Synthesis of 1′-Homo-N-nucleosides from Hexitols

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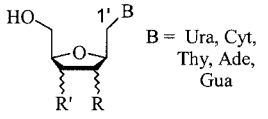
This paper describes a new route for the synthesis of *N*-(1′-homo-L-gulitol)nucleosides and amino sugar analogues of *N*-(1′-homo-L-gulitol)nucleosides by nucleophilic epoxide ring-opening followed by *O*-heterocyclization of 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-D-mannitol and 1,2:5,6-dianhydro-3,4-diazido-D-iditol, respectively. Magnesium perchlorate [$Mg(ClO_4)_2$] was found to be the best catalyst for the reaction of silylated bases, derived from uracil, thymine and adenine, with these bis(epoxides).

Introduction

The design and preparation of novel nucleoside analogues as antiviral and antitumor agents is a well-defined branch of medicinal chemistry.[1] Modification of the sugar residue of nucleosides has yielded a large variety of viral inhibitors against DNA, RNA and retroviruses. These modified nucleosides include therapeutically useful agents such as azidothymidine (AZT), dideoxycytidine (ddC), and dideoxyinosine (ddI),[2−4] potent antiherpetics in which the carbohydrate ring is replaced by acyclic side-chains, such as 9-alkylpurine derivatives (Acyclovir, Penciclovir and Famciclovir),[5] and *N*-thioxonucleosides such as Lamivudine.[6] During the last decades attention has also been focused on biologically active cyclopentylnucleosides (carbanucleosides),[7] derived from nucleosides by replacement of the furanose ring oxygen atom by a methylene moiety. Due to the absence of the natural *N*-glycosidic bond, these carbanucleosides possess greater metabolic stability due to their inertness towards hydrolytic activity of cellular phosphorylases. The resistance to enzymatic degradation is the rational basis for the synthesis of other analogues such as 2′,5′-anhydro-1′-substituted-1′-deoxyhexitols (1′-homo-N-nucleosides **1a**−**b**), in which a methylene group is inserted between the heterocyclic base and C1′ of the hexitol residue (Figure 1).[8] A further incentive for the synthesis and biological evaluation of these compounds is based on the anticipated interaction of the base moiety with DNA (or RNA) as base-pair complements.[9]



1a: R = H, R' = OH.
1b: R = OH, R' = OH

Figure 1. 1′-Homo-N-nucleosides

1′-Homo-N-nucleosides **1a**−**b** are generally prepared by two main methods.[8] In the first, heterocyclic bases can be introduced by nucleophilic displacement of a leaving group at the C-1′ exocyclic methyl group of the pentofuranose.[10] In the second method, the nucleobases are constructed from a C-1′ pentofuranosyl methylamino derivative.[11] These methods have been implemented with varying degrees of success due to side-reactions.

1,2:5,6-Dianhydro-3,4-di-*O*-protected hexitols have been widely used for the synthesis of biologically active compounds such as enzyme inhibitors,[12] amino acids,[13] and aziridines.[14] It has been observed that the selectivity and efficiency of the nucleophilic ring-opening of the oxiranyl moieties depend on various experimental factors, such as the nature of the nucleophile, the reaction solvent, and the type of 3,4-*O*-protecting groups used. The newly formed hydroxy moiety, resulting from the ring-opening process of one of the epoxides, can attack the second terminal epoxide to give mainly anhydro derivatives. Thus, enantiomerically pure amino carboxylic acids or "pseudo-azadisaccharides" have been obtained from C_2-symmetric bis(epoxides) on azidolysis followed by *O*-ring closure.[15]

Herein, we describe a novel synthesis of *N*-(2′,5′-anhydro-1′-deoxy-L-gulitol)nucleosides by nucleophilic ring opening of 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-D-mannitol (**3**) with purine and pyrimidine nucleophiles followed by *O*-

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heterocyclization to 2,5-anhydro derivatives. A similar procedure, starting from 1,2:5,6-dianhydro-3,4-diazido-D-iditol (**12**), is also reported for the synthesis of *N*-(1′-homo-L-glucitol)nucleosides bearing vicinal amino moieties on the hexitol residue.

