: 346.1379).

4.15. Preparation of 2,5-anhydro-3-azido-4-*O*-benzyl-3-deoxy-D-altruronic acid dimethyl acetal, 7

A solution of **21** (32.5 mg, 0.101 mmol) in acetone (1 mL) was treated with 300 μL of a 15% aqueous sodium hydrogen carbonate. To the mixture, cooled at 0 °C, sodium bromide (2.02 mg, 0.0202 mmol), 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO, 0.3 mg, 0.002 mmol), and trichloroisocyanuric acid (TCCA, two portions, each 23.5 mg, 0.101 mmol, over 10 min) were successively added. The mixture was stirred at room temperature for 45 min and filtered through a celite layer. The filtrate was treated with saturated aqueous sodium carbonate (30 mL) and washed with ethyl acetate (3 × 25 mL). The aqueous layer was acidified with 2 M HCl, then extracted with ethyl acetate (4 × 100 mL). The combined organic extracts were dried

(Na_2SO_4), and concentrated under reduced pressure to give 33.1 mg (98%) of **7**; R_f 0.42 (5:1 dichloromethane/methanol); $[\alpha]_D^{24} = -108.2$ (*c* 0.68, dichloromethane); IR ν_{max} 3295 (OH), 2110 (N_3), 1736 (CO), 1111 and 1065 cm^{-1} (C–O–C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.32 (m, 5H, Ph), 4.77 and 4.71 (each d, each 1H, J_{gem} = 11.7, CH_2Ph), 4.60 (d, 1H, $J_{1,2}$ = 6.9, H-1), 4.53 (d, 1H, $J_{4,5}$ = 7.2, H-5), 4.39 (dd, 1H, $J_{3,4}$ = 4.5, H-4), 4.08–4.00 (m, 2H, H-2 and H-3), and 3.46 and 3.45 (each s, each 3H, 2OMe); ^{13}C NMR (75.4 MHz) δ 175.4 (*C*OOH), 136.7–128.1 (m, Ph), 102.7 (C-1), 82.6 (C-4), 79.6 (C-2), 79.1 (C-5), 73.4 (CH_2Ph), 63.2 (C-3), and 55.7 and 53.9 (2OMe); FABHRMS: *m*/*z* 360.1161 (calcd for $C_{15}H_{19}N_3O_6$+Na^+: 360.1172).

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