Glycosylation of Cyclitols: Synthesis of Neamine-Type Aminoglycosides

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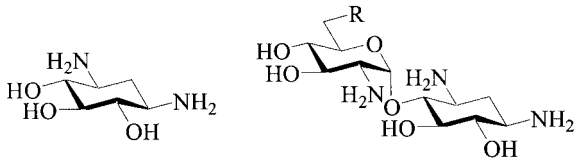
Keywords: Aminoglycoside antibiotics / Cyclitols / Glycosylations / RNA recognition

In this paper, a glycosylation-based approach towards novel aminoglycoside analogues is presented. Three different cyclitol building blocks were condensed with different thioglycosides to give, after removal of the protective groups, several neamine-type analogs varying in the positioning and the stereochemistry of the amino functions.

Introduction

Aminoglycosides, pseudo-oligosaccharide derivatives having several amine groups, are important lead compounds in the development of therapeutics for the treatment of infectious diseases. Members of this class of compounds, such as streptomycin and kanamycin, are widely used as antibiotics in combating bacterial infections. The mechanism of action relies on the capability of binding to the A-site of the bacterial ribosome. Recently, it has been found that aminoglycosides can also bind to several viral RNA structures including hepatitis delta virus ribozyme,[1] HIV trans-activating region[2] and HIV rev responsive element[3] These findings have spurred new research activities aimed at the generation of aminoglycoside derivatives with improved binding capabilities[4]

A common strategy for the synthesis of aminoglycoside analogues comprises the derivatisation of natural aminoglycosides, or their substructures. Recent efforts in this direction are the manipulation of the pseudo-disaccharides neamine[5−9] (**2**) and paromamine[10,11] (**3**; Figure 1). Following this strategy, large numbers of compounds can readily be prepared. However, the stereochemistry and positioning of the amine functionalities appended to the pseudo-disaccharide core remain largely unaltered. More structural and functional diversity can be achieved when starting from the aminocyclitol core, the common structural entity found in most natural aminoglycosides. For instance, glycosylation of 2-deoxystreptamine (**1**)[12,13] and 2,5-dideoxystreptamine[14] with a variety of (di)aminoglycosides was reported to give non-natural analogues of neamine and kanamycin, respectively.



1 **2** R = NH_2, **3** R = OH

Figure 1. 2-Deoxystreptamine (**1**), neamine (**2**) and paromamine (**3**)

Our strategy towards new aminoglycoside analogues is based on the premise that maximum structural diversity can be achieved through de novo synthesis of a set of carbocyclic cores, followed by glycosylation with a variety of aminoglycoside donors. We present here the synthesis of a set of structurally and functionally diverse neamine analogues from three (diamino)cyclitols and four (di)aminopyranosides.

Results and Discussion

We selected the suitably protected thioglycosides **4**, **5**, **8**, and **11** (Scheme 1), having one or two azides as masked amino functions, for ensuing attachment to the carbocyclic cores. Phenyl thioglycosides **4** and **5** were obtained following published procedures (Scheme 1).[12] Thioglycoside **8** was readily prepared from the known[15] phenyl 2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside (**6**) by mesylation of the free hydroxy groups and subsequent nucleophilic substitution of the di-mesylate **7** using an excess of sodium azide at 80 °C. Deacetylation of phenyl 2,4,6-tri-*O*-acetyl-3-azido-1-thio-β-D-glucopyranoside (**9**)[12] and subsequent selective

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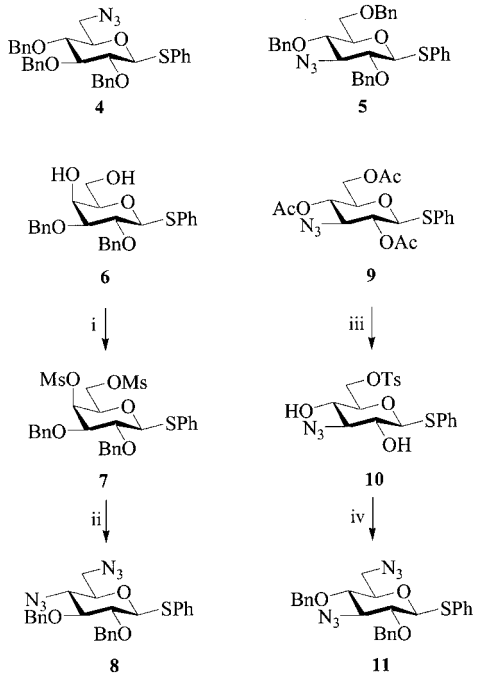
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

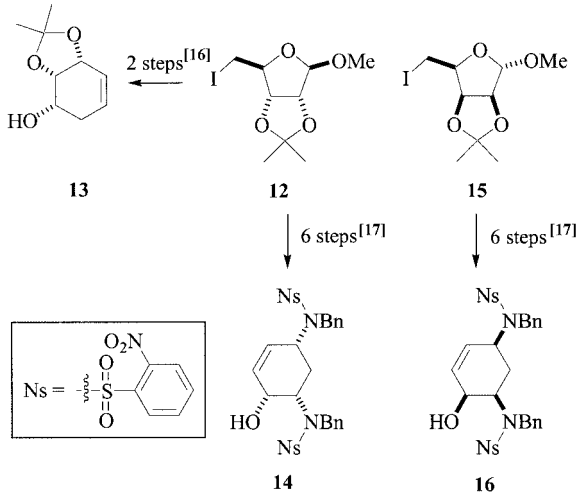
  DOI: 10.1002/ejoc.200400020



Scheme 1. Reagents and conditions: i. MsCl (2.5 equiv.), pyridine, 90%. ii. NaN_3 (4 equiv.), DMF, 80 °C, 78%. iii. a. KO*t*Bu (0.1 equiv.), MeOH. b. TsCl (1.1 equiv.), pyridine, 67%. iv. a. NaN_3 (3.0 equiv.), DMF, 80 °C. b. NaH (2.1 equiv.), BnBr (2.1 equiv.), DMF, 93%

tosylation yielded compound **10**, which was transformed into donor **11** by nucleophilic displacement of the tosylate by the azide ion, followed by benzylation of the remaining free hydroxy groups.

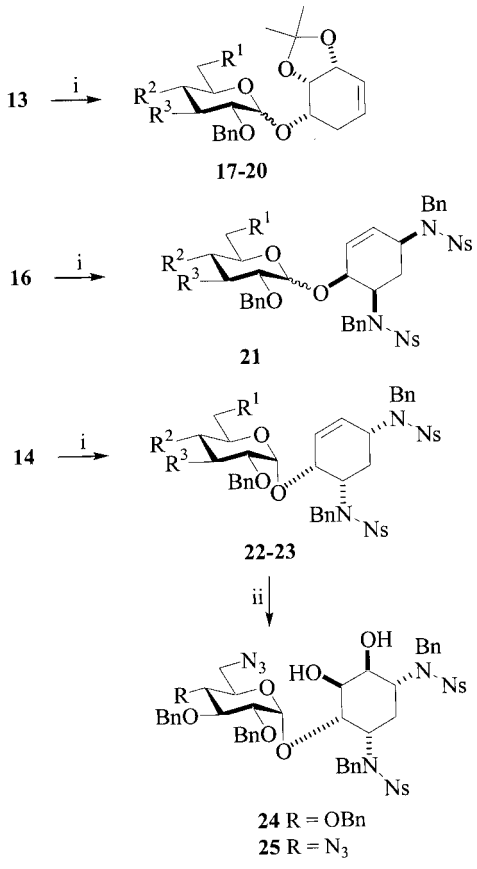
The synthesis of (diamino)cyclitol cores **13**, **14** and **16** (Scheme 2) was accomplished following well-established literature procedures. Briefly, cyclitol acceptor **13** was obtained from known methyl 5-deoxy-5-iodo-2,3-isopropylidene-β-D-ribofuranoside (**12**) after a one-pot Vasella−Barbier reaction followed by ring-closing metathesis (RCM).[16] Partially protected diaminocyclitol **14** and its enantiomer **16** were prepared in six steps from D-ribofuranoside (**12**) and the isomeric D-lyxoside **15**, respectively, following the protocol previously reported by us.[17]



