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2-Nitroglycals as Powerful Glycosyl Donors: Application in the Synthesis of Biologically Important Molecules

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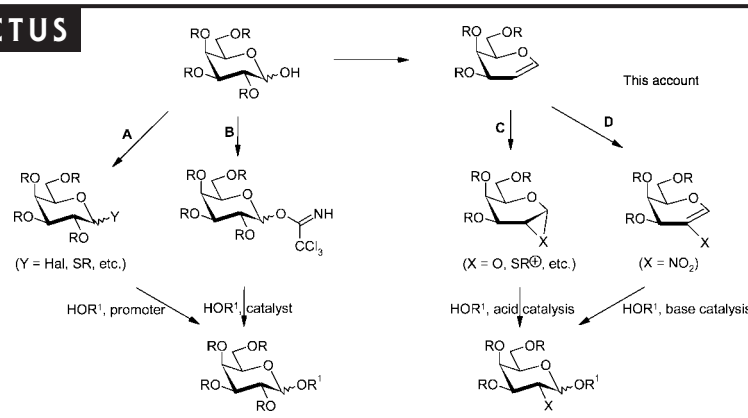
CONSPECTUS



The biological significance of oligosaccharides and glycoconjugates is profound and wide-ranging. For example, the mucins have attracted attention because of their role in fundamental cellular processes such as fertilization, parasitic infection, inflammation, immune defense, cell growth, and cell—cell adhesion. Increased expression of mucins is implicated in malignant transformation of cells. Antifreeze glycoproteins also are of interest because they are important for the survival of many marine teleost fishes that live in polar and subpolar waters.

The synthesis of glycoconjugates requires methods for glycoside bond formation, the most difficult aspect of which is the assembly of monosaccharide building blocks. This Account discusses a valuable addition to the repertoire of methods for glycoconjugate synthesis: an approach that involves 2-nitroglycal concatenation.

For a long time, methods for glycosylation via glycosyl donor generation required either an *anomeric oxygen exchange* reaction or *anomeric oxygen retention*. In the case of an anomeric oxygen exchange reaction, activation of the glycosyl donors demands a promoter in at least equimolar amounts. However, anomeric oxygen retention, such as base-catalyzed formation of *O*-glycosyl trichloroacetimidates, can be activated by catalytic amounts of acid or Lewis acid.

Alternatively, glycals, which are readily available from sugars, can be an attractive starting material for glycoside bond formation. Their nucleophilic character at C-2 permits reactions with oxygen, nitrogen, and sulfur electrophiles that under high substrate stereocontrol generally lead to three-membered rings; ring opening under acid catalysis furnishes the corresponding glycosides, which—depending on the electrophile X—are also employed for 2-deoxyglycoside synthesis.

Glycals also can be transformed into derivatives that have at C-2 an electron-withdrawing group and are amenable to Michael-type addition. A good example are 2-nitroglycals. In this case, glycoside bond formation is achieved under base catalysis and leads to 2-deoxy-2-nitroglycosides. These intermediates are readily converted into 2-amino-2-deoxyglycosides, which are constituents of almost all glycoconjugates. This 2-nitroglycal concatenation has been extensively investigated with 2-nitrogalactal derivatives. When alcohols are used as nucleophiles and strong bases used as catalysts, the result is primarily or exclusively the α-galacto-configured adducts. Some studies show that weaker bases may lead to preferential formation of the β-galacto-configured products instead.

The reaction was very successfully extended to other nucleophiles and also to other 2-nitroglycals that undergo base-catalyzed stereoselective Michael-type additions. Thus, 2-nitroglycals are versatile synthons in glycoconjugate and natural-products synthesis, and it is foreseeable that many more applications will be based on these readily available and highly functionalized skeletons.

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1. Introduction

2-Aminosugars, particularly their *O*-glycosides, constitute an integral part of various glycoconjugates.[1,2] These amino sugars usually exist in N-acylated form, and many α- and β-glycosidically linked glycoconjugates carry these units. Among these, the α-glycosidic linkage between 2-acetamido-2-deoxy-D-galactopyranose and the side chain hydroxy group of L-serine and L-threonine is a common motif in numerous glycoproteins. It is found in mucins, cell membrane glycoproteins, blood group determinants, immunoglobulins, antifreeze glycoproteins, and glycoprotein hormones.[3]

Particularly, the mucins, a family of highly glycosylated glycoproteins that are found in mucus and on cell surfaces of epithelial cells, have attracted much attention in recent years[4,5] because they subsume numerous structures of fundamental importance in biological processes such as fertilization, parasitic infection, inflammation, immune defense, cell growth, and cell−cell adhesion. Malignantly transformed cells show increased expression of mucins and, because of incomplete glycosylation, are covered with shorter carbohydrate chains. Thus, changes in glycosylation and accumulation of unusual glycosidic structures have often been described in cancer cells.[6] The T-antigen [Galβ(1→3)GalNAc] (Galβ = β-galactose; GalNAc = *N*-acetylgalactose) is one of these tumor-associated carbohydrate antigens, which is present in a cryptic form in normal tissue but exposed at the cell surface in carcinoma.[6]

Antifreeze proteins and glycoproteins collectively abbreviated as AF(G)Ps are important for the survival of many marine teleost fishes since they reside in polar and subpolar waters with temperatures being below the colligative freezing points of their body fluids.[7] It is believed that the AF(G)Ps function by binding to the surface of embryonic ice crystals to inhibit their growth. This binding results in the formal depression of the freezing point without a substantial difference in the melting point. The AF(G)Ps consist of repeating tripeptide units (Ala-Thr-Ala)$_n$ with a disaccharide moiety [Galβ(1−3)GalNAcα(1-*O*)] attached to each threonyl residue. Therefore, the synthesis of the antifreeze glycoproteins and the understanding of the role of the structural motif required for antifreeze activity are areas of great importance.[8−10]

2-Amino-2-deoxy-*O*-glycosides are constituents also of several nucleoside and aminoglycosidic antibiotics,[11] including streptomycin, kanamycin B, neomycins, paromomycins, kasugamycin, pyranmycins, and lividomycins. As a result, several methods have been introduced[12−14] to secure a 2-amino functionality or its equivalent on sugar units. Of these, the introduction of an azido group, originally introduced by

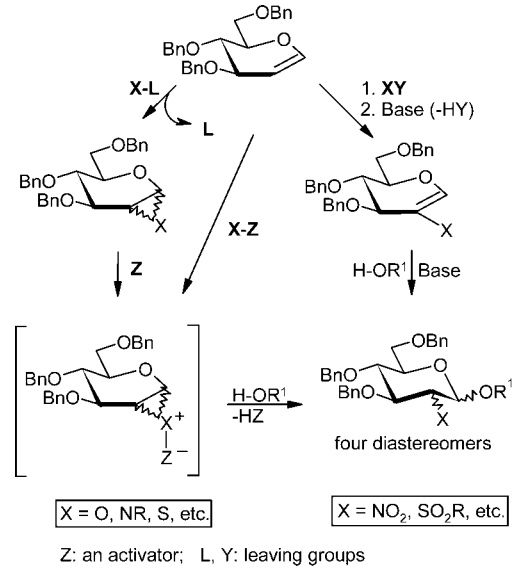


FIGURE 1. Reactions of glycals.

