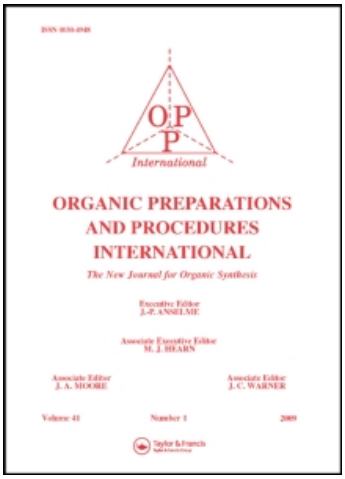

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SYNTHETIC GLYCODIVERSIFICATION. FROM AMINOSUGARS TO AMINOGLYCOSIDE ANTIBIOTICS. A REVIEW

Ravi Rai[a]; Ian McAlexander[a]; Cheng-Wei Tom Chang[a]
[a] Department of Chemistry and Biochemistry, Utah State University, Logan, Utah, USA

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Ravi Rai, Ian McAlexander and Cheng-Wei Tom Chang*

Department of Chemistry and Biochemistry
Utah State University, 0300 Old Main Hill
Logan, Utah 84322-0300, USA
e-mail: chang@cc.usu.edu

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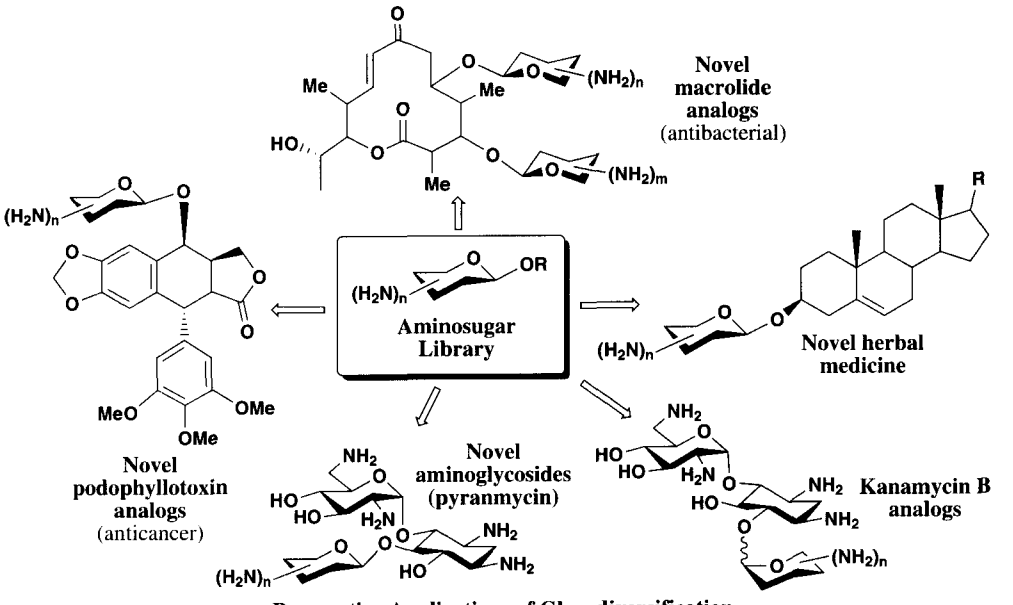
INTRODUCTION

Aminosugars have attracted burgeoning interest due to their widespread applications in chemistry, biochemistry, medicine and other pharmaceutical areas.[1-6] These are a group of structurally diverse unusual sugars bearing amino substitution on a normal sugar scaffold, which have been shown to closely relate to the activity of the aminosugar-containing antibiotics.[7-10]



Prospective Applications of Glycodiversification

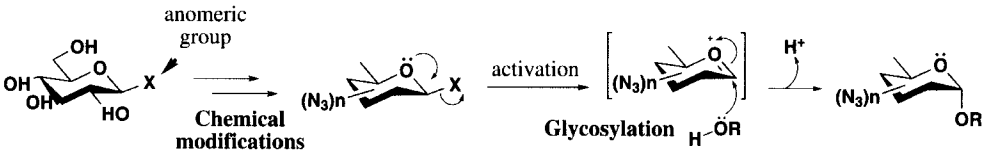
Fig. 1

Since aminosugars are often found in naturally occurring antibiotics, it would be useful to construct a library of naturally occurring antibiotic analogs with the original sugars replaced with synthetic ones. This strategy is termed glycodiversification, a concept with fruitful applications (*Figure 1*).

Unlike furanoses, many pyranoses exist in a chair conformation with distinct axial and equatorial hydroxy groups, which have been utilized as the controls for many stereo- and regioselective chemical transformations.[11] These methods allow for regio- and stereoselective introduction of amino groups onto the sugar generating library of aminosugars. This review will focus on the stereoselective and regioselective introduction of amino groups in a pyranose system and provide a brief coverage of the general synthetic protocols in glycodiversification.

I. SYNTHESIS OF AMINOSUGARS

The syntheses of naturally and non-naturally occurring aminosugars have been well documented.[12-14] Even so, there are several shortcomings in the current synthetic methodology of aminosugars. 1) There is no systematic protocol for the synthesis of a carbohydrate library. In-depth knowledge covering a wide range of carbohydrate-associated reactions is often essential. Therefore, carbohydrate synthesis is considered to be one of the most challenging synthetic tasks. 2) The syntheses of most of the aminosugars begin with different starting materials. For the synthesis of a library of unusual sugars, this will increase the synthetic challenge. In addition, structural variations often alter the chemical reactivity of carbohydrates. For example, a reaction that works on a glucose scaffold may not be effective on a 6-amino (or 6-azido) glucose scaffold, making it very difficult to extend the reported methods to a different sugar. 3) There is a deficiency in current methodologies for the conversion of synthetic aminosugars into glycosyl donors for glycosylation due to a paradox (*Figure 2*). For the introduction of functional groups, such as deoxygenation and aminosubstitution, harsh conditions are often needed, thus, a stable anomeric group is desirable. On the other hand, a labile anomeric group that can be activated under mild conditions is beneficial for effective glycosylation. Clearly, these two criteria are working against each other. To avoid complications during glycosylation, Wong, Crich, and others[15-25] have used arylthio or alkylthio groups, such as phenylthio or ethylthio, as the protecting group on C-1. Phenylthio or ethylthio groups are stable enough to withstand the conditions for amino group incorporation and deoxygenation, and can also be activated for glycosylation directly.



Challenges:
- X group needs to be **stable** enough to endure the conditions for chemical modifications
- X group needs to be **labile** enough to be activated for glycosylation

Challenges in Making the Unusual Sugar Donors

Fig. 2

1. Choice of Starting Sugars

Most of the glycosyl donors, such as glycosyl halides, glycosyl acetates, and glycosyl trichloroacetimidates, are not suitable for the procedures of aminosugar synthesis because of their instability at room temperature and long term storage. Therefore, arylthio or alkylthio groups, such as phenylthio or ethylthio groups, are often used for the synthesis of aminosugars and corresponding derivatives. In addition, methyl glycosides, such as methyl glucoside, are often used as starting materials since the anomeric methoxy group can withstand most of the chemical conditions employed for aminosugar synthesis. Nevertheless, the methoxy group is far too stable to be activated for direct glycosylation. Several Lewis acid-catalyzed hydrolyses are often used for such a purpose but these methods lack generality, especially for perbenzyl protected carbohydrates. However, we have discovered a protocol giving modest to excellent yields for the conversion of diverse modified methyl glycosides into acetyl glycosides, which can be transformed into different glycosyl donors following the reported procedures.

2. Divergent Synthesis

The idea of divergent synthesis is to begin the construction of a library of aminosugars from the same starting sugar, after which the synthesis can be branched into separate routes, leading to different aminosugars at the end.[26] Divergent synthesis reduces the synthetic burden and expedites the timeline for library construction, while still allowing one to obtain a structurally diverse aminosugar library. The drawback, however, is the large-scale initial synthetic steps.

Methyl glucoside is commercially available at relatively low cost, which makes it one of the ideal starting materials for the divergent approach, as long as the synthetic challenges of converting the synthesized carbohydrate derivatives into glycosyl donors can be overcome. We also favor the use of phenylthioglucopyranoside for two reasons. First, unlike ethylthioglucopyranoside, phenylthioglucopyranoside is easy to crystallize and thereby avoids the formidable task of column chromatography. Second, the synthesis of thioglycoside often requires the use of excess thiol. However, the excess thiophenol can be readily removed by co-evaporating with other organic solvents. On the other hand, *p*-thiocresol is a solid at room temperature, making its removal more challenging. Examples of employing these pyranoses as starting material will be discussed later.

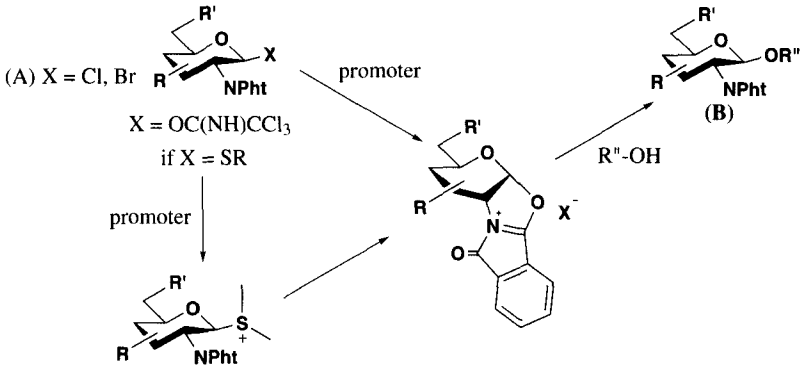
3. General Synthetic Protocols

Three synthetic approaches for the development of general protocols should be considered in advance: amino group incorporation (non-azido and azido approaches), hydroxy group epimerization, and regioselective deoxygenation.

a) Amino Group Incorporation. Non-azido Approach

Introduction of amino groups at C-1 and C-2 positions of a pyranose scaffold *via* the glycal has been reported extensively. Alternatively, commercially available glucosamine and galactosamine can serve as the starting material for 2-aminopyranose. Incorporation of amino groups at C-3 and C-4 is relatively indirect since nucleophilic substitution using amine as the nucleophile is often competed by elimination. Reductive amination (for example: using NH_4OAc and $NaBH_3CN$) of a ketosugar is suitable for installing amino groups only with equatorial configuration. Attaching an alkylamino group at C-6 can be achieved by reductive amination or nucleophilic substitution. In general, we find that it is less convenient to employ amino groups in the synthesis of aminosugars than azido groups. Nevertheless, several representative examples will be discussed below.

