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Article

General Method for the Synthesis of α- or β-Deoxyaminoglycosides Bearing Basic Nitrogen

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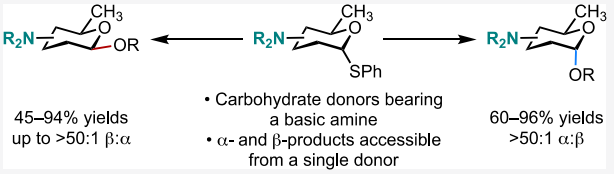
ABSTRACT: The introduction of glycosides bearing basic nitrogen is challenging using conventional Lewis acid-promoted pathways owing to competitive coordination of the amine to the Lewis acid promoter. Additionally, because many aminoglycosides lack a C2 substituent, diastereomeric mixtures of *O*-glycosides are often produced. Herein, we present a method for the synthesis of α- or β- 2,3,6-trideoxy-3-amino- and 2,4,6-trideoxy-4-amino *O*-glycosides from a common precursor. Our strategy proceeds by the reductive lithiation of thiophenyl glycoside donors and trapping of the resulting anomeric anions with 2-methyltetrahydropyranyl peroxides. We apply this strategy to the synthesis of α- and β-forosamine, pyrrolosamine, acosamine, and ristosamine derivatives using primary and secondary peroxides as electrophiles. α-Linked products are obtained in 60−96% yield and with >50:1 selectivity. β-Linked products are obtained in 45−94% yield and with 1.7−>50:1 stereoselectivity. Contrary to donors bearing an equatorial amine substituent, donors bearing an axial amine substituent favored β-products at low temperatures. This work establishes a general strategy to synthesize *O*-glycosides bearing a basic nitrogen.



INTRODUCTION

Aminosugars bearing a basic nitrogen are found in approximately 40% of glycosylated bacterial secondary metabolites.[1] In many instances, the aminoglycoside is essential for biological activity. The vast majority of these carbohydrates lack a C2 substituent, which makes stereocontrolled glycosylations challenging,[2] and the preparative-scale separation of diastereomeric glycosylation products is often not possible by flash-column chromatography. Additionally, competitive coordination of a basic amine to a Lewis acid promoter renders many glycosylation reactions inefficient.[3] For example, the β-glycoside **1** was prepared from the corresponding α-glycosyl phosphinate with 2:3 α-to-β selectivity (57% combined yield) using boron trifluoride diethyl etherate as promoter (Figure 1a).[4] The macrolide spinosyn A (**2**) was obtained as a 3:2 mixture of α and β diastereomers (17% combined yield) by a Koenigs−Knorr coupling.[5] By strategic use of a C2-directing group, the methymycin macrolactone precursor **3** was obtained with high β-selectivity, but the yield remained modest (43%).[6] Glycosylation reactions employing softer Lewis acids (e.g., gold)[5d] or electron-deficient aminosugars (e.g., such as azide, carbamate, and sulfonamide derivatives) have been employed to circumvent or decrease the basicity of the amine substituent,[7] but these strategies do not provide a general approach to stereocontrol in the 2-deoxy series. Finally, while glycosides bearing a basic nitrogen are stable toward acidic hydrolysis owing to preferential *N*-protonation, protection of the amine with electron-withdrawing groups renders the glycosides acid-labile and prone to anomerization (Figure 1b).[7c]

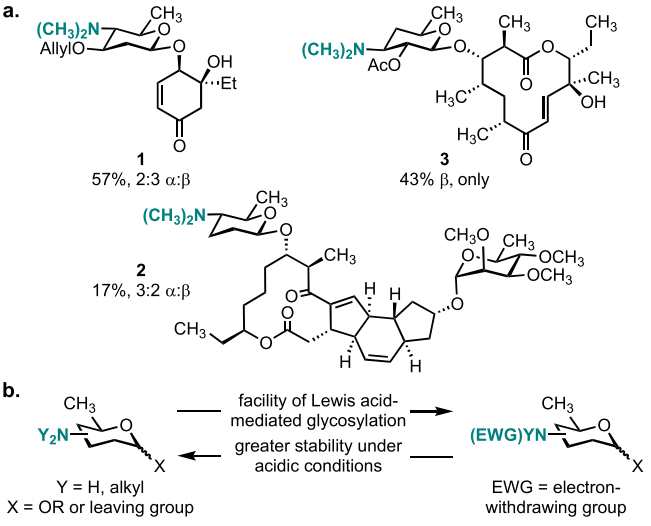


Figure 1. (a) Selected examples of *O*-glycosides containing basic nitrogen. Yields and stereoselectivities in the glycosylation step are shown. (b) Aminosugars bearing basic nitrogen are difficult to install via Lewis acid-mediated glycosylation reactions, but are stable toward acidic hydrolysis. Introduction of an electron-withdrawing group (EWG) facilitates Lewis acid-promoted glycosylation pathways, but renders the products acid-labile.