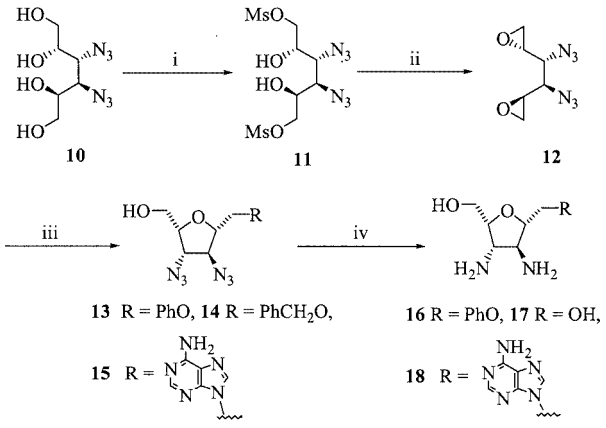
Amino sugar nucleosides, such as polyoxin or puromycin, are known to possess important antibacterial and antitumor properties.[16] Different procedures involving the reduction of the azidosugar analogue,[17] Mitsunobu reactions or intramolecular neighboring-group-assisted delivery of amine nucleophiles[18] have been reported to obtain the 2′- or 3′-aminodeoxynucleoside derivatives.[19] To the best of our knowledge, this is the first synthesis of an aminohexitol derivative of 1′-homo-N-nucleoside reported in the literature (Scheme 2).

Results and Discussion

The route developed to prepare *N*-(1′-homo-L-gulitol)nucleosides **7**−**9** and their precursors **4**−**6** is shown in Scheme 1. The starting material 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-D-mannitol (**3**) was prepared from D-mannitol, according to the procedure reported by Zhang.[20] Initially, the sodium salt of adenine, uracil, or thymine, generated by the treatment of the nucleic base with sodium hydride (NaH, 1.2 equiv.) in DMF (5 mL),[21] was condensed with freshly prepared bis(epoxide) **3** at room temperature.

Under these experimental conditions, 2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-1-(uracil-1-yl)-L-gulitol (**4**), 2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-1-(thymin-1-yl)-L-gulitol (**5**), and 2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-1-(6-amino-9*H*-purin-9-yl)-L-gulitol (**6**) were obtained in low yields (13, 19, and 11%, respectively). Improvements in the reaction yields were obtained using Lewis acids as catalysts under Vorbruggen conditions.[22] Typically, the trimethylsilylated nucleobases were prepared from uracil, thymine, and adenine with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide [BSTFA (5.0 equiv.); CH_3CN; 50 °C]. The reaction mixture containing either the trimethylsilylated pyrimidine or purine derivative and the bis(epoxide) **3** was then refluxed in the presence of tin(IV) chloride ($SnCl_4$; 1.0 equiv.; in acetonitrile) to afford compounds **4**, **5**, and **6** in 28, 32, and 35% yields, respectively. It is known that magnesium perchlorate [$Mg(ClO_4)_2$] is more selective as catalyst than $SnCl_4$ in ring-opening reactions of 1,2:5,6-dianhydro-3,4-di-*O*-isopropyliden-D-mannitols.[23] Accordingly, the condensation of the bis(trimethylsilyl) derivatives of adenine, uracil, and thymine with **3** was performed in the presence of magnesium perchlorate [$Mg(ClO_4)_2$] at reflux temperature, to give **4**, **5**, and **6** in yields of 51, 54, and 52%, respectively. Finally, catalytic hydrogenation of 1′-homo-3′,4′-di-*O*-benzyl-L-gulitol-N-nucleosides **4**, **5**, and **6** with 10% palladium/charcoal under ambient pressure afforded the corresponding 2,5-anhydro-1-deoxy-1-(uracil-1-yl)-L-gulitol (**7**), 2,5-anhydro-1-deoxy-1-(thymin-1-yl)-L-gulitol (**8**) and 2,5-anhydro-1-deoxy-1-(6-amino-9*H*-purin-9-yl)-L-gulitol (**9**) in high yields.