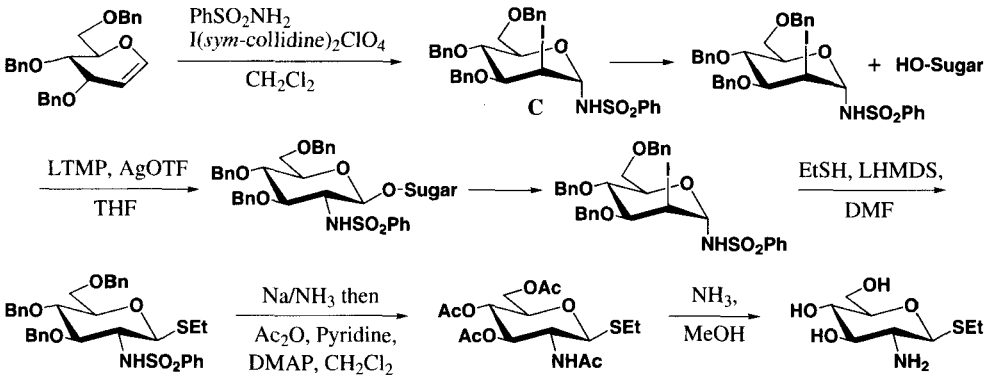
C2-Azaglycosides are ubiquitous building blocks in various biologically important glycoconjugates including glycoproteins, peptidoglycans, glycolipids, and glycosaminoglycans. In this context, the selective *C2-N*-functionalization as well as glycosidic bond formation is synthetically challenging. In 1976, Lemieux *et al.* introduced the use of 2-deoxy-2-phthalimido-glycosyl halides (**A**) in glycosylation reactions as a convenient method for the synthesis of 2-amino-2-deoxy-β-D-glycopyranosides (*Scheme 1*).[27] The β-selectivity comes from the neighbouring group assistance being offered by the bulky phthalimido group.



Synthesis of 2-Amino-2-deoxy-β-D-glycopyranosides

Scheme 1

The participating nature of the phtalimido group governs the stereochemistry of the glycosidic linkage. After glycosylation, the deprotection of the phtalimido to the free amine requires refluxing conditions which could be too harsh for other functional groups to endure. Another novel approach for the introduction of amino groups on both C-1 and C-2 positions was reported by Griffith *et al.*[28] which utilizes the stereoselective iodoglycosylation of glycals with iodonium di-*sym*-collidine perchlorate (IDCP) and benzene sulfonamide to afford 2-iodo-α-sulfonamidopyranoside (*Scheme 2*). The benzenesulfonamide acts as a participating group in glycosylations and gives 2-β-iodo-1-α-sulfonamidohexoses (**C**). In addition, it was found that

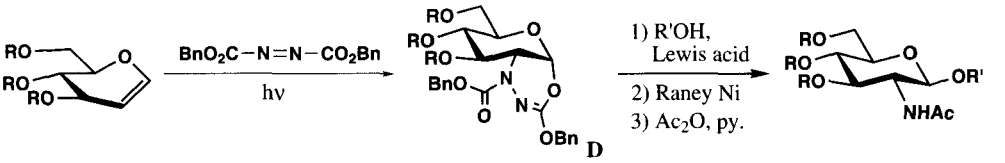


Griffith and Danishefsky Sulfonamidoglycosylation Using Glycals

Scheme 2

the sulfonamide could migrate in the presence of lithium ethanethiolate to give β-glycosides. Deprotection of the sulfonamide followed by acetylation provides 2-*N*-acetamido-β-pyranosides in good yields. The utility of the sulfonamidoglycosylation methodology has been demonstrated in the total synthesis of the natural product chitinase inhibitor, allosamidin and more recently in the total chemical synthesis of an *N*-linked glycopeptide.

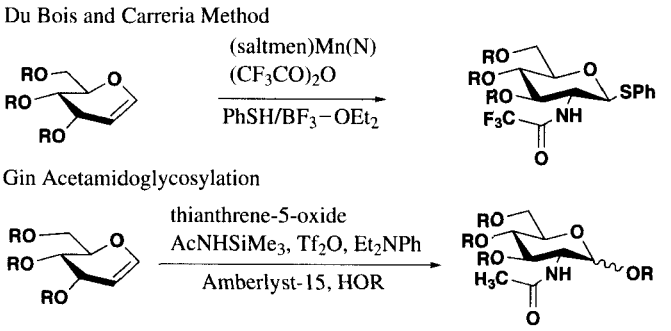
While azidonitration is an extremely useful method for introduction of nitrogen at C-2 of the pyranose ring, amination and glycosylation remain two separate steps requiring the conversion of the azidonitrate into a suitable glycosyl donor for glycosylation. An elegant method was developed by Fitzsimmons/LeBlanc to couple amination with glycosylation into a more concise sequence of synthetic manipulations (*Scheme 3*).[29] The approach taken by Fitzsimmons and LeBlanc involves a photoinduced [4 +2] cycloaddition of dibenzyl azodicarboxylate ($BnO_2CN{=}NCO_2Bn$, DBAD) with glycals to stereoselectively introduce nitrogen at C-2. The resulting cycloadducts (**D**) could then be used directly as donors for glycosylation reactions. Raney Ni deprotection of nitrogen followed by acetylation affords 2-*N*-acetamido-β-pyranosides.



Fitzimmons and Leblanc Cycloaddition Using Gycals

Scheme 3

Recent advances in synthetic methodology have provided new opportunities for one-pot amination and glycosylation of glycals. The extension of the nitrogen transfer nitridomanganese(V) complexes by Du Bois and Carreira allowed the aziridination of glycals with (saltmen)Mn(N) and trifluoroacetic anhydride (*Scheme 4*).[30] In the presence of acid and water the initial product, *N*-trifluoroacetyl aziridine, opens to afford the corresponding free reducing



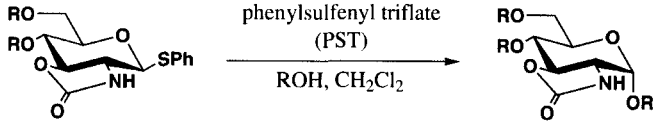
One-pot Syntheses of 2-Aminosugars from Glycals

Scheme 4

sugars. However, treatment of the *N*-trifluoroacetylaziridine with a Lewis acid and thiophenol affords the thioglycoside in good yield and high stereoselectivities. More recently, the introduction of one pot acetamidoglycosylation by Gin[31] and coworkers provides direct access to 2-*N*-acetamido-β-pyranosides. The reaction of the glycal with the first set of reagents results in the formation of an oxazoline intermediate, which upon treatment with acidic resin and alcohol acceptors, opens to afford the β-glycoside products in good to moderate yield. This is the first method that directly affords the desired 2-*N*-acetamido-β-pyranosides from glycals, which should facilitate the synthesis of glycoconjugates containing these monosaccharides.

b) Amino Group Incorporation. Azido Approach

Typically, the amino group needs to be protected in order to make the synthesis of the glycosyl donor and glycosylation feasible. Unfortunately, most of the nitrogen protecting groups that have been developed participate in glycosylation reactions and afford the β-glycoside as the major product. Therefore, the synthesis of 2-*N*-acetamido-α-pyranosides relies upon 2-azidoglycosyl donors or other non-participating protecting groups on the nitrogen.[32] Very recently, Kerns and coworkers have utilized the oxazolidinone protecting group between the 3-OH and 2-NH of the pyranose ring to effectively eliminate neighboring group participation in glycosylation reactions (*Scheme 5*).[33] This simple and elegant strategy provides a general and useful solution to the synthesis of α-linked glycosides of 2-aminosugars.



Oxazolidinone Protection of 2-Aminosugars for the Synthesis of α-Linked Glycosides

Scheme 5

A brief review of the commonly used amine protecting groups is shown in *Table 1*. The protecting groups that influence the stereoselectivity of glycosylation are specifically cited.

Table 1. Commonly Used Amine Protecting Groups

Protecting Group	Formation	Cleavage	Nature of Protecting Group	Ref.
N-Phthalimido (if present on C-2)	a) Phthalic anhydride, $CHCl_3$, 70°C b) Et_3N, 0°C	NH_2NH_2•OAc, reflux	Participating, favors β-glycoside	34
Acetyl	Ac_2O, Pyridine	a) $(Boc)_2O$, DMAP, THF b) NaOMe, MeOH c) TFA, NaOH	----	35
Fmoc (9-fluorenyl-methyl chloroformate)	Fmoc-Cl, dioxane, Na_2CO_3, 14 h	20% piperidine	----	36
Troc (trichloroethyl oxycarbonyl) (if present on C-2)	Cl_3CCH_2OCOCl, Pyridine	NaOMe, MeOH	Armed effect, increases reactivity, favors β-glycoside	37
TCP (tetrachlorophthaloyl) (if present on C-2)	Tetrachlorophthalic anhydride, microwaves, 90%	a) $NaBH_4$ b) AcOH	Armed effect, increases reactivity, favors β-glycoside	38
Trifluoroacetyl (if present on C-2)	a) NH_2NH_2, EtOH b) TFAA, Pyridine, Ac_2O, Pyridine	K_2CO_3, MeOH	Participating group	39
CBZ (benzyl chloroformate)	$PhCH_2OCOCl$, Na_2CO_3, H_2O, 0°C	H_2/Pd-C or TMSBr, PhSMe, TFA, 0°C	----	40
$(Boc)_2O$ (ditertbutyl dicarbonate)	$(Boc)_2O$, Et_3N, CH_2Cl_2, 0°C	TFA/CH_2Cl_2	----	----

We favor the popular azido group as an amino group surrogate for the synthesis of aminosugars (or azidosugars) because of the following advantages: 1) An azido group can be easily installed from an activated hydroxy group *via* S_N2 substitution; 2) The azido group is relatively stable to many reductive and oxidative conditions; 3) Unlike the carbamate type protecting group for amines, azido compounds have good solubility in organic media, allowing expedient chromatographic purification; 4) Azido groups can be converted to amino groups conveniently by hydrogenation or the Staudinger reaction; 5) Azido groups can be modified to the corresponding amide *via* a Staudinger ligation. These reactions are particularly useful for the synthesis of oligosaccharides as shown below in *Table 2*. In addition there are some literature procedures where azides can selectively be reduced to the corresponding amino group.