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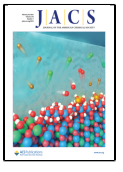

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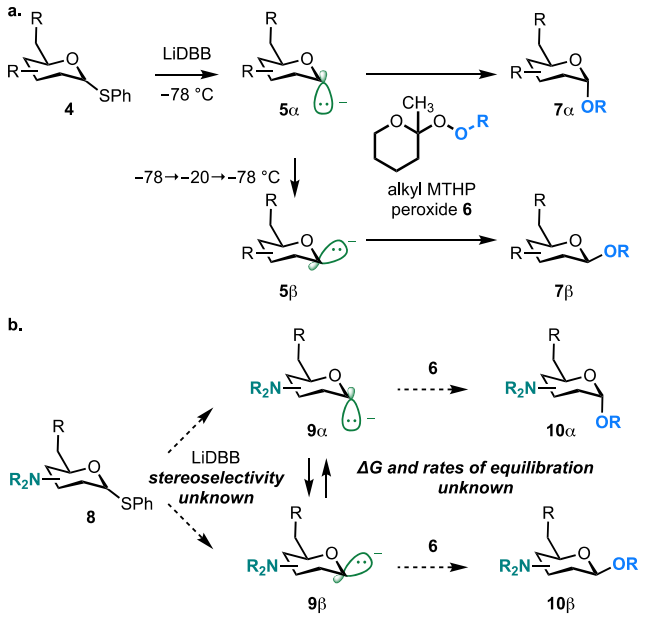
We recently reported a synthesis of 2-deoxyglycosides wherein the conventional polarity of the donor and acceptor is reversed.[8] In this approach, reductive lithiation of thiophenyl glycosides **4** using lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB)[9] forms the axial (α) anion **5α** as the kinetic product (Scheme 1a).[10] Addition of an alkyl (2-methyl)-tetrahydropyranyl (MTHP) peroxide **6**[11] results in formal alkoxenium ion transfer to provide the α-linked glycosides **7α**. An essential component of this approach is utilization of the thermodynamically favored equilibration[8,10a,c,d] of the axial (α) anion to the more stable[12] equatorial (β) anion **5β**. Thus, warming the α anion to −20 °C, followed by re-cooling to −78 °C and peroxide addition, forms the β-linked products **7β**.

Scheme 1. Anomeric Anion Approach to Glycosides and Aminoglycosides[a]



[a](a) Reductive lithiation of thiophenyl glycosides **4** forms the axial (α) anion **5α**. Warming to −20 °C promotes equilibration to the equatorial (β) anion **5β**. The addition of alkyl MTHP peroxides **6** to either anion provides the α- or β-linked products **7α** and **7β**, respectively. (b) The stereoselectivity in the reductive lithiation of amine-substituted thiophenyl glycosides **8** and their rates of interconversion were unknown. Addition of **6** to either **9α** or **9β** would provide the α- or β-aminoglycosides **10α** or **10β**, respectively.

Given the well-known compatibility of basic amines with organolithium reagents,[13] we reasoned that this method might provide an entry to 2-deoxyaminoglycosides (Scheme 1b). In particular, we sought to synthesize 4-amino-2,4,6-trideoxy and 3-amino-2,3,6-trideoxy pyranoses, which are important classes of carbohydrates present in anticancer drugs and natural products such as the saccharomicins, doxorubicin, and daunomycin.[1,14] However, the incorporation of basic nitrogen into the donors raises several interesting, but potentially complicating, issues. While the reductive lithiation of all oxygen-substituted thiophenyl glycosides reliably forms the axial (α) anion as the kinetic product, we anticipated that the amine might alter the preferred conformation of the anomeric radical intermediate. In addition, formation of a stable chelate might decrease the nucleophilicity of the organolithium intermediate, rendering the C−O bond-forming step inefficient. The extent to which an amine might influence the rates of epimerization was also not apparent.

