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SHORT COMMUNICATION

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A Divergent Method to Prepare 5-Amino-, 5-*N*-Acetamido-, and 5-*N*-Glycolylsialosides

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Sialic acids are essential mediators of biological processes involving carbohydrate recognition. A major determinant of sialic acid recognition is the N-5 substituent, which can be an *N*-acetyl (human), *N*-glycolyl (non-human), or amine (cancer associated) functionality. Access to homogeneous sialosides with distinct substitution patterns is essential to determine structure–activity relationships. Herein, we report a divergent chemical approach to enable the synthesis of a library of specifically substituted sialosides by using a single sialic acid building block.

Introduction

Sialic acids (also known as neuraminic acids) are a diverse family of naturally occurring 2-keto-3-deoxynononic acids that are found on the termini of glycan chains in all cell types.[1] Sialic acids are involved in a wide range of biological processes such as fertilization, leukocyte migration, neuronal plasticity, protein half-life, malignant transformation, and pathogen recognition and invasion.[1c,2] More than 50 derivatives of sialic acid are known, including a human derivative called Neu5Ac. Notably, small differences in the N-5 substituent differentiates human (Neu5Ac, 5-*N*-acetyl), non-human (Neu5Gc, 5-*N*-hydroxyacetyl), and cancer-associated (Neu, 5-amino) sialic acids.[3] Human biosynthesis of Neu5Ac is a consequence of a mutation of the hydroxylase required for the biosynthesis of Neu5Gc, as a defense mechanism to prevent pathogen recognition.[4] However, this difference in sialylation may also lead to adverse effects on human disease.[3a,4,5] For example, trace amounts of Neu5Gc incorporated in human glycans through the uptake of dietary Neu5Gc may lead to anti-Neu5Gc antibodies that are linked to chronic inflammatory disease and cancer progression.[6] Similarly, therapeutic approaches that rely on the use of therapeutic cells or glycoproteins can be affected by differences in sialylation, as these products are often contaminated with Neu5Gc.[7]

Hence, homogeneous sialosides with distinct substitution patterns are essential tools to determine structure–activity relationships. However, due to the complex sialylation pattern, it is difficult to obtain pure and well-defined sialosides for biological studies by isolation from natural sources. A versatile alternative to obtain well-defined glycans is by chemical synthesis.[8] However, glycosidations with sialic acid donors are also far from trivial because they are 3-deoxyketo sugars. This makes the stereochemical outcome of sialylation difficult to control, and activation of a sialyl donor may lead to extensive elimination as a result of the C-1 carboxylic acid(ester) and the sterically hindered nature of the tertiary oxacarbenium ion.[9] In addition, the protecting group at the N-5 position of the sialic acid can influence the reactivity and α-selectivity of sialic acid donors,[10] which has led to the use of a variety of N-5 protecting groups such as *N*-diacetyl (Ac_2),[11] *N*-trifluoroacetyl (TFA),[12] *N*-2,2,2-trichloroethoxycarbonyl (Troc),[13] 9-fluorenylmethoxycarbonyl (*N*-Fmoc),[14] azide (N_3),[15] and *N*-phthalimide (Phth).[16] A most recent iteration employs the highly electron-withdrawing 4,5-*O*,*N*-oxazolidinone group to provide excellent α-selectivity.[17] A major drawback of the oxazolidinone group, however, is that harsh basic conditions at high temperature are required for its removal.[17b] Although prior installment of an additional 5-*N*-acetyl group allows 5*N*,4*O*-oxazolidinone cleavage under much milder conditions, this procedure is not applicable to *N*-glycolylsialosides, as the *N*-glycolyl moiety, in contrast to the *N*-acetyl group, is readily cleaved.[17c,18] On the basis of the above, it is clear that a robust and versatile method to prepare 5-*N*-differentiated sialosides with excellent stereoselectivity and reactivity, combined with mild cleavage conditions, is highly desirable.

Herein, we report such a modular strategy to prepare 5-*N*-glycolyl-, 5-*N*-acetamido-, and 5-aminosialosides by means of novel 5-*N*-Boc-protected 5*N*,4*O*-oxazolidinone sialic acid donors **3** and **6** (Figure 1, Ada = adamantyl, Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, Bz = benzoyl). After glycosylation, the oxazolidinone and *N*-Boc group can be sequentially cleaved under mild conditions to afford a 5-amino building block that can be converted into any type of 5-*N*-sialoside.