Table 2. Transformation of Azido Groups

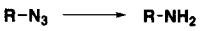
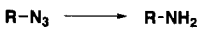
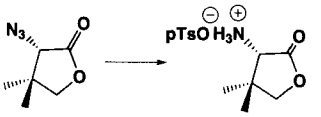
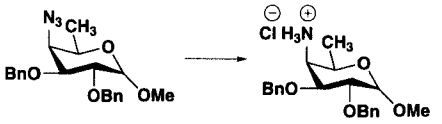
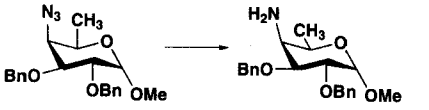
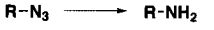
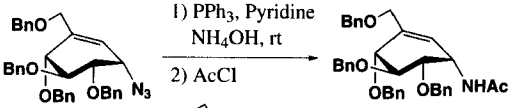
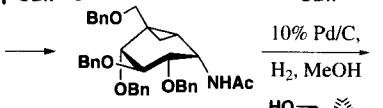
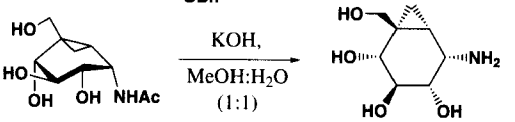
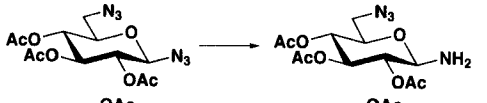
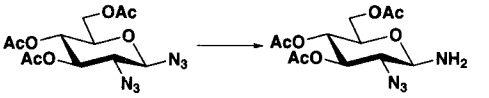
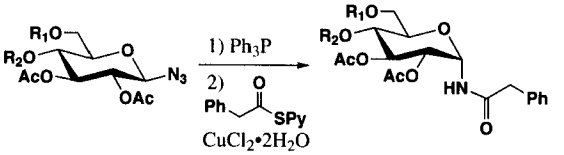
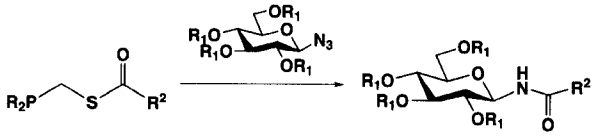
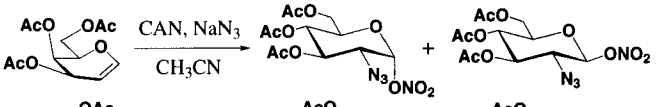
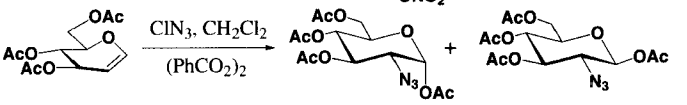
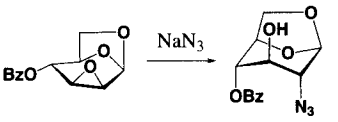
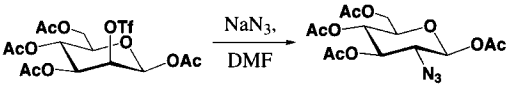
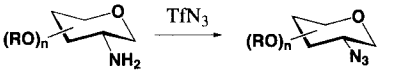
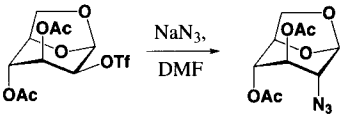
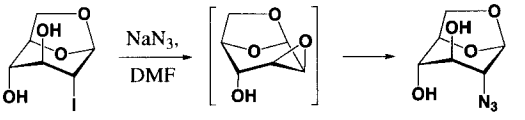
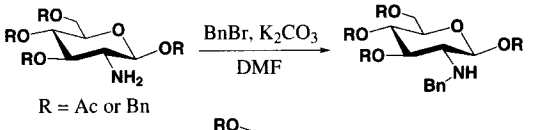
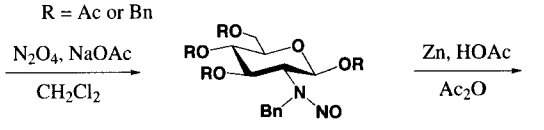
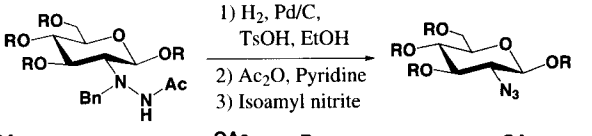
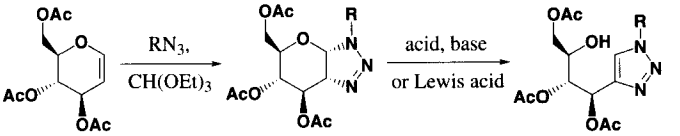
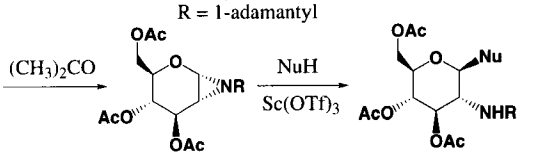
Reaction	Conditions	Ref.
	H_2, Ra-Ni, THF	41
	Pd/C, H_2, EtOH/PMe_3, THF, 0.1 N NaOH	42, 78
	DTT, Et_3N	43
	Pd/C, H_2, pTsOH, MeOH	44
	1) $LiAlH_4$, 1,4-dioxane 2) HCl, ether	----
	$SnCl_2$, Et_3N, PhSH	45
	TMSCl, NaI, CH_3CN	46
	Ph_3P, Pyridine, NH_4OH, rt	47
		
		
	benzyltriethylammonium tetrathiomolybdate ($[BnNEt_3]_2$-MoS_4), CH_3CN:H_2O, rt	48
		
	Ph_3P	49
	----	50

Table 3. Methods for the Synthesis of 2-Azidopyranoses

Transformations	Notes	Ref.
Azidonitration of glycal		51
Haloazides to glycals		52
Opening of the corresponding 2,3-epoxide derivatives		53, 56, 57
Substitution of 2-sulfonate derivatives		54, 55, 58, 59
diazo transfer of 2-amino-2-deoxyaldoses		65, 65, 66, 67
1,6-anhydro-β-mannopyranoses		60-62
Azide displacement in 2-deoxy-2-iodo-1,6-anhydroglucopyranose		63
Through 2-deoxy-2-hydrazino-glucopyranose	 R = Ac or Bn  	68
Through triazolines (*via* glycal)	 R = Bn R = 3,5-DMB R = 1-adamantyl 	69, 70

In general, there are two main strategies for introducing azido groups onto the pyranose scaffold: addition and substitution reactions. The procedures for the diastereoselective incorporation of azido groups *via* addition reactions have attracted a lot of attention, especially for the 2-azidopyranoses. There are various approaches to introduce an azido group. These include, azidonitration of glycal,[51] addition of haloazides to glycals,[52] from 1,6-anhydro sugars by opening of the corresponding 2,3-epoxide derivatives,[53,56,57] azide substitution of 2-sulfonate derivatives,[54,55,58,59] diazo transfer of 2-amino-2-deoxyaldoses using TfN_3,[64-67] azide substitution 1,6-anhydro-β-mannopyranoses,[60-62] azide displacement in 2-deoxy-2-iodo-1,6-anhydroglucopyranose,[63] or through 2-deoxy-2-hydrazinoglucopyranose (*Table 3*).[47,68]

The procedures for the substitution of a hydroxy group for an azido group have also been well-documented and can be grouped into two types of transformations: direct hydroxy group substitution and two-step substitution processes. The former can be achieved by using DPPA (or HN_3), PPh_3 and DEAD (or DIAD) through a Mitsunobu reaction. It is a one-pot reaction, however, purification is often complicated by the multiple reagents used. The second method involves converting the hydroxy group into a leaving group *via* tosylation, mesylation, or triflation, followed by nucleophilic substitution with azide ion. The crude tosylate, mesylate, or triflate can be used directly for azide substitution. Selective tosylation of a primary hydroxy group in the presence of secondary hydroxy groups is one of the advantages of employing TsCl. Unlike tosylation, mesylation can be used for converting both primary and secondary hydroxy groups to azido groups. Nevertheless, higher temperatures (up to 120°C) are needed for the azide substitution of a secondary mesylated hydroxy group. Triflation facilitates azide substitution at room temperature, albeit the reagent, triflic anhydride, is more expensive than TsCl and MsCl. A summary of typical azide substitution conditions is shown in *Table 4*.

Table 4. Common Protocols for Azide Substitution of a Hydroxy Group

Types of transformations	Reagents	Typical conditions	Types of hydroxy groups	Notes	Ref.
One-pot	DPPA(or HN_3), PPh_3 and DEAD (or DIAD)	Low temp. (–40° to 0°C), overnight	1° and 2°	Complex mixture may be obtained	70
Two-step	TsCl then NaN_3	80°C, overnight	1° (2° tosylated cannot be replaced with N_3^-)	Can be used for selective azide substitution	26
Two-step	MsCl then NaN_3	120°C, 1-2 days	1° and 2°	MsCl is cheaper than Tf_2O	71
Two-step	Tf_2O then NaN_3	0°C to R.T., overnight	1° and 2°	Most expedient	26

c) Epimerization of Hydroxy Group

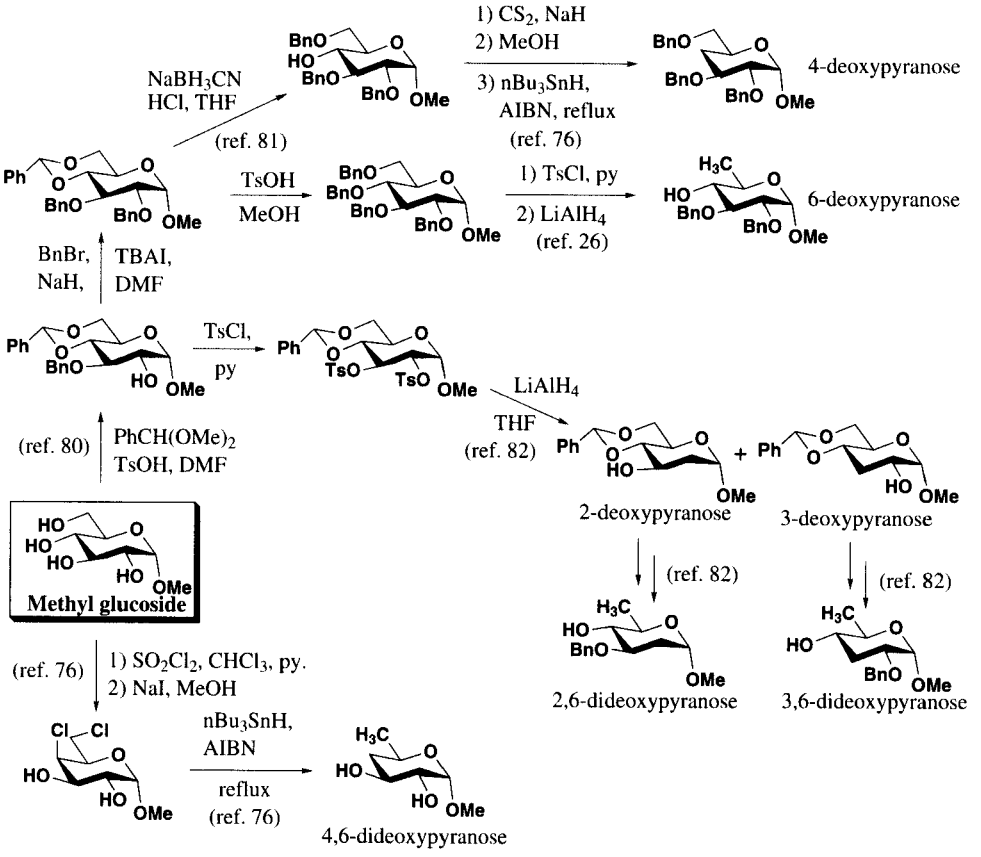
Since the substitution of a hydroxy group with an azido group is often carried out *via* S_N2 substitution, it is essential to be able to stereoselectively epimerize a hydroxy group on the glucopyranose scaffold to ensure the desired stereochemistry of the installed azido group. Many procedures have been reported in the literature, which include oxidation-reduction and nucleophilic substitution processes. The former involves an oxidation of a hydroxy group to a keto group followed by stereoselective hydride reduction. In this method, the vicinal protecting groups influence the stereoselectivity. The latter can be carried out by converting the secondary hydroxy group into a leaving group followed by S_N2 substitution using, for example, OAc^- or NO_2^- as nucleophiles. Due to steric hindrance of the secondary hydroxy groups on a pyranose scaffold, it is often unsatisfactory to use the Mitsunobu reaction for epimerization. A summary of typical epimerization conditions is shown in *Table 5*.