RESULTS AND DISCUSSION

We recognized that the highly deoxygenated thiophenyl glycoside **11α** (Table 1), a precursor to forosamine (2,3,4,6-tetradeoxy-4-dimethylamino-*erythro*-hexopyranose) derivatives, represented a singularly challenging substrate for study. Both α- and β-linked forosamine are found in natural products (for example, the griseusin naphthoquinones,[15] the spinosyn[16] and spiramycin[17] macrolides, and the forazoline polyketides[18]), and historically, the synthesis[19] and stereocontrolled introduction[5,20] of forosamine has been challenging. We developed a synthesis of **11α** from 3-deoxy-4,6-di-*O*-acetyl D-galactal[21] that proceeds in eight steps and 19% overall yield (see the Supporting Information).

We found that reductive lithiation of **11α** at −78 °C, followed by addition of the MTHP monoperoxy acetal **12**, furnished the α-linked disaccharide **13α** in 80% yield and >50:1 α-to-β selectivity (as determined by ^{1}H NMR analysis of the unpurified product mixture) using the conditions we previously established (Table 1, entry 1). To our knowledge, this constitutes the first stereoselective synthesis of an α-forosyl glycoside. Unfortunately, however, application of our prior conditions[8] to the synthesis of β-forosamine yielded no observable β-disaccharide (entry 2). Considering the lower inductive stabilization of the anion derived from **11α** relative to the mono- and dideoxyglycosides employed in our previous study,[8] we hypothesized that proton transfer from solvent was competitive with isomerization.[22] Upon decreasing the equilibration time to 30 min, the β-disaccharide **13β** was produced with 1:2.5 β-to-α selectivity (46% combined yield, entry 3). Conducting the equilibration at −30 °C for 60 min increased the yield of product to 56%, but eroded the selectivity (1:3.2 β-to-α, entry 4). Although changing the solvent to exclusively tetrahydrofuran improved the selectivity, the α-disaccharide **13α** still predominated (73%, 1:1.5 β-to-α, entry 5). Attempts to improve the selectivity by introducing salt additives, or using other solvent systems, were unsuccessful (entries 6−9). However, increasing the equilibration time to 90 min provided the β-disaccharide **13β** with 1:1 β-to-α selectivity (46% combined yield; entry 10). On further extending the equilibration time to 150 min, the β-disaccharide **13β** was obtained with 3:1 β-to-α selectivity, although in only 10% yield (entry 11). These results support the notion that proton abstraction from solvent by the more reactive α-anion is competitive with isomerization. Consistent with this, **13β** was obtained with 4.7:1 β-to-α selectivity and in 46% combined yield when THF-d_8 was employed as solvent (entry 12).[23,24] Alternatively, the β-disaccharide **13β** was formed with 5.3:1 β-to-α selectivity (69% combined yield) when 10 equiv of the donor **11α** was employed (entry 13). These results constitute the most β-selective glycosylations using a forosamine-derived donor to date. The best prior example of which we are aware was reported in 2016 by Dai and co-workers and proceeded in 71% yield and with 1:1 β-to-α selectivity (2:1 ratio of donor and acceptor).[5d] Additionally, these experiments underscore the higher basicity of the tetradeoxygenated anomeric anions. More electron-deficient derivatives transformed with greater efficiency, as anticipated (*vide infra*).

We then synthesized a series of 2,3,6-trideoxy-3-amino-thioglycoside and 2,4,6-trideoxy-4-aminothioglycoside pronu-

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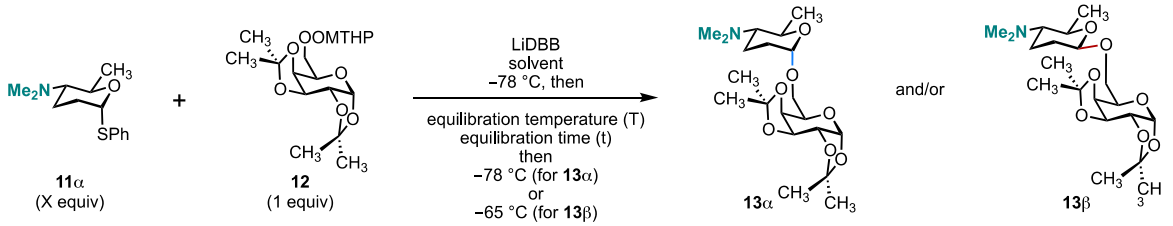
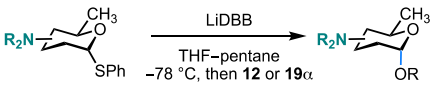
Table 1. Optimization of α- and β-Glycoside Synthesis Using the Forosamine Derivative 11α