Scheme 2. Synthesis of acceptors

Having the donor and acceptor moieties in hand, we set out to examine their condensations to give neamine-type pseudo-disaccharides (Scheme 3). NIS/TfOH-promoted glycosylation of cyclitol **13** with donor thioglycosides **4**, **5**, **8**, and **11** in diethyl ether at room temperature proceeded smoothly to give fully protected pseudo-disaccharides **17−20**, respectively, with high α-selectivity (Table 1). Glycosylation of **13** with donors **8** and **11** resulted in a higher α-selectivity (entries 3 and 4) than those with the donors **4** and **5** (entries 1 and 2). The α-anomers in entries 1, 3 and 4 were readily isolated in pure form after silica gel column chromatography. Unfortunately, separation of the α/β-mixture of dimer **18** was unsuccessful (entry 2). Moreover, removal of the isopropylidene protecting group in **18** did not result in the isolation of the individual anomers. Attempts to increase the α-selectivity of the glycosylation by decreasing the reaction temperature were unsuccessful because of the insolubility of the starting materials in diethyl ether at lower temperatures. Execution of the condensation in dichloromethane/diethyl ether mixtures did not have a beneficial effect in terms of yield or α-selectivity.

Due to the insolubility of the diaminocyclitols **14** and **16** in pure diethyl ether, glycosylations of the these two compounds had to be performed in dichloromethane/diethyl



Scheme 3. Reagents and conditions: i. Donor (1.2 equiv.), NIS (1.2 equiv.), TfOH (0.1 equiv.). ii. $K_2OsO_4{\cdot}2H_2O$ (0.5 mol %), NMO (2.2 equiv.), acetone/H_2O (2.5:1, v/v) **24**: 99%, **25**: 88%

Table 1. Glycosylations of cyclitols **13**, **14** and **16**

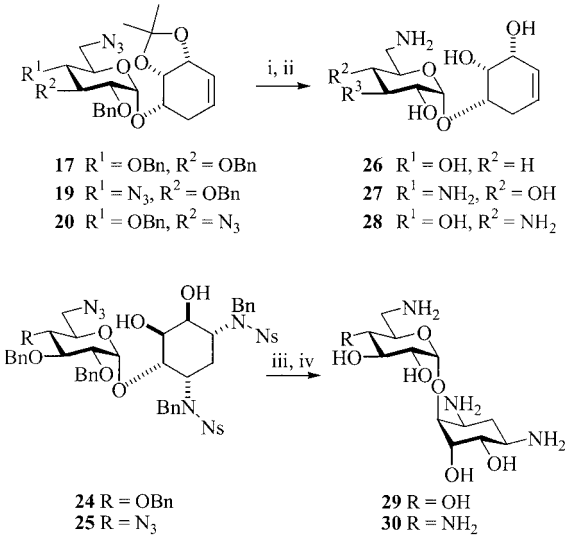
Entry	Acceptor	Donor	Dimer	*T* [°C]	DCM/Et_2O	R^1	R^2	R^3	Yield [%]	α/β[a]
1	**13**	**4**	**17**	room temp.	0:1	N_3	OBn	OBn	77	5.0:1
2	**13**	**5**	**18**	room temp.	0:1	OBn	OBn	N_3	78	4.3:1[b]
3	**13**	**8**	**19**	room temp.	0:1	N_3	N_3	OBn	80	6.6:1
4	**13**	**11**	**20**	room temp.	0:1	N_3	OBn	N_3	81	6.9:1
5	**16**	**4**	**21**	room temp.	1:9	N_3	OBn	OBn	77	1.4:1[b]
6	**14**	**4**	**22**	room temp.	1:11	N_3	OBn	OBn	92	2.0:1
7	**14**	**4**	**22**	−60 → −20	2:5	N_3	OBn	OBn	84	3.3:1
8	**14**	**5**	**23**	−60 → −20	2:5	N_3	N_3	OBn	77	5.0:1

[a] Ratios were determined by NMR spectroscopy. [b] Anomers could not be separated by column chromatography.

ether mixtures (Scheme 3). At room temperature, the stereoselectivity of the condensation of **4** with **16** turned out to be low (entry 5; α/β = 1.4:1), affording **21** as an inseparable mixture of anomers. Unfortunately, after dihydroxylation of the double bond in **21**, separation of the anomers could also not be achieved.

Condensation of **4** and **14** proceeded in higher yield and slightly higher selectivity to give **22** (entry 6; α/β = 2:1), the individual anomers of which could be readily separated by column chromatography. The stereoselectivity proved to be more pronounced when the glycosylation was performed at lower temperature (entry 7). Finally, pseudo-disaccharide **23** was obtained (entry 8) in reasonable yield and good α-selectivity. Dihydroxylation of the double bonds in dimers **22** and **23** proceeded stereoselectively to furnish protected pseudo-disaccharides **24** and **25** (Scheme 3).

As the next research objective, the deprotection of the anomerically pure neamine analogues **17**, **19**, **20**, **24** and **25** was studied. Acidic removal of the isopropylidene group of the α-anomers of **17**, **19** and **20** (82−88%), and subsequent removal of the benzyl protective groups employing Birch reduction conditions (sodium in liquid ammonia, 52−67%), furnished the projected unprotected aminoglycoside analogs **26**−**28**, respectively (Scheme 4). Deprotection of the nitrosulfonyl groups in **24** and **25** was effected by reaction with thiophenol and *N*,*N*-diisopropyl-*N*-ethylamine (dipea).[18] Removal of both *N*- and *O*-benzyl protective groups was accomplished using 10% Pd on charcoal and atmospheric hydrogen pressure, to give unprotected dimers **29** and **30** in 68% and 42% yield, respectively (Scheme 4).[19] All unprotected neamine analogues were readily purified by chromatography on Amberlite CG-50.



Scheme 4. Reagents and conditions: i. HOAc/H_2O 8:2, reflux, 80−88% ii. Na (s), NH_3 (l), THF, −40 °C, 52−67%. iii. PhSH, dipea, DMF; 48−53% iv. H_2/ Pd-C, 0.1 M HCl; H_2O/EtOH, 1:1; **29**: 68% **30**: 42%

Conclusion

By varying both the carbohydrate donor and the cyclitol acceptor, a structurally diverse set of neamine analogs was synthesized. Glycosylation of cyclitol **13**, which lacks amino functions, resulted in neamine analogs with a reduced number of amino groups. Glycosylation of diaminocyclohexene derivative **14**, followed by dihydroxylation, provided novel neamine-type analogs that are stereochemically distinct from the natural ones. Altogether, the results presented in this paper illustrate the versatility of glycosylation of cyclitols in the synthesis of aminoglycoside analogs.

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-200 (200 MHz, 50.1 MHz, respectively), a Bruker DPX-300 (300 MHz and 75.1 MHz, respectively) or a Bruker AV-400 (400 MHz, 100 MHz respectively). Chemical shifts (δ) are given in ppm relative to tetramethylsilane (δ = 0.0 ppm) or $CDCl_3$ (δ = 77.0 ppm) as an internal standard. Optical rotations were determined at 20 °C using a Propol automatic polarimeter. Mass spectrometry was performed on a PE/SCIEX API 165. IR spectra were recorded on a Shimadzu FTIR-8300. IR data are reported in cm^{-1}.