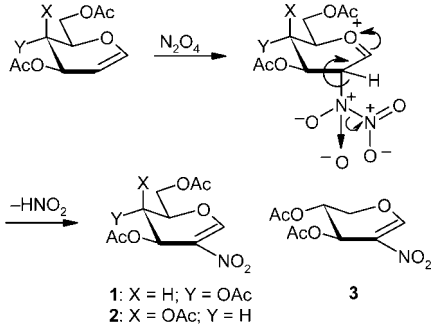
Lemieux et al.,[15,16] has found widespread application. Further, because of the stability of *C*-glycosides toward enzymes, acids, and bases, 2-amino-2-deoxy-*C*-glycosides have received attention.[17−19]

The nitro group is an important functionality in organic synthesis, especially since it can be readily reduced to an amino or a hydroxylamino group.[20] However, the chemistry of 2-nitrosugars en route to 2-amino-2-deoxy-*O*-(or *C*-)glycosides has received scant attention until a few years ago. Recently a number of useful carbohydrate molecules have been synthesized using 2-nitroglycals as intermediates. Here we present an overview of the developments that have taken place in this area and highlight the scope of 2-nitroglycal chemistry.

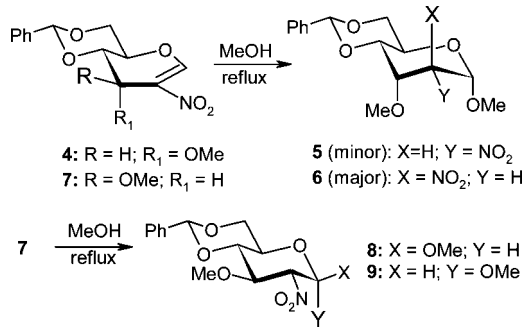
2. Glycals as Nucleophiles and Electrophiles

Glycals, being enol ethers, possess nucleophilic character and react with a variety of electrophiles of type X−L, releasing nitrenes, oxene, etc.,[10] or with typical electrophiles XZ that are stabilized by a leaving group Z (Figure 1). The latter include reagents such as iodine[21] in the presence of silver salts and a base, *N*-bromosuccinimide (NBS),[22] *N*-iodosuccinimide (NIS),[23] PhSeCl,[24] PhSOR,[25] PhSCl,[26,27] nitrene precursors,[12,13] and epoxidizing agents.[10] Reactions of glycals with these electrophiles in the presence of a glycosyl acceptor R^{1}OH leads to the corresponding *O*-glycosides. On the other hand, via addition/elimination reactions of electrophilic reagents XY, glycals can be readily transformed into the corresponding electron-poor vinyl derivatives (X = SO_2R,[28] NO_2) (Figure 1), which, in turn, are expected to react in Michael-type fashion with glycosyl acceptors (R^{1}OH) in the presence of a base leading to *O*-glycosides. The *O*-glycosides obtained from both

SCHEME 1. Formation of 2-Nitroglycals with N_2O_4 as Nitrating Agent



SCHEME 2. Early Results of Methanol Addition



these processes could show different anomeric selectivities and hence studies of such reactions are important. 2-Sulfonylglycals were found to react with nucleophiles[29] but not as well as 2-nitroglycals, which are highly reactive and lead to a variety of significant compounds; the details will be described below.

3. Synthesis and Early Work with 2-Nitroglycals

The first report on formation and reactions of 2-nitroglycals is from Lemieux et al.[30] who performed the synthesis of 2-nitroglycals **1**−**3** (Scheme 1) from the corresponding glycals upon reaction with N_2O_4. However, reactions of these 2-nitroglycals with alcohols were found to enter a multistage reaction sequence presumably because of the labile acetyl groups and hence were not found useful. Addition of methanol was subsequently reported by Sudoh et al.[31,32] Thus, 2-nitroallal **4** gave a mixture of **5** (minor) and **6** (major), whereas 2-nitroglucal **7** gave a 1:1 mixture of **8** and **9** (Scheme 2).

4. Synthetic Utility of 2-Nitroglycals

Recently, reactions of 2-nitroglycals as glycosyl donors with *O*-, *N*-, *S*-, *C*- and *P*-nucleophiles as glycosyl acceptors have successfully been carried out. Typical examples are compiled in Figure 2. Details are provided in the sections given in parentheses.

4.1. *O*-Glycoside synthesis. In 1988, Holzapfel et al.[33] reported an improved procedure for the preparation of 2-nitroglycals by reacting glycals with NO_2BF_4, followed by elimination of HF from the resultant 1-fluoro-2-nitro sugars with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). Although the yields of 2-nitroglycals were good, this method required the use of an excess of expensive NO_2BF_4.

Reactions of tri-*O*-acetyl-2-nitroglucal **1** with simple alcohols were found to give diastereomeric adducts of type **10** (Scheme 3). Reaction of tri-*O*-benzyl 2-nitroglycals **11** and **12** with lithium and particularly thallium salts of simple *O*-, *S*-, and *C*-nucleophiles gave preferentially products **13** of formal *cis*-β-addition. This difference in stereoselectivity is due to preferential attack of the nucleophile from the stereoelectronically favored β-side of the 2-nitroglucal, which prefers, supported by the allylic effect, the $^5H_4$ conformation. Subsequent protonation of the nitronate from the β-side yields the product with the nitro group in equatorial orientation.[33]

Further developments toward the synthesis and reactivity of 2-nitroglycals were not explored until we found that these compounds and particularly 2-nitrogalactals are excellent Michael-type acceptors in terms of yield and α/β selectivity that can be controlled by the base[34] and by the protecting groups (see below). Thus, 3,4,6-tri-*O*-benzyl-2-nitrogalactal **12** (Scheme 4), prepared by reacting 3,4,6-tri-*O*-benzylgalactal with readily available acetyl nitrate, undergoes convenient Michael-type addition of alcohols to furnish the corresponding 2-deoxy-2-nitro-*O*-galactosides **14** in high yields. High α-selectivity was observed with stronger bases like NaOMe and *t*-BuOK, whereas weaker bases like NEt_3 led mainly to the formation of β-galactopyranosides (Table 1). Transition states **A**α and **A**β may play a decisive role in these stereoselectivities though the starting material prefers the $^5H_4$ conformation. Reduction of the nitro group with Raney nickel followed by acetylation to form an *N*-acetylamino group, as shown for **15**, illustrates the power of this methodology.

This direct addition of glycosyl acceptors to 2-nitrogalactals using *t*-BuOK as base is particularly useful for synthesizing 2-deoxy-2-nitro-*O*-glycosides with preferential α-selectivity.

Formation of *O*-glycosides from 2-nitroglycals was further exploited in the synthesis of a derivative of D-lividosamine **20**, a 3-deoxy-sugar, which is a constituent of a few antibiotics such as lividomycins and 3′-deoxykanamycin.[35] Addition of methanol to 2-nitroglucal derivative **17** gave a mixture of **18**