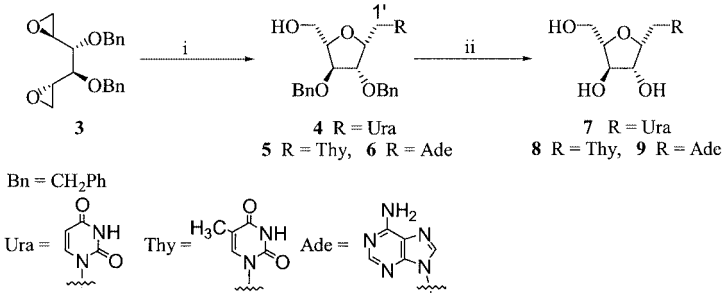
We next turned our attention to the synthesis of *N*-(1′-homo-L-hexitol)nucleosides bearing vicinal amino groups in the 2,5-anhydro ring. 1,2:5,6-Dianhydro-3,4-diazido-D-iditol (**12**) was prepared starting from diazidohexitol (**10**) under the experimental conditions described in the literature for cisplatinum analogues of alditol derivatives (Scheme 2).[24]



Scheme 2. Reagents and conditions: i. CH_3SO_2Cl, Py, 48 h, −15 °C; ii. KOH/H_2O, Et_2O, 3 h, 25 °C; iii. ROH/NaH or adenine/NaH, DMF, 4 h, 25 °C or adenine/BSTFA, CH_3CN, 50 °C then $Mg(ClO_4)_2$, CH_3CN, 6 h, 85 °C (R = Ph, $PhCH_2$); iv. H_2, Pd/C, MeOH/H_2O, 16 h, 25 °C

Diazido compound **10**, which is readily available from D-mannitol,[24] was converted into the desired bis(epoxide) **12** by treatment of the dimesylate **11** with an ethereal solution of potassium hydroxide (Scheme 2).

The opening of the bis(epoxide) **12** was examined with different nucleophiles. Firstly, sodium phenoxide, in DMF



Scheme 1. Reagents and conditions: i. BH/NaH, DMF, 4 h, 25 °C or BH/BSTFA, CH_3CN, 50 °C then $Mg(ClO_4)_2$, CH_3CN, 6 h, 85 °C (BH = Ura, Thy, Ade); ii. H_2/Pd−C, MeOH/H_2O, 16 h, 25 °C

at 25 °C, was used in a model reaction. Regiospecific ring-opening of one epoxide moiety followed by an *O*-heterocyclization was observed giving 2,5-anhydro-3,4-diazido-1-*O*-phenyl-L-glucitol (**13**) selectively. Subsequent reduction of the azido groups led to 2,5-anhydro-3,4-diamino-1-*O*-phenyl-L-glucitol (**16**) in a 40% overall yield (Scheme 2). The same procedure was repeated using sodium benzylate as the nucleophile to give 2,5-anhydro-3,4-diamino-1-*O*-benzyl-L-glucitol (**17**) in 58% yield starting from **12** (Scheme 2).

Application of the same protocol using sodium salts of adenine was equally successful. Thus, treatment of **12** with adenine and NaH in DMF resulted in a regioselective epoxide ring-opening to give 1-(6-amino-9*H*-purin-9-yl)-2,5-anhydro-3,4-diazido-1-deoxy-L-glucitol (**15**, 32%), as the only isolated product. It is noteworthy that when the reaction was carried out in the presence of magnesium perchlorate and a trimethylsilylated base in acetonitrile at 85 °C, **15** was obtained in 73% yield (Scheme 2). Catalytic hydrogenation afforded the desired 1-(6-amino-9*H*-purin-9-yl)-2,5-anhydro-3,4-diamino-1-deoxy-L-glucitol (**18**, 86%) (Scheme 2).

Conclusion

In summary, this paper describes a new route for the synthesis of *N*-(1′-homo-L-gulitol)nucleosides and amino sugar analogues of *N*-(1′-homo-L-glucitol)nucleosides by nucleophilic epoxide ring-opening followed by *O*-heterocyclization of 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-D-mannitol (**3**) and 1,2:5,6-dianhydro-3,4-diazido-D-iditol (**12**), respectively. Magnesium perchlorate was found to be the best catalyst for the reaction of silylated bases derived from uracil, thymine, and adenine with these bis(epoxides). This procedure was also applied to the synthesis of the corresponding 2′,3′-diamino analogues. In contrast, the sodium salt method for nucleophilic ring opening of epoxides gave modest to acceptable yields of the corresponding 1′-homo-N-nucleosides. The 1′-homo-N-nucleosides prepared by the methods described in this paper will be used as biological probes to explore RNA binding as well as potential antiviral or related activities.