Column chromatography was performed on silica gel 60 (230−400 mesh, Fluka). TLC analysis was conducted on TLC plastic sheets 60 F_{254} (Merck) with detection by UV absorption (254 nm) where applicable and/or by spraying with 20% H_2SO_4 in EtOH or a solution of molybdate (ammonium molybdate 25 g/L) and ceric ammonium sulfate (10 g/L in 10% aq. H_2SO_4) followed by charring at about 150 °C.

Acetic acid (Baker, p.a.) and ethyl acetate (extra pure, Riedel-de Haën) were used as received. For glycosylations, diethyl ether (extra pure, Riedel-de Haën) was freshly distilled from $LiAlH_4$ and DCM (Biosolve) was distilled from P_2O_5. Tetrahydrofuran (Baker p.a.) was freshly distilled from $LiAlH_4$. 1,2-Dichloroethane (Baker, p.a.), *N*,*N*-dimethylformamide (Baker, p.a.), pyridine (Baker, p.a.) and toluene (Baker, p.a.) were stored over 4-Å molecular sieves. Methanol (Biosolve, HPLC grade) was stored over molecular sieves (3 Å).

Ammonium hydroxide (25%, Baker, p.a.), ammonia (Air products), benzyl bromide (Fluka), diisopropyl ethyl amine (Biosolve), hydrogen (Air products), *N*-iodosuccinimide (Fluka), magnesium sulfate (BUFA), methanesulfonyl chloride (Merck), 10% palladium on activated charcoal (Aldrich), potassium *tert*-butoxide (Aldrich), sodium (Acros), sodium azide (Merck), sodium hydride (60% dispersion in mineral oil, Acros), tetrabutylammonium trifluoromethanesulfonate (Fluka), thiophenol (Acros) and *p*-toluenesulfonyl chloride (Merck) were used without purification. Amberlite IR-120 (Fluka) was rinsed with methanol before use. Amberlite CG-50 (Fluka) was converted into its NH_4^+-form before use. Trifluoromethanesulfonic acid (Acros) was distilled and stored under argon.

General Procedure for NIS/TfOH-Promoted Glycosylation: Generally, glycosylations were performed on a 0.5−2 mmol scale. Acceptor (1 equiv.) and donor (1.2 equiv.), dried by coevaporation of water with 1,2-dichloroethane, were dissolved in Et_2O or Et_2O/DCM. Molecular sieves (3 Å) were added and the mixture was stirred for 15 min under argon. NIS (1.2 equiv.) and TfOH (0.1 equiv.) were then added, after which the mixture turned red. When TLC analysis indicated complete consumption of the acceptor or that the reaction did not proceed any further, the reaction mixture was diluted with EtOAc, washed with 1 M NaS_2O_3 and sat. $NaHCO_3$. The aqueous layers were extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by silica column chromatography afforded the protected pseudodisaccharide.

General Procedure for Isopropylidene Cleavage: A mixture of AcOH and H_2O (8:2, v/v) was added to the isopropylidene-containing compound and the resulting mixture was heated to reflux. After 1−2 h, TLC analysis indicated complete conversion into a lower running product. The reaction mixture was diluted with toluene and the solvents evaporated to dryness under reduced pressure. Traces of AcOH were removed by coevaporation with toluene, after which the crude product was purified by silica column chromatography.

General Procedure for Dihydroxylation: *N*-Methylmorpholine *N*-oxide (NMO; 2.2 equiv.) and potassium osmate dihydrate (0.5 mol %) were added to a solution of the olefin (1.0 equiv.; 0.1 M in acetone/water, 5:2, v/v). After TLC analysis indicated complete conversion into a lower running product (ca. 48 h), excess NMO was quenched with a solution of $NaHSO_3$. The mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by silica column chromatography yielded the dihydroxylated compounds.

General Procedure for Birch Reductions: A solution of the protected carbohydrate derivative in THF (1 mL) was added to a dark-blue mixture of liquid ammonia (5−10 mL) and sodium (50−100 mg). The temperature was maintained between −60 °C and −40 °C. More sodium was added if the blue color disappeared. After 15−20 min the reaction was quenched with aqueous ammonium formate and the mixture was allowed to warm to room temperature, during which the ammonia evaporated. The reaction mixture was concentrated under reduced pressure and purified on a column loaded with Amberlite CG-50 (elution: 0 → 1.5 M NH_4OH for carbohydrates containing up to two amino groups; 0 → 2.5 M NH_4OH for products containing more than two amino groups). Fractions were evaporated to dryness. Residues were dissolved in water, acidified with aqueous HCl and lyophilized, giving the deprotected saccharides as white or slightly yellow fluffy solids.

Phenyl 2,3-Di-*O*-benzyl-4,6-di-*O*-methylsulfonyl-1-thio-β-D-galactopyranoside (7): A solution of diol **6** (9.43 g, 20.9 mmol) in pyridine (100 mL) was treated with methylsulfonyl chloride (4.03 mL, 52.1 mmol, 2.5 equiv.) and stirred for 2 h. The excess of methylsulfonyl chloride was quenched with methanol and the reaction solvents were evaporated to dryness. 1 M HCl was added and the mixture was extracted twice with EtOAc. The combined organic layers were washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography to yield dimesylate **7** (11.42 g, 18.8 mmol, 90%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.56−7.25 (m, 15 H, H_{arom}), 5.23 (d, *J* = 2.2 Hz, 1 H, H4), 4.88−4.62 (m, 5 H, H1, 2 × CH_2 Bn), 4.45 (dd, *J* = 6.6, *J* = 11.0 Hz, 1 H, C6−H_a), 4.29 (dd, *J* = 6.6, *J* = 11.0 Hz, 1 H, C6−H_b), 3.92−3.85 (m, 1 H, H2), 3.72−3.59 (m, 2 H, H3, H5), 3.04 (s, 3 H, Ms), 3.01 (s, 3 H, Ms). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ = 137.4, 136.6, 132.7 (C_q arom), 131.6, 128.8, 128.3, 128.2, 128.0, 127.7, 127.6 (CH_{arom}), 87.2 (C1), 80.1, 76.0, 75.3, 73.6 (C2, C3, C4, C5), 75.4, 72.9 (CH_2 Bn), 67.1 (C6), 38.7, 37.0 (Ms). ESI-MS: *m*/*z* = 631.3 $[M + Na]^+$.

Phenyl 4,6-Diazido-2,3-di-*O*-benzyl-4,6-dideoxy-1-thio-β-D-glucopyranoside (8): Sodium azide (4.9 g, 75 mmol, 4 equiv.) and a catalytic amount of tetrabutylammonium triflate were added to a solution of compound **7** (11.40 g, 18.7 mmol) in DMF (90 mL). The resulting mixture was stirred overnight at 80 °C. TLC analysis indicated complete conversion into a higher running product. The solvent was then removed in vacuo. Water was added to the residue and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was purified by silica column chromatography to yield the title compound **8** (7.34 g, 14.2 mmol, 78%). IR (neat): $\tilde{\nu}$ = 3032, 2916, 2870, 2106, 1358, 1271, 1113, 1084, 1061, 1051, 1024. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.58−7.55 (m, 2 H, H_{arom}), 7.42−7.25 (m, 15 H, H_{arom}), 4.94 (d, *J* = 10.3 Hz, 1 H, benzylic H), 4.90 (d, *J* = 10.6 Hz, 1 H, benzylic H), 4.82 (d, *J* = 10.6 Hz, 1 H, benzylic H), 4.72 (d, *J* = 10.3 Hz, 1 H, benzylic H), 4.63 (d, *J* = 8.3 Hz, 1 H, H1), 3.62−3.41 (m, 5 H, H2, H3, H4, H6), 3.28 (ddd, *J* = 2.3, *J* = 5.4, *J* = 9.5 Hz, 1 H, H5). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ = 137.8, 137.5 (C_q arom), 123.8, 129.1, 128.5, 128.2, 128.1, 126.4 (CH_{arom}), 87.8, 84.7, 80.6, 77.1 (C1, C2, C3, C5), 75.7, 75.4 (CH_2 Bn), 62.3 (C4), 51.8 (C6). ESI-MS: *m*/*z* = 525.2 $[M + Na]^+$.