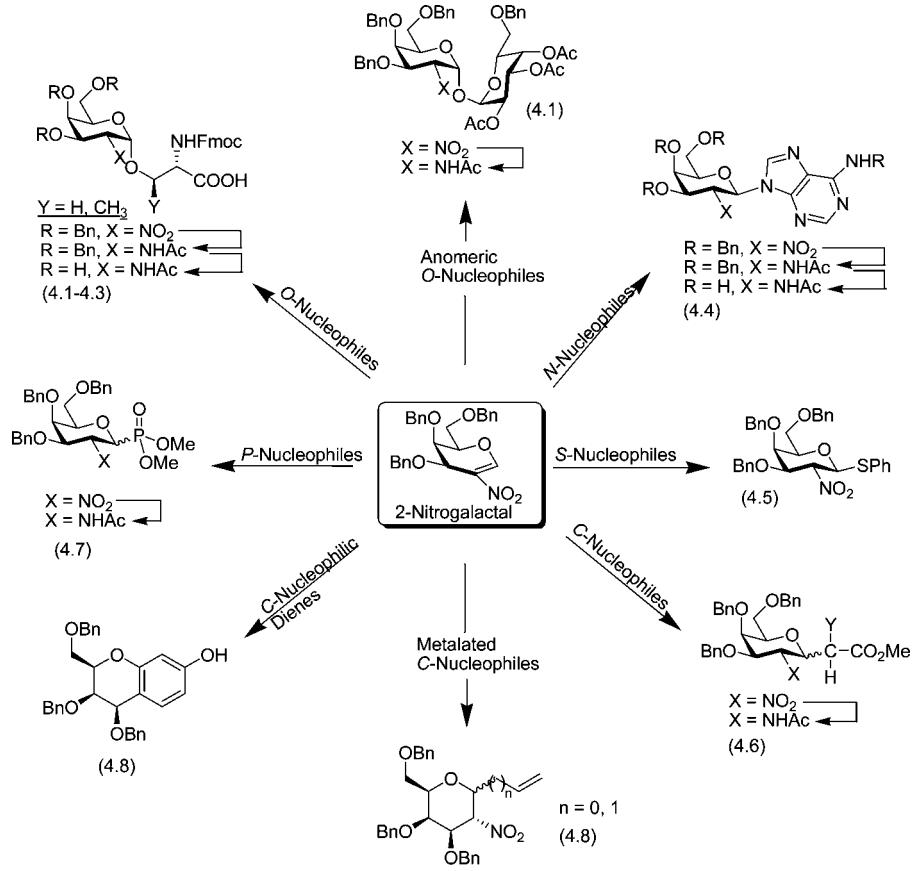
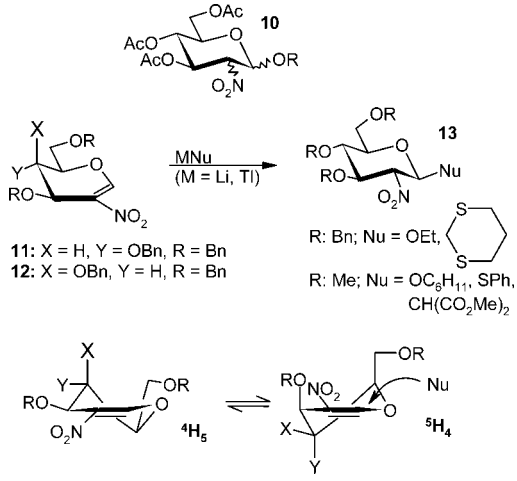


FIGURE 2. Michael-type addition of *O*-, *N*-, *S*-, *C*-, and *P*-nucleophiles.

SCHEME 3. Nucleophile Addition under Various Conditions



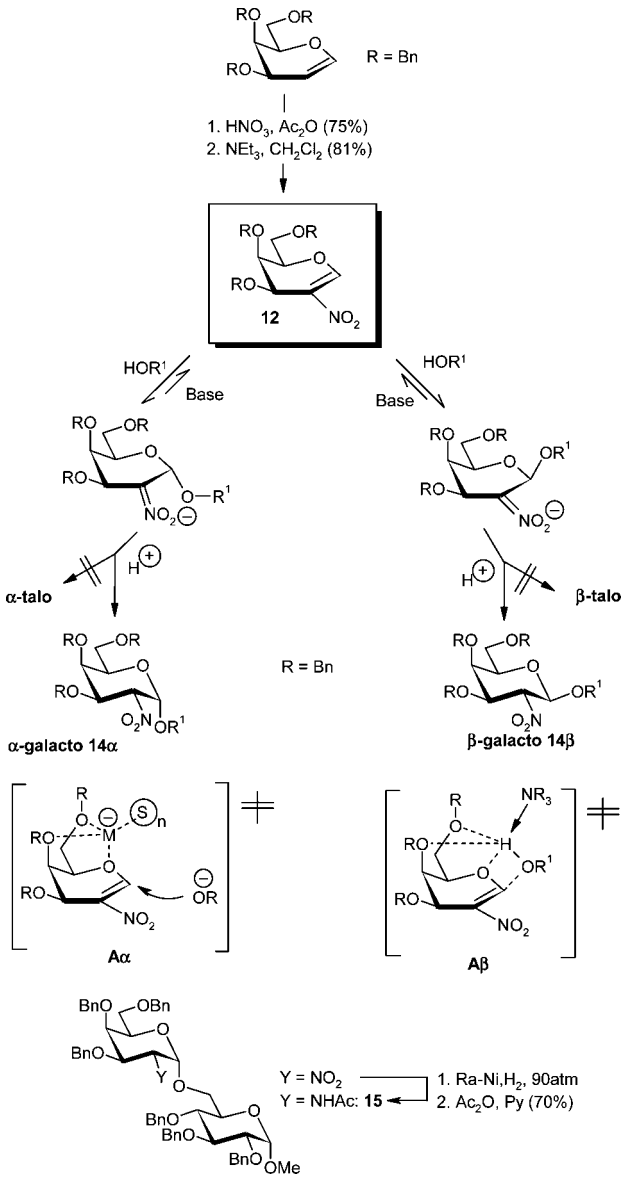
and **19** in a 2.5:1 ratio. Compound **18** was then converted via **20** into methyl *N*-acetyl-α-D-lividosamine **21** as shown in Scheme 5.

Aryl *O*-glycosides are important constituents of a number of useful natural products.[36] However, acid-promoted glycosylations using phenols are often low yielding due their low nucleophilicity.[1,13] 2-Nitrogalactal **12** acts as an excellent substrate for the addition of phenols under basic conditions permitting high-yielding syntheses of aryl *O*-glycosides **22** (Scheme 6).[37] These aryl *O*-glycosides can be readily transformed via **23** to aryl 2-acetamido-2-deoxygalactopyranosides **24**. This strategy has been utilized for the synthesis of *O*-galactopyranosyl tyrosine derivative **25** by using the N-Boc-protected tyrosine methyl ester as glycosyl acceptor.

Aminotrehaloses are promising candidates for designing novel antibiotics and trehalase inhibitors,[38] and a few methods for their synthesis have been reported in the literature.[39] 2-Nitrogalactals are excellent Michael-type acceptors for 1-*O*-unprotected sugars in the presence of *t*-BuOK leading predominantly to α-glycosidic bond formation in all the cases studied.[40] The selectivity at the anomeric carbon of the reducing end sugar was α or β depending on aldose and *O*-substituents. An example for the formation of trehalose-type derivative **28** is shown in Scheme 7.

4.2. Synthesis of *O*-Glycosyl Amino Acids and Glycopeptides. Construction of the 1,2-cis-glycosidic bond of 2-acetamido-2-deoxy-D-galactopyranosides is difficult since it necessitates a nonparticipating latent amino functionality at the C-2 atom of the glycosyl donor.[41] High α-selectivity was observed in the reaction of 3,4,6-tri-*O*-benzyl-2-nitrogalactals **12** with L-serine and L-threonine derivatives **29a**,**b** and

SCHEME 4. Base-Catalyzed Addition of Alcohols to 2-Nitrogalactal **12**



30a that gave practically exclusively 2-deoxy-2-nitro-α-D-galactopyranosides **31a**,**b** and **32a** (Scheme 8) in excellent yields.[42,43] Reduction of the nitro group with platinized Raney nickel T_4 followed by manipulation of the protecting groups afforded *N*-Fmoc-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranosyl)-L-serine and L-threonine **35a**,**b** (T_N antigens), which are valuable building blocks for *O*-glycopeptide synthesis.

4.3. Core Structures of the Mucin Type. All mucin core structures contain at the reducing end an *N*-acetylaminogalactose residue, which is α-glycosidically linked to L-serine and L-threonine. Eight core structures (Figure 3) of mucin-type glycopeptides have been identified to date, and they bear additional glycosyl residues at either position 3 or position 6 or both positions to form complex glycans. The above-described progress in terms of achieving reactivity and selectivity in *O*-glycoside bond formation with GalNAc is useful in the synthesis of these mucin-type structures including the T_N and ST_N antigens.