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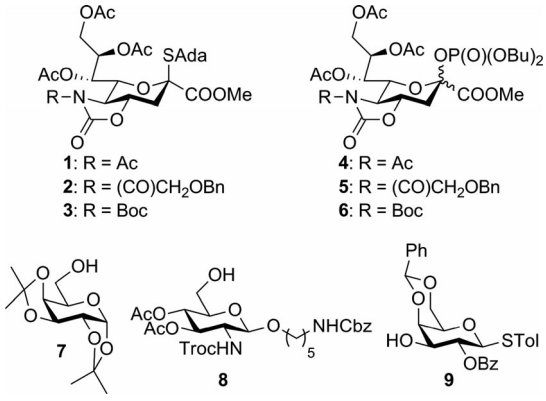


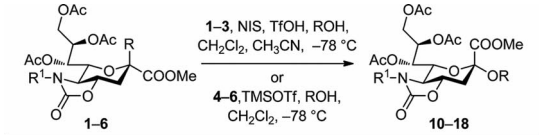
Figure 1. *N*-Acetyl-, *N*-glycolyl-, and *N*-Boc-protected sialyl donors **1**–**6** and glycosyl acceptors **7**–**9**.

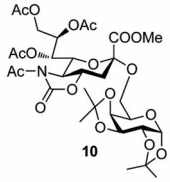
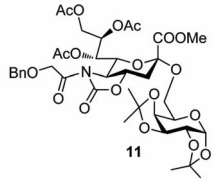
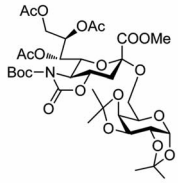
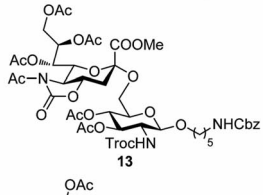
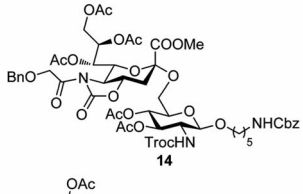
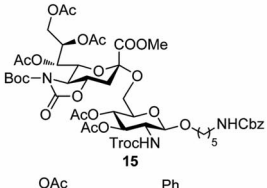
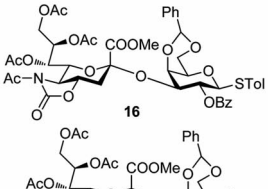
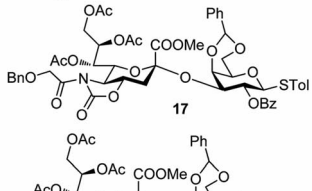
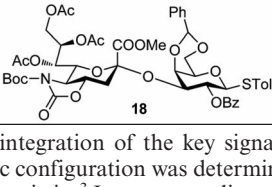
Results and Discussion

We started our investigation with the evaluation of the stability of a 5-*N*-Boc functionality of **3** and **6** under commonly used sialylation conditions, as well as its influence on the anomeric reactivity and stereoselectivity. For this purpose, well-established 5-*N*-acetyl sialyl donor **1**[17d] and 5-*N*-glycolyl donor **2** were prepared for comparison to 5-*N*-Boc-protected donor **3**. The synthesis of donors **1**–**3** was achieved by treating a known sialic acid 4,5-*O*,*N*-oxazolidinone derivative[17d] with acetyl chloride, benzyloxyacetyl chloride, and Boc_2O, respectively (see the Supporting Information). A similar range of phosphate ester sialic acid donors **4**–**6** was also prepared.[19] In addition, glycosyl acceptors **7**–**9** were used to represent common naturally occurring linkages of sialic acid to an underlying glycan, namely, α-2,6-linkage to galactose or glucosamine and α-2,3-linkages to galactose, respectively (Figure 1).[19]

