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2′-Modified Neamine Analogues from Thiomannosides through Glycosidation–Stereoinversion

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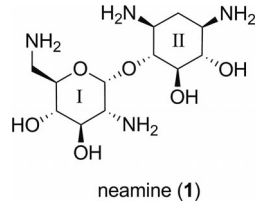
Conveniently protected neamine analogues were synthesized with a free 2′-OH group for further functionalization. An approach was investigated involving a stereoselective α-glycosidation reaction of 3,4-*O*-dimethoxybutanediyl-2-*O*-silyl protected thiomannosides with a 2-deoxystreptamine derivative. Subsequent 2-O-deprotection followed by an oxidation–reduction sequence led to α-glucosides with stereoinversion at C-2′. The scope of the procedure for the syntheses of α-glucosides was explored with three distinct model acceptors. Thiomannoside coupling, 2-O-deprotection, and oxidation were straightforward, whereas the outcome of the reduction step was clearly acceptor-dependent.

Introduction

Aminoglycosides form a class of compounds with strong bactericidal activity, because of the ability to interfere with the fidelity of mRNA translation to the appropriate protein.[1–6] Unfortunately, the clinical usefulness of aminoglycosides is diminished by emerging resistance of bacteria, in particular because of aminoglycoside-modifying enzymes.[7] In recent years, there has been a search for synthetic aminoglycoside analogues to circumvent this resistance and other undesired effects such as nephro- and ototoxicity.[8] However, the synthesis and functionalization of aminoglycoside structures are synthetically challenging. The regioselective protection of the heteroatoms followed by chemical modification is laborious, thus thwarting the rapid preparation of structural libraries as is usual in a medicinal chemistry setting.

The structure of pseudodisaccharide neamine (**1**, Figure 1) is the central scaffold of most relevant aminoglycosides. It consists of a 2,6-diaminoglucose ring (I) and a 2-deoxystreptamine ring (II), linked by an α-configured glycosidic bond. Interestingly, the aminocyclitol 2-deoxystreptamine (2-DOS) is universally conserved in aminoglycoside antibiotics, thus suggesting an essential role for the binding of aminoglycosides to ribosomal RNA. Neamine is easily obtained from natural sources. However, the plethora of amino and hydroxy groups impedes a facile differentiation, leading to lengthy protective group manipulation strategies.



neamine (**1**)

Figure 1. Structure of neamine (**1**).

We are particularly interested in the selective manipulation of the neamine 2′-position. Most of the reported libraries of neamine analogues focus on the functionalization of other positions in neamine,[9] mainly because of the difficulty of solely exposing the 2′-position. Additionally, NMR and crystallographic studies of the neomycin and paromomycin families have shown the presence of an internal hydrogen bond that involves the 2′-position in the bioactive conformation.[2,3] We reasoned that the availability of a neamine intermediate with an uniquely exposed heteroatom at the 2′-position would be valuable for further investigations.

We intend to construct protected neamine analogues, ready for selective 2′-functionalization, by employing a convergent strategy commencing with individual building blocks. An essential element of the present study towards such neamine analogues involves the α-stereodirected glycosidation reaction between a thioglycoside derivative (**2**) and the suitably protected 2-DOS (**3**, Scheme 1).

In this direction, there is no broadly applicable solution for the stereoselective installation of a 1,2-*cis*-glycosidic bond,[10,11] often leading to α/β mixtures with ratios depending on the coupling conditions and carbohydrate acceptor. There are coupling methods that aim to circumvent this problem, such as intramolecular aglycon delivery.[12,13] Several authors have obtained good results with different techniques. Demchenko et al. reported a promising modi-

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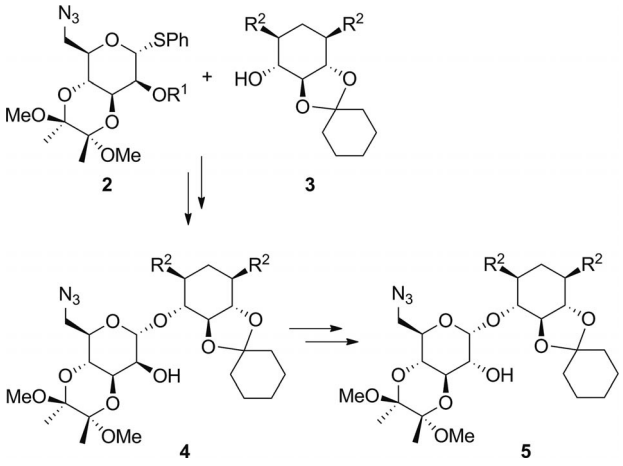


Scheme 1. Synthesis of neamine analogues; R^1 = silyl ethers, R^2 = NHCbz (Cbz = carbobenzyloxy) or N_3.

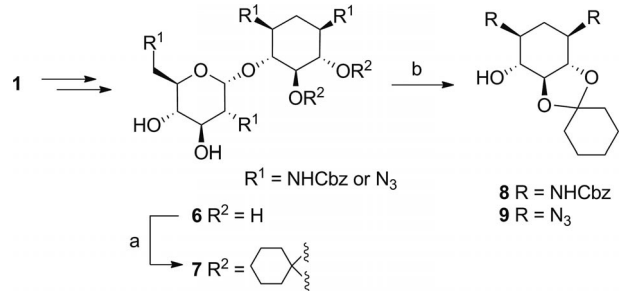
fied thiocyanide method[14] and more recently used *S*-benzoxazolyl glycosides,[15] both are promoters of 1,2-*cis* glycosylation. Lemieux's halide-catalyzed glycosidation conditions,[16] with preference for α-linked dissacharide formation, have been extensively applied to the syntheses of α-glucosides.[10,11] Another promising strategy was recently introduced by Boons et al. to control the stereoselectivity of glycosidation reactions,[17,18] but its straightforward application was hampered by the prerequisite of the enantiopure formation of a 2′-*O*-thioether. A method for the formation of 1,2-*cis*-*manno*-configured carbohydrates involves stereoinversion at C-2′. Such β-mannosides can be obtained from the oxidation of 2-hydroxy-β-glucosides to 2-ketoglycosides intermediates followed by a stereoselective reduction.[19–25] Additionally, the stereoselective reduction of α-2-ulosides to 1,2-*cis*-α-glycosides has been reported for several deoxysugars.[26–29]

We utilized thiomannosides in the glycosidation step, as the α-glycosidation reaction of mannoses is particularly facile and stereoselective. Next, we investigated the conditions for inversion at C-2′, leading to the syntheses of α-configured glucosides with high stereoselectivity. This paper reports the successful syntheses of 2′-modified neamine and other α-glucosides, preceded by the coupling of thiomannosides and the inversion of the configuration at C-2′.

Results and Discussion

2-Deoxystreptamine as a Building Block

2-Deoxystreptamine plays a central role in the bioactivity of most aminoglycoside antibiotics.[30] The asymmetrical functionalization of 2-DOS can be obtained by the selective hydrolysis of neomycin to afford neamine[31] (**1**), followed by the sequential protection and hydrolysis of the glycosidic bond. The procedure reported by Vourloumis et al. was applied to generate the conveniently protected 2-DOS derivative **8** (Scheme 2).[32] First, the amino groups of neamine (**1**) were protected by Cbz groups upon treatment with benzyl chloroformate, and the differentiation of the two vicinal diols was performed by selectively introducing a cyclohexylidene group at O-5 and O-6. Next, the residual sugar diol was oxidatively cleaved to give a dialdehyde, followed by β-elimination. In addition to carbamates, an alternative mode of amine masking was also performed by introducing azide as reported by Arenz et al.[33] A diazo-transfer reaction on neamine (**1**) with triflyl azides generated tetraazido compound **6** in good yield.[34–36] The differentiation of the two vicinal diols was performed, as before, by introducing a cyclohexylidene group.[37] The oxidative cleavage of the sugar diol, followed by β-elimination, afforded diazido 2-DOS precursor **9** (Scheme 2). Both **8** and **9** served as useful building blocks for the generation of neamine analogues.[38]

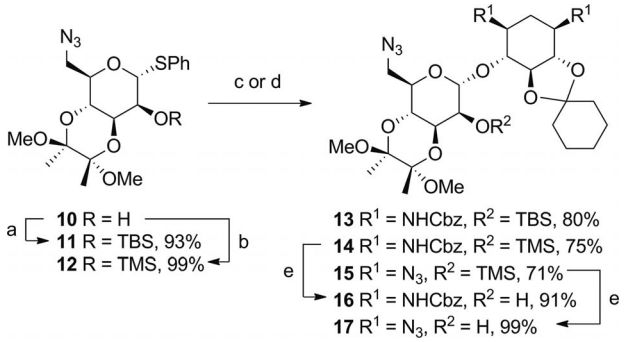


Scheme 2. Reagents and conditions: (a) 1,1-dimethoxycyclohexane, TsOH (*p*-toluenesulfonic acid), DMF (dimethylformamide) or MeCN; (b) (1) $NaIO_4$, MeOH or THF/H_2O, (2) Et_3N or *N*-butylamine, MeOH.

Thioglycoside Coupling and O-2′ Deprotection

Crich et al.[39] reported the use of a Ley's bis(acetal)-type protecting group[40–43] on thiomannoside donors. The 3,4-*O*-dimethoxybutanediyl (DMB) protection was found to have excellent features for the promotion of α-stereoselective couplings.[44] In addition, it allowed the straightforward differentiation between the 2- and 6-OH positions.[45] Thus, thiomannoside **10** was readily obtained from phenyl-1-thio-α-D-mannopyranoside by the preferential protection with a DMB moiety on the *trans*-vicinal alcohols[44] and the conversion of the 6-OH into an azido group.[45]

The protection of the 2-OH was required for glycosidation. We opted for using a silyl group with the advantage that it can be readily and selectively removed by treatment with a fluoride source. Thus, the treatment of **10** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine in dichloromethane afforded compound **11** in 93% yield (Scheme 3). Glycosidation was performed with 2-DOS derivative **8** as the acceptor. The activation of the thioglycoside was generated by using the system of 1-(phenylsulfinyl)piperidine/triflic anhydride (PSP/Tf_2O),[46–49] which formed a potent metal-free thiophile. The reaction was quenched with triethyl phosphite,[50,51] improving the yield and facilitating purification. The glycosidation gave **13** in good yield and complete α-stereoselectivity (Scheme 3).