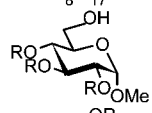
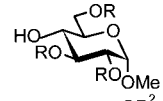
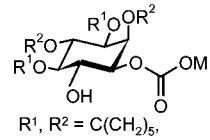
For the synthesis of these core structures, different approaches are available: (i) acid-catalyzed elongation of appropriately protected T_N antigen; (ii) acid-catalyzed glycosylation of galactals at 3-*O*/6-*O*, then introduction of the nitro group at *C*-2, and finally concatenation with the 2-nitrogalactal residue; (iii) reiterative base-catalyzed elongation with 2-nitroglycals as glycosyl donors. Examples of successful applications of these approaches are discussed below.

4.3.1. Acid-Catalyzed Elongation of the T_N Antigen. 2-Nitroglycal-based chemistry has been utilized for the synthesis of 6-*O*-branched structures (ST_N antigen and core 7) and one molecule with 3-*O*-branched structure (core 1).[43,44] For the synthesis of the T_N building block, the nitrogalactal **37** was reacted with **29a**,**b** to form compounds **38a**,**b** in excellent yields and high α-selectivity. Compound **38b** was subsequently transformed via 6-*O*-deprotected **39b** followed by sialylation with phosphite donor **40** into ST_N antigen **41** in a few steps (Scheme 9).

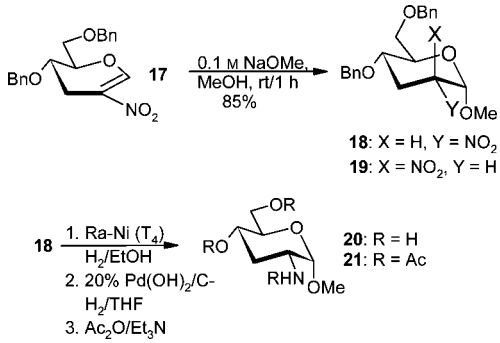
4.3.2. Galactal Glycosylation and then 2-Nitrogalactal Concatenation: Synthesis of Core 1, 2, 6, and 8 Structures. The efficient direct glycosylation of the particularly acid-sensitive galactal derivatives with *O*-glycosyl trichloroacetimidates as glycosyl donors in the presence of $Sn(OTf)_2$ as mild catalyst[45] and the extension of the nitrogalactal concatenation[46] permits a versatile approach to the synthesis of the mucin core structures and derivatives. The design of this approach is outlined in Figure 4. This approach involves (1) regioselective glycosylation of galactal derivatives at 3-*O* or 6-*O* requiring minimal protecting group manipulations, (2) nitro group introduction at *C*-2 of the galactal moiety, (3) Michael-type addition of alcohols at the anomeric carbon being α-selective with the nitro group at *C*-2 adopting the equatorial position, thus with high stereocontrol generating two stereogenic centers leading directly to the desired α-galacto-configured compounds, and (4) transformation of the nitro group into an amino group providing the target compounds. The application of this synthesis design is demonstrated in successful core 1, core 2, core 6, core 7, and core 8 syntheses. The same approach was also successfully applied to the synthesis of core 3 and core 5 structures.

Glycosylation of 3,4-*O*-unprotected galactal **43** with galactosyl donor **42** in the presence of $Sn(OTf)_2$ as catalyst afforded β-linked disaccharide **44** in high yield (Scheme 10). *O*-Acetyl

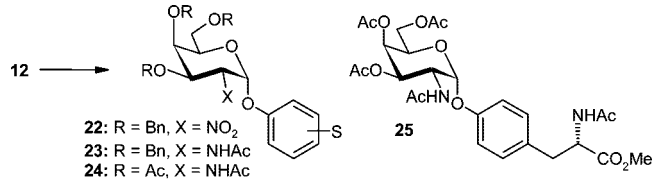
TABLE 1. Michael-Type Addition of HOR[1] to 2-Nitrogalactal **12** (R = Bn)

H-OR[1] (R = Bn)	Base	Yield [%]	α:β	Base	Yield [%]	α:β
$HOCH_3$	NaH	92	8:1	NEt_3	90	1:8
HOC_8H_{17}	KO*t*Bu	72	8:1	NEt_3	66	1:8
	$KN(SiMe_3)_2$	89	1:0	NEt_3	86	1:1
				DBU	79	2:3
	$KN(SiMe_3)_2$	79	1:0	not invest.		
 R^1, R^2 = $C(CH_2)_5$, M = (-)-Mnt	KO*t*Bu	80	8:1	not invest.		

SCHEME 5. Snythesis of Lividosamine **20**



SCHEME 6. Reaction of **12** with Phenol and Phenol Derivatives



group removal and *O*-benzylation furnished **45** whose nitration gave **46**. Reactions of **46** with serine and threonine derivatives **29a**,**b** in presence of *t*-BuOK gave **47a**,**b**, which were readily transformed to core structures **48a**,**b** in only five steps.

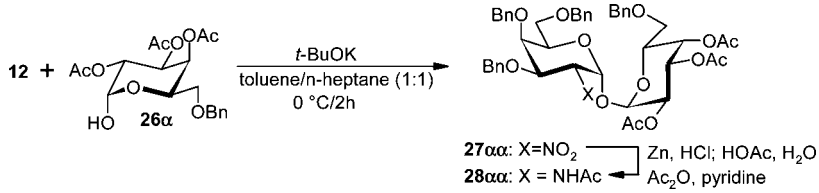
For the synthesis of core 2 structure, disaccharide **45** was 6-*O*-desilylated with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF); subsequent glycosylation with azidoglucosyl donor **49** in acetonitrile as solvent in the presence of $Sn(OTf)_2$ led exclusively to the β-linked trisaccharide **50**. Nitration (leading to **51**) and serine addition under standard conditions furnished target molecule **52a** with α-linked serine as the only product.

α-Selective galactosylation of galactal **43** with galactosyl donor **53**[1] under $Sn(OTf)_2$ catalysis afforded mainly α-linked disaccharide **54** (α/β = 10:1) (Scheme 11).[45] 4a-*O*-Benzylation (leading to **55**), then nitration (leading to **56**), and addition of amino acid derivatives **29a**,**b** furnished the desired core 8 intermediates **57a**,**b**, which were subsequently transformed to **58a**,**b** and, for instance, to core 8 derivative **59a**. Similarly, the core 6 building block was obtained.[46]

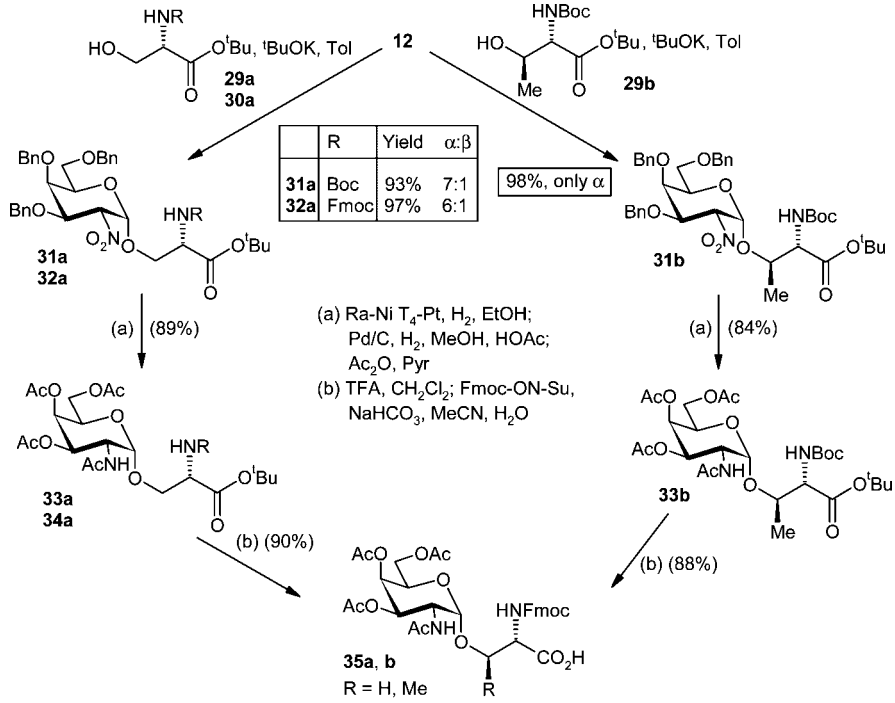
4.3.3. Reiterative 2-Nitroglycal Concatenation: Synthesis of Core Structures 6 and 7. Following the synthesis design in Figure 4, for amino sugars attached to the reducing end GalNAc residue (core structures 2−7), Michael-type addition to 2-nitroglycals can be employed for sugar ligation as first step. Steps 2−4 would remain identical. Thus, glycoside bond formation is based on reiterative 2-nitroglycal concatenation. The success of this concept is demonstrated for core structures 6 and 7. It has been also successfully applied to the synthesis of core structures 5 and 3.[43]