Next, we explored the glycosylation behavior of sialyl donors **1**–**3**. Low-temperature (–78 °C) activation with *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH)[20] in the presence of glycosyl acceptor **7** or **8** in a mixture of CH_2Cl_2/acetonitrile (2:1) afforded in all cases disaccharides **10**–**15** in high isolated yield with excellent stereoselectivity (Table 1). Importantly, the 5-*N*-Boc group of **3** proved compatible with 0.4 equiv. of TfOH, and there was no noticeable adverse effect on the α-selectivity. Similarly, phosphate ester donors **4**–**6** were readily activated at low temperature (–78 °C) with a stoichiometric amount of TMSOTf and then treated with glycosyl acceptor **9** to afford α-2,3-sialosides **16**–**18** in moderate to good yield (Table 1). The stereoselectivity was excellent for the 5-*N*-acetyl (i.e., **4**) and 5-*N*-Boc (i.e., **6**) derivatives, but in the case of 5-*N*-glycolyl donor **5**, a mixture of anomers was obtained. Again, the 5-*N*-Boc group proved to be stable at –78 °C even in the presence of an equimolar amount of TMSOTf. Taken together, the results in Table 1 show that the 5-*N*-Boc group of **3** and **6** is stable under the commonly used conditions to activate thioglycosides and glycosyl phosphates, and glycosylation to prepare 2,6- and 2,3-linkages proceeds with excellent α-selectivity and high yield. Next, we investigated the selective removal of the 5*N*,4*O*-

Table 1. Stereoselectivity of sialylations with donors **1**–**6**.

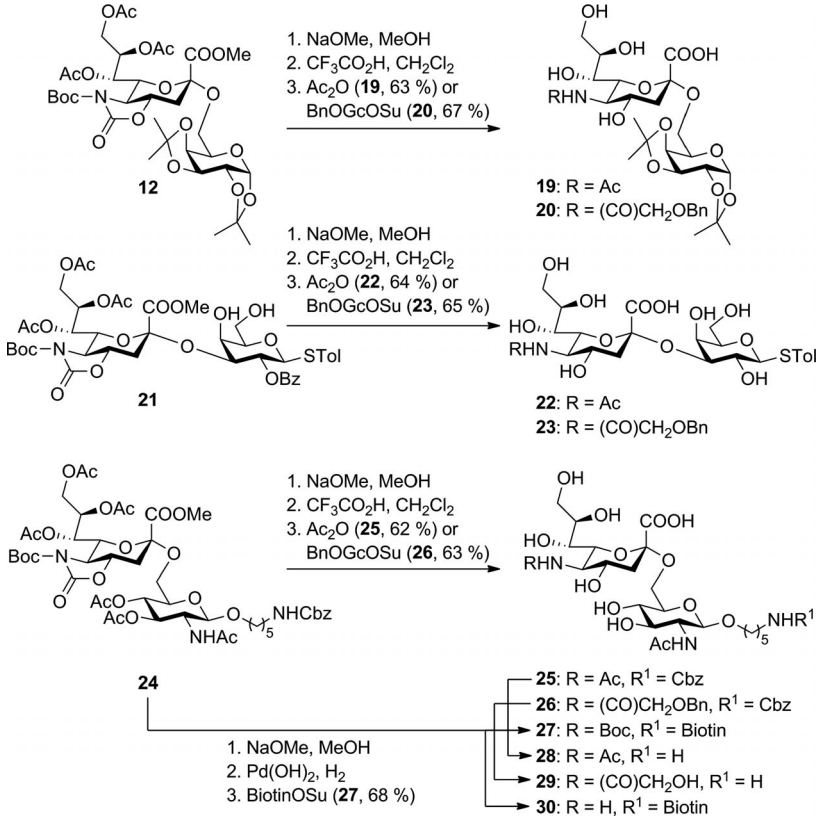


Entry	Sialyl donor + acceptor	Disaccharide product	α/β ratio[a]	Yield[b] [%]
1	**1** + **7**	 **10**	>20:1	85
2	**2** + **7**	 **11**	>20:1	76
3	**3** + **7**		>20:1	88
4	**1** + **8**	 **13**	>20:1	82
5	**2** + **8**	 **14**	>20:1	73
6	**3** + **8**	 **15**	>20:1	80
7	**4** + **9**	 **16**	>20:1	65
8	**5** + **9**	 **17**	3:1	43
9	**6** + **9**	 **18**	20:1	62