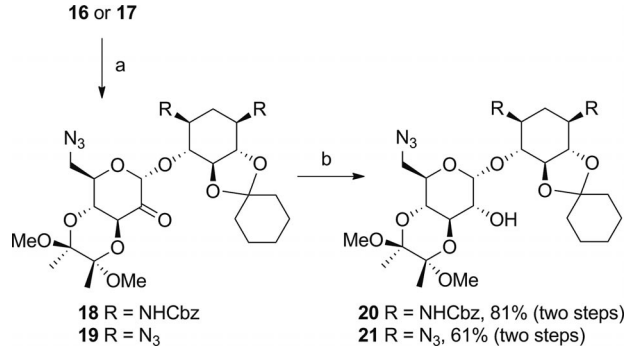
Scheme 3. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, r.t.; (b) HMDS (hexamethyldisilazane), cat. TMSCl (trimethylsilyl chloride) CH_3CN; (c) **8**, PSP, Tf_2O, TTBP (2,4,6-tri-*tert*-butylpyrimidine), 4 Å MS (molecular sieves), CH_2Cl_2, –60 °C; (d) **9**, PSP, Tf_2O, TTBP, 4 Å MS, CH_2Cl_2, –60 °C; (e) TBAF (tetra-*n*-butylammonium fluoride), THF (tetrahydrofuran), r.t.

The next step was the removal of the silyl group with the aim to expose the 2′-OH functionality uniquely. However, the TBS protection proved to be invulnerable under the influence of TBAF. An alternative treatment with HF/pyridine led to slow degradation of **13**. The unexpected stability of the TBS group prompted us to attempt the coupling and deprotection sequence with a more labile silyl ether. Thus, thiomannoside **10** was treated with hexamethyldisilazane and a catalytic amount of trimethylsilyl chloride in acetonitrile to give, after filtration and evaporation, trimethylsilyl (TMS) protected **12** in excellent yield and purity.

Under the influence of PSP/Tf_2O activation, **12** and **8** were coupled without affecting the TMS group. The reaction afforded only α-isomer **14**. Moreover, TMS deprotection with TBAF proceeded rapidly and smoothly to obtain the pseudodisaccharide **16** with a free 2′-OH group in 91% yield. Finally, TMS-protected thiomannoside **12** was glycosidated with the diazido 2-DOS derivative **9**, and **15** was obtained after purification in 71% yield, along with a small inseparable fraction (2% yield) of the α/β mixture (ratio 4:5). As expected in this case, treatment of **15** with TBAF in THF removed the TMS group uneventfully to afford **17** in quantitative yield (Scheme 3).

Inversion of Configuration at C-2′

After the successful syntheses of free 2′-OH α-mannosides **16** and **17**, we envisaged their application as intermediates towards free 2′-OH α-glucosides. An epimerization at C-2′ was conducted by an oxidation–reduction sequence. Compound **16** was exposed to Dess–Martin periodinane leading to the rapid and complete oxidation at C-2′. The resulting crude 2-ulose **18**, isolated in acceptable purity (>90%) as indicated by NMR analysis, was subjected to reduction without purification as a consequence of its inherent instability. Reduction under the action of L-selectride proceeded with excellent stereoselectivity (Scheme 4), and the analysis of the crude product by ^1H NMR revealed a 49:1 *gluco*/*manno* ratio. Purification by silica gel column chromatography afforded the desired α-D-glucoside **20** in 81% yield.[52,53]



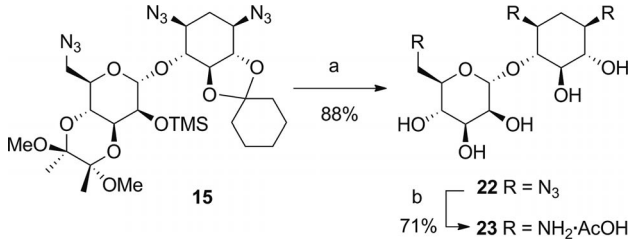
Scheme 4. Reagents and conditions: (a) Dess–Martin periodinane, CH_2Cl_2, r.t.; (b) reduction for **18**: L-selectride, THF, r.t.; reduction for **19**: $NaBH_4$, MeOH, r.t.

When L-selectride was applied to **19**, bearing azides instead of benzyloxy carbamates on the 2-DOS moiety, the crude *gluco*/*manno* ratio dropped to 8:5. In search for an improvement in the stereoselectivity, lithium tri-*tert*-butoxyaluminiumhydride and sodium borohydride were also tested, giving crude *gluco*/*manno* ratios of 10:6 and 13:5, respectively. Sodium borohydride gave the best result with preference for the desired stereoisomer, and α-D-glucoside **21** was isolated in 61% yield, along with recovery of **19** in 20% yield.[52,53]

Deprotection of 15 and 20

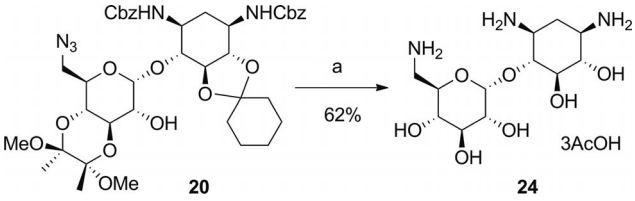
We considered it important to prove that the removal of the protecting groups employed in the synthesis was possible, therefore compounds **15** and **20** were subjected to deprotection conditions. Additionally, **15** would generate an interesting new neamine analogue, displaying a *manno*-configuration on the sugar ring. Compound **15** was subjected to a 9:1 mixture of TFA (trifluoroacetic acid)/H_2O for 4 min, leading to the hydrolysis of the DMB, cyclohexylidene acetal, and TMS groups in a single step to afford **22** in good yield.[54] The reaction time was found to be critical, as longer exposure led to hydrolysis of the glycosidic bond. The azide reduction of **22** was successfully performed by a Staudinger reaction with trimethylphosphane. Chromatography on silica gel followed by ion-exchange chromatographic purification gave the new neamine analogue **23** containing a 6-deoxy-6-aminomannose ring. After treatment with acetic acid, the product was isolated as a triammonium acetate salt (Scheme 5).

The removal of the protecting groups of **20** was performed in three steps without intermediate purification. Under acidic conditions as aforementioned, the hydrolysis of the acetals was followed by the reduction of the 6′-azido group in the crude intermediate under Staudinger conditions. The remaining benzyloxycarbonyl groups were hydrogenolyzed, and again, performing chromatography on silica gel followed by ion-exchange purification afforded 2′-de-



Scheme 5. Reagents and conditions: (a) TFA/H_2O (9:1, v/v), r.t.; (b) (1) $P(CH_3)_3$, THF/H_2O/1 M NaOH (10:1:0.1, v/v/v), (2) AcOH.

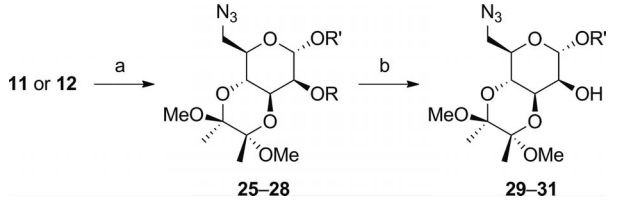
amino-2′-hydroxyneamine **24** (Scheme 6). Although synthesized in a different manner, the same neamine analogue had been reported earlier by Wong et al.[55]



Scheme 6. Reagents and conditions: (a) (1) TFA/H_2O (9:1, v/v), r.t., (2) $P(CH_3)_3$, THF/H_2O/1 M NaOH (10:1:0.1, v/v/v), (3) cat. Pd/C, H_2 (1 atm), MeOH/AcOH (1:1, v/v).

Scope of the Coupling–Epimerization Methodology

The previous positive results led us to investigate the validity of the coupling–epimerization sequence with other substrates. Three model acceptors were selected and coupled to either **11** or **12** under PSP/Tf_2O conditions (see Scheme 7 and Table 1).



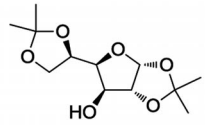
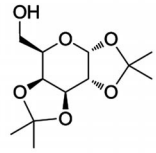
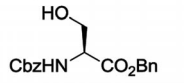
Scheme 7. (a) R′OH (see Table 1), PSP, Tf_2O, TTBP, 4 Å MS, CH_2Cl_2, –60 °C; (b) TBAF, THF, r.t.

Diisopropylidene-D-glucose was glycosylated with thiomannoside **11** to afford **25** in 93% yield and complete α stereoselectivity. Here, the TBS protecting group was cleanly removed upon treatment with 1.1 equiv. of TBAF, leading to **29** in high yield (Table 1, Entry 1).

Glycosylation of diisopropylidene-D-galactopyranose with **11** afforded 85% of disaccharide **26** as a 41:1 ratio of the α/β mixture. By employing silica chromatography, compound **26** was partially separated from its β isomer in 69% yield. Treatment with TBAF liberated the 2′-OH group to afford **30** (Table 1, Entry 2).