Table 5. Common Protocols for Epimerization of Hydroxy Group

Transformations	Examples of Reagents	Notes	Ref.
Oxidation/ reduction	1) $(COCl)_2$, DMSO; DIPEA 2) $NaBH_4$	Vicinal protecting groups (ex. Bn) are essential for the selectivity. Others (ex. Bz) may offer lower or no selectivity toward epimerization	72
Multi-step	1) Tf_2O 2) $(n\text{-}Bu)_4N^+ NO_2^-$	$(n\text{-}Bu)_4N^+ NO_2^-$ can be soluble in CH_2Cl_2, providing better results than reagents like $NaNO_2$	73
Multi-step	1) Tf_2O 2) $(n\text{-}Bu)_4N^+ OAc^-$ 3) hydrolysis of OAc	$(n\text{-}Bu)_4N^+ OAc^-$ can be soluble in CH_2Cl_2, providing better result than reagent like KOAc or CsOAc	74

d) Regioselective Deoxygenation

Many aminosugars contain the features of deoxygenation. There are many well-established methods in the literature for deoxygenation, nevertheless, harsh conditions are often employed. Therefore, deoxygenation generally proceeds before the introduction of the azido group. Tosylation followed by hydride reduction is the most convenient method for 6-deoxygenation. For deoxygenation of a secondary hydroxy group, Barton reduction[75] or dehalogenation[76] are the commonly employed methods. Dideoxysugars can be synthesized in a similar fashion. Typical procedures for deoxysugars synthesis are summarized in *Scheme 6*. Azido groups can be reduced under conditions for deoxygenation using $LiAlH_4$ or $n Bu_3SnH$. Therefore, to avoid an additional protection step, it is recommended that azido incorporation be carried out after deoxygenation.



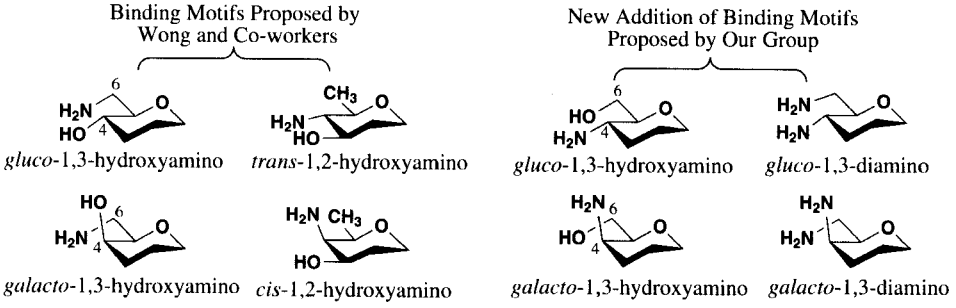
Examples of Deoxygenation

Scheme 6

4. Examples for the Synthesis of Aminosugars

a) Synthesis of 4- and/or 6-Aminopyranoses - Binding Motif-based Aminosugar Synthesis

Given the complexity of the aminosugars found in naturally occurring aminoglycoside antibiotics, it is arduous to outline or predict conclusions regarding the structure-activity relationship

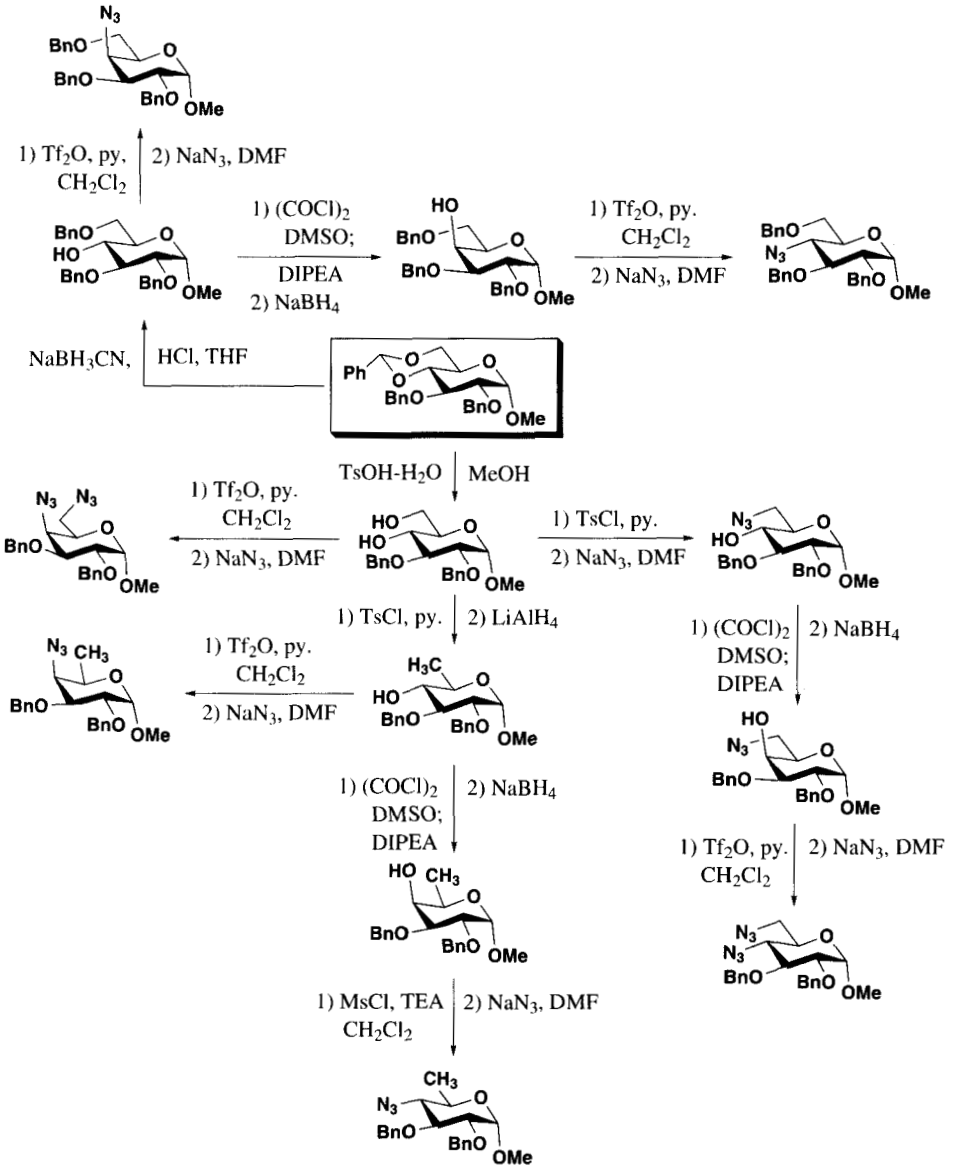


Proposed Binding Motifs of Aminosugars

Fig. 3

of unusual sugars among the vast numbers of unusual sugar-containing antibiotics. Therefore, Wong and coworkers have proposed several binding motifs based on the commonly observed structural features of unusual sugars on aminoglycosides (*Figure 3*).[77,78] These include *gluco-/galacto*-1,3-hydroxyamino and *cis-/trans*-1,2-hydroxyamino substructures. Following these binding motifs, four new natural and non-natural binding motifs, including *gluco-/galacto*-1,3-diamino and variants of *gluco-/galacto*-1,3-hydroxyamino substructures have also been proposed (*Figure 3*).[79]

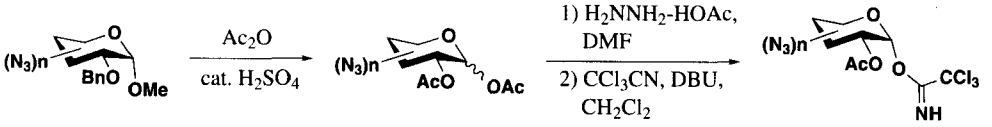
The divergent synthesis of the aminosugar library is outlined in *Scheme 7*.[26] Since



Divergent Synthesis of Aminosugars with Designed Binding Motifs

Scheme 7

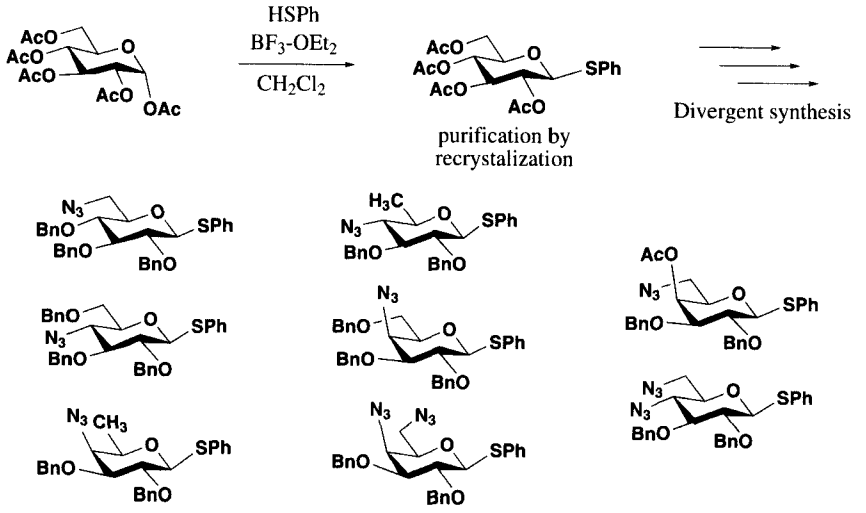
methyl glucopyranoside was used as the starting material, a general procedure for converting the synthesized azidosugars into glycosyl donors is necessary. Selective hydrolysis of the anomeric methoxy group to a hydroxy group for the perbenzylated azidosugars based on the reported methods[83-87] was problematic due to the concomitant deprotection of the benzyl groups. However, a general protocol for converting these azidosugars into glycosyl donors was developed. The anomeric methoxy group and all the benzyl groups can be converted into acetyl groups using Ac_2O with a catalytic amount of H_2SO_4 (*Scheme 8*). The resulting acetyl glycosides can then be transformed into the glycosyl trichloroacetimidate as the glycosyl donor,[88] which could then be coupled to the acceptor of choice. The constructed aminosugar library will undergo glycosylation in favor of the formation of the β-glycosidic bond due to the presence of an acetyl group at the *O*-2 position.



General Procedure for the Synthesis of Glycosyl Donors

Scheme 8

Employing the philosophy of divergent synthesis and phenylthioglucopyranoside as the starting material, the other library can be constructed in a similar fashion as previously described (*Scheme 9*).[89] The importance of having a 2-*O*-benzyl group in this library will be discussed later.

