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Regioselective Glycosylation of Neamine Core: A Facile Entry to Kanamycin B Related Analogues

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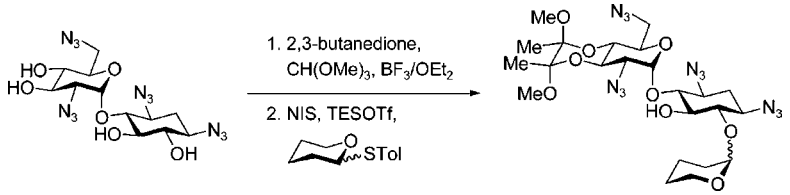
ABSTRACT



Introduction of a sugar unit at either the O5 or O6 position of various neamine derivatives in excellent selectivity and yields is described here. Application to the synthesis of kanamycin analogues is also highlighted.

Aminoglycosides are a group of structurally diverse and clinically important antibiotics with a unique ability to recognize RNA specifically.[1] They function through binding to specific sites in the bacterial ribosome and interfere with protein biosynthesis in a cascade of events that ultimately leads to bacterial cell death.[2] Structural[3] and synthetic[4] studies over the past few years have contributed significantly to our understanding of small molecule−RNA interactions.[5] The emergence of bacterial resistance[6] to these antibiotics has, however, triggered a search for new, smaller, and simpler structures that would essentially retain the antibiotic activity but avoid the problems of resistance.

The 2-deoxystreptamine-based antibiotics share a common pseudodisaccharide core, neamine (Scheme 1), which is regioselectively glycosylated either at the O5 (e.g., neomycin B) or O6 position (e.g., kanamycin B) with various saccharides. Neamine, is one such optimal structural motif that has received much of the attention[7−10] owing to its structural

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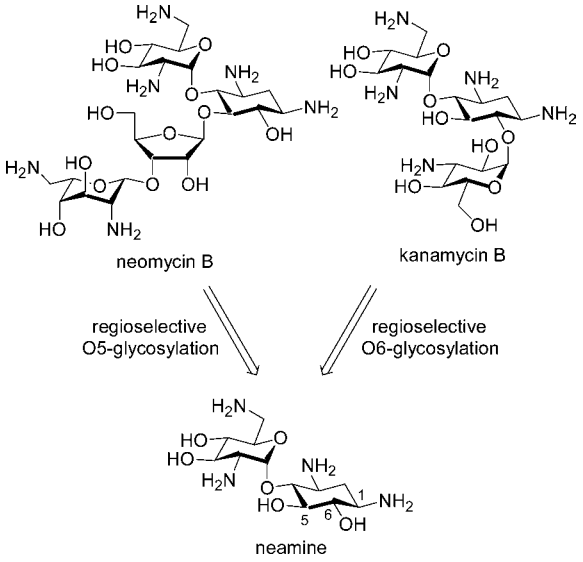
Scheme 1



simplicity, its ease of accessibility, and its ability to be readily modified chemically compared with the parent antibiotic. A chemical approach to create libraries of neomycin and related analogues of therapeutic potential via O5-assembly of the tri-OBn[8,9] or tri-OAc[10] analogues of **2** with a variety of molecules has been intensely investigated. In comparison, O6-functionalization has proven more challenging and only one literature report has appeared on this topic, which exploited a lengthy procedure to introduce a 6-*O*-allyl group and several other groupings at this position.[11] Surprisingly, there has been no literature precedent for O6-glycosylation on neamine derivatives. Herein, we now report a novel and straightforward approach for coupling a sugar unit to the neamine core at either O5 or O6 to provide a concise synthesis of various glycosylated kanamycin B analogues.

Our synthesis (Scheme 2) commenced with regioselective benzoylation of the neamine derivative **1**, obtained from

Scheme 2

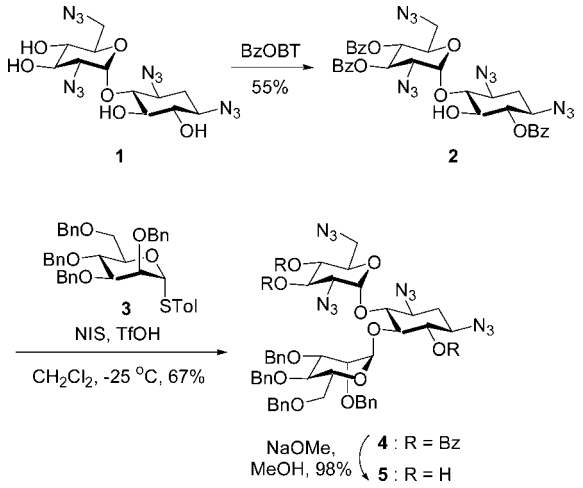
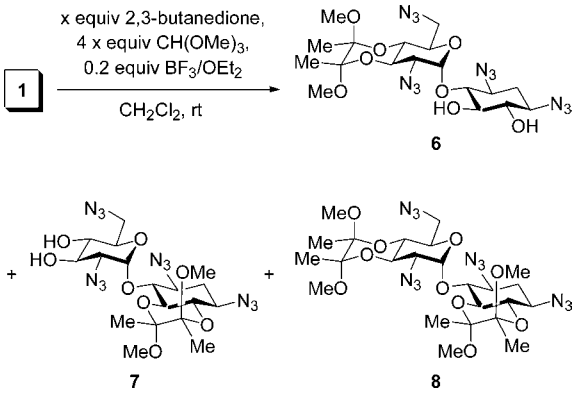