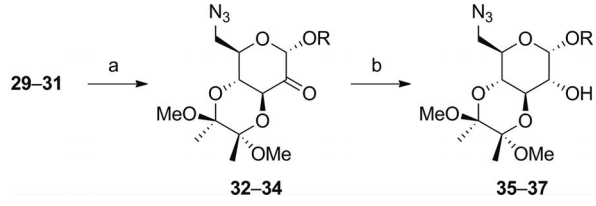
Glycosylation of *N*-Cbz-L-serine benzyl ester with **11** gave solely the α-coupled product **27** in good yield (Table 1, Entry 3). However, subsequent treatment with TBAF induced only the basic hydrolysis of the benzyl ester, instead of the removal of the silyl ether. The addition of acetic acid to reduce the basicity of TBAF avoided the undesired carbamate hydrolysis, but the silyl ether remained unaffected. To circumvent this problematic, TMS-protected thiomannoside **12** was employed. *N*-Cbz-L-serine benzyl ester was coupled to **12**, and removal of the TMS group from **28** occurred smoothly with TBAF in THF to afford **31** in near quantitative yield (Table 1, Entry 4).

Table 1. Results for coupling reaction of **11** and **12** and 2′-*O*-deprotection.

Entry	Donor	R'OH	Dimer	α/β[a]	Yield [%][b]	Alcohol	Yield [%][a]
1	**11**		**25**	1:0	93	**29**	86
2	**11**		**26**	41:1	69	**30**	95
3	**11**		**27**	1:0	83	**31**	0
4	**12**		**28**	28:1	75	**31**	96

[a] Based on crude ^1H NMR spectroscopy. [b] Isolated yield.

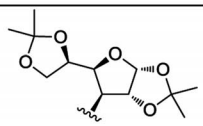
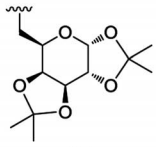
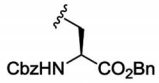
Finally, the oxidation–reduction protocol was applied to the *manno*-configured glycosides **29**–**31**. In all cases, Dess–Martin periodinane oxidation worked uneventfully, and the crude 2-ulose intermediates **32**–**34** were subjected to reduction without purification. The reduction conditions were explored by using 1–2 equiv. of reducing agent (see Scheme 8 and Table 2). The stereoselectivity results were based on ^1H NMR analyses of the stereogenic C-2 center in the crude products.[52,53]



Scheme 8. Reagents and conditions: (a) Dess–Martin periodinane, CH_2Cl_2, r.t.; (b) reduction (see Table 2).

The reduction of intermediate **32** under the action of bulky L-selectride proceeded with complete stereoselectivity. No trace of mannoside could be detected, and α-D-glucoside **35** was isolated in 84% yield (Table 2, Entry 1). For **33**, the application of the bulky reducing agent lithium tri-*tert*-butoxyaluminiumhydride gave better stereoselective results than those obtained by using L-selectride (Table 2, Entry 6). Finally, the treatment of the crude L-serine α-D-*arabino*-hexosidulose **34** with hydride sources led to degradation of the substrate. The milder borane–dimethyl sulfide complex induced a completely stereoselective reduction, but instead

Table 2. Reaction conditions and results for reduction of **32**–**34**.[a]

Entry	R	Reducing agent	Solvent	Glc/Man[b]	Glc product	Glc [%][c]	Man [%][c]
1	 **32**	L-selectride	THF	1:0	**35**	84	0
2		$NaBH_4$	MeOH	5:2			
3		$NaBH_4/CeCl_3$	MeOH	4:1			
4		$NaBH_4$	CH_2Cl_2	3:2			
5	 **33**	L-selectride	THF	4:3	**36**	49	17
6		$LiAl(OtBu)_3H$	THF	10:3			
7	 **34**	L-selectride	THF	–	**37**	0	70
8		$LiAl(OtBu)_3H$	THF	–			
9		$NaBH_4$	MeOH	–			
10		$BH_3 \cdot Me_2S$	THF	0:1			

[a] All reactions were performed at room temperature. [b] Crude ^1H NMR analysis. [c] Isolated yield for the best ratio.

of affording the desired *gluco*-configured alcohol **37**, the *manno*-configured **31** was isolated as the sole product (Table 2, Entry 10).

Conclusions

The enantiopure and asymmetrically protected 2-DOS derivatives were obtained in a few straightforward steps from readily available neamine (**1**). The resulting 2-DOS precursors served as versatile scaffolds for new neamine-type aminoglycosides.

Acetal-protected thiomannoside donors proved to be efficient in promoting the α-glycosidation reaction. The installation of a TMS protecting group at the 2-O-position gave access to free 2′-OH neamine analogues **16** and **17** by straightforward deprotection. The epimerization at C-2′ was performed by an oxidation–reduction method. A Dess–Martin oxidation followed by reduction with a hydride source successfully yielded α-glucosides **20** and **21**. These compounds may find suitable application in the syntheses of new 2′-modified neamine analogues by further functionalization at the free 2′-OH group.

The scope of the coupling–stereoinversion sequence was studied with three model acceptors, leading to glycosidation with excellent stereoselectivity in all cases. However, the reduction step required optimization for each individual substrate. Nevertheless, with one exception, all of the α-mannosides were efficiently converted into the corresponding α-glucosides in 49–84% yield.

The presented methodology may find suitable application in the target-oriented synthesis of α-glucosides, specifically when the presence of a free 2′-OH group is desired. For example, it would be of interest to generate 2′-*O*-alkylated or 2′-*O*-functionalised neamine-type derivatives in search for enhanced antibacterial activity.

Experimental Section

General Methods and Materials: The solvents were distilled from the appropriate drying agents prior to use and stored under nitrogen. The reactions were carried out under an inert atmosphere of dry nitrogen or argon. Standard syringe techniques were applied for the transfer of dry solvents and air- or moisture-sensitive reagents. The R_f values were obtained by using thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254) with the indicated solvent mixture. The compounds were detected by UV light, ammonium molybdate solution, potassium permanganate, ninhydrin, or anisaldehyde/H_2SO_4. The melting points were measured with a Büchi melting point B-545. The IR spectra were recorded with an ATI Mattson Genesis Series FTIR or a Bruker Tensor 27 FTIR spectrometer. The NMR spectroscopic data were recorded with Bruker DMX 300 (300 MHz) and Varian 400 (400 MHz) spectrometers, using $CDCl_3$ or D_2O solutions (unless otherwise reported). The chemical shifts are given in ppm with respect to tetramethylsilane (TMS) or HDO (δ = 4.79 ppm)[56] as the internal standard. The coupling constants are reported as *J* values in Hz. The peak assignments in the ^{13}C NMR spectra were made on the basis of 2D gHSQC (gradient heteronuclear single quantum correlation) and gHMBC (gradient heteronuclear multiple-bond correlation) spectra. Column or flash chromatography was carried out using ACROS silica gel (0.035–0.070 mm, and ca. 6 nm pore diameter). Ion-exchange column chromatography was carried out using Amberlite CG-50 resin in the NH_4^+ form. The optical rotations were determined with a Perkin–Elmer 241 polarimeter. The high resolution mass spectra were recorded with a JEOL AccuTOF (ESI) or a MAT900 (EI, CI, and ESI). The elemental analyses were carried out with a Carlo Erba Instruments CHNS-O EA 1108 element analyser.

General Procedure for Glycosidation of Thiomannosides: The thiomannoside donor of choice and PSP (1.2 equiv.) were added to a flask, and the mixture was coevaporated with dry toluene (3×). The mixed reagents were redissolved in dry CH_2Cl_2 under an argon atmosphere. TTBP (2.0–2.5 equiv.), which was previously dried in a desiccator, and activated powdered MS (4 Å) were added. The reaction mixture was cooled to –60 °C, and Tf_2O (1.2 equiv.) was

added slowly. After 15 min, a solution of the glycosyl acceptor of choice (1.2–1.3 equiv.) in dry CH_2Cl_2 was slowly added. The reaction mixture was stirred for 20 min at –60 °C, then slowly warmed to –20 °C, and quenched with $P(OEt)_3$ (1.1–1.2 equiv.). The mixture was warmed to room temperature and filtered. The filtrate was washed with saturated $NaHCO_3$ and then brine, dried with $MgSO_4$, and concentrated under reduced pressure. Purification was performed by silica gel chromatography to afford the desired product.

Phenyl 6-Azido-2-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-1-thio-α-D-mannopyranoside (11): To a solution of thiomannoside **10** (50 mg, 0.122 mmol) and 2,6-lutidine (39 μL, 0.336 mmol, 3.0 equiv.) in dry CH_2Cl_2 (5 mL) was added *tert*-butyldimethylsilyl triflate (TBSOTf, 42 μL, 0.183 mmol, 1.5 equiv.). After 2 h, the TLC showed that starting material remained, and extra 2,6-lutidine (3.0 equiv.) and TBSOTf (1.5 equiv.) were added. After 10 h, the reaction was quenched with MeOH, and the solvents were evaporated under reduced pressure. Purification by silica gel chromatography afforded **11** (60 mg, 0.114 mmol, 93%) as a thick oil that solidified slowly to give an amorphous solid. R_f = 0.5 (EtOAc/heptane, 1:9). $[\alpha]_D^{20}$ = +177.7 (*c* = 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.46 (m, 2 H), 7.34–7.24 (m, 3 H), 5.33 (d, *J* = 0.98 Hz, 1 H), 4.34–4.29 (m, 1 H), 4.15–4.10 (m, 2 H), 3.87 (dd, *J* = 9.9 Hz, *J* = 2.6 Hz, 1 H), 3.53 (dd, *J* = 13.2 Hz, *J* = 2.3 Hz, 1 H), 3.37 (dd, *J* = 13.2 Hz, *J* = 5.9 Hz, 1 H), 3.29 (s, 3 H), 3.21 (s, 3 H), 1.28 (s, 3 H), 1.27 (s, 3 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.98, 131.24, 128.87, 127.19, 99.77, 99.45, 89.73, 71.92, 71.37, 68.56, 63.91, 50.65, 48.00, 47.70, 25.82, 18.38, 17.92, 17.77, –4.49, –4.65 ppm. IR (neat): $\tilde{\nu}$ = 2828, 2094, 1143, 1052 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{39}N_3O_6SSiNa$ $[M + Na]^+$ 548.2227; found 548.2276.