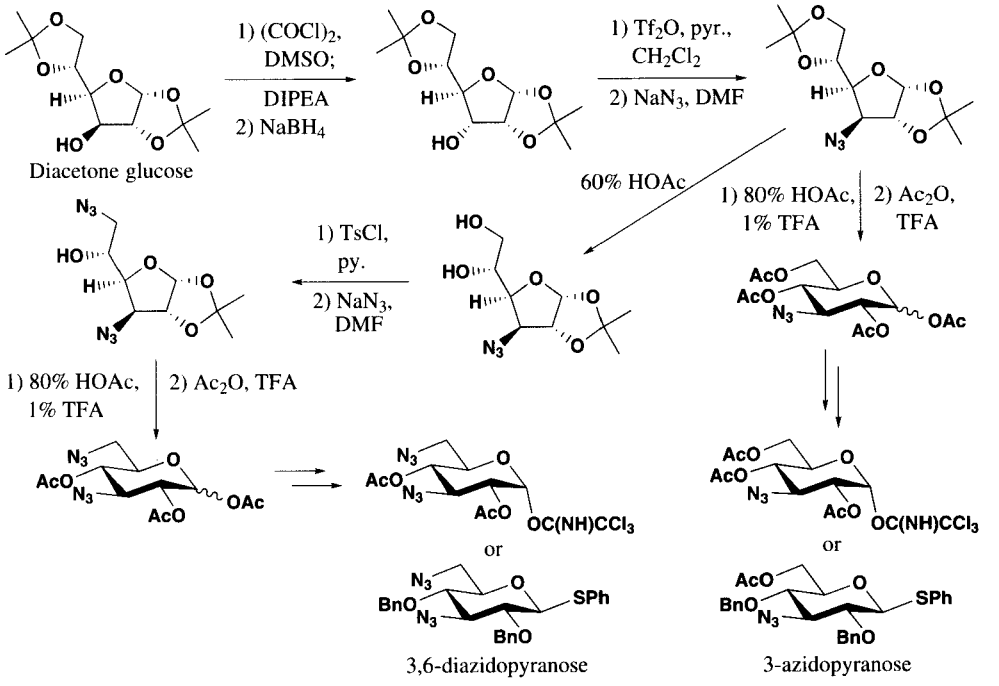


Synthesis of Glycosyl Donors from Phenylthioglucose

Scheme 9

b) Synthesis of 3-Aminoglycopyranoses

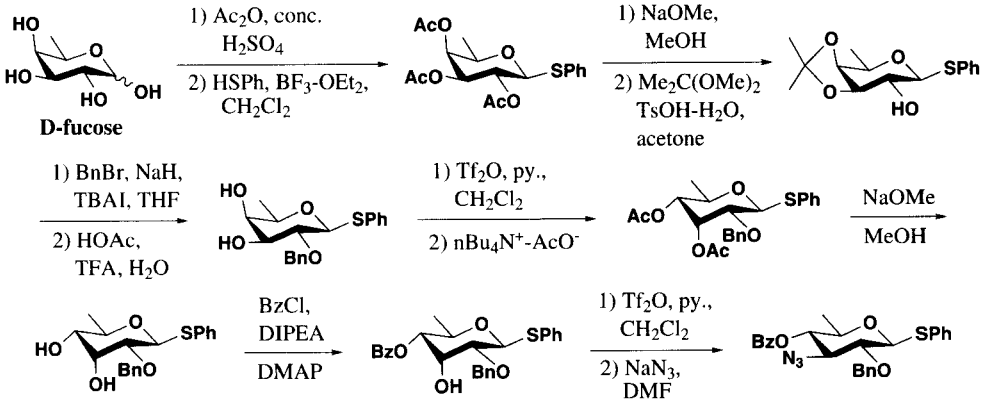
The trichloroacetimidate and phenylthio glycosyl donors of 3-azidoglucopyranose or 3,6-diazidoglucopyranose can be readily obtained from diacetone-D-glucose *via* reported methods (*Scheme 10*).[88] While 3-azidopyranoses can be prepared readily from diacetone-D-



Examples for the Synthesis of 3-Azidosugars

Scheme 10

glucose, the synthesis of 3-azidopyranoses with deoxygenation is rather challenging although it can be achieved from D-fucose (*Scheme 11*).[152] Alternatively, 3,6-dideoxy-3-aminopyranoses can



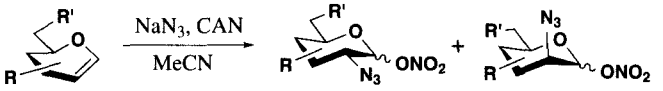
Synthesis of 3,6-Dideoxy-3-aminopyranoses

Scheme 11

be prepared from the route using diacetone-D-glucose.[153] Nevertheless, the azido group was reduced and protected as a carbamate.

c) Synthesis of 2-Aminoglycopyranoses

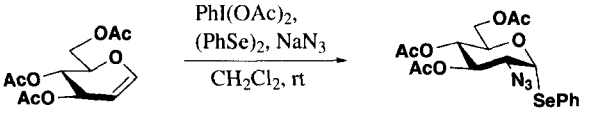
Of the above methods,[51-68] the most widely used reaction for the preparation of 2-azido analogues was the azidonitration of glycals developed by Leimieux and co-workers in 1979 (*Scheme 12*).[51] This reaction occurred by the addition of ceric ammonium nitrate and sodium azide on protected glycals to afforded epimeric mixtures of 2-azido-2-deoxy-1-*O*-nitropyranoses. The stereochemistry of the addition favored the formation of the equatorial 2-azido derivative with respect to the axial epimer.



Synthesis of 2-Azido Sugars from Glycals

Scheme 12

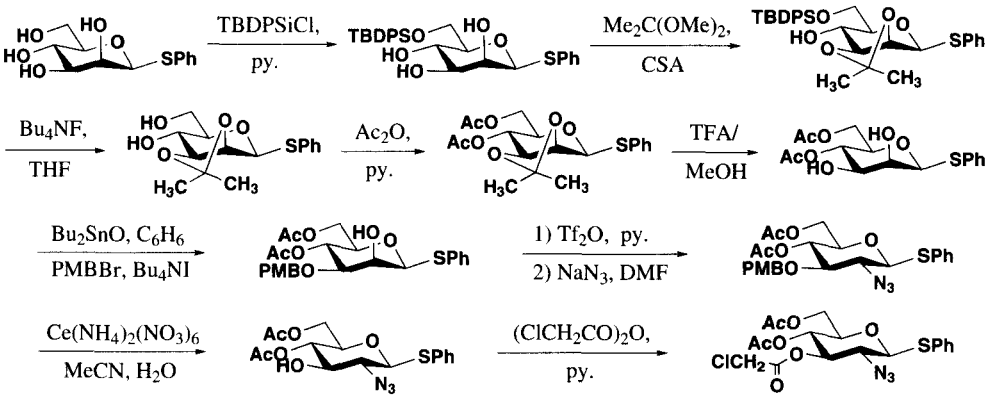
This protocol, however, brings with it an additional step, that of the conversion to the corresponding glycosyl donor. Azidophenylselenylation of the glycal double bond is a one-step approach to introduce two molecules as reported by Tingoli *et al.*[91] When this reaction is initiated by an electrophilic phenylselenium species like PhSeCl in the presence of azides, Markovnikov adducts are usually obtained. Nevertheless, Tingoli *et al.* obtained anti-Markovnikov addition products by treatment of an olefin with sodium azide and diphenyl diselenide in the presence of (diacetoxyiodo) benzene. They proposed a mechanism initiated by addition to the olefin of an azido radical formed by oxidation of the azido ion. This reaction was incorporated by Santoyo-Gonzalez *et al.* and others[92,93] to carry out a one-step regiospecific preparation of 2-azido-2-deoxy glycosides bearing a leaving group with good glycosylating properties (*Scheme 13*). Another approach, used by Pozsgay *et al.*,[94] capitalizes on the observation of van Boom *et al.*, who found that azide substitution of a triflyloxy group at C-2 of β-linked



Santoyo-Gonsalez Approach

Scheme 13

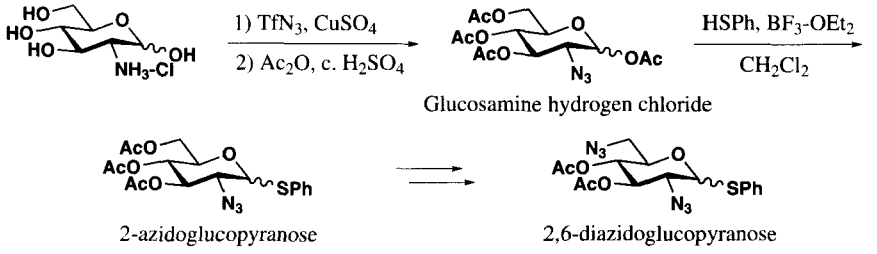
mannopyranose derivatives affords 2-azido-*gluco*-compounds, whereas the corresponding α-diastereomers are unreactive.[58] Pozsgay *et al.* used a manno precursor that already contained a good leaving group at the anomeric position which did not interfere with the nucleophilic introduction of the azido group and could be exploited for anomeric activation (*Scheme 14*).



Pozsgay Approach

Scheme 14

Alternatively, the 2-azidoglucopyranose or 2,6-diazidoglucopyranose can be obtained from commercially available glucosamine (*Scheme 15*).[90]

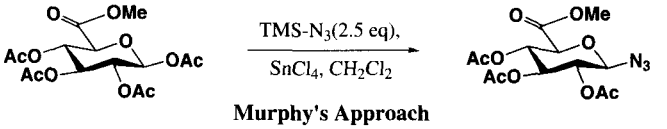


Examples for the Synthesis of 2-Azidosugars

Scheme 15

d) Synthesis of 1-Aminoglycopyranoses

The synthesis of C-1 azido sugars has been reported on numerous occasions.[95,96] The general protocol as adopted by Murphy *et al.* involves the introduction of a stable azide at the anomeric center using $SnCl_4$ and TMS-N_3 (*Scheme 16*)



Murphy's Approach

Scheme 16

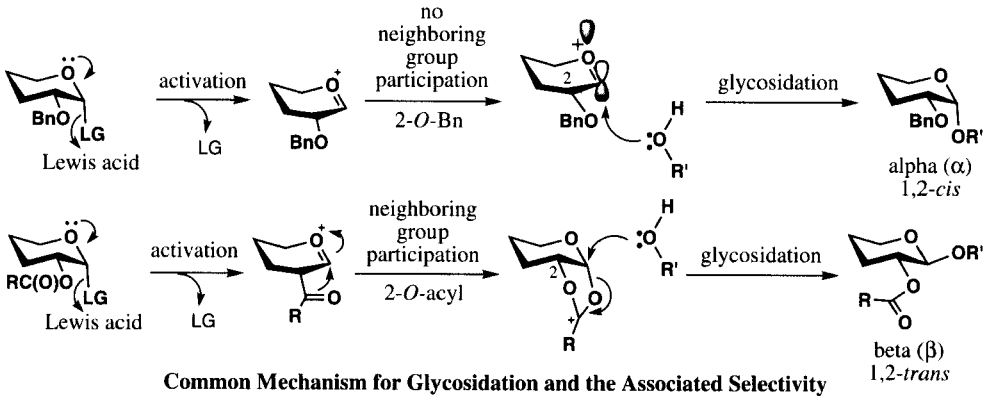
II. STEREOSELECTIVE GLYCOSYLATION

1. Background in Glycosylation

It has long been acknowledged that "half of the sugar chemistry resides at the anomeric carbon atom". Indeed, soon after the total synthesis of glucose by Emil Fischer,[97] he demon-

strated the unique properties of the hemiacetal function by an acid-catalyzed condensation reaction with methanol to give the corresponding methyl glucoside. We now know this method as the Fischer glycoside synthesis.[98] Remarkably, there was no need for protecting groups, as more often is the case today in such transformations. Since then, generations of 20th century carbohydrate chemists have instinctively and steadily contributed to the art and science of glycoside synthesis while experiencing many challenges.[99] Today, the total synthesis of an oligosaccharide comprising over a dozen sugar units can be achieved in relatively good yield and with impressive stereocontrol, especially under optimized conditions. Newer methods of sterocontrolled glycoside synthesis, including oligosaccharides, have been a great source of challenge and inspiration for several decades since the venerable Koenigs-Knorr methods and its variations.[100]