Phenyl 3-Azido-3-deoxy-6-*O*-*p*-tolylsulfonyl-1-thio-β-D-glucopyranoside (10): Potassium *tert*-butoxide (20 mg, 0.18 mmol, 0.1 equiv.) was added to a solution of phenyl 2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-1-thio-β-D-glucopyranoside (764 mg, 1.81 mmol) in MeOH (10 mL). After 1 h the reaction was quenched with Amberlite IR-120 (H^+-form). The mixture was filtered and concentrated under reduced pressure. Traces of methanol and water were removed by coevaporation with pyridine. The residue was dissolved in pyridine (10 mL), cooled to 0 °C, and *p*-toluenesulfonyl chloride (380 mg, 1.99 mmol, 1.1 equiv.) was added. The reaction mixture was allowed to warm to room temperature. After TLC analysis indicated complete conversion into a higher running product, the reaction

was quenched with a few drops of MeOH and concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with 1 M HCl and a sat. $NaHCO_3$ solution. The aqueous layers were separately extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography yielded the title compound (550 mg, 1.22 mmol, 67%). ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.82 (m, 2 H, H_{arom}), 7.51−7.26 (m, 7 H, H_{arom}), 4.47 (d, *J* = 9.7 Hz, 1 H, H1), 4.36−4.27 (m, 2 H, H6), 3.48−3.25 (m, 4 H, H2, H3, H4, H5), 2.45 (s, 3 H, Me Ts). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ = 144.9 (C_q arom), 132.3 (CH_{arom}), 132.0 (C_q arom), 131.8 (CH_{arom}), 131.3 (C_q arom), 129.7, 128.9, 128.7, 127.9, 127.7 (CH_{arom}), 87.7 (C1), 77.2, 70.8, 69.6 (C2, C4, C5), 68.4 (C6), 67.8 (C3), 21.3 (Me Ts).

Phenyl 3,6-Diazido-2,4-di-*O*-benzyl-3,6-dideoxy-1-thio-β-D-glucopyranoside (11): Sodium azide (240 mg, 3.7 mmol, 3 equiv.) was added to a solution of compound **10** (550 mg, 1.22 mmol) in DMF (5 mL). The mixture was stirred overnight at 70 °C after which the solvent was removed in vacuo. The residue was dissolved in water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Traces of water were removed from the residue by coevaporation with toluene. The residue was dissolved in DMF, cooled to 0 °C and BnBr (0.31 mL, 2.6 mmol, 2.1 equiv.) and NaH (105 mg, 2.6 mmol, 2.1 equiv.) were subsequently added. After TLC indicated conversion into a higher running product, the reaction mixture was concentrated in vacuo. Water was added to the residue and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Silica column chromatography gave donor **11** as a white solid (566 mg, 1.13 mmol, 93%). IR (neat): ṽ = 2922, 2855, 2093, 1070. ^1H NMR ($CDCl_3$, 200 MHz): δ = 7.59−7.24 (m, 15 H, H_{arom}), 4.94 (d, *J* = 10.2 Hz, 1 H, benzylic H), 4.87 (d, *J* = 11.0 Hz, 1 H, benzylic H), 4.75 (d, *J* = 10.2 Hz, 1 H, benzylic H), 4.64−4.50 (m, 2 H, H1, benzylic H), 3.64−3.28 (m, 6 H, H2, H3, H4, H5, H6). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ = 136.5, 136.4 (C_q arom), 132.0, 128.3, 127.8, 127.7, 127.5, 126.9, 126.8 (CH_{arom}), 87.0 (C1), 78.5, 77.5, 75.6 (C2, C4, C5), 74.5, 74.0 (CH_2 Bn), 96.6 (C3), 50.3 (C6). ESI-MS: *m*/*z* = 525.5 $[M + Na]^+$.

1-*O*-(6-Azido-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranosyl)-(1*S*,2*S*,3*R*)-2,3-*O*-isopropylidenecyclohex-4-ene-1,2,3-triol (17): Yield: 483 mg (77%); α/β = 5.0:1. Spectroscopic data α-anomer: IR (neat): ṽ = 2988, 2918, 2862, 2098, 1068, 1026. $[\alpha]_D$ = +64.4 (*c* = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.37−7.22 (m, 15 H, H_{arom}), 5.72−5.68 (m, 1 H, C=CH), 5.59−5.55 (m, 1 H, C=CH), 5.01 (d, *J* = 10.9 Hz, 1 H, benzylic H), 4.94−4.91 (m, 2 H, H1′, benzylic H), 4.82 (d, *J* = 10.9 Hz, 1 H, benzylic H), 4.76 (d, *J* = 12.0 Hz, 1 H, benzylic H), 4.65 (d, *J* = 12.0 Hz, 1 H, benzylic H), 4.61−4.58 (m, 2 H, H3, benzylic H), 4.52 (br. d, *J* = 5.3 Hz, 1 H, H2), 4.12−4.06 (m, 2 H, H3′, H5′), 3.75 (ddd, *J* = 2.0, *J* = 5.4, *J* = 10.5 Hz, 1 H, H1), 3.54 (dd, *J* = 3.7, *J* = 9.6 Hz, 1 H, H2′), 3.51−3.46 (m, 2 H, H4′, C6′−H_a), 3.38 (dd, *J* = 5.0, *J* = 13.1 Hz, 1 H, C6′−H_b), 2.53−2.45 (m, 1 H, C6−H_a), 2.22 (dt, *J* = 5.4, *J* = 16.4 Hz, 1 H, C6−H_b), 1.40 (s, 3 H, CMe_2), 1.38 (s, 3 H, CMe_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.6, 138.1, 137.8 (C_q arom), 128.4, 128.3, 128.2, 127.9 127.8, 127.7, 127.4 (CH_{arom}, 126.6, 125.9 (C4, C5), 109.8 (C_q isoprop), 96.8 (C1′), 81.4 (C3′), 80.1 (C2′), 78.2 (C4′), 75.5 (C1, C2), 75.4, 75.1, 72.8 (3 CH_2 Bn), 74.5 (C3), 70.0 (C5′), 51.3 (C6′), 27.7, 27.0 (2 CMe_2), 25.2 (C6). ESI-MS: *m*/*z* = 645.6 $[M + NH_4]^+$, 650.4 $[M + Na]^+$, 666.4 $[M + K]^+$.