Table 1. Regioselective Protection of the Neamine-Derived Tetraol **1**



entry	*x*	yield (%) **6**	**7**	**8**	recovered yield (%) of **1**
1	1	17	8	7	66
2	2	33	17	20	26
3	3	33	25	13	27
4	4	58	8	13	17
5	5	58	17	6	15
6	6	42	17	13	25
7	7	42	17	20	16

commercially available neomycin B by sequential methanolysis[7a] followed by amino−azido conversion.[12] Treatment of **1** with a mild benzoylation reagent (1-*N*-benzoyloxybenzotriazole, BzOBT) afforded the 3′,4′,6-tri-OBz derivative **2** as a major product in 55% yield. To test the viability of **2** as a glycosyl acceptor, its coupling with D-mannopyranosyl thioglycoside **3** was promoted via a combination of *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH), and the corresponding α-linked trisaccharide **4** was obtained in 67% yield. The concomitant de-*O*-benzoylation proceeded smoothly under standard conditions to give triol **5** almost quantitatively. This constitutes a short and efficient route for the synthesis of neomycin B analogues.

Next, we turned our attention to the regioselective protection-glycosylation of the tetraol derivative **1**, so as to access kanamycin B analogues. Of the various protective groups tried for the regioselective discrimination of the two *trans*-diequatorial dihydroxy motifs, Ley's method of 1,2-butane diacetal (BDA) formation[13] worked the best. Treatment of compound **1** with various amounts of 2,3-butanedione and trimethylorthoformate in the presence of boron trifluoride

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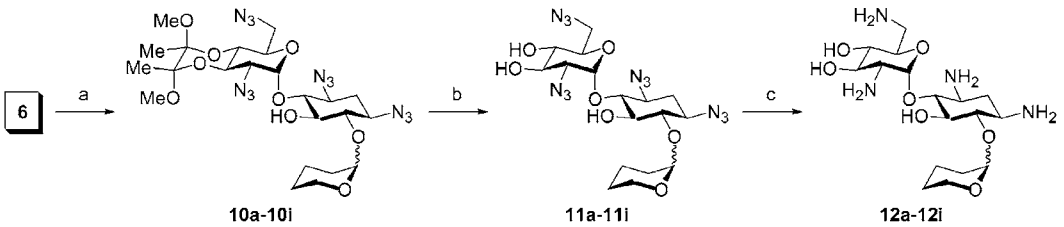
Table 2. Regioselective Glycosylation of the Diol **6** Followed by Sequential Deprotections to Kanamycin Analogues[a]



entry	thioglycoside donor	yield of **10a-10i**	yield of **11a-11i**	yield of **12a-12i**
1	**9a** : L = β-STol, R^1 = R^2 = OBn	**10a** : 78%, α only	**11a** : α, 96%	**12a** : α, 71%
2	**9b** : L = α-STol, R^1 = Bn, R^2 = N_3	**10b** : 80%, α/β = 4/1	**11b** : α, 90%	**12b** : α, 63%
3	**9c** : L = β-STol, R^1 = Bz, R^2 = OBn	**10c** : 67%, β only	**11c** : β, 95%	**12c** : β, 65%
4	**9d** : L = β-STol, R^1 = Bz, R^2 = N_3	**10d** : 65%, β only	**11d** : β, 94%	**12d** : β, 69%
5	**9e** : R = OBn	**10e** : 82%, α/β = 5/1	**11e** : α, 95%	**12e** : α, 64%
6	**9f** : R = N_3	**10f** : 82%, α/β = 2/1	**11f** : α, 91%	**12f** : α, 72%
7	**9g** : L = β-STol, R = OBn	**10g** : 85%, α/β = 2/1	**11g** : α, 84%	**12g** : α, 63%
8	**9h** : L = α-STol, R = N_3	**10h** : 81%, α/β = 6/1	**11h** : α, 90%	**12h** : α, 71%
9	**9i**	**10i** : 84%, α/β = 3/1	**11i** : α, 87%	**12i** : α, 68%