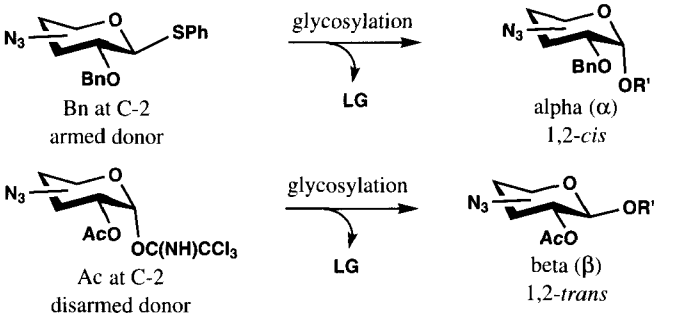
The formation of a β-glycosidic bond can be achieved by the presence of an acyl protecting group at the *O*-2 position *via* neighboring group participation (*Figure 4*). The formation of a α-glycosidic bond is, however, more challenging, despite great advances. The stereocontrolled synthesis of α-glycosides can be affected by such factors as electronic effects, steric hindrance, solvent, and conformation. To date, there is no general protocol for stereoselective glycosylation for formation of a α-glycosidic bond despite numerous efforts.



Common Mechanism for Glycosidation and the Associated Selectivity

Fig. 4

There are myriad glycosylation methods documented in the literature. Nevertheless, few of these methods are compatible with the synthesized aminosugar donors. In addition, the armed and disarmed effects (defined below) of protecting groups and azido groups on the reactivity of pyranose further limit the options for available donors.[101] The reactivity of glycosyl donors can be enhanced with an electron-donating protecting group, such as benzyl (Bn), leading to the term "armed glycosyl donor" (*Figure 5*). On the other hand, having an electron-withdrawing protecting group, such as acetyl (Ac), benzoyl (Bz), or azido group, will decrease the reactivity of the glycosyl donor, which is classified as a "disarmed glycosyl donor" (*Figure 5*). To simplify the options, accommodate the variation in the reactivity of glycosyl donors, and acquire essential stereoselectivity for glycodiversification, we have discovered that, for the formation of β-linked



Concept for Stereoselective Glycosidation of Diverse Glycosyl Donors

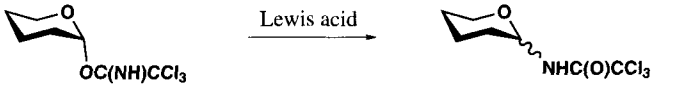
Fig. 5

aminosugar, trichloroacetimidate group is superior for disarmed donors bearing an Ac group at *C*-2. The phenylthio group is suitable for armed donors bearing a Bn protecting group at *C*-2, which can be used for the formation of α-linked aminosugars. The discussion of glycosylation in this review will follow this narrative.

2. Formation of a β-Glycosidic Bond

The selectivity for the β-glycosidic bond is better referred to as the preference for the formation of a 1,2-*trans*-glycosidic linkage in pyranoses with *galacto*- or *gluco*-configurations. For the pyranoses with *manno*-configuration, 1,2-*trans* (or 1,2-*cis*) is the better description for the preferred glycosidic bonds. As mentioned previously, high selectivity for the formation of the β-glycosidic bond can be achieved by the presence of an acyl protecting group at the *O*-2 position *via* neighboring group participation. However, it is known that the presence of electron-withdrawing groups, such as Ac, Bz, and N_3 groups, will lower the reactivity of azidosugars toward glycosylation,[101] therefore, a more reactive anomeric group is desirable. Glycosyl trichloroacetimidate,[102] prepared by the reaction of sugars with an anomeric hydroxy group and trichloroacetonitrile in the presence of DBU, is used frequently due to its superior reactivity for glycosylation. Thus, for a library of azidosugars with peracetyl groups, glycosyl trichloroacetimidates are more advantageous than phenylthioglycosides.

Two problems often encountered with glycosyl trichloroacetimidates are the formation of undesired acetylamidoglycoside by-product *via* the Chapman rearrangement (*Figure 6*),[103-105]



Chapman Rearrangement

Fig. 6

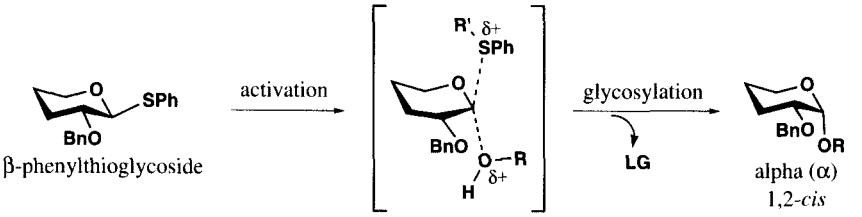
and the lack of stability for long-term storage. Therefore, variants of trichloroacetimidate donors, such as *N*-phenyl trichloroacetimidate, have also been developed.[106-108]

3. Formation of a α-Glycosidic Bond

The selectivity for the α-glycosidic bond is better referred to as the preference for the formation of a 1,2-*cis*-glycosidic linkage in pyranoses with *galacto*- or *gluco*-configurations. The preference for the α-glycoside can be directed most conveniently by both the kinetic anomeric effect, and by avoidance of neighboring group participation at C-2.[109] The former can be further tuned by the control of temperature and solvent. Nevertheless, a general and stereospecific protocol has yet to be established. The latter can be achieved by the introduction of ether type protecting groups such as Bn or PMB. The presence of electron-donating groups, such as Bn or PMB, will, however, increase the reactivity of glycosyl donors toward glycosylation, making the anomeric trichloroacetimidate too reactive to be properly purified. Therefore, a more stable but readily accessible phenylthioglycoside is more suited for the formation of the α-glycosidic bond.

Thioglycosides have been extensively studied as useful glycosyl donors due to their high stability under many organic operations.[154] On the other hand, other glycosyl donors, such as, glycosyl trichloroacetimidates and bromides are preferably prepared just before the glycosylation step. Thioglycosides are stable for long-term storage, and can be activated by various thiophilic agents such as NBS,[110] PhHgOTf,[111] DMTST,[112] IDCP,[113] NIS,[114] and $TrClO_4$.[115]

It is also proposed that a β-phenylthioglycoside may provide superior 1,2-*cis*-selectivity than an α-phenylthioglycoside due to a S_N2 type glycosylation mechanism. The combined features of 2-*O*-Bn and β-phenylthioglycoside can be generated as described previously. The use of ether mixed with CH_2Cl_2 is also known to increase the selectivity for the α-glycosidic bond, presumably due to the preference for this S_N2 type of glycosylation mechanism, which is favored in less polar solvents like ether (*Figure 7*).[22,116]



S_N2-type Glycosylation Mechanism and Associated Selectivity

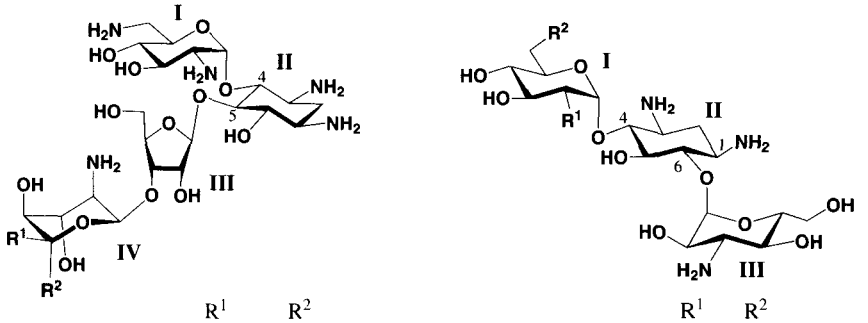
Fig. 7

III. AMINOGLYCOSIDE ANTIBIOTIC SYNTHESIS

1. Background

One of the immediate applications of an aminosugar library is the synthesis of aminoglycoside antibiotics since they consist of, primarily, aminosugars that are assembled *via* specific glycosidic linkages. Aminoglycoside antibiotics, such as neomycin and kanamycin, have been widely used against both gram-positive and gram-negative bacteria for over fifty years (*Figure 8*).[4,117] Unlike vancomycin, the so-called last line of defense, which is active only

against gram-positive pathogens, aminoglycoside antibiotics have the advantages of high and broad-spectrum activity.



Structures of Neomycin and Kanamycin

Fig. 8

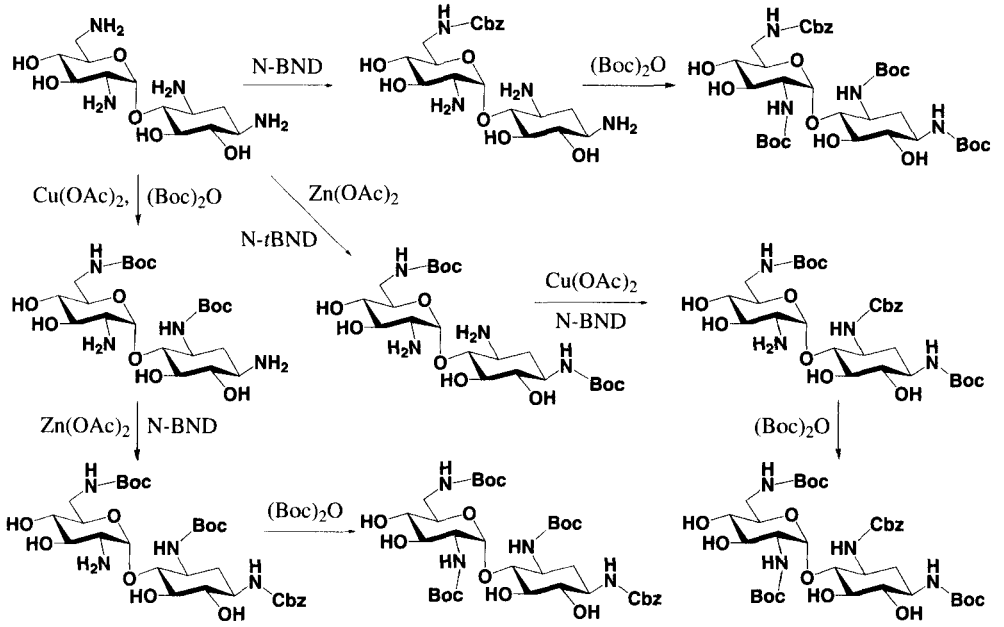
Neomycin and kanamycin are two of the most studied aminoglycoside antibiotics. Neomycin belongs to a group of aminoglycosides containing a 4,5-disubstituted 2-deoxystreptamine core, while kanamycin contains a 4,6-disubstituted 2-deoxystreptamine core. These two antibiotics exert their antibacterial activity by binding selectively toward the A-site decoding region of 16S rRNA, thereby disrupting protein synthesis.