Core 7 bears a second α-linked galactosamine moiety at position 6 of the T_N-antigen. This unit can be installed using reiterative Michael addition (Scheme 12). The 6-position of

SCHEME 7. Reaction of **12** with Anomeric Hydroxy Groups



SCHEME 8. Synthesis of *O*-Glycosyl Amino Acids



nitroglycoside **38a** is unmasked as mentioned before and the nitro group reduced to the amine and N-acetylated (leading to **60**). Glycosyl acceptor **60** is glycosylated making repeated use of nitrogalactal **12** affording stereoselectively the α-glycoside **61** in 70% yield. This glycosylation cycle is completed by reduction of the nitro group and acetylation of the resulting amine to afford **62**. Exchange of all protecting groups on the carbohydrate moiety for acetyl groups, removal of both Boc and *tert*-butyl protection, and installation of the Fmoc protecting group leads to **63**.

The synthesis of core structure 6 via reiterative 2-nitroglycal concatenation requires stereoselective Michael-type addition to 2-nitroglucal. Because previous experiments with this glycosyl donor led mainly to modest results, particularly concerning the anomeric selectivity,[30–33] it was hypothesized that a bulky group on the α-side would enforce via the $^5H_4$ conformer an increase

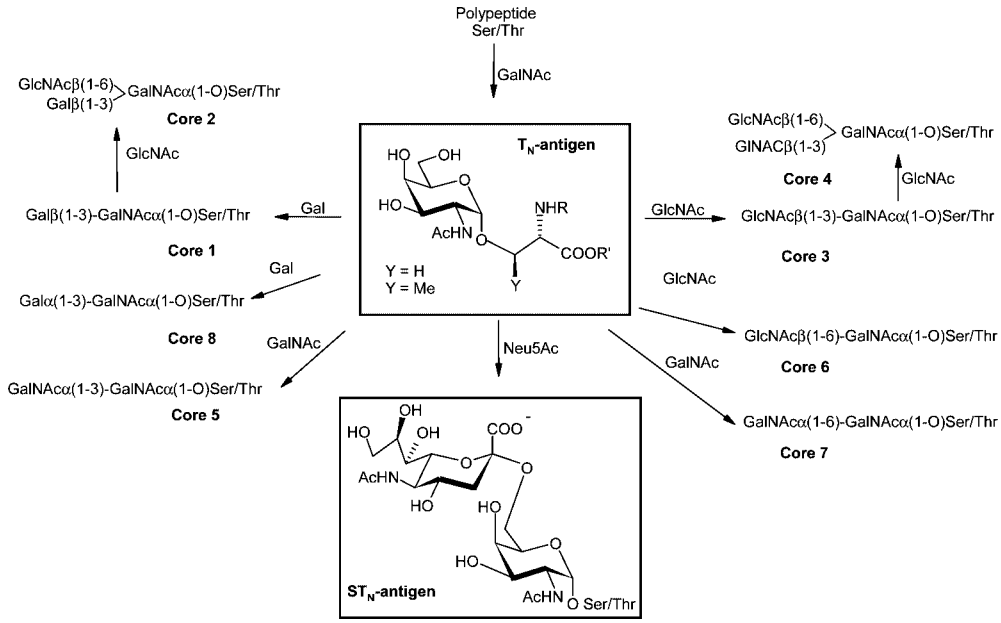
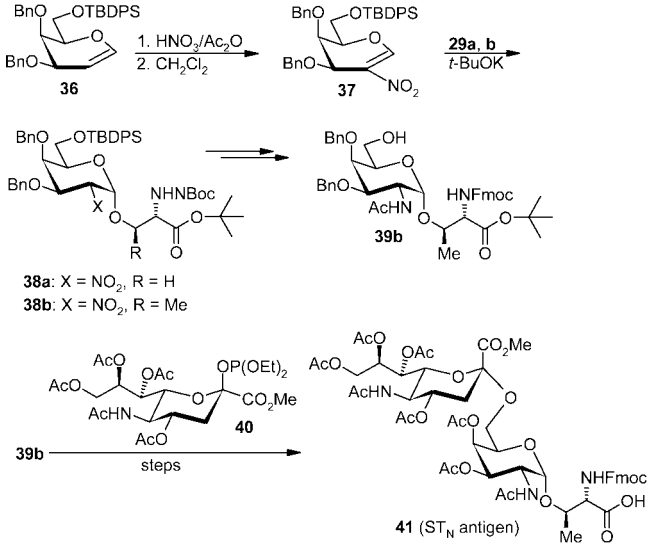
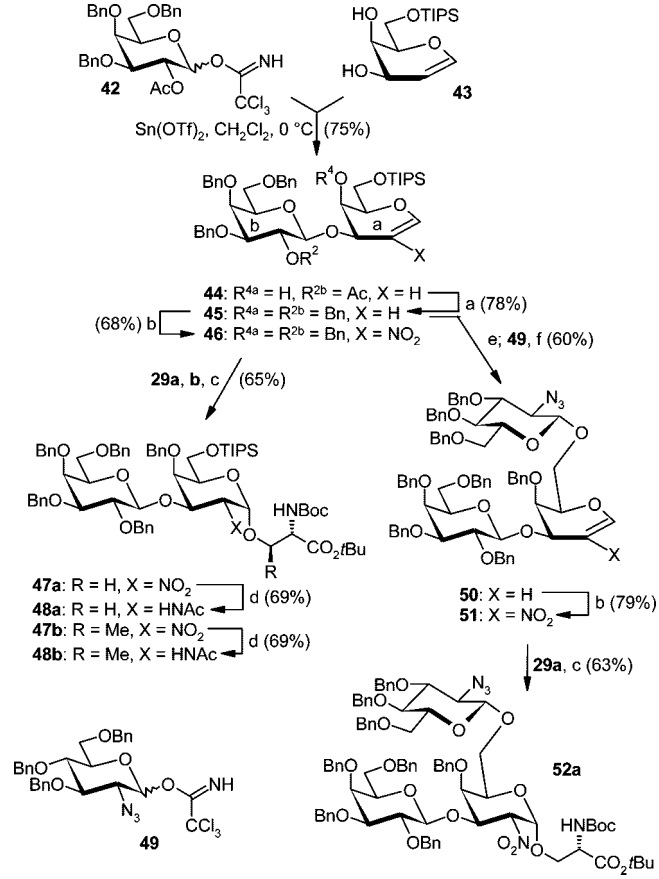


FIGURE 3. Mucin core structures.