Phenyl 6-Azido-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-2-*O*-(trimethylsilyl)-1-thio-α-D-mannopyranoside (12): To a solution of thiomannoside **10** (1.8 g, 4.374 mmol) in acetonitrile (90 mL) were added MS (4 Å, 1 g), HMDS (4.53 mL, 21.87 mmol, 5.0 equiv.), and a catalytic amount of TMSCl (55.5 μL, 0.437 mmol, 0.1 equiv.). After 24 h, the reaction mixture was filtered through diatomaceous earth, and the solvent was evaporated under reduced pressure to afford analytically pure **12** (2.10 g, 4.350 mmol, 99%) as a white powder, m.p. 103–104 °C. R_f = 0.36 (EtOAc/heptane, 1:12). $[\alpha]_D^{20}$ = +191.6 (*c* = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.49 (m, 2 H), 7.34–7.24 (m, 3 H), 5.39 (s, 1 H), 4.36–4.31 (m, 1 H), 4.17–4.15 (m, 1 H), 4.00 (t, *J* = 10.0 Hz, 1 H), 3.86 (dd, *J* = 10.0 Hz, *J* = 2.7 Hz, 1 H), 3.52–3.43 (m, 2 H), 3.29 (s, 3 H), 3.22 (s, 3 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 0.16 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.39, 131.42, 129.22, 127.51, 100.23, 99.85, 90.25, 72.45, 71.72, 69.01, 64.62, 51.10, 48.39, 48.14, 18.31, 18.18, 1.06 ppm. IR (neat): $\tilde{\nu}$ = 2828, 2098, 1138, 1124, 864, 845 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{33}N_3O_6SSiNa$ $[M + Na]^+$ 506.1757; found 506.1780. $C_{21}H_{33}N_3O_6SSi$ (483.65): calcd. C 52.15, H 6.88, N 8.69; found C 52.17, H 6.87, N 8.49.

4-*O*-{6-Azido-2-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-α-D-mannopyranosyl}-1,3-bis[*N*-(benzyloxycarbonyl)]-5,6-*O*-cyclohexylidene-2-deoxystreptamine (13): The general procedure for glycosidation was applied to thiomannoside **11** (302 mg, 0.575 mmol) and PSP (144.4 mg, 0.690 mmol, 1.2 equiv.) in dry CH_2Cl_2 (15 mL). TTBP (286 mg, 1.150 mmol, 2.0 equiv.) and activated powdered MS (4 Å, 150 mg) were added at room temperature, followed by Tf_2O (116.6 μL, 0.690 mmol, 1.2 equiv.) at –60 °C. Then, 2-DOS **8**[57] (382 mg, 0.748 mmol, 1.3 equiv.) in dry CH_2Cl_2 (9 mL) was added. After 20 min, the reaction was slowly warmed to –20 °C and quenched with $P(OEt)_3$ (118.3 μL, 0.690 mmol, 1.2 equiv.). Purification was performed by silica gel chromatography using a mixture of EtOAc/heptane with Et_3N (1%) to afford **13** (426 mg, 0.460 mmol, 80%) as a white powder, m.p. 140–142 °C. R_f = 0.26 (EtOAc/heptane, 2:5). $[\alpha]_D^{20}$ = +84.0 (*c* = 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 10 H), 5.21 (d, *J* = 11.9 Hz, 1 H), 5.13–5.05 (m, 4 H), 4.85 (br. s, 1 H), 4.79 (d, *J* = 8.0 Hz, 1 H), 3.98–3.90 (m, 3 H), 3.83–3.74 (m, 4 H), 3.54–3.51 (m, 2 H), 3.39–3.27 (m, 5 H), 3.18 (s, 3 H), 2.55–2.52 (m, 1 H), 1.69–1.43 (m, 9), 1.33–1.30 (m, 2 H), 1.24 (s, 3 H), 1.18 (s, 3 H), 0.90 (s, 9 H), 0.11 (3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.44, 155.30, 136.17, 135.99, 128.31, 128.22, 128.18, 127.95, 127.85, 112.75, 100.31, 99.46, 99.34, 80.54, 78.35, 77.20, 70.94, 70.37, 67.56, 67.09, 66.93, 63.76, 51.11, 50.98, 49.62, 47.89, 47.61, 36.64, 36.32, 35.99, 25.83, 25.04, 23.83, 23.66, 18.40, 17.96, 17.87, –4.57, –4.87 ppm. IR (neat): $\tilde{\nu}$ = 3300, 2096, 1691, 1126, 1038 cm^{-1}. HRMS (ESI): calcd. for $C_{46}H_{67}N_5O_{13}SiNa$ $[M + Na]^+$ 948.4402; found 948.4429.

4-*O*-{6-Azido-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-2-*O*-(trimethylsilyl)-α-D-mannopyranosyl}-1,3-bis[*N*-(benzyloxycarbonyl)]-5,6-*O*-cyclohexylidene-2-deoxystreptamine (14): The general procedure for glycosidation was applied to thiomannoside **12** (600 mg, 1.241 mmol) and PSP (311.7 mg, 1.489 mmol, 1.2 equiv.) in dry CH_2Cl_2 (25 mL). TTBP (771 mg, 3.102 mmol, 2.5 equiv.) and activated powdered MS (4 Å, 350 mg) were added at room temperature, followed by Tf_2O (250.5 μL, 1.489 mmol, 1.2 equiv.) at –60 °C. Then, 2-DOS **8**[57] (823.7 mg, 1.613 mmol, 1.3 equiv.) in dry CH_2Cl_2 (20 mL) was added. After 20 min, the reaction was slowly warmed to –20 °C and quenched with $P(OEt)_3$ (255.3 μL, 1.489 mmol, 1.2 equiv.). Purification was performed by silica gel chromatography using a mixture of EtOAc/heptane with Et_3N (1%) to afford **14** (826 mg, 0.934 mmol, 75%) as a white powder, m.p. 89–90 °C. R_f = 0.24 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ = +79.3 (*c* = 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 10 H), 5.21 (d, *J* = 11.9 Hz, 1 H), 5.14–5.04 (m, 4 H), 4.94 (br. s, 1 H), 4.88 (d, *J* = 8.4 Hz, 1 H), 3.97–3.70 (m, 7 H), 3.55–3.47 (m, 2 H), 3.41–3.36 (m, 2 H), 3.30 (s, 3 H), 3.18 (s, 3 H), 2.54–2.52 (m, 1 H), 1.68–1.50 (m, 8 H), 1.48–1.44 (m, 1 H), 1.38–1.27 (m, 2 H), 1.26 (s, 3 H), 1.19 (s, 3 H), 0.15 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.63, 155.46, 136.35, 136.14, 128.44, 128.35, 128.23, 128.09, 127.94, 112.85, 100.65, 99.66, 99.52, 80.68, 78.47, 77.40, 71.03, 70.45, 67.64, 67.20, 67.07, 64.17, 51.21, 51.16, 49.71, 48.01, 47.83, 36.76, 36.46, 36.18, 25.18, 24.10, 23.89, 18.12, 18.03, 0.63 ppm. IR (neat): $\tilde{\nu}$ = 3309, 2099, 1694, 1127, 1039 cm^{-1}. HRMS (FAB): calcd. for $C_{43}H_{62}N_5O_{13}Si$ $[M + H]^+$ 884.4113; found 884.4122.

4-*O*-{6-Azido-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-2-*O*-(trimethylsilyl)-α-D-mannopyranosyl}-1,3-diazido-1,3-dideamino-5,6-*O*-cyclohexylidene-2-deoxystreptamine (15): The general procedure for glycosidation was applied to thiomannoside **12** (82 mg, 0.170 mmol) and PSP (42.7 mg, 0.204 mmol, 1.2 equiv.) in dry CH_2Cl_2 (3 mL). TTBP (106 mg, 0.425 mmol, 2.5 equiv.) and activated powdered MS (4 Å, 70 mg) were added at room temperature, followed by Tf_2O (34.3 μL, 0.204 mmol, 1.2 equiv.) at –60 °C. Then, 2-DOS **9**[58] (60 mg, 0.204 mmol, 1.2 equiv.) in dry CH_2Cl_2 (2 mL) was added. After 20 min, the reaction was slowly warmed to –20 °C and quenched with $P(OEt)_3$ (35 μL, 0.204 mmol, 1.2 equiv.). Purification was performed by silica gel chromatography using a mixture of EtOAc/heptane with Et_3N (1%) to afford α-coupled product **15** (80 mg, 0.120 mmol, 71%) as a white solid and an inseparable fraction of the α/β mixture in a 4:5 ratio (2 mg, 0.003 mmol, 2%). Analytical data are given for α-coupled product **15**. M.p. 144–146 °C; R_f = 0.24 (EtOAc/heptane, 1:12). $[\alpha]_D^{20}$ =

+119.2 (c = 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.19 (s, 1 H), 4.10–4.05 (m, 1 H), 3.97–3.91 (m, 2 H), 3.88–3.79 (m, 2 H), 3.64–3.58 (m, 1 H), 3.50–3.36 (m, 5 H), 3.21 (s, 3 H), 3.20 (s, 3 H), 2.32 (dt, J = 13.7 Hz, J = 5.0 Hz, 1 H), 1.68–1.46 (m, 11 H), 1.26 (s, 3 H), 1.25 (s, 3 H), 0.15 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.65, 100.81, 99.82, 99.65, 79.85, 79.36, 76.84, 71.52, 70.49, 67.62, 63.92, 60.75, 57.55, 50.78, 47.93, 47.77, 36.40, 36.19, 33.92, 24.98, 23.92, 23.71, 17.90, 17.80, 0.40 ppm. IR (neat): $\tilde{\nu}$ = 2100, 1127, 1036 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{45}N_9O_9SiNa$ $[M + Na]^+$ 690.3007; found 690.3002.