Experimental Section

General: All commercially available reagents were used without further purification. Solvents when necessary were dried prior to use according to standard procedures. NMR (^{1}H, ^{13}C) spectra were recorded with a Bruker (200 MHz) spectrometer and are reported in δ values. Elemental microanalyses were performed with a C. Erba 1106 analyser. Optical rotations were recorded with a Perkin−Elmer 241 polarimeter in a 1-dm cell at ambient temperature (ca. 25°C). Thin layer chromatography was carried out using Merck 60 F_{254} precoated silica gel plates. Visualization was done by UV light (254 nm), followed by heating with ethanolic phosphomolybdic acid. Chromatographic purifications were performed on columns packed with Merck 60 silica gel, 230−400 mesh, for flash technique.

General Procedure for the Preparation of Compounds 4−6: A solution of 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-D-mannitol (**3**, 100 mg, 0.3 mmol)[20] in dry CH_3CN (5 mL) was carefully added to a previously prepared solution of silylated nucleic base [1.0 mmol of either adenine, uracil or thymine and 5.0 mmol of bis(trimethylsilyl) trifluoroacetamide (BSTFA) in dry CH_3CN (5.0 mL)] under argon. The mixture was heated to 85 °C and magnesium perchlorate [$Mg(ClO_4)_2$; 1.0 mmol] was added. After 6 h at 85 °C, the mixture was cooled, diluted with EtOAc, washed with NaCl (aq.; satd.), and the solvent evaporated. The crude mixture was purified by flash chromatography (EtOAc/hexane, 60:40).

2,5-Anhydro-3,4-di-*O*-benzyl-1-deoxy-1-(uracil-1-yl)-L-gulitol (4): Yield: 67 mg (51%; clear oil). ^{1}H NMR ($CDCl_3$): δ = 3.56 (dd, *J* = 11.70, 4.16 Hz, 2 H, C*H*$_2$OH), 3.68 (dd, *J* = 12.90, 6.28 Hz, 2 H, C*H*$_2$N), 3.55 (m, 2 H, 3-H and 4-H), 3.84 (m, 1 H, 5-H), 4.51 (s, 4 H, 2 × OC*H*$_2$Ph), 4.63 (m, 1 H, 2-H), 5.79 (d, *J* = 7.71 Hz, 1 H, *UraH-5*), 6.12 (d, *J* = 7.71 Hz, 1 H, *UraH-6*), 7.32 (m, 5 H, Ph), 8.18 (m, 5 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 44.16 (CH_2), 61.88 (CH_2), 71.33 (CH), 72.11 (CH_2), 72.89 (CH_2), 77.56 (CH), 83.22 (CH), 86.45 (CH), 103.12 (CH), 128.90 (CH), 129.42 (CH), 133.71 (C), 135.59 (CH), 144.52 (CH), 151.03 (C), 160.16 (C), 160.86 (C), 164.50 (C) ppm. $C_{24}H_{26}N_2O_6$ (438.5): calcd. C 65.74, H 5.98, N 6.39; found C 66.09, H 6.12, N 6.36.

2,5-Anhydro-3,4-di-*O*-benzyl-1-deoxy-1-(thymin-1-yl)-L-gulitol (5): Yield: 70 mg (54%; clear oil). ^{1}H NMR ($CDCl_3$): δ = 1.91 (s, 3 H, C*H*$_3$), 3.43 (dd, *J* = 11.87, 4.21 Hz, 2 H, C*H*$_2$OH), 3.54 (dd, *J* = 12.54, 5.39 Hz, 2 H, C*H*$_2$N), 3.62 (m, 2 H, 3-H and 4-H), 3.84 (m, 1 H, 5-H), 4.32 (s, 4 H, 2 × OC*H*$_2$Ph), 4.68 (m, 1 H, 2-H), 6.54 (s, 1 H, *ThyH-6*), 7.43 (m, 5 H, Ph), 7.66 (m, 5 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.22 (CH_3), 44.87 (CH_2), 59.24 (CH_2), 68.72 (CH), 72.31 (CH), 73.56 (CH_2), 73.98 (CH_2), 74.65 (CH), 77.18 (CH), 111.84 (C), 128.12 (CH), 129.87 (CH), 133.04 (CH), 135.16 (CH), 137.59 (C), 141.34 (C), 151.33 (CH), 162.38 (C), 168.10 (C) ppm. $C_{25}H_{28}N_2O_6$ (452.5): calcd. C 66.36, H 6.24, N 6.19; found C 66.47, H 6.14, N 6.32.