1-*O*-(3-Azido-2,4,6-tri-*O*-benzyl-3-deoxy-α/β-D-glucopyranosyl)-(1*S*,2*S*,3*R*)-2,3-*O*-isopropylidenecyclohex-4-ene-1,2,3-triol (18): Yield: 215 mg (78%); α/β = 4.3:1. Spectroscopic data α/β-mixture: IR (neat): ṽ = 2916, 2868, 2104, 1070, 1026. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.46−7.20 (m, H_{arom}), 5.70−5.65 (m, C=CH), 5.53 (br. d, *J* = 10.1 Hz, C=CH), 4.88 (d, *J* = 3.6 Hz, H1α), 4.82−4.75 (m, 2 H, 2 × CH_aH_bPh), 4.63−4.42 (m, H2, H3, H1β, 1 × CH_aH_bPh, 3 × CH_aH_bPh), 4.05−3.96 (m, H3′, H5′), 3.76−3.64 (m, H1, C6′−H_a), 3.60−3.56 (m, C6′−H_b), 3.51−3.41 (m, H4′), 3.39−3.34 (m, H2′), 2.49−2.39 (m, C6−H_a), 2.22 (m, C6−H_b). 1.35 (s, CMe_2), 1.29 (s, CMe_2). ^{13}C NMR ($CDCl_3$, 50.1 MHz): δ = 137.8, 137.5, (C_q arom), 128.3, 128.1, 127.9, 127.7, 127.6, 126.5, 125.9 (C4, C5, CH_{arom}) 109.6 (C_q isoprop), 102.7 (C1β), 96.4 (C1α), 77.9, 76.2, 75.7, 75.3, 74.3 (C1, C2, C3, C2′, C4′), 74.7, 73.4, 72.8 (CH_2 Bn), 69.8, 64.9 (C3′, C5′), 68.0 (6′), 27.6, 26.9 (CMe_2), 25.2 (C6). ESI-MS: *m*/*z* = 650.5 $[M + Na]^+$.

1-*O*-(4,6-Diazido-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl)-(1*S*,2*S*,3*R*)-2,3-*O*-isopropylidenecyclohex-4-ene-1,2,3-triol (19): Yield: 542 mg (80%); α/β = 6.6:1. Spectroscopic data α-anomer: $[\alpha]_D$ = +131 (*c* = 1.0, $CHCl_3$). IR (neat): ṽ = 2986, 2922, 2868, 2100, 1072, 1024. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.39−7.19 (m, 10 H, H_{arom} Bn), 5.70−5.67 (m, 1 H, C=CH), 5.57−5.55 (m, 1 H, C=CH), 4.97−4.93 (m, 2 H, H1′, benzylic H), 4.78 (d, *J* = 10.5 Hz, 1 H, benzylic H), 4.71 (d, *J* = 12.0 Hz, 1 H, benzylic H), 4.60 (d, *J* = 12.0 Hz, 1 H, benzylic H), 4.57−4.55(m, 1 H, H3), 4.49 (br. d, *J* = 5.7 Hz, 1 H, H2), 3.96 (t, *J* = 9.5 Hz, 1 H, H3′), 3.90 (ddd, *J* = 2.4, *J* = 4.8, *J* = 10.5 Hz, 1 H, H5′), 3.70 (ddd, *J* = 2.0, *J* = 5.4, *J* = 10.5 Hz, 1 H, H1), 3.53 (dd, *J* = 3.6, *J* = 9.4 Hz, 1 H, H2′), 3.48−3.43 (m, 2 H, H4′, C6′−H_a), 3.39 (dd, *J* = 4.9, *J* = 13.3 Hz, 1 H, C6′−H_b), 2.51−2.44 (m, 1 H, C6−H_a), 2.21 (dt, *J* = 5.7, *J* = 16.5 Hz, 1 H, C6−H_b), 1.40 (s, 3 H, CMe_2), 1.37 (s, 3 H, CMe_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 137.9 (C_q arom), 128.3, 128.1, 128.0, 127.7, 127.6 (CH_{arom}), 126.5, 125.7 (C4, C5), 97.0 (C1), 79.9 (C2′), 79.3 (C3′), 76.0 (C1), 75.32 (C2), 75.29, 72.6 (CH_2 Bn), 74.3 (C3), 69.0 (C5′), 62.1 (C4′), 51.6 (C6′), 27.6, 26.9 (CMe_2), 25.3 (C6). ESI-MS: *m*/*z* = 563.4 $[M + H]^+$, 585.3 $[M + Na]^+$.

1-*O*-(3,6-Diazido-2,4-di-*O*-benzyl-3,6-dideoxy-α-D-glucopyranosyl)-(1*S*,2*S*,3*R*)-2,3-*O*-isopropylidenecyclohex-4-ene-1,2,3-triol (20): Yield: 232 mg (81%); α/β = 6.9:1. Spectroscopic data α-anomer: $[\alpha]_D$ = +74.4 (*c* = 1.0, $CHCl_3$). IR (neat): ṽ = 2988, 2901, 2098, 1066, 1026. ^1H NMR ($CDCl_3$, 400 MHz): *δ* = 7.40−7.28 (m, 10 H, H_{arom}), 5.68 (ddd, *J* = 1.6, *J* = 6.0, *J* = 10.0 Hz, 1 H, C=CH), 5.57−5.54 (m, 1 H, C=CH), 4.92−4.89 (m, 2 H, H1, CH_aH_bPh), 4.77 (d, *J* = 12.1 Hz, 1 H, CH_aH_bPh), 4.62 (d, *J* = 12.1 Hz, 1 H, CH_aH_bPh), 4.58−4.56 (m, 2 H, H3, CH_aH_bPh), 4.47 (br. d, *J* = 5.2 Hz, 1 H, H2), 4.07 (ddd, *J* = 2.6, *J* = 4.3, *J* = 9.8 Hz, 1 H, H5′), 4.01 (t, *J* = 9.8 Hz, 1 H, H3′), 3.68 (ddd, *J* = 2.0, *J* = 5.4, *J* = 10.5 Hz, 1 H, H1), 4.46 (dd, *J* = 2.5, *J* = 13.1 Hz, 1 H, C6′−H_a), 3.39−3.34 (m, 2 H, H2′, C6′−H_b), 3.28 (t, *J* = 9.7 Hz, 1 H, H4′), 2.48−2.41 (m, 1 H, C6−H_a), 2.18 (dt, *J* = 5.7, *J* = 10.5 Hz, 1 H, C6−H_b), 1.37 (s, 3 H, CMe_2), 1.35 (s, 3 H, CMe_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 137.7, 137.3 (C_q arom), 128.5, 128.4, 128.3, 128.0, 127.9 (CH_{arom}), 126.6, 125.9 (C4, C5), 109.9 (C_q isoprop), 96.2 (C1′), 78.2 (C2′), 76.8 (C4′), 75.9 (C1), 75.4 (C2), 75.0 (CH_2 Bn), 74.5 (C3), 72.8 (CH_2 Bn), 69.7 (C5′), 64.7 (C3′), 51.1 (C6′), 27.7, 27.1 (CMe_2), 25.3 (C6). ESI-MS: *m*/*z* = 585.2 $[M + Na]^+$.

(1*R*,4*R*,6*S*)-1-(6-Azido-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranosyl)4,6-bis[benzyl(*o*-nitrophenylsulfonyl)amino]cyclohex-2-enol (22): Yield: 1.88 g (84%), α/β = 3.3:1. Off-white foam. Spectroscopic data for α-anomer: $[\alpha]_D^{20}$ = −22 (*c* = 0.5, $CHCl_3$). IR (neat):