4-*O*-{6-Azido-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-α-D-mannopyranosyl}-1,3-bis[*N*-(benzyloxycarbonyl)]-5,6-*O*-cyclohexylidene-2-deoxystreptamine (16): TBAF (1 M in THF, 333 μL, 1.1 equiv.) was added to a stirred solution of **14** (268 mg, 0.303 mmol) in THF (10 mL). The reaction mixture was stirred for 1 h, and the solvent was evaporated under reduced pressure. Purification was performed by silica gel chromatography using a mixture of EtOAc/heptane with Et_3N (1%) to afford **16** (225 mg, 0.277 mmol, 91%) as a white powder, m.p. 110–111 °C. R_f = 0.24 (EtOAc/heptane, 2:3). $[\alpha]_D^{20}$ = +90.5 (c = 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 10 H), 5.30 (s, 1 H), 5.21 (d, J = 9.9 Hz, 1 H), 5.12–5.05 (m, 3 H), 4.96 (br. s, 1 H), 4.86 (d, J = 8.6 Hz, 1 H), 4.00–3.90 (m, 4 H), 3.79–3.75 (m, 3 H), 3.54–3.48 (m, 2 H), 3.40–3.35 (m, 2 H), 3.31 (s, 3 H), 3.21 (s, 3 H), 2.55–2.52 (m, 1 H), 2.45 (br. s, 1 H), 1.63–1.56 (m, 8 H), 1.37–1.33 (m, 3 H), 1.30 (s, 3 H), 1.21 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.53, 155.48, 136.29, 136.14, 128.46, 128.39, 128.24, 128.11, 128.02, 112.95, 100.25, 99.97, 98.78, 80.56, 78.38, 77.27, 70.47, 69.77, 67.90, 67.22, 67.08, 64.14, 51.24, 51.11, 49.63, 48.23, 48.09, 36.59, 36.40, 25.25, 24.07, 23.98, 18.11, 18.09 ppm. IR (neat): $\tilde{\nu}$ = 3413, 3313, 2098, 1697, 1134, 1115 cm^{-1}. HRMS (FAB): calcd. for $C_{40}H_{54}N_5O_{13}$ $[M + H]^+$ 812.3718; found 812.3712.

4-*O*-{6-Azido-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-α-D-mannopyranosyl}-1,3-diazido-1,3-dideamino-5,6-*O*-cyclohexylidene-2-deoxystreptamine (17): TBAF (1 M in THF, 268 μL, 1.1 equiv.) was added to a stirred solution of **15** (163 mg, 0.244 mmol) in THF (20 mL). The reaction mixture was stirred for 2 h, and the solvent was evaporated under reduced pressure. Purification was performed by silica gel chromatography using a mixture of EtOAc/heptane with Et_3N (1%) to afford **17** (144 mg, 0.242 mmol, 99%) as a colorless gum. R_f = 0.24 (EtOAc/heptane, 1:3). $[\alpha]_D^{20}$ = +111.7 (c = 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.38 (s, 1 H), 4.10–4.06 (m, 1 H), 40.3–3.99 (m, 2 H), 3.96 (br. s, 1 H), 3.86–3.81 (m, 1 H), 3.66–3.57 (m, 1 H), 3.53–3.37 (m, 5 H), 3.23 (s, 3 H), 3.22 (s, 3 H), 2.54 (br. s, 1 H), 2.30 (dt, J = 13.5 Hz, J = 5.0 Hz, 1 H), 1.65–1.58 (m, 8 H), 1.48 (q, J = 13.5 Hz, 1 H), 1.38–1.37 (m, 2 H), 1.30 (s, 3 H), 1.27 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.73, 100.35, 100.08, 98.74, 79.66, 79.42, 76.49, 70.95, 69.73, 67.82, 63.85, 60.89, 57.38, 50.71, 48.12, 48.04, 36.34, 36.20, 33.91, 25.00, 23.89, 23.75, 17.84, 17.80 ppm. IR (neat): $\tilde{\nu}$ = 3464, 2098, 1135, 1035 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{37}N_9O_9Na$ $[M + Na]^+$ 618.2612; found 618.2593.

4-*O*-{6-Azido-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-α-D-glucopyranosyl}-1,3-bis[*N*-(benzyloxycarbonyl)]-5,6-*O*-cyclohexylidene-2-deoxystreptamine (20): Dess–Martin periodinane (627 mg, 1.478 mmol, 2.0 equiv.) was added to a stirred solution of compound **16** (600 mg, 0.739 mmol) in CH_2Cl_2 (20 mL). After 10 h, the reaction was diluted with CH_2Cl_2 (20 mL), and the resulting solution was quenched with NaOH (1 M solution, 30 mL). The mixture was vigorously stirred for 10 min, after which the organic layer was separated. The water layer was extracted with CH_2Cl_2 (2×), and the combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and filtered. The solvent was evaporated. To the crude intermediate dissolved in THF (25 mL) was added L-selectride (1 M in THF, 1.478 mL, 2.0 equiv.). After 10 h, H_2O (20 mL) was added, and the reaction was neutralized with AcOH (127 μL, 2.217 mmol, 3.0 equiv.). The THF was evaporated, and the H_2O layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried with $MgSO_4$, and filtered. The solvent was evaporated. The crude product was purified by silica gel chromatography to afford a small quantity of *manno*-configured **16** (10 mg, 0.012 mmol, 1.6%) and **20** (488 mg, 0.601 mmol, 81%) as a white powder, m.p. 109–110 °C. R_f = 0.39 (EtOAc/heptane, 3:2). $[\alpha]_D^{20}$ = +108.2 (c = 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 10 H), 5.21 (br. s, 1 H), 5.18–5.06 (m, 6 H), 3.96–3.92 (m, 1 H), 3.87–3.89 (m, 5 H), 3.59–3.40 (m, 4 H), 3.31 (s, 3 H), 3.28–3.25 (m, 1 H), 3.23 (s, 3 H), 2.51 (br. s, 2 H), 1.68–1.53 (m, 9 H), 1.48–1.36 (m, 2 H), 1.32 (s, 3 H), 1.24 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.51, 155.47, 136.07, 128.41, 128.21, 128.09, 128.07, 113.26, 99.70, 99.62, 99.16, 80.12, 79.53, 78.20, 70.00, 69.94, 69.76, 67.20, 67.05, 66.60, 51.83, 50.54, 49.59, 48.18, 48.09, 36.58, 36.27, 25.12, 24.00, 23.90, 18.11, 17.96 ppm. IR (neat): $\tilde{\nu}$ = 3314, 2832, 2100, 1696, 1137, 1027 cm^{-1}. HRMS (FAB): calcd. for $C_{40}H_{53}N_5O_{13}Na$ $[M + Na]^+$ 834.3538; found 834.3591.

4-*O*-{6-Azido-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-α-D-glucopyranosyl}-1,3-diazido-1,3-dideamino-5,6-*O*-cyclohexylidene-2-deoxystreptamine (21): Dess–Martin periodinane (37 mg, 0.088 mmol, 2.0 equiv.) was added to a stirred solution of compound **17** (26 mg, 0.044 mmol) in CH_2Cl_2 (3 mL). After 10 h, the reaction was diluted with CH_2Cl_2 (3 mL), and the resulting solution was quenched with NaOH (1 M solution, 4 mL). The mixture was stirred for 20 min, after which the organic layer was separated. The water layer was extracted with CH_2Cl_2 (2×), and the combined organic layers were dried with $MgSO_4$, and filtered. The solvent was evaporated. The crude intermediate was dissolved in MeOH (2 mL), and $NaBH_4$ (3.3 mg, 0.088 mmol, 2.0 equiv.) was added. After 1 h, the solvent was evaporated, and the residue was dissolved in CH_2Cl_2. The resulting solution was washed with saturated NH_4Cl, dried with $MgSO_4$, and filtered. The solvent was evaporated again. The crude product was purified by silica gel chromatography to afford some quantity of *manno*-configured **17** (5.3 mg, 0.009 mmol, 20%) and **21** (16 mg, 0.027 mmol, 61%) as a colorless gum. R_f = 0.26 (EtOAc/heptane, 1:2). $[\alpha]_D^{20}$ = +168.2 (c = 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.36 (d, J = 3.9 Hz, 1 H), 4.13–4.08 (m, 1 H), 3.92 (t, J = 9.9 Hz, 1 H), 3.81–3.76 (m, 2 H), 3.67–3.56 (m, 3 H), 3.51–3.38 (m, 4 H), 3.27 (s, 3 H), 3.26 (s, 3 H), 2.35 (dt, J = 13.0 Hz, J = 5.0 Hz, 1 H), 1.68–1.59 (m, 8 H), 1.50 (q, J = 13.0 Hz, 1 H), 1.39–1.36 (m, 2 H), 1.33 (s, 3 H), 1.29 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 114.10, 99.89, 99.83, 98.88, 79.41, 79.24, 78.75, 70.11, 70.05, 69.86, 66.52, 61.18, 57.38, 50.45, 48.21, 48.11, 36.29, 36.27, 34.08, 24.95, 23.86, 23.79, 17.92, 17.78 ppm. IR (neat): $\tilde{\nu}$ = 3464, 2832, 2100, 1136, 1030 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{37}N_9O_9Na$ $[M + Na]^+$ 618.2612; found 618.2560.