1-(6-Amino-9*H*−purin-9-yl)-2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-L-gulitol (6): Yield: 72 mg (52%; clear oil). ^{1}H NMR ($CDCl_3$): δ = 3.64 (dd, *J* = 10.76, 4.11 Hz, 2 H, C*H*$_2$OH), 4.06 (dd, *J* = 14.03, 6.48 Hz, 2 H, C*H*$_2$N), 4.44 (s, 4 H, 2 × OC*H*$_2$Ph), 4.74 (m, 1 H, 5-H), 5.08 (m, 1 H, 3-H), 5.28 (m, 1 H, 4-H), 5.45 (m, 1 H, 2-H), 7.48 (m, 5 H, Ph), 8.07 (m, 5 H, Ph), 8.16 (s, 1 H, *AdeH-8*), 8.27 (s, 1 H, *AdeH-2*) ppm. ^{13}C NMR ($CDCl_3$): δ = 44.90 (CH_2), 59.24 (CH), 67.13 (CH), 72.11 (CH_2), 72.67 (CH_2), 74.41 (CH), 84.10 (CH), 86.51 (CH), 118.67 (C), 128.44 (CH), 129.73 (CH), 133.41 (CH), 135.26 (CH), 136.18 (C), 137.19 (C), 144.67 (CH), 155.19 (C), 160.86 (CH), 163.42 (C) ppm. $C_{25}H_{27}N_5O_4$ (461.5): calcd. C 65.06, H 5.90, N 15.17; found C 65.21, H 5.83, N 15.34.

General Procedure for the Preparation of Compounds 7−9: Compound **4**, **5**, or **6** (50 mg) was hydrogenated in the presence of a catalytic amount of Pd/C (10%) in a 8:1 mixture MeOH/H_2O. After 16 h, the mixture was filtered through Celite, the catalyst was washed with MeOH, and the solvent removed by evaporation.

2,5-Anhydro-1-deoxy-1-(uracil-1-yl)-L-gulitol (7): Yield: 26 mg (88%; brown oil). ^{1}H NMR (CD_3OD): δ = 3.69 (dd, *J* = 10.54, 3.57 Hz, 2 H, C*H*$_2$OH), 3.84 (dd, *J* = 12.87, 5.35 Hz, 2 H, C*H*$_2$N), 3.94 (m, 1 H, 4-H), 4.12 (m, 3 H, 2-H, 3-H and 5-H), 6.18 (d, *J* = 7.31 Hz, 1 H, *UraH-5*), 7.75 (d, *J* = 7.31 Hz, 1 H, *UraH-6*) ppm. ^{13}C NMR (CD_3OD): δ = 45.34 (CH_2), 60.63 (CH_2), 68.24 (CH), 70.65 (CH), 73.18 (CH), 83.90 (CH), 103.37 (CH), 144.73 (CH), 151.03 (C), 164.50 (C) ppm. $C_{10}H_{14}N_2O_6$ (258.2): calcd. C 46.51, H 5.46, N 10.85; found C 46.30, H 5.64, N 10.81.

2,5-Anhydro-1-deoxy-1-(thymin-1-yl)-L-gulitol (8): Yield: 25 mg (83%; yellow oil). ^{1}H NMR (CD_3OD): δ = 1.94 (s, 3 H, CH_3), 3.41 (dd, *J* = 11.43, 3.36 Hz, 2 H, CH_2OH), 3.66 (dd, *J* = 12.90, 4.15 Hz, 2 H, CH_2N), 3.96 (m, 2 H, 4-H and 5-H), 4.16 (m, 2 H, 2-H and 3-H), 7.34 (s, 1 H, *ThyH-6*) ppm. ^{13}C NMR (CD_3OD): δ = 16.14 (CH_3), 43.20 (CH_2), 60.23 (CH_2), 66.17 (CH), 71.56 (CH), 74.88 (CH), 85.26 (CH), 111.43 (C), 141.36 (CH), 151.44 (C), 166.64 (C) ppm. $C_{11}H_{16}N_2O_6$ (272.3): calcd. C 48.53, H 5.92, N 10.29; found C 48.51, H 5.86, N 10.23.