entry	equiv **11α**	solvent	T (°C)[a]	t (min)[b]	yield of **13** (%)[c]	selectivity
1	**1.5**	**THF−pentane**			**80**[d]	**>50:1 α:β**
2	2.0	THF−pentane	−20	60	0	n.d.[e]
3	2.0	THF−pentane	−20	30	46	1:2.5 β:α
4	2.0	THF−pentane	−30	60	56	1:3.2 β:α
5	2.0	THF	−30	60	73[d]	1:1.5 β:α
6[f]	2.0	THF	−30	60	80[d]	1:4 β:α
7	2.0	Et_2O	−30	60	62	1:10.8 β:α
8	2.0	2-methyl-THF	−30	60	65	1:3.9 β:α
9[g,h]	2.0	THP	−20	60	39	1.8:1 β:α
10	2.0	THF	−30	90	46	1:1 β:α
11	2.0	THF	−30	150	10	3:1 β:α
12	**2.0**	**THF-d_8**	**−30**	**150**	**46**[d]	**4.7:1 β:α**
13	**10.0**	**THF**	**−30**	**150**	**69**[d]	**5.3:1 β:α**

[a]Temperature of α-to-β equilibration. [b]Time of α-to-β equilibration. [c]Combined yield of both diastereomers as determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard, unless otherwise noted. [d]Isolated yields following purification by flash-column chromatography. [e]n.d. = not detected. [f]LiCl (5.0 equiv) was added prior to the reductive lithiation. [g]The reductive lithiation and the reaction temperature were conducted at −30 °C. THP = tetrahydropyran. [h]The reductive lithiation was conducted using a solution of LiDBB in THF. Use of LiDBB in THP led to recovery of starting material.

Table 2. Synthesis of α-Aminoglycosides[a,b]



pronucleophiles			electrophiles	
14α	**16β**		**12**	**19α**
15α	R = MOM, **17α**	R = PMB, **18α**		
20α	**21α**	**22α**	**23α**	**24α**
93%, >50:1 α:β	96%, >50:1 α:β	79%, >50:1 α:β	87%, >50:1 α:β	60%, >50:1 α:β
25α	**26α**	**27α**	**28α**	**29α**
88%, >50:1 α:β	92%, >50:1 α:β	79%, >50:1 α:β	78%, >50:1 α:β	80%, >50:1 α:β

[a]Stereoselectivities determined by ^{1}H NMR analysis of the unpurified product mixtures. [b]Isolated yields following purification.

cleophiles present in natural products, including pyrrolosamine, acosamine, and ristosamine derivatives, and evaluated their reactivities in this anionic glycosylation method. Cognizant that there may be variability in the α-to-β

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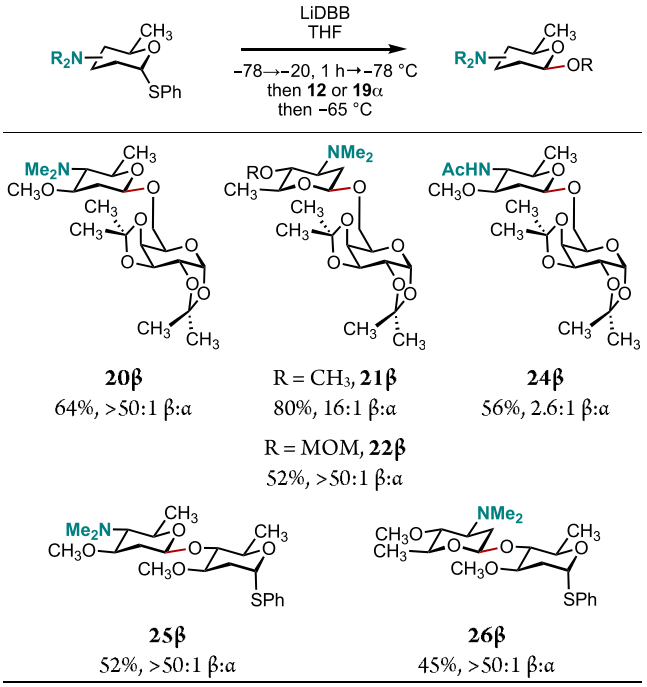
equilibration, we first evaluated the syntheses of α-aminoglycosides. Overall, this approach to α-2,6-dideoxyaminoglycosides proved general (Table 2). For example, reductive lithiation of the pyrrolosamine derivative **14α**, followed by addition of the MTHP monoperoxy acetal **12**, provided the α-linked disaccharide **20α** in 93% yield and with >50:1 α-to-β selectivity. Alternatively, addition of the secondary MTHP electrophile **19α** to the α-anion derived from **14α** furnished the disaccharide **25α** in 88% yield and with >50:1 α-to-β selectivity. Coupling of the acosamine derivatives **16β**−**18α** with the MTHP electrophile **12** provided the α-disaccharides **21α**−**23α** in 79−96% yield and with >50:1 selectivity for the α-anomer. These pronucleophiles also reacted efficiently with the secondary MTHP electrophile **19α** to furnish the α-disaccharides **26α**−**28α** in 78−92% yield and with >50:1 α-to-β selectivities. Finally, we turned our attention to the secondary amide **15α**, which bears an acidic proton. Sequential deprotonation (methyllithium, −78 °C), addition of LiDBB, and introduction of either MTHP electrophile **12** or **19α** provided the α-disaccharides **24α** and **29α** in 60% and 80% yields, respectively, and with >50:1 α-to-β selectivity in both instances.