4-*O*-(6-Azido-6-deoxy-α-D-mannopyranosyl)-1,3-diazido-1,3-dideamino-2-deoxystreptamine (22): Compound **15** (100 mg, 0.150 mmol) was dissolved in TFA/H_2O (9:1, v/v, 3 mL), and after stirring for 4 min, the solvent was rapidly evaporated under reduced pressure. Purification was performed by silica gel chromatography using 3% of MeOH in EtOAc as the eluent. After evaporation of the solvent, the product was coevaporated (3×) with MeOH[54] to afford **22** (53 mg, 0.132 mmol, 88%) as a colorless gum. R_f = 0.27 (MeOH/EtOAc, 3%). $[\alpha]_D^{20}$ = +71.1 (c = 0.35, MeOH). ^1H NMR

(400 MHz, CD_3OD): δ = 5.39 (d, J = 1.6 Hz, 1 H), 4.12–4.07 (m, 1 H), 3.96 (dd, J = 3.1 Hz, J = 1.8 Hz, 1 H), 3.72 (dd, J = 9.57 Hz, J = 3.1 Hz, 1 H), 3.64 (t, J = 9.57 Hz, 1 H), 3.51–3.34 (m, 6 H), 3.27–3.23 (m, 1 H), 2.22 (dt, J = 12.5 Hz, J = 4.1 Hz, 1 H), 1.39 (q, J = 12.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 102.47, 80.96, 77.90, 77.79, 74.17, 72.23, 72.01, 69.21, 61.89, 61.00, 52.95, 33.30 ppm. IR (neat): $\tilde{\nu}$ = 3361, 2102, 1039 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{19}N_9O_7Na$ $[M + Na]^+$ 424.1305; found 424.1299.

4-*O*-(6-Amino-6-deoxy-α-D-mannopyranosyl)-2-deoxystreptamine (23): Compound **22** (18 mg, 0.045 mmol) was dissolved in THF/H_2O/1 M NaOH (10:1:0.1, v/v/v, 2.5 mL) and $P(CH_3)_3$ (1 M in THF, 202 μL, 0.202 mmol, 4.5 equiv.) was added. The reaction was stirred for 12 h, and the solvent was evaporated. The residue was purified by silica gel column chromatography (R_f = 0.16, 25% NH_4OH/CH_2Cl_2/*n*BuOH/EtOH, 6:2:4:5). The remaining silica and organic solvents were removed by using ion-exchange column chromatography (0.5 × 5 cm) with Amberlite CG-50 in its NH_4^+ form (1 M NH_4OH as the eluent). The eluent was evaporated under reduced pressure. The product was dissolved in water (5 mL), and 2 drops of glacial acetic acid were added. After lyophilization, compound **23** (16 mg, 0.032 mmol, 71%) was obtained as a sticky powder. $[\alpha]_D^{20}$ = +52.6 (c = 0.35, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 5.43 (d, J = 1.8 Hz, 1 H), 4.14 (dd, J = 3.1 Hz, J = 2.1 Hz, 1 H), 3.97–3.92 (m, 1 H), 3.89 (dd, J = 9.6 Hz, J = 3.1 Hz, 1 H), 3.80 (dd, J = 10.2 Hz, J = 9.0 Hz, 1 H), 3.66 (t, J = 9.6 Hz, 1 H), 3.59 (t, J = 9.0 Hz, 1 H), 3.52 (t, J = 10.2 Hz, 1 H), 3.49–3.41 (m, 2 H), 3.33–3.27 (m, 1 H), 3.23 (dd, J = 13.5 Hz, J = 7.8 Hz, 1 H), 2.47 (dt, J = 12.5 Hz, J = 4.2 Hz, 1 H), 1.95 (s, 9 H), 1.85 (q, J = 12.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 179.77, 100.41, 78.45, 74.60, 72.14, 69.50, 69.17, 68.99, 67.15, 49.23, 47.99, 39.88, 27.76, 22.08 ppm. IR (neat): $\tilde{\nu}$ = 3170, 2912, 1538, 1402, 1044, 1009, 652 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{25}N_3O_7Na$ $[M + Na]^+$ 346.1590; found 346.1580.

4-*O*-(6-Amino-6-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine (24): Compound **20** (60 mg, 0.074 mmol) was dissolved in TFA/H_2O (9:1, v/v, 2.5 mL), and after stirring for 4 min, the solvent was rapidly evaporated under reduced pressure. The residue was dissolved in THF/H_2O/1 M NaOH (10:1:0.1, v/v/v, 4 mL), and $P(CH_3)_3$ (1 M in THF, 222 μL, 0.222 mmol, 3.0 equiv.) was added. The reaction was stirred for 12 h, and the solvent was evaporated. The crude intermediate was dissolved in MeOH/AcOH (10:1, v/v, 5.5 mL), and Pd on carbon (60 mg) was added. The reaction was stirred under H_2 (1 atm) for 20 h. The mixture was filtered through Celite, washing with H_2O, and the solvents were evaporated. The residue was purified by silica gel chromatography (25% NH_4OH/CH_2Cl_2/*n*BuOH/EtOH, 6:2:4:5). The remaining silica and organic solvents were removed by using ion-exchange column chromatography (0.5 × 5 cm) with Amberlite CG-50 in its NH_4^+ form (1 M NH_4OH as the eluent). The eluent was evaporated under reduced pressure. The product was dissolved in water (5 mL), and 2 drops of glacial acetic acid were added. After lyophilization, compound **24** (23 mg, 0.046 mmol, 62%) was obtained as a sticky powder. Analytical data were identical to those reported by Wong et al.[55]

3-*O*-{6-Azido-2-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-α-D-mannopyranosyl}-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (25): The general procedure for glycosidation was applied to thiomannoside **11** (50 mg, 0.095 mmol) and PSP (23.9 mg, 0.114 mmol, 1.2 equiv.) in dry CH_2Cl_2 (2.5 mL). TTBP (69 mg, 0.280 mmol, 2.0 equiv.) and activated powdered MS (4 Å, 30 mg) were added at room temperature, followed by Tf_2O (19.2 μL, 0.104 mmol, 1.2 equiv.) at –60 °C. Then, diisopropylidene-D-glucose[59] (32 mg, 0.123 mmol, 1.3 equiv.) in dry CH_2Cl_2 (1.5 mL) was added. After 20 min, the reaction was slowly warmed to –20 °C and quenched with $P(OEt)_3$ (17.9 μL, 0.104 mmol, 1.1 equiv.). Purification was performed by silica gel chromatography to afford **25** (60 mg, 0.089 mmol, 93%) as a colorless thick oil. R_f = 0.35 (EtOAc/heptane, 1:4). $[\alpha]_D^{20}$ = +103.0 (c = 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (d, J = 3.7 Hz, 1 H), 4.90 (d, J = 1.6 Hz, 1 H), 4.63 (d, J = 3.5 Hz, 1 H), 4.26 (d, J = 2.7 Hz, 1 H), 4.17–4.00 (m, 5 H), 3.91–3.87 (m, 2 H), 3.79 (dd, J = 10.0 Hz, J = 2.7 Hz, 1 H), 3.60 (dd, J = 13.1 Hz, J = 2.1 Hz, 1 H), 3.52 (dd, J = 13.1 Hz, J = 6.1 Hz, 1 H), 3.25 (s, 3 H), 3.20 (s, 3 H), 1.49 (s, 3 H), 1.40 (s, 3 H), 1.30 (s, 6 H), 1.27 (s, 3 H), 1.26 (s, 3 H), 0.90 (s, 9 H), 0.11 (s, 3 H), 0.06 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.21, 109.57, 105.51, 102.95, 100.08, 99.82, 84.20, 81.73, 81.16, 72.91, 71.82, 70.40, 68.17, 67.99, 64.05, 51.05, 48.51, 48.08, 27.43, 27.31, 26.60, 26.19, 25.87, 18.74, 18.31, 18.18, –4.20, –4.39 ppm. IR (neat): $\tilde{\nu}$ = 2832, 2098, 1129, 1039, 840 cm^{-1}. HRMS (FAB): calcd. for $C_{30}H_{54}N_3O_{12}Si$ $[M + H]^+$ 676.3477; found 676.3445.

6-*O*-{6-Azido-2-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-α-D-mannopyranosyl}-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (26): The general procedure for glycosidation was applied to thiomannoside **11** (193 mg, 0.367 mmol) and PSP (92 mg, 0.440 mmol, 1.2 equiv.) in dry CH_2Cl_2 (6 mL). TTBP (228 mg, 0.917 mmol, 2.5 equiv.) and activated powdered MS (4 Å, 100 mg) were added at room temperature, followed by Tf_2O (74 μL, 0.440 mmol, 1.2 equiv.) at –60 °C. Then, diisopropylidene-D-galactose[60] (115 mg, 0.440 mmol, 1.2 equiv.) in dry CH_2Cl_2 (5 mL) was added. After 20 min, the reaction was slowly warmed to –20 °C and quenched with $P(OEt)_3$ (76 μL, 0.440 mmol, 1.2 equiv.). Purification was performed by silica gel chromatography to afford α-coupled product **26** (170 mg, 0.252 mmol, 69%) as a colorless gum and an inseparable fraction of the α/β mixture in an 8:1 ratio (40 mg, 0.059 mmol, 16%). Analytical data are given for the α-coupled product **26**. R_f = 0.33 (EtOAc/heptane, 1:5). $[\alpha]_D^{20}$ = +82.2 (c = 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 (d, J = 4.9 Hz, 1 H), 4.77 (d, J = 1.2 Hz, 1 H), 4.61 (dd, J = 7.8 Hz, J = 2.3 Hz, 1 H), 4.31 (dd, J = 5.0 Hz, J = 2.4 Hz, 1 H), 4.20 (dd, J = 7.9 Hz, J = 1.8 Hz, 1 H), 4.06–3.99 (m, 2 H), 3.91–3.84 (m, 3 H), 3.81–3.71 (m, 2 H), 3.48 (dd, J = 13.1 Hz, J = 2.1 Hz, 1 H), 3.32 (dd, J = 13.1 Hz, J = 5.9 Hz, 1 H), 3.22 (s, 3 H), 3.19 (s, 3 H), 1.51 (s, 3 H), 1.44 (s, 3 H), 1.32 (s, 3 H), 1.31 (s, 3 H), 1.25 (s, 3 H), 1.24 (s, 3 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.43, 108.61, 100.18, 99.77, 99.51, 96.44, 71.34, 71.19, 70.92, 70.73, 70.48, 67.98, 65.16, 64.92, 63.82, 50.71, 48.14, 47.79, 26.42, 26.29, 26.02, 25.25, 24.86, 18.56, 18.08, 17.98, –4.35, –4.64 ppm. IR (neat): $\tilde{\nu}$ = 2832, 2097, 1126, 1070 cm^{-1}. HRMS (FAB): calcd. for $C_{30}H_{54}N_3O_{12}Si$ $[M + H]^+$ 676.3477; found 676.3434.