$\tilde{\nu}$ = 3030, 2970, 2922, 2102, 1740, 1541, 1365, 1354, 1229, 1217, 1159, 1072. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.03−8.01 (m, 1 H, H_{arom}), 7.66−6.94 (m, 28 H, H_{arom}), 6.87−6.83 (m, 2 H, H_{arom}), 6.54 (d, *J* = 7.3 Hz, 1 H, H_{arom}), 6.01 (ddd, *J* = 2.5, *J* = 5.1, *J* = 10.0 Hz, 1 H, C=CH), 5.57 (d, *J* = 10.2 Hz, 1 H, C=CH), 5.09 (d, *J* = 3.4 Hz, 1 H, H1′), 4.97−4.93 (m, 2 H, 2 × benzylic H), 4.92−4.84 (m, 2 H, 1 benzylic H, H4), 4.80−4.74 (m, 2 H, 3 × benzylic H), 4.62−4.58 (m, 2 H, 2 × benzylic H), 4.44−4.38 (m, 2 H, 2 × benzylic H), 4.11−4.07 (m, 2 H, H1, H6), 3.83 (t, *J* = 9.3 Hz, 1 H, H3′), 3.74, (ddd, *J* = 2.5, *J* = 5.1, *J* = 9.8 Hz, 1 H, H5′), 3.56 (dd, *J* = 3.3, *J* = 9.9 Hz, 1 H, H2′), 3.48 (t, *J* = 9.3 Hz, 1 H, H4′), 3.33 (dd, *J* = 2.5, *J* = 13.0 Hz), 1 H, C6′-H_a) 3.25 (dd, *J* = 5.2, *J* = 13.0 Hz, 1 H, C6′−H_b), 2.12−2.04 (m, 1 H, C5−H_a), 1.96−1.92 (m, 1 H, C5−H_b). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.6, 147.0, 138.2, 137.9, 137.6, 136.5, 134.8, 133.8 (C_q arom), 133.4, 132.7, 131.3, 129.0, 127.3, 126.9, 124.2, 123.6 (CH_{arom}, C2, C3), 99.3 (C1′), 81.0, 80.1, 78.6, 77.9 (C1, C2′, C3′, C4′), 75.4, 75.3, 73.6 (CH_2 OBn), 70.8 (C5′), 56.9, 56.0 (C4, C6), 51.4, 49.9, 49.0 (C6′, CH_2 NBn), 28.7 (C5). ESI-MS: *m*/*z* = 1158.7 [M + Na]$^+$.

(1*R*,4*R*,6*S*)-1-(4,6-Diazido-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl)-4,6-bis[benzyl(*o*-nitrophenylsulfonyl)amino]cyclohex-2-enol (23): Yield: 1.65 g (77%), α/β = 5.0:1. Off-white foam. Spectroscopic data for α-anomer: $[\alpha]_D^{20}$ = +8.4 (*c* = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3030, 2970, 2924, 2876, 2104, 1740, 1541, 1366, 1350, 1157. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.04 (d, *J* = 8.6 Hz, 1 H, H_{arom}), 7.68−7.10 (m, 24 H, H_{arom}), 6.98 (t, *J* = 7.3 Hz, 1 H, H_{arom}), 6.87 (t, *J* = 7.6 Hz, 1 H, H_{arom}), 6.57 (d, *J* = 7.4 Hz, 1 H, H_{arom}), 5.98 (ddd, *J* = 2.4, *J* = 5.0, *J* = 10.0 Hz, 1 H, C=CH), 5.61 (d, *J* = 10.2 Hz, 1 H, C=CH), 5.11 (d, *J* = 3.2 Hz, 1 H, H1′), 4.96−4.84 (m, 3 H, 2 × benzylic H, H4), 4.81−4.74 (m, 3 H, 3 × benzylic H), 4.59 (d, *J* = 16.3 Hz, 1 H, 1 benzylic H NBn), 4.44−4.35 (m, 2 H, 2 × benzylic H NBn), 4.12−4.09 (m, 2 H, H1, H6), 3.73 (t, *J* = 9.3 Hz, 1 H, H3′), 3.60−3.46 (m, 3 H, H2′, H4′, H5′), 3.39 (dd, *J* = 2.2, *J* = 13.1 Hz, 1 H, C6′−H_a), 3.33 (dd, *J* = 4.9, *J* = 13.1 Hz, 1 H, C6′−H_b), 2.35−1.98 (m, 2 H, H5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.6, 147.0, 137.63, 137.56, 137.4, 126.4, 134.8 (C_q arom), 133.7, 133.5, 132.7, 131.7, 131.2, 131.1, 130.7, 127.6, 127.0, 124.3, 123.7 (CH_{arom}, C2, C3), 99.4 (C1′), 80.0 (C2′), 78.8 (C3′), 78.2 (C1), 75.4, 73.6 (CH_2 OBn), 69.9 (C5′), 62.7 (C4′), 57.0 (C4), 56.0 (C6), 51.8 (C6′), 49.9, 49.1 (CH_2 NBn), 28.8 (C5).

1-D-(1,4,6/2,3)-1-(6-Azido-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranosyl)-4,6-bis[benzyl(*o*-nitrophenylsulfonyl)amino]cyclohexane-1,2,3-triol (24):[20] Yield: 1.15 g (99%). Off-white foam. $[\alpha]_D^{20}$ = −33 (*c* = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3020, 2901, 2102, 1740, 1541, 1350, 1161, 1070. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.17−8.14 (m, 1 H, H_{arom}), 7.74−6.89 (m, 31 H, H_{arom}), 6.78 (d, *J* = 7.4 Hz, 1 H, H_{arom}), 5.02 (d, *J* = 10.9 Hz, 1 H, benzylic H), 4.96 (d, *J* = 11.0 Hz, 1 H, benzylic H), 4.90−4.77 (m, 5 H, 4 benzylic H, H1′), 4.59 (d, *J* = 11.0 Hz, 1 H, benzylic H), 4.56−4.50 (m, 2 H, 2 benzylic H), 4.44−4.40 (m, 2 H, 1 benzylic H, H6), 4.14−4.07 (m, 2 H, H2, H4), 3.80 (br. s, 1 H, H1), 3.74−3.69 (m, 1 H, H3′), 3.57 (br. s, 1 H, H3), 3.53 (dd, *J* = 3.6, *J* = 10.0 Hz, 1 H, H2′), 3.43−3.37 (m, 2 H, H4′, H5′), 3.31 (br. d, *J* = 12.9 Hz, 1 H, H6′^{a}), 3.21 (dd, *J* = 5.3, *J* = 13.0 Hz, 1 H, H6′^{b}), 2.56 (br. s, 2 H, OH), 1.77−1.68 (m, 1 H, H5^a), 1.63−1.60 (m, 1 H, H5^b). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.6, 147.2, 138.0, 137.7, 137.3, 134.4 (C_q arom), 133.8, 133.0 (CH_{arom}), 132.7 (C_q arom), 132.3, 131.9, 131.4, 127.0, 124.4, 123.9 (CH_{arom}), 100.2 (C1′), 85.4 (C1), 81.0 (C3′), 79.5 (C2′), 78.2 (C4′), 75.5 (2 CH_2 OBn), 73.9 (CH_2 OBn), 71.8 (C5′), 70.4 (C2), 67.6 (C3), 56.9 (C4), 53.3 (C6), 51.3 (C6′), 49.7, 48.4 (NBn), 29.4 (C5). ESI-MS: *m*/*z* = 1195.6 [M + Na]$^+$.

1-D-(1,4,6/2,3)-1-(4,6-Diazido-2,3-di-*O*-benzyl-4,6-dideoxy-α-D-glucopyranosyl)-4,6-bis[benzyl(*o*-nitrophenylsulfonyl)amino]cyclohexane-1,2,3-triol (25): Yield: 903 mg (88%). Off-white foam. $[\alpha]_D^{20}$ = −4.4 (*c* = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3026, 2970, 2104, 1738, 1541, 1365, 1352, 1161, 1088, 1013. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.14−8.12 (m, 1 H, H_{arom}), 7.74−6.98 (m, 25 H, H_{arom}), 6.78 (d, *J* = 7.3 Hz, 2 H, H_{arom}), 4.97 (d, *J* = 10.7 Hz, 1 H, benzylic H), 4.91 (d, *J* = 3.1 Hz, 1 H, H1′), 4.87−4.81 (m, 3 H, benzylic H), 4.75 (d, *J* = 11.8 Hz, 1 H, benzylic H), 4.54−4.44 (m, 4 H, H6, 3 benzylic H), 4.19−4.17 (m, 1 H, H4), 4.06 (br. s, 1 H, H2), 3.82 (br. s, 1 H, H1), 3.61−3.53 (m, 3 H, H2′, H3, H3′), 3.42−3.37 (m, 2 H, H4′, C6′−H_a), 3.32−3.26 (m, 2 H, H5′, C6′−H_b), 2.92 (br. s, 1 H, OH) 2.69 (d, *J* = 5.2 Hz, 1 H, OH), 1.74−1.68 (m, 2 H, H5). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.5, 147.1, 137.4, 137.23, 137.18, 137.0 (CH_{arom}), 133.9, 133.0 (CH_{arom}), 132.6 (CH_{arom}), 132.2, 131.6, 131.4, 131.2, 128.9, 128.0, 127.1, 124.4, 123.8 (CH_{arom}), 100.0 (C1′), 85.8 (C1), 79.4 (C2′), 78.8 (C3′), 75.4, 73.7 (CH_2 OBn), 70.8 (C5′), 70.3 (C2), 67.6 (C3), 62.4 (C4′), 56.9 (C4), 53.4 (C6), 51.7 (C6′), 49.7, 48.5 (CH_2 NBn), 29.8 (C5). ESI-MS: *m*/*z* = 1128.6 [M + Na]$^+$.