(6-Amino-9*H*−purin-9-yl)-2,5-anhydro-1-deoxy-1-L-gulitol (9): Yield: 27 mg (89%; brown oil). ^{1}H NMR (CD_3OD): δ = 3.55 (dd, *J* = 10.38, 3.69 Hz, 2 H, CH_2OH), 3.92 (d, *J* = 13.65, 7.11 Hz, 2 H, CH_2N), 4.15 (m, 2 H, 3-H and 4-H), 4.78 (m, 2 H, 2-H and 5-H), 7.61 (s, 1 H, *AdeH-8*), 8.14 (s, 1 H, *AdeH-2*) ppm. ^{13}C NMR (CD_3OD): δ = 45.81 (CH_2), 63.76 (CH_2), 67.19 (CH), 70.43 (CH), 74.28 (CH), 85.11 (CH), 120.90 (C), 144.79 (CH), 151.22 (C), 153.47 (CH), 155.19 (C) ppm. $C_{11}H_{15}N_5O_4$ (281.3): calcd. C 46.97, H 5.38, N 24.90; found C 46.91, H 5.23, N 24.93.

3,4-Diazido-3,4-dideoxy-1,6-bis(*O*-mesyl)-D-iditol (11): 3,4-Diazido-3,4-dideoxy-D-iditol (**10**)[24] (600 mg, 2.5 mmol) in dry pyridine (10 mL) at −15 °C under argon was treated with methanesulfonyl chloride (420 μL, 2.1 equiv.). After 48 h, the mixture was diluted with EtOAc, washed with H_2O, and the solvent evaporated (to remove also the excess pyridine). The crude mixture was purified by flash chromatography (EtOAc/hexane, 80:20) to give 906 mg (93%) of **11** as a clear oil. ^{1}H NMR ($CDCl_3$): δ = 3.12 (s, 6 H, 2 × CH_3SO_2), 3.75 (dd, *J* = 11.30, 5.83 Hz, 4 H, 2 × CH_2OMs), 4.18 (m, 2 H, 2 × C*H*N$_3$), 4.37 (m, 2 H, 2 × C*H*OH) ppm. ^{13}C NMR ($CDCl_3$): δ = 35.15 (CH_3), 63.10 (CH_2), 68.21 (CH), 70.0 (CH) ppm. $C_8H_{18}N_6O_8S_2$ (390.4): calcd. C 24.61, H 4.65, N 21.53; found C 24.66, H 4.72, N 21.45.

1,2:5,6-Dianhydro-3,4-diazido-D-iditol (12): Compound **11** (585 mg, 1.5 mmol), dissolved in Et_2O (15 mL), at 25 °C, was treated with KOH (336 mg, 6.0 mmol, 4.0 equiv.) as a solution in H_2O (6 mL). After 3 h, the mixture was diluted with EtOAc, washed with NaCl (aq.; satd.), and the organic solvent removed by evaporation. The crude mixture was purified by chromatography (EtOAc/hexane, 90:10) to give the product **12** (213 mg, 72%) as a clear oil. $[\alpha]_D$ = −77.48 (*c* = 1.35, MeOH). ^{1}H NMR (CD_3OD): δ = 2.75 (dd, *J* = 4.85, 3.38 Hz, 2 H, CH_2O), 2.90 (dd, *J* = 4.20, 3.38 Hz, 2 H, CH_2O), 3.20 (m, 2 H, 2 × C*H*O), 3.35 (m, 2 H, 2 × C*H*N$_3$) ppm. ^{13}C NMR (CD_3OD): δ = 45.0 (CH_2), 52.10 (CH), 65.0 (CH) ppm. $C_6H_{10}N_6O_2$ (198.2): calcd. C 36.36, H 5.09, N 42.41; found C 36.31, H 5.11, N 42.44.

2,5-Anhydro-3,4-diazido-1-*O*-phenyl-L-glucitol (13): A solution of compound **12** (100 mg, 0.5 mmol) in dry DMF (4 mL) was carefully added to a previously prepared solution of sodium phenoxide [phenol (200 mg, 2.1 mmol) treated with NaH (57 mg, 2.4 mmol) in dry DMF (6 mL)] at 0 °C. After 4 h at 25 °C, the mixture was diluted with EtOAc, washed with NaCl (aq.; satd.), and the organic solvent evaporated. The crude material was purified by flash chromatography (EtOAc/hexane, 50:50) to give product **13** (76 mg, 52%) as a brown oil. ^{1}H NMR (CD_3OD): δ = 3.65 (dd, *J* = 10.62, 3.77, 2 H, CH_2OH), 3.85 (dd, *J* = 11.07, 3.27, CH_2OPh), 4.01 (m, 2 H, 3-H and 4-H), 4.15 (m, 1 H, 5-H), 4.35 (m, 1 H, 2-H) 6.80 (m, 3 H, phenyl), 7.18 (m, 2 H, phenyl) ppm. ^{13}C NMR (CD_3OD): δ = 62.07 (CH_2), 63.22 (CH_2), 70.94 (CH), 71.43 (CH), 73.43 (CH), 73.67 (CH), 114.10 (2 × CH), 122.11 (CH), 129.10 (2 × CH), 162.12 (C) ppm. $C_{12}H_{16}N_6O_3$ (292.3): calcd. C 49.31, H 5.52, N 28.75; found C 49.11, H 5.66, N 28.71.