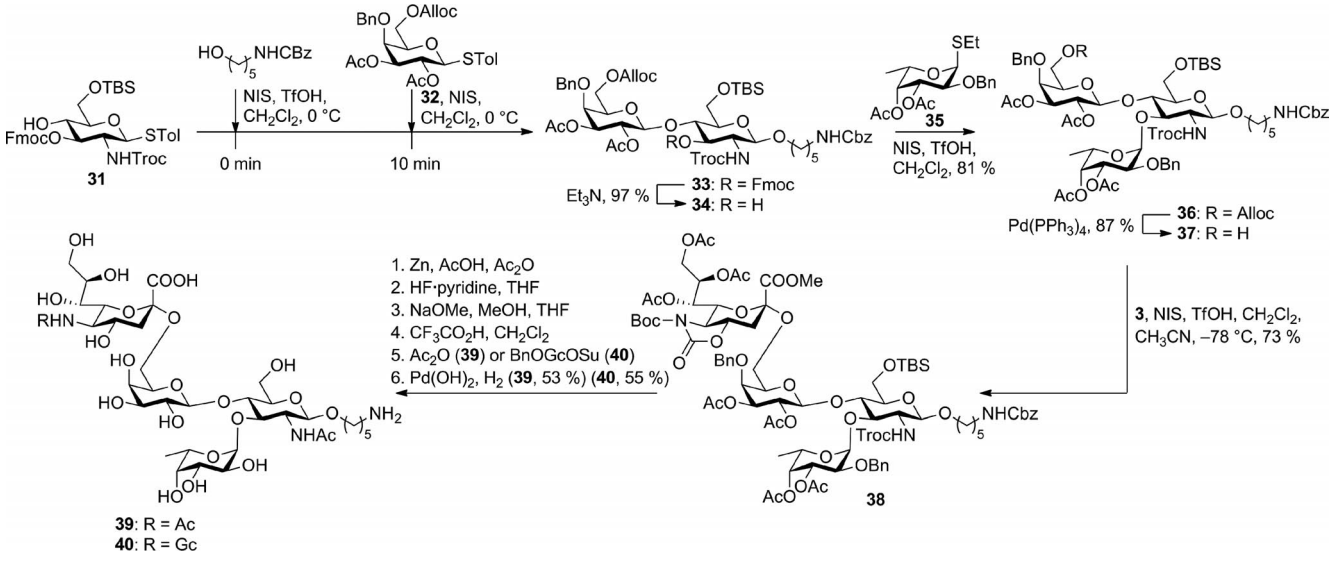
[a] Determined by integration of the key signals in the ^1H NMR spectrum. Anomeric configuration was determined by the measurement of the characteristic $^3J_{C1\text{-}H3ax}$ coupling constant.[21] [b] Isolated yield.

oxazolidinone moiety of sialosides **12**, **15**, and **18**. As mentioned in the Introduction, the 5-*N*-glycolyl moiety on a 5*N*,4*O*-oxazolidinone is not stable under basic conditions and is cleaved faster than the 5*N*,4*O*-oxazolidinone.[18] Indeed, when we treated compound **2** with NaOMe in MeOH, a mixture of compounds was obtained, and this is indicative of unselective cleavage. However, the 5-*N*-Boc group allowed the use of mild conditions to remove the oxazolidinone with retention of the carbamate function. The best results were obtained by treatment of disaccharide **12** with NaOMe in a mixture of MeOH and wet THF (Scheme 1). MS analysis showed that the Boc carbamate remained intact, and thus the crude product was treated with CF_3CO_2H in CH_2Cl_2 (1:9) for 10 min to afford the desired unprotected amine with no observable cleavage of the isopropylidene acetal or glycosidic linkage. The crude amine was converted into either 5-*N*-acetyl sialoside **19** by treatment with Ac_2O or 5-*N*-glycolylsialoside **20** by reaction with *N*-succinimidyl benzyloxyacetate. Disaccharide **18** was used to investigate the deprotection of α-2,3-sialosides, starting with removal of the 4,6-*O*-benzylidene acetal [camphorsulfonic acid (CSA), MeOH] to afford diol **21** (Scheme 1). Again, the aforementioned three-step reaction sequence of deacetylation, 5-*N*-Boc cleavage, and functionalization of the crude amine by acetylation or glycolylation afforded disaccharides **22** and **23** in good overall yields. Finally, more challenging disaccharide **15** containing two additional amino functions was converted into three different sialosides **28**–**30** containing a 5-*N*-acetyl, 5-*N*-glycolyl, or 5-amine functionality, respectively. Notably, the 5-*N*-Boc group of **18** is orthogonal to commonly used amine protecting groups such as the Troc and Cbz groups, which thereby allows selective functionalization and/or immobilization. Thus, the Troc-protected amino group of **15** was converted into an acetamide by treatment with zinc powder (→**24**), followed by conversion into 5-*N*-acetyl and 5-*N*-glycolyl derivatives **25** and **26** by the aforementioned three-step procedure. Hydrogenation led to **28** and **29**, which carry an aminopentyl spacer that can be used for further immobilization or functionalization. Alternatively, the Cbz-protected linker can be modified by deacetylation, hydrogenation, and biotinylation to afford **27** in good overall isolated yield (68%). Finally, the 5-*N*-Boc functionality was deprotected by using 10% CF_3CO_2H in CH_2Cl_2 to afford **30** in 99% yield. Deprotected α-sialosides **20**, **23**, and **28**–**30** proved to be stable compounds, as judged by their analysis by NMR spectroscopy, regardless of the N-5 substitution pattern. Hence, three derivatives (i.e., **28**–**30**) were prepared from a single intermediate (i.e., **15**), and the overall strategy is suitable to prepare any type of biologically relevant 5-N derivative of sialic acid from only one sialic acid building block.