SCHEME 9. Synthesis of T_N and ST_N Building Blocks



SCHEME 10. Core 1 and Core 2 Building Blocks[a]



[a] Reagents: (a) NaOMe, MeOH, BnBr, NaH, DMF; (b) HNO_3, Ac_2O, Et_3N, CH_2Cl_2; (c) KO*t*Bu, TolI; (d) Zn, HCl, H_2O, HOAc, THF, Ac_2O, Pyr; (e) TBAF, THF; (f) $Sn(OTf)_2$, MeCN.

in β-selectivity. Therefore, 2-nitroglucal **65**, obtained from glucal **64**, having 4-*O*-*tert*-butyldimethylsilyl protection was chosen as glycosyl donor (Scheme 13). Base-catalyzed addition of 6-*O*-unprotected galactal **66** afforded exclusively the desired $\beta(1-6)$-linked disaccharide **67**, which on nitration furnished Michael-type acceptor **68**. Reaction with **29a** under standard conditions led to clean α-addition, affording the desired core 6 intermediate **69a**, which was transformed into **70**.

4.3.4. Synthesis of a MUC 1 Mucin Type Glycopeptide and Antifreeze Glycoprotein Fragments. The ST_N antigen **41** (Scheme 9), obtained by 2-nitroglycal assembly, was further elaborated[43,44] to MUC 1 mucin-type glycopeptide **74**(Scheme 14). For the glycopeptide coupling, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBop)/*N*-hydroxybenzotriazole (HOBT) activation was chosen, and TentaGel 5 RAM Gly Fmoc, as the prefunctionalized resin, was used for the subsequent solid phase synthesis. Thus, protected glycopeptide **73** was assembled via intermediates **71** and **72** using standard procedures. The ST_N antigen derivative **41** was used in 2-fold excess and was activated in the same manner as the amino acids. After the peptide had been assembled, it was cleaved from the solid phase and partially deprotected using trifluoroacetic acid (TFA)/triisopropylsilane/H_2O. The desired glycopeptide **73** was deprotected under alkaline conditions to obtain the MUC 1 mucin-type glycopeptide **74**.

The above-described syntheses of various core structures of mucin-type *O*-glycosides demonstrate the wide applicability of the chemistry of 2-nitroglycals. Since the antifreeze glycoproteins contain 2-amino sugars and carry an α-threonine unit at the anomeric carbon, they are readily accessible by 2-nitroglycal concatenation. Basically, antifreeze glycoproteins are derived from the core 1 structure extended by two alanyl residues. This unit can be extended randomly or in a defined manner, as shown here (Scheme 15). To this end, core 1 inter-

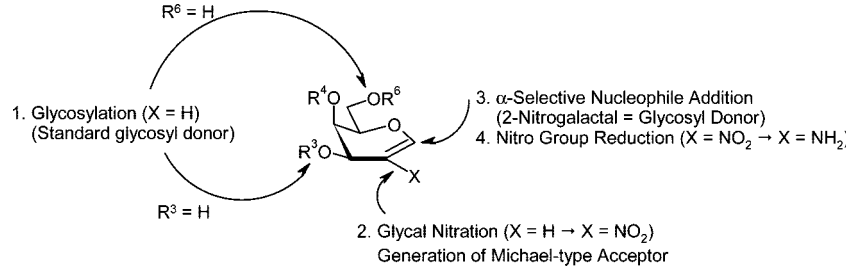
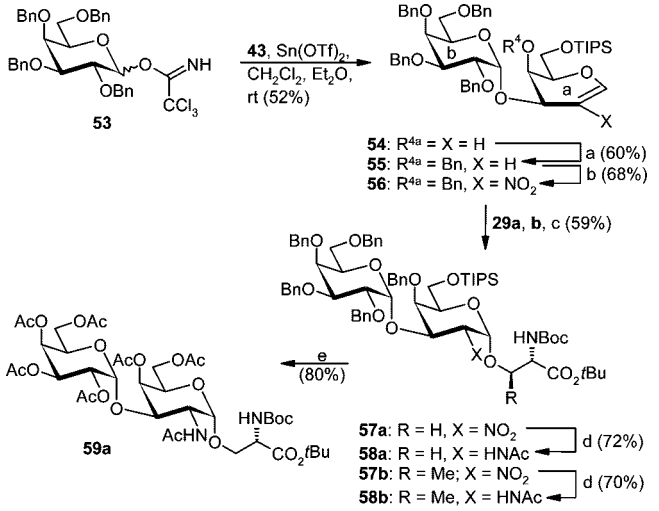


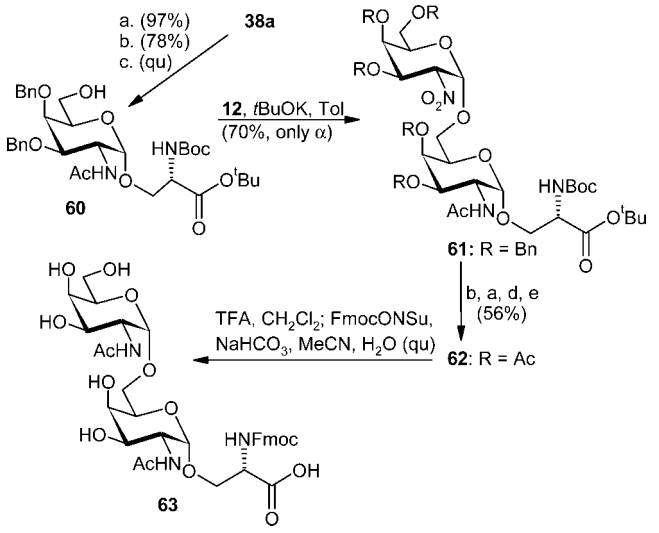
FIGURE 4. Synthesis design for 2-nitrogalactal concatenation.

SCHEME 11. Core 8 Building Blocks[a]



[a] Reagents: (a) BnBr, NaH, DMF; (b) HNO_3, Ac_2O, Et_3N, CH_2Cl_2; (c) KO*t*Bu, Tol; (d) Zn, HCl, H_2O, HOAc, THF, Ac_2O, Pyr; (e) HF-Pyr, THF, Pd/C, H_2, MeOH, HOAc, Ac_2O, Pyr.

SCHEME 12. Core 7 Building Block[a]

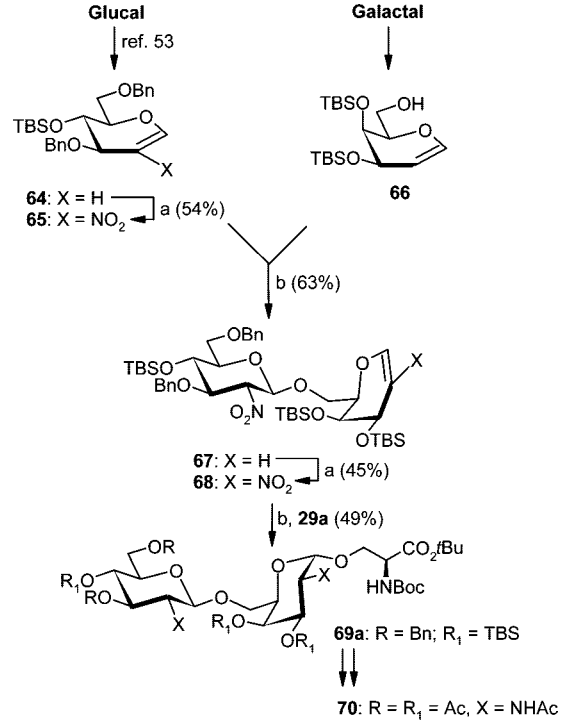


[a] Reagents: (a) TBAF, THF, HOAc, (b) Ra-Ni, T_4 (Pt), H_2, EtOH, Ac_2O, Pyr; (c) NaOMe, MeOH; (d) Pd/C, H_2, HOAc, MeOH; (e) Ac_2O, Pyr; (f) *t*BuOK, Tol.

mediate **48b** is *O*-desilylated, *O*-debenzylated, and then *O*-acetylated, thus affording core 1 intermediate **75** in almost quantitative yield. Peptide chain extension based on Fmoc strategy was adopted that gave the desired disaccharide-linked FmocThrAlaAla*t*Bu tripeptide, which is a suitably protected monomer unit for chain extension. Via the dimer, the tetramer **76** was obtained, which is ready for further chain extensions.