We then set out to develop a β-selective glycosylation (Table 3). The α- and β-diastereomers reported herein are

Table 3. Synthesis of β-Aminoglycosides[a,b]



[a]Stereoselectivities determined by ^{1}H NMR analysis of the unpurified product mixtures. [b]Combined yields of both diastereomers following purification.

readily distinguished by ^{1}H NMR spectroscopy. The anomeric proton of the α-diastereomers is generally observed as a doublet (J = 3.2−5.7 Hz) in the δ 4.75−5.59 ppm range. By comparison, the anomeric proton of the β diastereomers is generally observed as a doublet of doublets (J = 7.9−9.8, 2.0−2.4 Hz) in the δ 4.47−4.72 ppm range.

We anticipated that trideoxygenated donors would react more efficiently than the forosamine donor **11α** due to the inductive stabilization deriving from the oxygen substituents. Consistent with this, the β-linked disaccharide **20β** was obtained in 64% yield and with >50:1 β-to-α selectivity by reductive lithiation of the pyrrolosamine derivative **14α**, equilibration (−20 °C, 1 h), and addition of the electrophile **12** (Table 3). Lithiation and thermal equilibration of the acosamine derivative **16β** in a 1:1 tetrahydrofuran−pentane mixture, followed by the addition of **12**, provided the disaccharide **21β** in 83% yield and with 3:1 β-to-α selectivity (not shown). This result suggests that the position of the amine (C4 for pyrrolosamine and C3 for acosamine) influences the rate of equilibration.

Consistent with previous studies,[10c] higher rates of equilibration were observed when tetrahydrofuran was used exclusively as solvent, and the disaccharide **21β** was obtained in 80% yield and with 16:1 β-to-α selectivity using the same equilibration temperature and time. Alternatively, the disaccharide **26β** was obtained in 45% yield and >50:1 β-to-α selectivity following addition of the secondary electrophile **19α**. The methoxymethyl ether derivative **17α** was transformed to the disaccharide **22β** in 52% yield and with >50:1 β-to-α selectivity. When subjecting the amide **15α** to deprotonation (methyllithium, −78 °C), reductive lithiation, thermal equilibration, and addition of the MTHP electrophile **12**, the β-disaccharide **24β** was obtained in 56% yield and with 2.6:1 β-to-α selectivity.

Unexpectedly, the L-ristosamine derivative **30β**, which contains an axial amine substituent, provided the β-disaccharide **35β** as the major product (87%, 2.8:1 β-to-α) under nominally kinetic conditions (Table 4, entry 1). The stereochemistry of **35β** was confirmed by observation of an NOE correlation between H1 and H5. No significant change in diastereoselectivity was observed when the anion generated from **30β** was aged at −78 °C for 30 min prior to the addition of the electrophile **12** or when the reductive lithiation was carried out at warmer (−60 °C) or cooler (−100 °C) temperatures (see Table S1). These data suggest that a mixture of configurationally stable α- and β-anions are formed from **30β** at −78 °C. One possible explanation for this is that the axial amine in **30β** renders the energies of the two anomeric radical chair conformers, with the SOMO in an axial orientation, comparable to one another (see **34α** and **34β**). To test this, we synthesized the L-ristosamine derivative **30α**, which adopts the $^4C_1$ conformation (confirmed by nuclear Overhauser effect correlation between the C1 and C6 protons). Reductive lithiation of **30α** at −78 °C, followed by addition of the MTHP electrophile **12**, provided the disaccharide **35β** in 83% yield and with 9:1 β-to-α selectivity (entry 2). These data suggest that the β, axial-conformer of the radical derived from **30β** and **30α** is lower in energy than the respective α, axial-conformer, but that some isomerization between the two is occurring prior to anion formation.