1-*O*-(6-Amino-6-deoxy-α-D-glucopyranosyl)-(1*S*,2*S*,3*R*)-cyclohex-4-ene-1,2,3-triol (26): Yield: 26 mg (52%). ^{1}H NMR (D_2O, 400 MHz): δ = 5.87−5.82 (m, 1 H, C=CH), 5.64 (br. d, *J* = 10.1 Hz, 1 H, C=CH), 5.17 (d, *J* = 3.8 Hz, 1 H, H1′), 4.43 (br. s, 1 H, H3), 4.20−4.19 (m, 1 H, H2), 4.10−4.02 (m, 2 H, H1, H5′), 3.82 (t, *J* = 9.5 Hz, 1 H, H3′), 3.63 (dd, *J* = 3.9, *J* = 9.8 Hz, 1 H, H2′), 3.49 (dd, *J* = 2.9, *J* = 13.3 Hz, 1 H, C6′−H_a), 3.40 (t, *J* = 9.5 Hz, 1 H, H4′), 3.22 (dd, *J* = 8.5, *J* = 13.3 Hz, 1 H, C6′−H_b), 1054−2.47 (m, 1 H, C6−H_a), 2.32−2.24 (m, 1 H, C6−H_b). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 127.8, 127.0 (C4, C5), 97.0 (C1′), 75.2, 73.4, 72.2, 71.9, 71.2, 68.7, 68.6 (C2′, C3′, C4′, C5′, C1, C2, C3), 41.3 (C6′), 26.6 (C6). HRMS: found [M + H]$^+$ 292.1367 ppm; $C_{12}H_{22}NO_7^+$ requires 292.1390.

1-*O*-(4,6-Diamino-4,6-dideoxy-α-D-glucopyranosyl)-(1*S*,2*S*,3*R*)-cyclohex-4-ene-1,2,3-triol (27): Yield: 44 mg (67%). ^{1}H NMR (D_2O, 400 MHz): δ = 5.88−5.83 (m, 1 H, C=CH), 5.69−5.65 (m, 1 H, C=CH), 5.27 (d, *J* = 3.7 Hz, 1 H, H1′), 4.49−4.41 (m, 2 H, H3, H5′), 4.20−4.19 (m, 1 H, H2), 4.15−4.11 (m, 1 H, H1), 4.03 (t, *J* = 9.9 Hz, 1 H, H3′), 3.74 (dd, *J* = 3.7, *J* = 9.8 Hz), 1 H, H2′3.56 (dd, *J* = 2.9, *J* = 13.4 Hz, 1 H, C6′−H_a), 3.34−3.26 (m, 2 H, H4′, C6′−H_b), 2.56−2.48 (m, 1 H, C6−H_a), 2.35−2.28 (m, 1 H, C6−H_b). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 127.7, 127.0 (C4, C5), 96.9 (C1′), 74.5, 71.9, 71.0, 69.2, 68.3, 65.6 (C2′, C3′, C5′, C1, C2, C3), 54.3 (C4′), 40.9 (C6′), 26.9 (C6). HRMS: found [M + H]$^+$ 291.1539 ppm; $C_{12}H_{23}N_2O_6^+$ requires 291.1556.

1-*O*-(3,6-Diamino-3,6-dideoxy-α-D-glucopyranosyl)-(1*S*,2*S*,3*R*)-cyclohex-4-ene-1,2,3-triol (28): Yield: 24 mg (57%). ^{1}H NMR (D_2O, 400 MHz): δ = 5.87−5.82 (m, 1 H, C=CH), 5.65 (br. d, *J* = 10.1 Hz, 1 H, C=CH), 4.45 (br. s, 1 H, H3), 4.23−4.22 (m, 1 H, H2), 4.16−4.10 (m, 2 H, H1, H5′), 3.91 (dd, *J* = 3.7, *J* = 10.7 Hz, 1 H, H2′), 3.67 (t, *J* = 9.8 Hz, 1 H, H4′), 3.59−3.52 (m, 2 H, H3′, C6′−H_a), 3.23 (dd, *J* = 9.1, *J* = 13.3 Hz, 1 H, C6′−H_b), 2.57−2.50 (m, 1 H, C6−H_a), 2.33−2.26 (m, 1 H, C6−H_b). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 127.8, 126.9 (C4, C5), 95.7 (C1′), 74.2, 71.1, 68.8, 68.63, 68.59, 68.5 (C2′, C4′, C5′, C1, C2, C3), 55.8 (C3′), 41.0 (C6′), 26.6 (C6). HRMS: found [M + H]$^+$ 291.1561 ppm; $C_{12}H_{23}N_2O_6^+$ requires 291.1556.

1-D-(1,4,6/2,3)-1-(6-Amino-6-deoxy-α-D-glucopyranosyl)-4,6-diaminocyclohexane-1,2,3-triol (29): A solution of compound **24**

(0.50 g, 0.428 mmol), thiophenol (0.26 mL, 2.57 mmol, 6 equiv.) and dipea (0.37 mL, 2.14 mmol, 5 equiv.) in DMF (4 mL) was stirred for 72 h. TLC analysis showed complete conversion into a lower running product and the reaction mixture was concentrated in vacuo. Silica gel column chromatography (elution: 50% toluene in EtOAc → 10% MeOH in EtOAc containing 1% Et_3N) afforded the dimer without nitrobenzenesulfonyl groups (222 mg, 0.28 mmol, 65%). A mixture of the partially protected dimer (49 mg, 0.061 mmol) and 10% palladium on activated charcoal (25 mg) in EtOH/0.2 M aqueous HCl (ca. 1:1, v/v) was stirred under 1 atm hydrogen pressure for 72 h. The reaction mixture was filtered and the solvents evaporated to dryness. The resulting residue was purified on a column loaded with Amberlite CG-50 (elution: 0 → 2.5 M NH_4OH). Product-containing fractions were evaporated to dryness. The residue was redissolved in water, acidified with aqueous HCl and lyophilized, giving the hydrochloride salt of the title compound as a white solid (19 mg, 0.041 mmol, 68%). ^1H NMR (D_2O, 400 MHz): δ = 5.24 (d, J = 3.6 Hz, 1 H, H1′), 4.30−4.27 (m, 2 H, H2, H1 or H3), 4.01−3.90 (m, 3 H, H5′, H1 or H3, H4 or H6), 3.81 (dd, J = 8.8, J = 9.9 Hz, 1 H, H3′), 3.75 (dd, J = 3.6 Hz), J = 9.9 Hz, 1 H, H2′), 3.64−3.58 (m, 1 H, H4 or H6), 3.52−3.45 (m, 2 H, H4′, C6′−H_a), 3.32 (dd, J = 7.0, J = 13.5 Hz, 1 H, C6′−H_b), 2.41−2.35 (m, 1 H, C5−H_a), 2.13 (q, J = 12.5 Hz, 1 H, C5−H_b). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 105.0 (C1′), 82.6, 75.2, 74.2, 73.6, 72.9, 72.2, 71.2 (C2′, C3′, C4′, C5′, C1, C2, C3), 51.3, 50.1 (C4, C6), 43.3 (C6′), 29.9 (C5). HRMS: found $[M + H]^+$ 324.1777 ppm; $C_{12}H_{26}N_3O_7^+$ requires 324.1771.