3-*O*-{6-Azido-2-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-α-D-mannopyranosyl}-*N*-(benzyloxycarbonyl)-L-serine Benzyl Ester (27): The general procedure for glycosidation was applied to thiomannoside **11** (114 mg, 0.217 mmol) and PSP (54.4 mg, 0.260 mmol, 1.2 equiv.) in dry CH_2Cl_2 (5.5 mL). TTBP (135 mg, 0.543 mmol, 2.5 equiv.) and activated powdered MS (4 Å, 75 mg) were added at room temperature, followed by Tf_2O (44 μL, 0.260 mmol, 1.2 equiv.) at –60 °C. Then *N*-Cbz-L-serine benzyl ester (86 mg, 0.260 mmol, 1.2 equiv.) in dry CH_2Cl_2 (4.5 mL) was added. After 20 min, the reaction was slowly warmed to –20 °C and quenched with $P(OEt)_3$ (44.6 μL, 0.260 mmol, 1.2 equiv.). Purification was performed by silica gel

chromatography to afford **27** (135 mg, 0.181 mmol, 83%) as a colorless oil. R_f = 0.31 (EtOAc/heptane, 1:4). $[\alpha]_D^{20}$ = +108.3 (c = 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 10 H), 5.68 (d, J = 8.6 Hz, 1 H), 5.19 (s, 2 H), 5.14 (s, 2 H), 4.60–4.58 (m, 2 H), 4.05–3.93 (m, 3 H), 3.80–3.72 (m, 3 H), 3.46 (dd, J = 13.1 Hz, J = 2.0 Hz, 1 H), 3.27 (dd, J = 13.1 Hz, J = 6.0 Hz, 1 H), 3.21 (s, 3 H), 3.19 (m, 3 H), 1.26 (s, 3 H), 1.25 (s, 3 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.03 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.66, 155.75, 136.06, 135.04, 128.58, 128.46, 128.14, 128.06, 102.27, 99.80, 99.54, 71.50, 70.31, 68.79, 67.91, 67.57, 67.35, 63.49, 54.67, 50.57, 48.18, 47.82, 25.97, 18.51, 18.07, 17.97, –4.32, –4.64 ppm. IR (neat): $\tilde{\nu}$ = 3333, 2830, 2099, 1725, 1130, 1038 cm^{-1}. HRMS (FAB): calcd. for $C_{36}H_{52}N_4O_{11}SiNa$ $[M + Na]^+$ 767.3300; found 767.3312.

3-*O*-{6-Azido-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-2-*O*-(trimethylsilyl)-α-D-mannopyranosyl}-*N*-(benzyloxycarbonyl)-L-serine Benzyl Ester (28) and the β Isomer: The general procedure for glycosidation was applied to thiomannoside **12** (180 mg, 0.372 mmol) and PSP (93 mg, 0.446 mmol, 1.2 equiv.) in dry CH_2Cl_2 (6 mL). TTBP (231 mg, 0.930 mmol, 2.5 equiv.) and activated powdered MS (4 Å, 90 mg) were added at room temperature, followed by Tf_2O (75 μL, 0.446 mmol, 1.2 equiv.) at –60 °C. Then *N*-Cbz-L-serine benzyl ester (147 mg, 0.446 mmol, 1.2 equiv.) in dry CH_2Cl_2 (5 mL) was added. After 20 min, the reaction was slowly warmed to –20 °C and quenched with $P(OEt)_3$ (76 μL, 0.446 mmol, 1.2 equiv.). Purification was performed by silica gel chromatography to afford **28** (195 mg, 0.277 mmol, 75%) and its β isomer (7 mg, 0.010 mmol, 3%), both as colorless oils (α/β, 28:1). Analytical data are given for both isomers. Data for **28**: R_f = 0.28 (EtOAc/heptane, 1:4). $[\alpha]_D^{20}$ = +101.1 (c = 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.32 (m, 10 H), 5.69 (d, J = 8.6 Hz, 1 H), 5.24 (d, J = 12.3 Hz, 1 H), 5.18–5.14 (m, 3 H), 4.61–4.58 (m, 2 H), 3.98–3.88 (m, 3 H), 3.81–3.71 (m, 3 H), 3.44 (dd, J = 13.0 Hz, J = 2.2 Hz, 1 H), 3.37 (dd, J = 13.0 Hz, J = 6.5 Hz, 1 H), 3.21 (s, 3 H), 3.19 (s, 3 H), 1.28 (s, 3 H), 1.25 (s, 3 H), 0.14 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.64, 155.75, 136.06, 135.11, 128.55, 128.44, 128.10, 128.04, 102.45, 99.86, 99.55, 71.31, 70.45, 68.84, 68.00, 67.51, 67.34, 63.83, 54.62, 50.68, 48.18, 47.84, 18.07, 17.98, 0.83 ppm. IR (neat): $\tilde{\nu}$ = 3327, 2831, 2099, 1725, 1129, 1038 cm^{-1}. HRMS (FAB): calcd. for $C_{33}H_{47}N_4O_{11}Si$ $[M + H]^+$ 703.3011; found 703.3007. Data for β Isomer: R_f = 0.14 (EtOAc/heptane, 1:4). $[\alpha]_D^{20}$ = +66.4 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.31 (m, 10 H), 5.62 (d, J = 8.0 Hz, 1 H), 5.30–5.12 (m, 4 H), 4.59–4.57 (m, 1 H), 4.43 (s, 1 H), 4.36 (dd, J = 10.1 Hz, J = 3.6 Hz, 1 H), 3.95–3.83 (m, 3 H), 3.56–3.49 (m, 2 H), 3.38–3.36 (m, 2 H), 3.24 (s, 3 H), 3.18 (m, 3 H), 1.27 (m, 3 H), 1.24 (s, 3 H), 0.12 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.45, 155.73, 136.18, 135.27, 128.49, 128.46, 128.15, 128.11, 128.07, 100.78, 99.86, 99.61, 77.36, 74.92, 70.23, 69.12, 67.49, 67.24, 64.18, 54.56, 50.70, 48.19, 47.95, 18.05, 17.89, 0.76 ppm. IR (neat): $\tilde{\nu}$ = 3438, 3335, 2832, 2097, 1725, 1128, 1050 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{46}N_4O_{11}SiNa$ $[M + Na]^+$ 725.2830; found 725.2841.

3-*O*-{6-Azido-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-α-D-mannopyranosyl}-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (29): TBAF (1 M in THF, 81.4 μL, 1.1 equiv.) was added to a stirred solution of **25** (50 mg, 0.074 mmol) in THF (3 mL). The reaction mixture was stirred for 10 h, and the solvent was evaporated. The residue was dissolved in EtOAc, and the resulting solution was washed with H_2O. The H_2O layer was extracted with additional EtOAc, and the combined organic layers were washed with brine, dried with $MgSO_4$, and evaporated under reduced pressure. Purification by silica gel chromatography gave **29** (36 mg, 0.064 mmol, 86%) as a colorless oil. R_f = 0.42 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ = +94.6 (c = 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 (d, J = 3.3 Hz, 1 H), 5.11 (s, 1 H), 4.70 (d, J = 3.3 Hz, 1 H), 4.28 (br. s, 1 H), 4.16–4.06 (m, 3 H), 4.02–3.89 (m, 5 H), 3.56 (d, J = 13.0 Hz, 1 H), 3.43 (dd, J = 13.0 Hz, J = 7.0 Hz, 1 H), 3.26 (s, 3 H), 3.23 (s, 3 H), 2.54 (br. s, 1 H), 1.48 (s, 3 H), 1.39 (3 H), 1.31 (br. s, 9 H), 1.28 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 111.89, 109.14, 105.15, 101.24, 100.30, 99.94, 83.51, 81.63, 81.15, 72.47, 70.82, 69.38, 67.92, 67.73, 63.95, 50.80, 48.33, 48.08, 26.96, 26.92, 26.21, 25.47, 17.93, 17.87 ppm. IR (neat): $\tilde{\nu}$ = 3481, 2840, 2103, 1139, 1079, 1031 cm^{-1}. HRMS (FAB): calcd. for $C_{24}H_{40}N_3O_{12}$ $[M + H^+$ 562.2612; found 562.2620.

6-*O*-{6-Azido-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-α-D-mannopyranosyl}-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (30): TBAF (1 M in THF, 193 μL, 1.1 equiv.) was added to a stirred solution of **26** (118 mg, 0.175 mmol) in THF (8 mL). After 3.5 h, TLC showed only a half conversion. Additional TBAF (1 M in THF, 87 μL, 0.5 equiv.) was added. The reaction mixture was stirred for 10 h, and the solvent was evaporated. The crude product was purified by silica gel chromatography to afford **30** (94 mg, 0.167 mmol, 95%) as a colorless gum. R_f = 0.26 (EtOAc/heptane, 2:3). $[\alpha]_D^{20}$ = +93.2 (c = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (d, J = 5.1 Hz, 1 H), 4.90 (s, 1 H), 4.60 (dd, J = 7.9 Hz, J = 2.4 Hz, 1 H), 4.30 (dd, J = 5.0 Hz, J = 2.4 Hz, 1 H), 4.21 (dd, J = 7.9 Hz, J = 1.9 Hz, 1 H), 4.02–3.89 (m, 5 H), 3.81 (dd, J = 10.7 Hz, J = 6.9 Hz, 1 H), 3.73 (dd, J = 10.7 Hz, J = 6.6 Hz, 1 H), 3.48 (dd, J = 13.1 Hz, J = 2.5 Hz, 1 H), 3.42 (dd, J = 13.1 Hz, J = 5.7 Hz, 1 H), 3.25 (s, 3 H), 3.22 (s, 3 H), 2.52 (br. s, 1 H), 1.53 (s, 3 H), 1.43 (s, 3 H), 1.32 (br. s, 6 H), 1.30 (s, 3 H), 1.26 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.43, 108.64, 100.35, 99.97, 99.56, 96.36, 71.09, 70.81, 70.77, 70.50, 69.71, 68.15, 66.01, 65.46, 64.05, 50.76, 48.37, 48.16, 26.40, 26.27, 25.24, 24.87, 18.07, 18.02 ppm. IR (neat): $\tilde{\nu}$ = 3487, 2830, 2098, 1132, 1114, 1069, 1042 cm^{-1}. HRMS (FAB): calcd. for $C_{24}H_{39}N_3O_{12}Na$ $[M + Na]^+$ 584.2431; found 584.2444.