[a] Reagents and conditions: (a) donors **9a**−**i**, NIS/TESOTf, CH_2Cl_2, −78 °C; (b) 90% TFA; (c) for **12a**,**b**,**e**−**i**: $Pd(OH)_2$, H_2, EtOH/H_2O/$CHCl_3$ = 2/2/1; for **12c**,**d**: (i) NaOMe, MeOH; (ii) $Pd(OH)_2$, H_2, EtOH/H_2O/$CHCl_3$ = 2./2/1.

etherate as a catalyst furnished the required 3′,4′-diketal **6**, together with other isomers in variable ratios. Table 1 summarizes our efforts to tune the reaction conditions in favor of one of the isomers. As shown in entries 1−3, mostly unreacted starting material **1** was recovered, and the desired monoacetal **6** was isolated in low yields. Use of 4 (entry 4) or 5 equiv (entry 5) of 2,3-butanedione led to the formation of 5,6-diol **6** (58%) as a major product along with other two isomers **7** and **8** in minor proportions. Increasing the reagent concentration (entries 6 and 7) progressively resulted in the formation of higher proportions of the bis-acetal **8**. Compound **6** could be easily separated by column chromatography, as a diastereomeric mixture,[14] while the remaining mixture was subjected to hydrolysis conditions using 90% aqueous trifluoroacetic acid to recover tetraol **1** almost quantitatively.

With the key synthon **6** in hand, the regioselective O6-glycosylation to the kanamycin B analogues was further investigated. As illustrated in Table 2, coupling of diol **6** with the thioglycoside donors **9a**−**i** at −78 °C using NIS/TESOTf proceeded with excellent O6-regioselectivity to provide the corresponding trisaccharides **10a** (78%, α only), **10b** (80%, α/β = 4/1), **10c** (67%, β only), **10d** (65%, β only), **10e** (82%, α/β = 5/1), **10f** (82%, α/β = 2/1), **10g** (85%, α/β = 2/1), **10h** (81%, α/β = 6/1), and **10i** (84%, α/β = 3/1), respectively. Cleavage of the BDA-protecting group with aqueous trifluoroacetic acid followed by immediate removal of the reagent under diminished pressure yielded the corresponding triol derivatives **11a**−**11i** in very good yields, respectively. It should be noted that, particularly in the D-*galacto* case, the time factor of the TFA-hydrolysis reaction was very crucial. A delay in the evaporation of reagent showed a marked drop in the yield, presumably via the cleavage of the newly formed glycosidic linkage. All of these triols were carefully characterized through the analyses of their ^{1}H, ^{13}C, ^{1}H−^{1}H COSY, ^{13}C−^{1}H COSY, and NOESY NMR spectra, respectively.[15] Compound **11e** showed no resemblance with the previously synthesized analogue **5**,

(14) In the BDA-protection of diol **1**, although, the anomeric effect at the two acetal centers favored the formation of the isomer with anti-periplanar arrangement of OMe groups, the other isomer was also formed in minor proportion. This was not separated and the mixture was used as such for ensuing glycosylations. After the removal of BDA protecting group, individual products were obtained in pure form.

(15) A standard structural elucidation protocol involved ^{1}H, ^{13}C, and 2D NMR analysis. The anomeric carbons and protons were clearly distinguished from the ^{13}C−^{1}H COSY spectrum. ^{1}H−^{1}H COSY spectral analysis then established the correlation between all of the protons on each ring. The regioselectivity of glycosylation (O5 or O6) was determined by observation of the correlation with the OH protons in the COSY spectrum, wherever possible, and also judged from the multiplicity of H5 and H6 protons. NOESY spectral analysis was finally used to reaffirm the assignments. The α and β configurations were determined on the basis of coupling constant measurements of the respective anomeric protons (see the Supporting Information).

further reaffirming the well-analyzed regiochemical outcome of glycosylation. Hydrogenolysis of **11a**, **11b**, and **11e−i** and debenzoylation−hydrogenolysis of **11c** and **11d** afforded the desired kanamycin B analogues **12a−i**, respectively.

In conclusion, we have successfully developed an efficient strategy for the assembly of kanamycin B-like aminoglycosides via regioselective glycosylation of compound **6** at O6 in excellent yields. The strategy works well with commonly used glycosyl donors and holds a great promise to rapidly construct previously inaccessible and biologically significant analogues of kanamycins and structurally related aminoglycosides.

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Supporting Information Available: ^{1}H, ^{13}C, and 2D NMR spectra for all new compounds and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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