Nevertheless, there are two problems associated with aminoglycoside antibiotics. The first one is the rapid emergence of drug resistance from infectious microorganisms.[118-120] The second problem is their relatively high cytotoxicity; therefore, aminoglycosides are generally administered orally with close monitoring or are limited to external use. However, with recent discoveries from structural studies involving aminoglycoside-bound rRNA molecules,[121-123] the X-ray structure of aminoglycoside-modifying enzymes,[124-130] and advances in carbohydrate synthesis, aminoglycoside antibiotics have become a focus for new drug development.[117] In general, there are two types of approaches reported for syntheses of new aminoglycoside antibiotics. The first one is modification of existing aminoglycosides, which is well-reviewed by Mobashery and co-workers.[117a] The second approach is to apply glycosylation strategies on selected cores, such as 2-deoxystreptamine (ring II) and neamine (rings I and II), and create libraries of new aminoglycosides. The first strategy has been pioneered by Umezawa,[117b] Remers,[140] and others followed by Mobashery[117c] and Hannessian.[147,148] An example will be given below. The latter arises from the concept of glycodiversification.

2. Approach from Modifications of Existing Aminoglycosides

Due to the amino groups present on aminoglycoside, one of the challenging tasks in this approach is the regioselective protection and modification of amino groups. Over the years there

have been numerous protecting groups employed to protect the amine functionality in non-regio- or regioselective fashions. For example, Mobashery and his co-workers have used *N*-benzyloxycarbonyloxy-5-norbornene-endo-2,3-dicarboximide (*N*-BND) for introduction of the carbobenzyloxy (Cbz) group on free neamine (*Scheme 17*).[131] They also used *N*-butoxycarbonyloxy-5-norbornene-endo-2,3-dicarboximide (*N*-*t*BND), a sterically encumbered reagent, for introduction



Selective Protection of Amino Groups

Scheme 17

of the butoxycarbonyl (Boc) in the presence of zinc acetate to furnish a di-Boc analogue as the major product. Next, they found that Neamine coordinates the copper(II) ion differently than the zinc ion. When they reacted di-*tert*-butyldicarbonate with neamine in the presence of the copper (II) ion they could selectively protect the N3 and N6' amines. Subsequently, reaction with N-BND in the presence of zinc acetate furnished the mono-Cbz protected analogue along with a small quantity of the di-Cbz derivative, which could be separated by column chromatography.

However, the above protocol has its limitations. First, the poor solubility of polycarbamate groups used for protection of amino groups results in difficulties in purification and characterization of these compounds. Second, the aminoglycoside scaffolds impose limited options for structural modifications. Third, the regioselective methods for amino group protection may vary among various classes of aminoglycosides, thus increasing the synthetic burden. Nevertheless, it is more cost-efficient in producing large quantity of modified aminoglycosides, such as amikacin.

Wong and his co-workers have used N_3 as an surrogate of amino group for most of their sugars[22,101] whereas E. Riguet *et al.* have used trityl groups to protect their amino groups.[132] The azido group-modified aminoglycosides are less convenient for scale-up production. In the latter case, the bulkiness of the trityl group influences the regioselective modification of the hydroxy groups. However, these methods are valuable in producing guidelines for possible modifications on existing aminoglycosides.

3. Glycodiversification Approach. Preparation of a Pyranmycin Library

The glycodiversification approach is advantageous in expedient construction of a library of aminoglycosides for revealing the essential structure activity relationship (SAR). The introduced structural features can be free of limits imposed by the existing aminoglycoside scaffold. However, it is generally more difficult for scale-up synthesis. We will use pyranmycin (neomycin class) and kanamycin as examples for the following discussion.

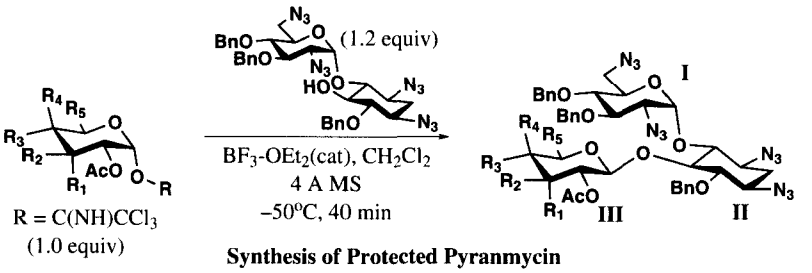
Pyranmycin prepared by chemical synthesis can be viewed as a neomycin type of antibiotic.[26,88] However, pyranmycin differs from neomycin in two aspects: (1) pyranmycin contains a β-linked pyranose as the ring III component, while neomycin contains a furanose, and (2) pyranmycin represents a family of over thirty structurally different members bearing modifications on ring III.

Neomycin is also known to be labile under acidic conditions due to the presence of a glycosidic bond from ring III furanose, which degrades readily into less active neamine (rings I and II) and inactive neobiosamine (rings III and IV). Since the corresponding glycosidic bond of pyranmycin is made from a pyranose, this gives pyranmycin superior stability to acidic conditions.[133] It has been reported that the neamine component (ring I and ring II) is essential for the antibacterial activity of aminoglycoside antibiotics, such as neomycin and kanamycin.[22] Therefore, it is expected that using the glycodiversification strategy to replace ring III and ring IV with a pyranose will generate a library of new aminoglycoside antibiotics, pyranmycins, with improved acid-stability. It is also likely that the cytotoxicity of aminoglycosides can be reduced due to the lower orally administered dosage needed for achieving the therapeutically effective concentration of antibiotics.

Several neomycin and ribostamycin (rings I, II and III of neomycin) analogs have been synthesized and studied.[134-142] Some of them show remarkable antibacterial activity. However, the acid-labile glycosidic bond is present in these designs. Only two examples use D-glucopyranose as the ring III component *via* the α and β linkages.[143,144] Nevertheless, these glucopyranose incorporated adducts are less active than neamine, and no further modification has been documented since.

From the reported studies, the intramolecular hydrogen bonding between the 2'-amino group of ring I and the *O*-4'' atom of ring III help to orient ring I for specific binding with RNA.[121] According to molecular modeling studies, similar intramolecular hydrogen bonding can

be mimicked only by a ring III pyranose bearing a β-glycosidic bond, which can be readily achieved using the library of glycosyl trichloroacetimidates. The synthesis of a library of pyranmycins was achieved by glycosylation of the neamine derivatives (*Scheme 18*), followed by hydrolysis, Staudinger reaction, and hydrogenation (*Scheme 19*).

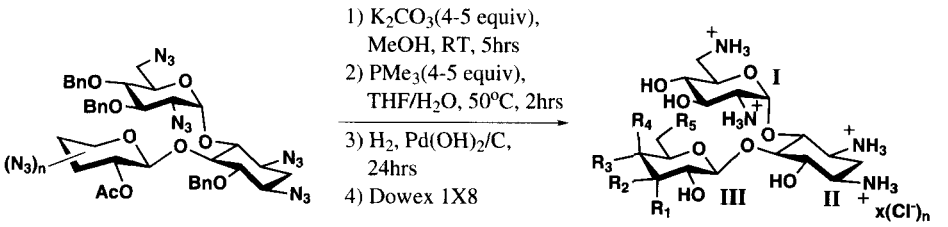


Synthesis of Protected Pyranmycin

Scheme 18

R_1	R_2	R_3	R_4	R_5	Yield (%)
H	OAc	OAc	H	CH_2OAc	71
H	OAc	OAc	H	CH_2N_3	87
H	OAc	N_3	H	CH_2N_3	73
H	OAc	H	OAc	CH_2N_3	42
H	OAc	N_3	H	CH_3	79
H	OAc	H	N_3	CH_3	55
H	N_3	OAc	H	CH_2OAc	66
OAc	H	OAc	H	CH_2OAc	33
H	OAc	N_3	H	CH_2OAc	71
H	N_3	OAc	H	CH_2N_3	64
H	OAc	H	H	CH_3	89
H	OAc	H	N_3	CH_2OAc	50
H	OAc	Tetraacetyl-β-D-galactopyranosyl	H	CH_2OAc	30
H	OAc	OAc	H	CH_3	61
H	OAc	tetraacetyl-β-D-glucopyranosyl	H	CH_2OAc	0 6
H	OAc	OAc	H	H	92

After the determination of minimum inhibitory concentration (MIC), the structure activity relationship (SAR) of ring III D-pyranose on pyranmycin is summarized as follows (*Figure 9*): 1) there is no significant difference in the antibacterial activity among the pyranoses with *allo*-, *gluco*-, and *galacto*-configurations; 2) deoxygenation at C-6" (6"-CH_3) substantially increases the activity; 3) a NH_2 group at C-4" position is essential for activity; deoxygenation of 4"-OH or glycosylation on 4"-OH results in a dramatic decrease in activity; 4) amino group substitution at C-3" has less effect on activity compared to substitution at C-4" and C-6".

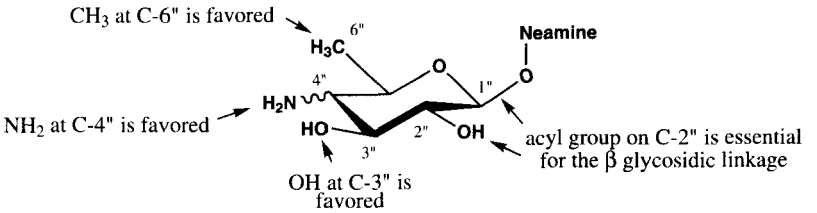


Synthesis of the Designed Pyranmycin

Scheme 19

Products	R_1	R_2	R_3	R_4	R_5	MIC (μM)[a]	Yield(%)
Neomycin B	----	----	----	----	----	2	----
Neamine	----	----	----	----	----	36	----
TC001	H	OH	OH	H	CH_2OH	42	37
TC002	H	OH	OH	H	CH_2NH_3	16	32
TC003	H	OH	NH_3	H	CH_2NH_3	19	66
TC004	H	OH	H	OH	CH_2NH_3	25	40
TC005	H	OH	NH_3	H	CH_3	9	99
TC006	H	OH	H	NH_3	CH_3	9	25
TC007	H	NH_3	OH	H	CH_2OH	26	87
TC008	OH	H	OH	H	CH_2OH	29	66
TC012	H	OH	NH_3	H	CH_2OH	20	60
TC016	H	NH_3	OH	H	CH_2NH_3	28	99
TC017	H	OH	H	H	CH_3	45	56
TC018	H	OH	H	NH_3	CH_2OH	12	19
TC019	H	OH	β-D-Gal	H	CH_2OH	Inactive	69
TC020	H	OH	OH	H	CH_3	19	60
TC021	H	OH	β-D-Glc	H	CH_2OH	Inactive	78
TC022	H	OH	OH	H	H	Inactive	76

a) Minimum inhibitory concentration (MIC) obtained from antibacterial assay against *Escherichia coli* (ATCC 25922)