3-*O*-{6-Azido-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-α-D-mannopyranosyl}-*N*-(benzyloxycarbonyl)-L-serine Benzyl Ester (31): TBAF (1 M in THF, 219 μL, 1.1 equiv.) was added to a stirred solution of **28** (140 mg, 0.199 mmol) in THF (25 mL). After 1.5 h, TLC showed a half conversion. Additional TBAF (1 M in THF, 100 μL, 0.5 equiv.) and 2 drops of AcOH were added.[61] After 4 h, the solvent was evaporated under reduce pressure. Purification was performed by silica gel chromatography to afford **31** (120 mg, 0.191 mmol, 96%) as a colorless gum. R_f = 0.40 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ = +102.9 (c = 1.15, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.32 (m, 10 H), 5.67 (d, J = 8.4 Hz, 1 H), 5.27 (d, J = 12.1 Hz, 1 H), 5.14–5.11 (m, 3 H), 4.66 (s, 1 H), 4.61–4.59 (m, 1 H), 3.99–3.94 (m, 3 H), 3.83–3.77 (m, 2 H), 3.67–3.66 (m, 1 H), 3.44 (dd, J = 13.1 Hz, J = 2.3 Hz, 1 H), 3.36 (dd, J = 13.1 Hz, J = 6.0 Hz, 1 H), 3.23 (s, 3 H), 3.22 (s, 3 H), 2.41 (br. s, 1 H), 1.30 (s, 3 H), 1.27 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.50, 155.72, 136.01, 135.08, 128.59, 128.50, 128.45, 128.27, 128.14, 128.13, 100.90, 100.35, 99.99, 70.69, 69.37, 69.13, 67.98, 67.56, 67.37, 63.73, 54.60, 50.58, 48.43, 48.18, 18.03, 18.00 ppm. IR (neat): $\tilde{\nu}$ = 3434, 3339, 2833, 2098, 1720, 1133, 1114, 1036 cm^{-1}. HRMS (FAB): calcd. for $C_{30}H_{39}N_4O_{11}$ $[M + H]^+$ 631.2615; found 631.2623.

3-*O*-{6-Azido-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-α-D-glucopyranosyl}-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (35): Dess–Martin periodinane (147 mg, 0.346 mmol,

1.5 equiv.) was added to a stirred solution of compound **29** (130 mg, 0.231 mmol) in CH_2Cl_2 (6 mL). After 10 h, the reaction was diluted with CH_2Cl_2 (6 mL), and the resulting solution was quenched with NaOH (1 M solution, 10 mL). The mixture was stirred for 30 min, after which the organic layer was separated. The water layer was extracted with CH_2Cl_2 (2×), and the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was evaporated. The crude intermediate **32** was dissolved in THF (6 mL), and L-selectride (1 M in THF, 346 μL, 1.5 equiv.) was added. After 2 h, the reaction was quenched with MeOH, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2, and the resulting solution was washed with saturated NH_4Cl, dried with $MgSO_4$, and filtered. The solvent was evaporated again. The crude product was purified by silica gel chromatography to give solely compound **35** (109 mg, 0.194 mmol, 84%) as a colorless oil. R_f = 0.24 (EtOAc/heptane, 1:2). $[\alpha]_D^{20}$ = +112.3 (*c* = 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (d, *J* = 3.5 Hz, 1 H), 5.07 (d, *J* = 3.7 Hz, 1 H), 4.83 (d, *J* = 3.5 Hz, 1 H), 4.29–4.22 (m, 2 H), 4.19–4.14 (m, 2 H), 4.02–3.95 (m, 2 H), 3.80 (t, *J* = 10.0 Hz, 1 H), 3.69 (td, *J* = 10.0 Hz, *J* = 3.7 Hz, 1 H), 3.57–3.53 (m, 2 H), 3.38–3.32 (m, 2 H), 3.29 (s, 3 H), 3.24 (s, 3 H), 1.49 (s, 3 H), 1.41 (s, 3 H), 1.33 (s, 3 H), 1.32 (s, 6 H), 1.29 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.50, 109.82, 105.98, 101.64, 100.00, 99.99, 85.40, 83.25, 81.86, 73.63, 70.75, 70.51, 70.31, 68.54, 67.22, 51.13, 48.48, 48.21, 27.42, 27.15, 26.63, 25.45, 18.27, 18.15 ppm. IR (neat): $\tilde{\nu}$ = 3450, 2833, 2099, 1138, 1027 cm^{-1}. HRMS (FAB): calcd. for $C_{24}H_{40}N_3O_{12}$ $[M + H]^+$ 562.2612; found 562.2600.

6-*O*-{6-Azido-6-deoxy-3,4-*O*-[(2*S*,3*S*)-2,3-dimethoxybutane-2,3-diyl]-α-D-glucopyranosyl}-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (36): Dess–Martin periodinane (80 mg, 0.188 mmol, 2.0 equiv.) was added to a stirred solution of compound **30** (53 mg, 0.094 mmol) in CH_2Cl_2 (4 mL). After 10 h, the reaction was diluted with CH_2Cl_2 (4 mL), and the resulting solution was quenched with NaOH (1 M solution, 5 mL). The mixture was stirred for 30 min, after which the organic layer was separated. The water layer was extracted with CH_2Cl_2 (2×), and the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was evaporated. The crude intermediate **33** was dissolved in THF (4 mL), and LiAl(O*t*Bu)$_3$H (1.1 M in THF, 128 μL, 1.5 equiv.) was added. After 2 h, the reaction was quenched with MeOH, and the solvent was evaporated. The residue was dissolved in CH_2Cl_2, and the resulting solution was washed with saturated NH_4Cl, dried with $MgSO_4$, and filtered. The solvent was evaporated again. The crude product was purified by silica gel chromatography to afford *manno*-configured product **30** (9 mg, 0.016 mmol, 17%) and **36** (26 mg, 0.046 mmol, 49%) as a colorless gum. R_f = 0.27 (EtOAc/heptane, 1:1). $[\alpha]_D^{20}$ = +129.8 (*c* = 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (d, *J* = 5.1 Hz, 1 H), 4.93 (d, *J* = 3.9 Hz, 1 H), 4.62 (dd, *J* = 7.9 Hz, *J* = 2.4 Hz, 1 H), 4.33 (dd, *J* = 5.0 Hz, *J* = 2.4 Hz, 1 H), 4.25 (dd, *J* = 7.8 Hz, *J* = 2.0 Hz, 1 H), 4.02–3.92 (m, 3 H), 3.85 (t, *J* = 9.9 Hz, 1 H), 3.74–3.70 (m, 2 H), 3.62 (t, *J* = 9.9 Hz, 1 H), 3.53 (dd, *J* = 13.3 Hz, *J* = 2.3 Hz, 1 H), 3.36 (dd, *J* = 13.1 Hz, *J* = 5.3 Hz, 1 H), 3.29 (s, 3 H), 3.25 (s, 3 H), 2.58 (br. s, 1 H), 1.54 (s, 3 H), 1.44 (s, 3 H), 1.33 (s, 9 H), 1.28 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.59, 108.81, 99.75, 99.74, 99.37, 96.26, 71.22, 70.81, 70.65, 70.40, 69.92, 69.68, 67.78, 66.68, 65.87, 50.53, 48.29, 48.18, 26.38, 26.25, 25.23, 24.81, 18.12, 17.98 ppm. IR (neat): $\tilde{\nu}$ = 3469, 2829, 2100, 1135, 1070, 1032 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{39}N_3O_{12}Na$ $[M + Na]^+$ 584.2432; found 584.2437.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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[58] Compound **9** = 1,3-diazido-1,3-dideamino-5,6-*O*-cyclohexylidene-2-deoxystreptamine.
[59] Diisopropylidene-D-glucose = 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose.
[60] Diisopropylidene-D-galactose = 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose.
[61] Compound **28** showed partial degradation upon exposure to basic conditions. AcOH was added to neutralize the basicity of TBAF.

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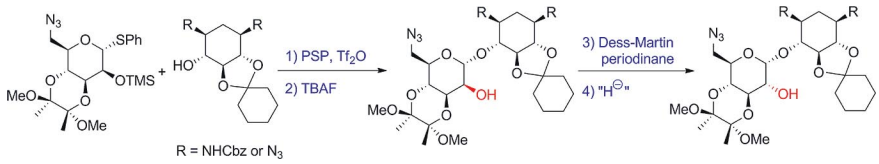
Neamine Analogues



Neamine analogues with a free 2′-OH group were synthesized through a stereoselective α-glycosidation reaction of 3,4-*O*-dimethoxybutanediyl-2-*O*-silyl-protected thiomannosides, followed by a 2-O-deprotection and an oxidation–reduction sequence, leading to stereoinversion at C-2′. The scope of such a procedure for the syntheses of α-glucosides was explored with three distinct model acceptors.

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2′-Modified Neamine Analogues from Thiomannosides through Glycosidation–Stereoinversion

Keywords: Carbohydrates / Oxygen heterocycles / Glycosidation / Oxidation / Reduction