Finally, we investigated the applicability of the above-described technology to the preparation of fucose-bearing tetrasaccharide **39** (Scheme 2). Fucose is often present in sialylated glycan chains and essential for binding to selectins. However, we were aware that, although the glycosidic linkages of **12**, **21**, and **24** were stable during Boc deprotection, acidic treatment in the assembly of **39** could well be



Scheme 1. Deprotection to afford 5-amino-, 5-*N*-acetyl-, and 5-*N*-glycolylsialosides.



Scheme 2. Synthesis of *N*-acetyl- and *N*-glycolylsialosides in the presence of an acid-labile fucose residue.

problematic with respect to the acid lability of fucosyl linkages. Thus, orthogonally protected disaccharide **33** was prepared by one-pot reaction of **31** (TBS = *tert*-butyldimethylsilyl) with an aminopentyl linker, followed by glycosylation with galactosyl donor **32** by using NIS and TfOH. After Fmoc deprotection (→**34**), fucosylation with **35**[22] promoted by NIS/TfOH afforded trisaccharide **36** in good yield with good stereoselectivity (α/β = 10:1). Removal of the allyloxycarbonyl (Alloc) group with $Pd(PPh_3)_4$ afforded trisaccharide acceptor **37** in excellent yield, and finally sialylation of the primary alcohol with **3** led to desired complex tetrasaccharide **38** in good yield with excellent stereoselectivity. Deprotection of the Troc carbamate with Zn/AcOH was followed by desilylation with HF·pyridine. Thus, the stage was set for the pivotal deprotection–functionalization sequence. First, deacetylation with NaOMe/MeOH/THF readily hydrolyzed acetyl and methyl esters as well as the oxazolidinone. Next, the resulting intermediate was briefly treated (10 min) with only 10% CF_3CO_2H in CH_2Cl_2 to obtain the free amine. Much to our satisfaction, MS analysis of the crude reaction mixture showed that the Boc carbamate was selectively cleaved and the fucosyl linkage was unaffected. Acylation of the amine afforded the acetamido and glycolyl derivatives and final hydrogenation afforded **39** and **40** in good overall yields.

Conclusions

In conclusion, the method described herein enables the synthesis of complex 5-*N*-acetyl-, 5-*N*-glycolyl-, and 5-aminosialosides from a single 5-*N*-Boc sialic acid building block. The Boc group is stable under commonly used sialylation conditions, ensures excellent α-selectivity, and affords α-2,6- and α-2,3-sialosides in high yields. Furthermore, the Boc group allows mild and selective cleavage of the 5*N*,4*O*-oxazolidinone, and the resulting amine can be functionalized to afford human (Neu5Ac) and non-human (Neu5Gc) sialosides as well as sialosides found in cancer cells (Neu), as demonstrated by the selective synthesis of nine sialosides from only four building blocks. In addition, this method is applicable to the synthesis of complex oligosaccharides that contain highly acid-labile fucose residues.

Experimental Section

General Procedures: ^1H NMR and ^{13}C NMR spectra were recorded with a Varian Inova 400 MHz or Bruker Avance III 500 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as the internal standard. NMR spectroscopic data is presented as follows: Chemical shift, multiplicity (s = singlet, br. s = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet and/or multiple resonances), integration, coupling constant in Hz. All NMR signals were assigned on the basis of ^1H NMR, ^{13}C NMR, COSY, and HSQC experiments. Mass spectra were recorded with a JEOL JMS-T100CS AccuTOF mass spectrometer. Column chromatography was performed on silica gel, 0.035–0.070 mm, 60 Å, Acros organics and automatic column Büchi fraction-collector C-660, Büchi pump-manager C-615, Column-silicycle FLH-R10030B-ISO25 cartridge, 4–40 g. TLC analysis was conducted on TLC Silicagel, 60, F_{254}, Merck, with detection by UV absorption (254 nm) if applicable, and by spraying with 20% sulfuric acid in ethanol followed by charring at about 150 °C or by spraying with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$ (25 g L^{-1}) in 10% sulfuric acid in ethanol followed by charring at about 150 °C. Molecular sieves (3 Å, AW-300) were flame-activated under vacuum prior to use. All reactions were carried out under an argon atmosphere.