1-D-(1,4,6/2,3)-1-(4,6-Diamino-4,6-dideoxy-α-D-glucopyranosyl)-4,6-diaminocyclohexane-1,2,3-triol (30): A solution of compound **25** (0.45 g, 0.408 mmol), thiophenol (0.25 mL, 2.45 mmol, 6 equiv.) and dipea (0.36 mL, 2.04 mmol, 5 equiv.) in DMF (4 mL) was stirred for 72 h. The reaction mixture was concentrated in vacuo and the residue was purified by silica column chromatography (elution: 50% toluene in EtOAc → 5% MeOH in EtOAc containing 1% Et_3N) afforded the dimer without nitrobenzenesulfonyl groups (196 mg, 0.27 mmol, 66%). 10% Palladium on activated charcoal was added to a solution of the partially protected dimer (21 mg, 0.029 mmol) in 0.2 M HCl (aq.)/EtOH (2 mL, ca. 1:1 v/v). The mixture was stirred under 1 atm hydrogen pressure for 72 h. After filtration and concentration under reduced pressure, the residue was purified on a column loaded with Amberlite CG-50 (elution: 0 → 4 M NH_4OH). Fractions with product were collected and the solvents evaporated to dryness. The residue was redissolved in water, acidified with 1 M HCl and lyophilized yielding the hydrochloride salt of the title compound (6 mg, 0.012 mmol, 42%) as a white solid. ^1H NMR (D_2O, 400 MHz): δ = 5.25 (d, J = 3.8 Hz, 1 H, H1′), 4.29−4.17 (m, 3 H, H5′, H2, H1 or H3), 3.96−3.89 (m, 2 H, H3′, H1 or H3), 3.87−3.82 (m, 1 H, H4 or H6), 3.75 (dd, J = 3.8 Hz, J = 9.7 Hz, 1 H, H2′), 3.56−3.47 (m, 2 H, C6′-H_a, H4 or H6), 3.31−3.23 (m, 2 H, H4′, C6′−H_b), 2.30−2.26 (m, 1 H, C5−H_a), 2.03 (q, J = 12.5 Hz, 1 H, C5−H_b). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 102.6 (C1′), 80.7, 71.9, 70.5, 69.0, 68.9, 66.8 (C2′, C3′, C5′, C1, C2, C3), 53.4 (C4′), 48.9, 47.9 (C4, C6), 40.6 (C6′), 27.6 (C5). HRMS: found $[M + H]^+$ 323.1928 ppm; $C_{12}H_{27}N_4O_6^+$ requires 323.1931.

Acknowledgments

The authors thank Hans van den Elst for performing mass spectrometry, Bertil Hofte for high-resolution mass spectrometry and Organon N.V. for funding.

[1] J. Rogers, A. H. Chang, U. von Ashen, R. Schroeder, J. Davies, *J. Mol. Biol.* **1996**, *259*, 916−925.
[2] H.-Y. Mei, D. P. Mack, A. A. Galan, N. S. Halim, A. Heldsinger, J. A. Loo, D. W. Moreland, K. A. Sannes-Lowery, L. Sharmeen, H. N. Truong, A. W. Czarnik, *Bioorg. Med. Chem.* **1997**, *5*, 1173−1184.
[3] M. L. Zapp, S. Stern, M. R. Green, *Cell* **1993**, *74*, 969−978.
[4] For recent reviews on aminoglycoside−RNA interactions, see: [4a] S. J. Sucheck, C.-H. Wong, *Curr. Opin. Chem. Biol.* **2000**, *4*, 678−686. [4b] L. P. Kotra, S. Mobashery, *Curr. Org. Chem.* **2001**, *5*, 193−205. [4c] J. Gallego, G. Varani, *Acc. Chem. Res.* **2001**, *34*, 836−843. [4d] Y. Tor, *ChemBioChem* **2003**, *4*, 998−1007. [4e] G. J. R. Zaman, P. J. A. Michiels, C. A. A. van Boeckel, *DDT* **2003**, *8*, 297−306.
[5] W. K. C. Park, M. Auer, H. Jaksche, C.-H. Wong, *J. Am. Chem. Soc.* **1996**, *118*, 10150−10155.
[6] S. J. Sucheck, W. A. Greenberg, T. J. Tolbert, C.-H. Wong, *Angew. Chem. Int. Ed.* **2000**, *39*, 1080−1084.
[7] C. L. Nunns, L. A. Spence, M. J. Slater, D. J. Berrisforld, *Tetrahedron Lett.* **1999**, *40*, 9341−9345.
[8] K. Hamasaki, M.-C. Woo, A. Ueno, *Tetrahedron Lett.* **2000**, *41*, 8327−8332.
[9] J. Haddad, L. P. Kostra, B. Llano-Sotelo, C. Kim, E. F. Azucena, Jr., M. Liu, S. B. Vakulenko, C. S. Chow, S. Mobashery, *J. Am. Chem. Soc.* **2002**, *124*, 3229−3237.
[10] S. Hanessian, M. Tremblay, A. Kornienko, N. Moitessier, *Tetrahedron* **2001**, *57*, 3255−3265.
[11] K. B. Simonsen, B. K. Ayida, D. Vourloumis, M. Takahashi, G. C. Winters, S. Barluenga, S. Qamar, S. Shandrick, Q. Zhao, T. Hermann, *ChemBioChem* **2002**, *3*, 1223−1228.
[12] W. A. Greenberg, E. S. Priestley, P. S. Sears, P. B. Alper, C. Rosenbohm, M. Hendrix, S.-C. Hung, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 6527−6541.
[13] D. H. Ryu, C.-H. Tan, R. R. Rando, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 901−903.
[14] P. H. Seeberger, M. Baumann, G. Zhang, T. Kanemitsu, E. E. Swayze, S. A. Hofstadler, R. H. Griffey, *Synlett* **2003**, *9*, 1323−1326.
[15] K. Tatsuta, M. Kitagawa, *Tetrahedron Lett.* **1995**, *36*, 6717−6720.
[16] [16a] L. Hyldtoft, C. S. Poulsen, R. Madsen, *Chem. Commun.* **1999**, 2101−2102. [16b] L. Hyldtoft, R. Madsen, *J. Am. Chem. Soc.* **2000**, *122*, 8444−8452.
[17] S. H. L. Verhelst, W. Wiedenhof, H. Ovaa, G. A. van der Marel, H. S. Overkleeft, C. A. A. van Boeckel, J. H. van Boom, *Tetrahedron Lett.* **2002**, *43*, 6451−6455.
[18] [18a] T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373−6374. [18b] J. J. Turner, N. Wilschut, H. S. Overkleeft, W. Klaffke, G. A. van der Marel, J. H. van Boom, *Tetrahedron Lett.* **1999**, *40*, 7039−7042.
[19] Surprisingly, deprotection using Birch conditions resulted in the cleavage of the *O*- but not the *N*-benzyl functionalities.
[20] For nomenclature on cyclitols, see the IUPAC recommendations on the internet at www.chem.qmul.ac.uk/iupac/cyclitol/

Received January 13, 2004