Hence, the concept of mild acid-catalyzed *O*-glycosylation of galactals, enol ether nitration to generate a Michael acceptor, stereoselective addition of alcohols as nucleophiles, and then nitro group reduction to the amino group can be successfully employed to the synthesis of all mucin core structures. In addition, a wide variety of structurally related compounds like antifreeze glycopeptides can be readily obtained.

SCHEME 13. Core 6 Building Block[a]

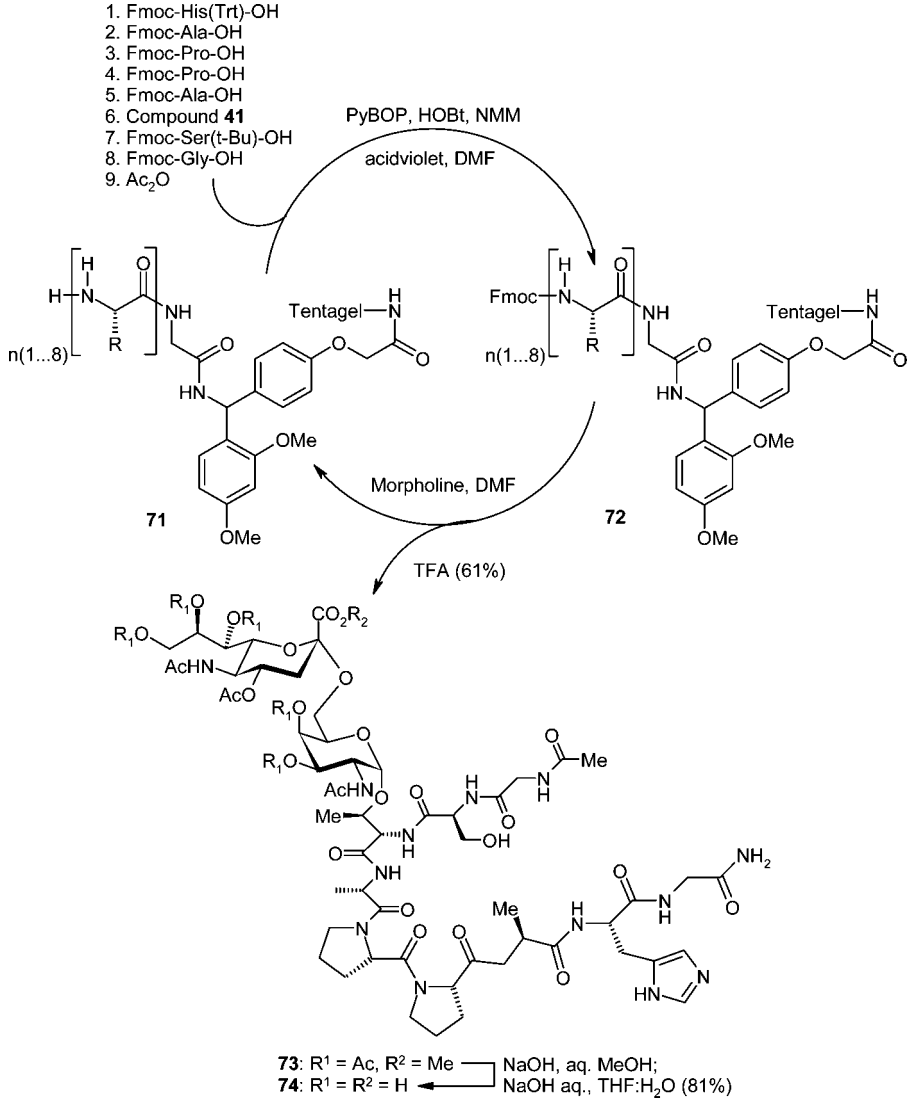


[a] Reagents: (a) Ac_2O, HNO_3, Et_3N, CH_2Cl_2; (b) KO*t*Bu, Tol.

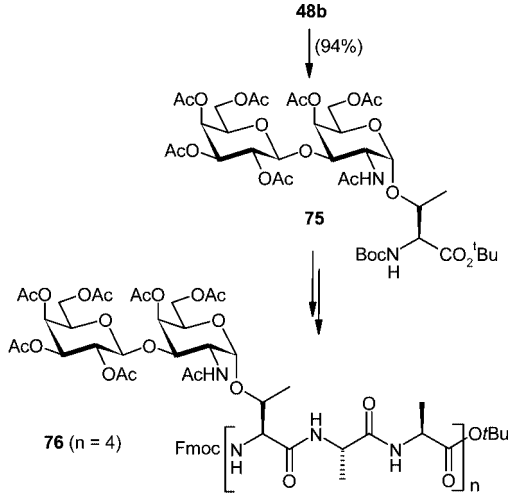
4.4. Some Studies toward the Synthesis of *N*-Glycosides. The 2-nitroglycal chemistry has been extended[47] to the synthesis of some nucleosides of 2-nitrogen-substituted pyranoses **78** (Scheme 16). Literature methods to obtain such compounds employ rather harsh conditions. In contrast, the 2-nitrogalactals permit high-yielding addition products **77** of a variety of bases like purine, *N*-benzyl adenine, pyridone, imidazole, benzimidazole, indazole, benzotriazole. These addition products were found to possess β-configuration at the anomeric carbon as the reactions were performed in the presence of catalytic amounts of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

4.5. Synthesis of Thioglycosides and Their Use As Glycosyl Donors. 2-Nitro-thioglycosides were prepared by addition of thiophenol to 2-nitrogalactal derivatives in the presence of *t*-BuOK.[48] They have been found[48] to be good glycosyl donors leading to the corresponding *O*-glycosides with β-selectivity (Scheme 17). To this end, 2-nitro-thioglycosides are activated by NIS/trimethylsilyl trifluoromethanesulfonate (TMSOTf) followed by reaction with glycosyl acceptors. The β-selectivity can be generally improved by performing the reactions in nitriles as solvent.[49] During addition of thiophenol to **12**, the α/β ratio of thioglycosides **79**$\boldsymbol{\alpha,\beta}$ was

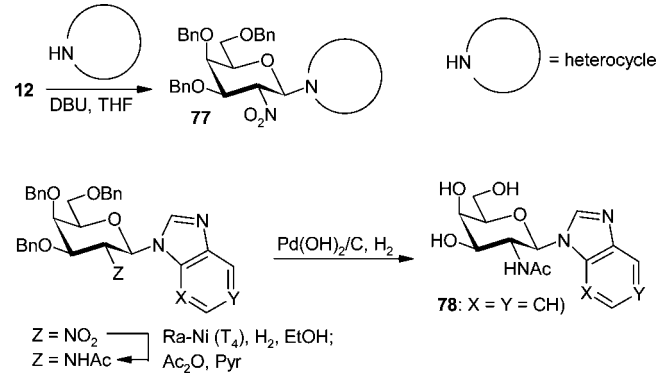
SCHEME 14. MUC 1 Mucin Type Glycopeptide



SCHEME 15. Synthesis of Antifreeze Glycopeptide **76**.