2,5-Anhydro-3,4-diazido-1-*O*-benzyl-L-glucitol (14): A solution of compound **12** (100 mg, 0.5 mmol) in dry DMF (4 mL) was carefully added to a previously prepared solution of sodium benzylate [benzyl alcohol (200 mg, 1.8 mmol) treated with NaH (48 mg, 2.0 mmol) in dry DMF (6 mL)] at 0 °C. After 4 h at 25 °C, the mixture was diluted with EtOAc, washed sequentially with H_2O and NaCl (aq.; satd.), and the solvent evaporated. The crude material was purified by flash chromatography (EtOAc/hexane, 50:50) to give product **14** (105 mg, 69%) as a yellow oil. $[\alpha]_D$ = −13.46 (*c* = 0.92, MeOH). ^{1}H NMR (CD_3OD): δ = 3.48 (dd, *J* = 10.04, 4.12, 2 H, CH_2O), 3.76 (dd, *J* = 11.22, 4.09, 2 H, CH_2OH), 3.88 (m, 2 H, 3-H and 4-H), 4.37 (m, 2 H, 2-H and 5-H), 4.44 (s, 2 H, OCH_2Ph), 7.29 (m, 5 H, phenyl) ppm. ^{13}C NMR (CD_3OD): δ = 60.63 (CH_2), 60.88 (CH_2), 70.94 (CH), 71.34 (CH), 72.25 (CH), 73.40 (CH_2), 73.52 (CH), 126.83 (2 × CH), 127.34 (CH), 128.26 (2 × CH), 137.56 (C) ppm. $C_{13}H_{18}N_6O_3$ (306.3): calcd. C 50.97, H 5.92, N 27.44; found C 50.92, H 5.88, N 27.33.

1-(6-Amino-9*H*-purin-9-yl)-2,5-anhydro-3,4-diazido-1-deoxy-L-glucitol (15). Method A: A solution of compound **12** (100 mg, 0.5 mmol) in dry DMF (4 mL) was carefully added to a previously prepared solution of sodium adenylate [adenine (200 mg, 1.48 mmol) treated with NaH (40 mg, 1.7 mmol) in dry DMF (6 mL)] at 0 °C. After 4 h at 25 °C, the mixture was diluted with EtOAc, washed sequentially with H_2O and NaCl (aq.; satd.), dried and the solvent evaporated. The crude material was purified by flash chromatography (EtOAc/hexane, 50:50) to give product **15** (54 mg, 32%) as a yellow oil. ^{1}H NMR (CD_3OD): δ = 3.68 (m, 4 H, CH_2OH and 3-H and 4-H), 3.90 (dd, *J* = 13.82, 5.09, 2 H, CH_2N), 4.47 (m, 1 H, 5-H), 4.84 (m, 1 H, 2-H), 7.82 (s, 1 H, *AdeH-8*), 8.08 (s, 1 H, *AdeH-2*) ppm. ^{13}C NMR ($CDCl_3$/CD_3OD): δ = 47.32 (CH_2), 60.90 (CH_2), 69.28 (CH), 71.84 (CH), 72.65 (CH), 74.35 (CH), 123.10 (C), 145.02 (CH), 153.18 (CH), 156.65 (C), 159.92 (C) ppm. $C_{11}H_{15}N_{11}O_2$ (333.3): calcd. C 39.64 H, 4.54 N, 46.23; found C 39.37 H, 4.56 N, 46.35. **Method B:** A solution of compound **12** (100 mg, 0.5 mmol) in dry CH_3CN (5 mL) was added under argon to a previously prepared solution of silylated adenine [adenine (1.0 mmol) and BSTFA (5.0 mmol) in dry CH_3CN (5.0 mL)]. The resulting mixture was heated to 85 °C. Magnesium perchlorate [$Mg(ClO_4)_2$, 1.0 mmol] was then added. After 6 h at 85 °C, the mixture was cooled, diluted with EtOAc, washed with NaCl (aq.; satd.), and the solvent evaporated. The crude product was purified by flash chromatography (EtOAc/hexane, 60:40) to give **12** (121 mg, 73%) as a yellow oil.