General Procedure for Sialylation with Thioglycosides 1–3 (GP1): Glycosyl acceptor (0.1 mmol) and glycosyl donor (0.15 mmol, 1.5 equiv.) were dissolved in a mixture of dichloromethane (2.0 mL) and acetonitrile (1.0 mL) and activated molecular sieves were added. The resulting mixture was stirred for 10 min at room temperature and then cooled to –78 °C, and NIS (0.15 mmol, 1.5 equiv.) was added. TfOH (0.04 mmol, 0.4 equiv.) was added, and the mixture was stirred for 20 min at –78 °C. Et_3N (0.05 mL) was added, and the mixture was warmed to room temperature.

EtOAc (5 mL) and $Na_2S_2O_3$ (1 M in H_2O, 5 mL) were, added and the organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography.

General Procedure for Sialylation with Glycosyl Phosphates 4 and 5 (GP2): Glycosyl acceptor (0.1 mmol) and glycosyl donor (0.15 mmol, 1.5 equiv.) were dissolved in dichloromethane (2.0 mL) and activated molecular sieves were added. The resulting mixture was stirred for 10 min at room temperature and then cooled to –78 °C, and TMSOTf (0.15 mmol, 1.5 equiv.) was added. The mixture was stirred for 60 min at –78 °C. Et_3N (0.05 mL) was added, and the mixture was warmed to room temperature. EtOAc (5 mL) and water (5 mL) were added, and the organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography.

General Procedure for 4,5-*O*,*N*-Oxazolidinone and Boc Cleavage (GP3): Starting material **12**, **21**, **24**, or **38** (0.1 mmol) was dissolved in a mixture of wet THF (2 mL) and MeOH (0.5 mL). KO*t*Bu (0.3 mmol, 3.0 equiv.) was added, and the resulting mixture was stirred for 16 h at room temperature. Dowex H^+ was added, and the mixture was filtered and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (1.8 mL) and CF_3CO_2H (0.2 mL) was added. The mixture was stirred for 10 min at room temperature and toluene (2 mL) was added. The mixture was concentrated in vacuo, and the residue was coevaporated with toluene (3 × 2 mL) to afford the crude amine, which was used without further purification.

General Procedure for 5-*N*-Acetylation (GP4): Crude amine (0.1 mmol) was dissolved in MeOH (2.0 mL), and the resulting mixture was cooled to 0 °C. Et_3N (1.0 mmol, 10.0 equiv.) and Ac_2O (0.5 mmol, 5.0 equiv.) were added, and the mixture was stirred for 5 h at 0 °C. The mixture was concentrated in vacuo, and the residue was redissolved in MeOH (2 mL). $NaHCO_3$ (0.05 g) was added, and after 5 min, the mixture was filtered and concentrated in vacuo. The residue was purified by RP-C18 HPLC (0–20% CH_3CN/H_2O).

General Procedure for 5-*N*-Glycoylation (GP5): Crude amine (0.1 mmol) was dissolved in DMF (2.0 mL), and the resulting mixture was cooled to 0 °C. Et_3N (1.0 mmol, 10.0 equiv.) and *N*-succinimidyl benzyloxyacetate (0.12 mmol, 1.2 equiv.) were added, and the mixture was stirred for 5 h at 0 °C. The mixture was concentrated in vacuo, and the residue was redissolved in MeOH (2 mL). $NaHCO_3$ (0.05 g) was added, and after 5 min, the mixture was filtered and concentrated in vacuo. The residue was purified by RP-C18 HPLC (0–20% CH_3CN/H_2O).

Supporting Information (see footnote on the first page of this article): ^1H NMR and ^{13}C NMR spectra and experimental procedures for compounds **2**, **3**, **5**, **6**, **8**, and **10**–**40**.

Acknowledgments

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