Summary of SAR of Ring III of Pyranmycin

Fig. 9

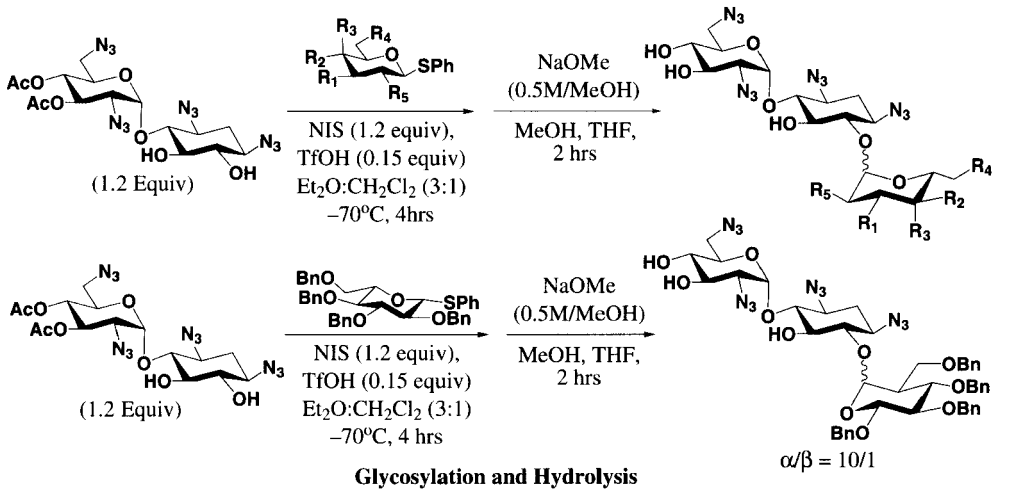
These two compounds, **TC002** and **TC005**, from the pyranmycin family and neomycin were subjected to acid-degradation experiments. These two compounds were dissolved in D_2O purged with anhydrous HCl (*p*H *ca.* 1) then sealed in NMR tubes, incubated at 37°C, and monitored by ^1H NMR. Neomycin underwent a time-dependent acid degradation (20%, 40%, 60%, and 80% degradation after 2, 6, 10, and 14 days), and lost significant antibacterial activity (MIC of acid-treated neomycin increased from 2 μM to 50 μM). In contrast, both **TC002** and **TC005** showed no sign of degradation and maintained the same level of antibacterial activity.

4. Glycodiversification Approach. Preparation of a Kanamycin Library

Kanamycin belongs to a group of aminoglycoside antibiotics with 4,6-disubstituted 2-deoxystreptamine.[4,118] Like neomycin, kanamycin also exerts prominent antibacterial activity against both gram positive and gram negative susceptible strains of bacteria. Nevertheless, kanamycin has become clinically obsolete due to the emergence of aminoglycoside resistant bacteria.[118-120] In order to revive the activity of kanamycin against drug resistant bacteria, numerous attempts have been devoted to the chemical modification of kanamycin.[145-148] Except for a few publications,[116,149,150] most works use various carbamates as protecting groups for kanamycin resulting in the production of kanamycin with polycarbamate groups. Two drawbacks were often encountered: the poor solubility of polycarbamates, which produce great difficulties in purification and characterization of these compounds, and the limited options for structural modifications imposed by the kanamycin scaffold.

The α-glycosidic bond between rings II and III is important as the kanamycin analogs with a β-glycosidic bond manifest much weaker antibacterial activity.[151] However, unlike the synthesis of the β-glycosidic bond, the control for the stereoselective formation of a glycosidic bond is challenging since no neighboring group assistance can be exploited. Nevertheless, the optimal condition for making the α-glycosidic bond was discovered.

Having a 2-*O*-Bn group, the phenylthioglycoside library is ideal for forming the α-glycosidic bond due to the anomeric effect. The neamine acceptor underwent regiospecific glycosylation at the *O*-6 position resulting in the desired 4,6-disubstituted 2-deoxystreptamine motif (*Scheme 20*). The optimal stereoselectivity for the formation of the α-glycosidic bond is accomplished by running the reaction in a solution of Et_2O and CH_2Cl_2 in a 3:1 ratio.[22,116] Further increase in the content of Et_2O has no effect on the stereoselectivity; however, decreasing the Et_2O content results in lower stereoselectivity. The glycosylated compounds were often mixed with inseparable impurities. Nevertheless, after hydrolysis of the acetyl groups, the triols can be obtained in good purity and improved α/β ratio. The final products were synthesized as chloride salts using the Staudinger reaction followed by hydrogenation and ion-exchange (*Scheme 21*).

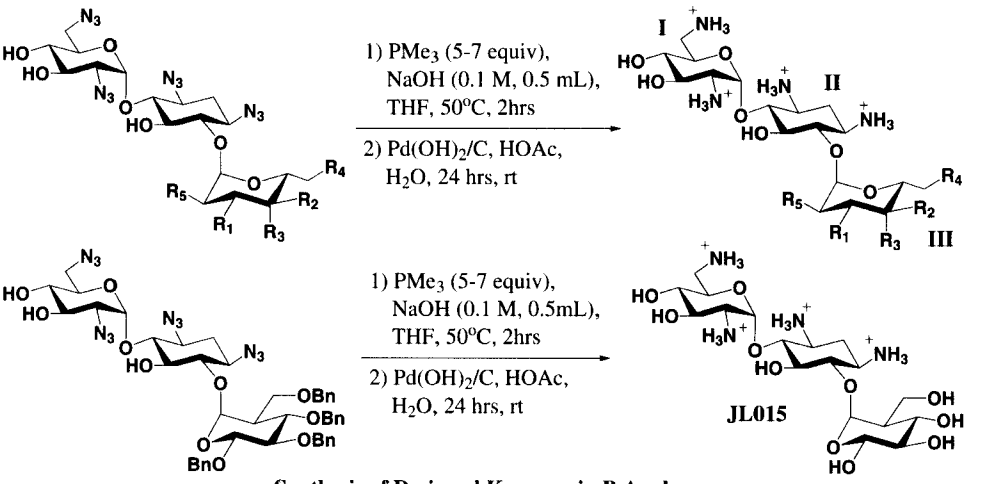


Glycosylation and Hydrolysis

Scheme 20

R_1	R_2	R_3	R_4	R_5	Yield (%)	α : β
OBn	OBn	H	OBn	OBn	35	8:1
OBn	OBn	H	N_3	OBn	32	11:1
OBn	N_3	H	N_3	OBn	33	Only α
OBn	H	OH	N_3	OBn	44	Only α
OBn	N_3	H	H	OBn	61	7:1
OBn	H	N_3	H	OBn	45	Only α
N_3	OBn	H	OBn	OBn	62	10:1
OBn	N_3	H	OBn	OBn	40	Only α
OBn	OBn	H	OBn	N_3	54	2.5:1
OBn	H	N_3	N_3	OBn	36	Only α
N_3	OBn	H	N_3	OBn	48	10:1
OBn	H	N_3	OBn	OBn	54	Only α
OBn	Tetrabenzyl-α-D-Galactopyranosyl	OBn	OBn	OBn	23	Only α
N_3	H	N_3	OBn	OBn	45	Only α

These kanamycin analogs were tested against *Escherichia coli* (ATCC 25922), and *Staphylococcus aureus* (ATCC 25923) using kanamycin B as the control. The SAR of kanamycin B analogs is summarized as follows (*Figure 10*): (1) a 3"-NH_2 group is essential, (2) similar to the pyranmycin family, the presence of a 6"-CH_3 group also increases the activity, (3) unlike the pyranmycin family, an equatorial 4"-NH_2 group is superior to an axial one. An axial 4"-NH_2 group actually decreases the activity.

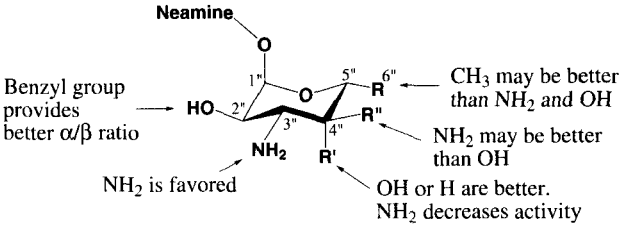


Synthesis of Designed Kanamycin B Analogs

Scheme 21

Cmpd	R_1	R_2	R_3	R_4	R_5	Yield (%)	MIC (μM)[a] *E. coli*[b]	MIC (μM)[a] *S. aureus*[c]
Kanamycin B	$^+NH_3$	OH	H	OH	OH		1.4	0.5
JL001	OH	OH	H	OH	OH	14	50	8
JL002	OH	OH	H	$^+NH_3$	OH	22	Inactive	30
JL003	OH	$^+NH_3$	H	$^+NH_3$	OH	55	22	29
JL004	OH	H	OH	$^+NH_3$	OH	54	22	8
JL005	OH	$^+NH_3$	H	H	OH	39	12	2
JL006	OH	H	$^+NH_3$	H	OH	89	Inactive	16
JL007	$^+NH_3$	OH	H	OH	OH	76	6	1
JL012	OH	$^+NH_3$	H	OH	OH	50	23	4
JL013	OH	OH	H	OH	$^+NH_3$	39	23	4
JL014	OH	H	$^+NH_3$	$^+NH_3$	OH	68	Inactive	57
JL015	----	----	----	----	----	32	Inactive	Inactive
JL016	$^+NH_3$	OH	H	$^+NH_3$	OH	49	22	2
JL018	OH	H	$^+NH_3$	OH	OH	85	Inactive	16
JL019	OH	α-D-Gal	OH	OH	OH	59	Inactive	Inactive
JL024	$^+NH_3$	H	$^+NH_3$	OH	OH	83	----	4

a) MIC: minimum inhibitory concentration; b) ATCC 25922; c) ATCC 25923



Summary of the SAR of Ring III of Kanamycin B Analogs

Fig. 10

IV. CONCLUSIONS

Carbohydrate synthesis is one of the most formidable tasks in organic synthesis. The synthesis of aminosugar libraries for practical applications represents an even greater challenge. Nevertheless, through the use of standardized protocols and a divergent synthetic approach, systematic procedures have been developed. Two separate aminosugar libraries, ready for stereoselective glycosylation, will further fuel carbohydrate focused research. The potential of glycodiversification has also been demonstrated in the library construction of pyranmycin and kanamycin B analogs.

V. GLOSSARY

AIBN: 2,2' -azobisisobutyronitrile
Bn: benzyl
Bz: benzoyl
CSA: camphorsulfonic acid
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD: diethylazodicarboxylate
DIAD: diisopropylazodicarboxylate
DIPEA: N,N-diisopropylethylamine
DMSO: dimethyl sulfoxide
DPPA: diphenyl phosphorylazide
DMTST: dimethyl(methylthio)sulfonium triflate
IDCP: iodinium dicollidine perchlorate
NBS: N-bromosuccinimide
NIS: N-iodosuccinimide
PMB: p-methoxybenzyl
PPTS: pyridinium p-toulenesulfonate
TBAI: tetrabutylammonium iodide
Tf_2O: trifluoromethanesulfonyl acid anhydride
TsOH: toluenesulfonic acid
TsCl: toluenesulfonyl chloride
$TrClO_4$: triphenylmethyl perchlorate

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