3,4-Diamino-2,5-anhydro-1-*O*-phenyl-L-glucitol (16): Compound **13** (70 mg, 0.24 mmol) was hydrogenated in the presence of a catalytic amount of Pd/C (10%) in a 8:1 mixture of MeOH/H_2O. After 16 h, the mixture was filtered through Celite, the catalyst washed with MeOH, and the organic solvent removed to give product **16** (43 mg, 76%) as a yellow oil. $[\alpha]_D$ = +12.13 (*c* = 0.85, MeOH). ^{1}H NMR (CD_3OD): δ = 3.79 (dd, *J* = 10.70, 4.19, 2 H, CH_2OH), 3.89 (dd, *J* = 11.07, 4.91, 2 H, CH_2OPh), 4.01 (m, 2 H, 3-H and 4-H), 4.42 (m, 2 H, 2-H and 5-H), 6.79−7.24 (m, 5 H, phenyl) ppm. ^{13}C NMR (CD_3OD): δ = 52.94 (CH), 55.08 (CH), 61.65 (CH_2), 64.04 (CH_2), 74.66 (CH), 75.16 (CH), 116.42 (2 × CH), 121.18 (CH), 126.85 (2 × CH), 158.21 (C) ppm. $C_{12}H_{18}N_2O_3$ (238.3): calcd. C 60.49, H 7.61, N 11.76; found C 60.65, H 7.32, N 11.74.

3,4-Diamino-2,5-anhydro-1-deoxy-L-glucitol (17): Compound **14** (50 mg, 0.16 mmol) was hydrogenated in the presence of a catalytic amount of Pd/C (10%) in a 8:1 mixture of MeOH/H_2O. After 16 h, the mixture was filtered through Celite, the catalyst washed with MeOH, and the solvent removed to give product **17** (21 mg, 84%) as a yellow oil. $[\alpha]_D$ = −2.60 (*c* = 0.5, MeOH). ^{1}H NMR (D_2O): δ = 3.72 (m, 4 H, 2 × CH_2OH), 4.02 (m, 2 H, 3-H and 4-H), 4.35 (m, 2 H, 2-H and 5-H), 5.58 (br. s, 2 H, 2 × CH$_2$O*H*) ppm. ^{13}C

NMR (D_2O): δ = 52.66 (2 × CH), 61.07 (2 × CH_2), 74.67 (2 × CH) ppm. $C_{13}H_{20}N_2O_3$ (252.3): calcd. C 44.43, H 8.70, N 17.27; found C 44.39, H 8.64, N 17.33.

3,4-Diamino-1-(6-amino-9*H*−purin-9-yl)-2,5-anhydro-1-deoxy-L-glucitol (18): Compound **15** (50 mg, 0.15 mmol) was hydrogenated in the presence of a catalytic amount of Pd/C (10%) in a 8:1 mixture of MeOH/H_2O. After 16 h, the mixture was filtered through Celite, the catalyst washed with MeOH, and the organic solvent removed to give product **18** (36 mg, 86%) as a brown oil. ^{1}H NMR (CD_3OD): δ = 3.60 (dd, *J* = 9.88, 4.15 Hz, 2 H, C*H*$_2$OH), 3.79 (m, 2 H, 3-H and 4-H), 3.91 (dd, *J* = 13.32, 6.40, 2 H, C*H*$_2$N), 4.12 (m, 1 H, 5-H), 4.57 (m, 1 H, 2-H), 6.15 (br. s, 1 H, CH$_2$O*H*), 7.88 (s, 1 H, *AdeH-8*), 8.18 (s, 1 H, *AdeH-2*) ppm. ^{13}C NMR (CD_3OD): δ = 44.64 (CH_2), 52.54 (CH), 56.30 (CH), 59.09 (CH_2), 74.26 (CH), 76.46 (CH), 119.46 (C), 143.57 (CH), 149.70 (C), 151.71 (CH), 157.39 (C) ppm. $C_{11}H_{17}N_7O_2$ (279): calcd. C 47.30, H 6.14, N 35.10; found C 47.23, H 6.21, N 35.15.

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