On the basis of these observations, we synthesized the ristosamine derivatives **31β**−**33β**. We reasoned that the products derived from **31β** and **32β** should show an increased preference for the α-disaccharides, as the respective radicals should favor the α, axial-conformer **34α** due to the increased steric bulk on the C4 oxygen. Consistent with this hypothesis, reductive lithiation of **31β** and trapping with the peroxide **12** provided the disaccharide **36β** in 93% yield and with 1.7:1 β-to-α selectivity. Although we expected the glycosylation with **32β** to show an even further enhancement of α-selectivity due to the bulky silyl protecting group, the product **37β** was formed with only marginally greater selectivity (2.0:1 β-to-α,

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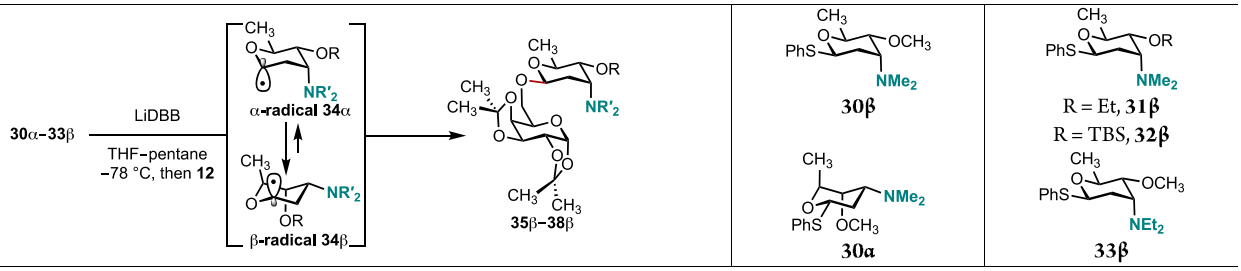
Table 4. Glycosylations Using the Ristosamine Derivatives 30α−33β



entry	SM	R	R′	product	yield (%)[a,b]	selectivity
1	**30*β***	CH_3	CH_3	**35*β***	87	2.8:1 *β*:*α*
2	**30*α***	CH_3	CH_3	**35*β***	83	9.1:1 *β*:*α*
3	**31*β***	Et	CH_3	**36*β***	93	1.7:1 *β*:*α*
4	**32*β***	TBS	CH_3	**37*β***	94	2.0:1 *β*:*α*
5	**33*β***	CH_3	Et	**38*β***	86	6.4:1 *β*:*α*

[a]Stereoselectivities determined by ^{1}H NMR analysis of the unpurified product mixtures. [b]Combined yields of both diastereomers following purification.

94%). However, this observation may be due to solvent effects.[25] Finally, we synthesized ristosamine derivative **33*β***, with the expectation that the radical derived from **33*β*** would favor adopting the *β*, axial-conformation **34*β***, and thus, the product derived from **33*β*** should show an increased *β*-preference. In line with our expectations, the glycosylation with **33*β*** yielded **38*β*** in 86% yield and 6.4:1 *β*-to-*α* selectivity. These data suggest that by manipulating the conformation of the thioglycoside pronucleophiles,[26] *β*-selective glycosylation reactions can be favored at −78 °C (e.g., without thermal equilibration), a finding that has important implications for the synthesis of oligosaccharides.

CONCLUSION

In conclusion, we have developed a synthesis of deoxyaminoglycosides bearing basic amine residues. Both *α*- and *β*-aminoglycosides are accessible in 45−96% yield. *α*-Linked products are formed with >50:1 selectivity. While the selectivities for *β*-linked products are variable, many products are attainable with synthetically useful levels of selectivity. In the course of these studies, we discovered that the conformations of thioglycoside pronucleophiles can be utilized to control the kinetic selectivity in the anion generation step, which has important implications for the synthesis of oligosaccharides. These findings constitute the first general strategy to synthesize *α*- or *β*-glycosides bearing a basic nitrogen.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11262.

Detailed experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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