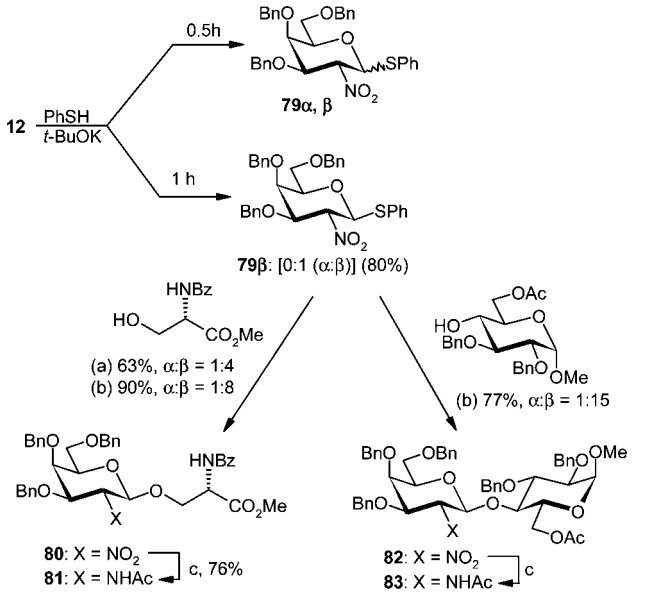


SCHEME 16. Reactions with *N*-Nucleophiles



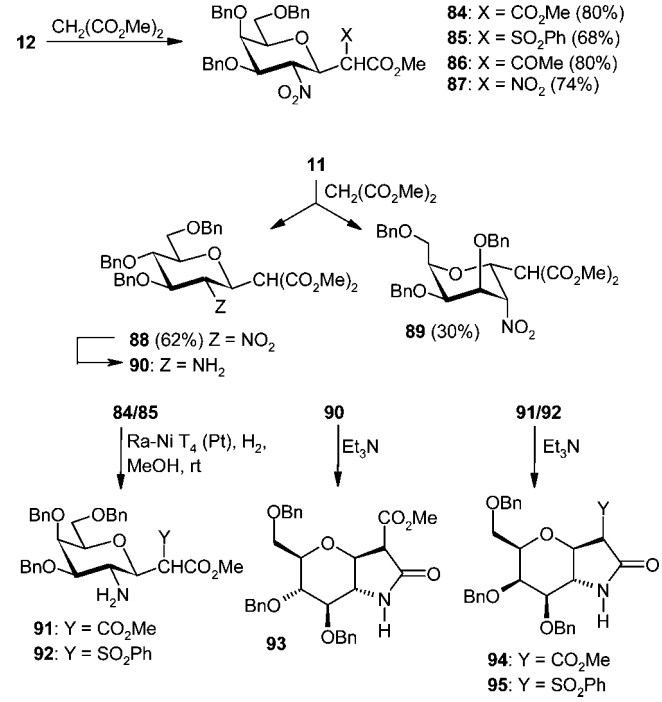
found to be time dependent. Thus, the α-anomer is formed in the beginning in substantial amounts, and with time the β-anomer **79*β*** became the exclusive product. In the subse-

SCHEME 17. Reactions with Thiophenol and Use of the Products As Glycosyl Donors[a]



[a] Reagents and conditions: (a) NIS (2 equiv), TMSOTf (0.15 equiv), CH_2Cl_2, 0 °C; (b) NIS (2 equiv), TMSOTf (0.15 equiv), C_2H_5CN, −15 °C; (c) Zn, 1 N HCl, HOAc.

SCHEME 18. Synthesis of *C*-Glycosides and Bicyclic Compounds



quent glycosylations with alcohols in the presence of NIS/TMSOTf, formation of the β-products **80** and **82** was major. Nitro group reduction led to amino sugar glycosides **81** and **83**, respectively.

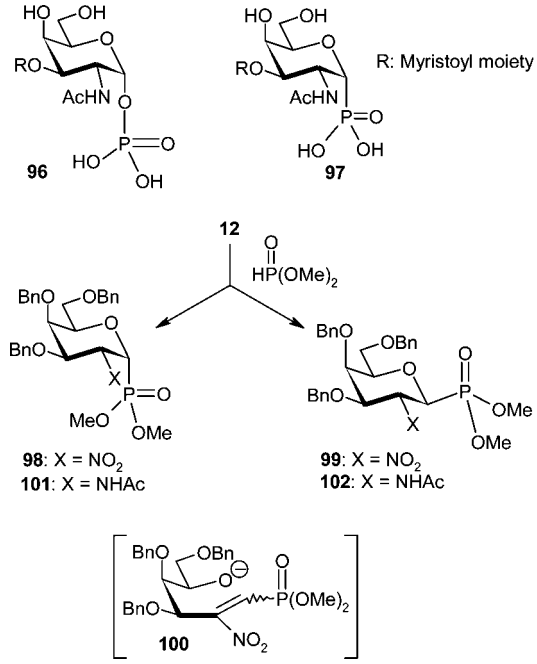
4.6. Reactions with *C*-Nucleophiles. Synthesis of α-linked *C*-glycosyl derivatives of 2-amino sugars is somewhat difficult by common *C*-glycosylation strategies[17−19,50] due to incompatibility of neighboring nitrogen-based functional groups (i.e., amides and carbamates). Therefore, not many methods for their synthesis are reported in the literature.[51,52] Likewise, methods for the synthesis of β-linked 2-amino-*C*-glycosides are also limited.[53−55] The 2-nitroglycals are useful synthons in dealing with these problems since the anions derived from dimethyl malonate, methyl sulfonylacetate, methyl acetoacetate, and methyl nitroacetate add across 2-nitrogalactal derivative **12** to form the corresponding β-*C*-glycosides **84**−**87** (Scheme 18), respectively, in good yields.[56] Not surprisingly, the 2-nitroglucal derivative **11** gave a 1:2 mixture of α/β *C*-glycosides **88** and **89** when reacted with dimethyl malonate in the presence of *t*-BuOK. The adducts **84**, **85**, and **88** were subsequently converted into the corresponding bicyclic compounds **93**−**95** via reduction with Raney Ni (leading to **90**−**92**) followed by treatment with NEt_3.

4.7. Reactions with *P*-Nucleophiles. The outer surface of the outer membrane of *Escherichia coli* and other Gram-negative bacteria is made up primarily of lipid A, anchoring lipopolysaccharides. Lipid A is a β-(1′−6)-linked D-glucosamine disaccharide with phosphate residues at C-1 and C-4′, and several N- and O-bound long-chain acyl groups. Lipid X monosaccharide isolated from *E. coli* mutants as derived from **96** is a biosynthetic precursor of lipid A. The use of phosphonic acids as analogues of natural phosphates represents a systematic approach to metabolic regulation, enhancement, or inhibition studies[57,58] because the C−P bond is not easily hydrolyzed by the enzymes involved in phosphate cleavage. Since the function of the phosphate group is not fully understood, it is presumed that phosphonate analogues of type **97** might help to study these functions. Therefore, some syntheses are reported[58] on such types of nonisosteric glycosyl phosphate analogues.

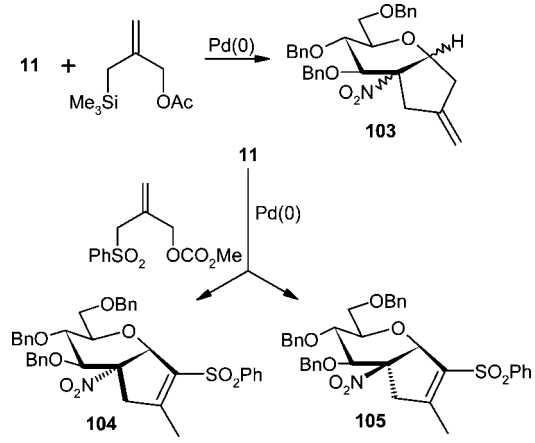
2-Nitroglycals permit[59] addition of dimethyl hydrogen phosphonate leading to the desired α and β isomers in high yields. Formation of the β product was found to be time dependent. Thus, the initial α/β ratio, being 1:1.2 within 5 min, increased to only β isomer after 2 h. The initially formed α-isomer **98** gets equilibrated to the β-isomer **99** via the intermediate **100** (Scheme 19). Reduction of the nitro group followed by acetylation led to the target glycosyl phosphonates **101** and **102**.

4.8. Annellated Compounds. Synthesis of some annellated compounds by employing cycloaddition reactions and Michael addition followed by cyclizations has been reported. Thus, 2-nitroglucal derivative **11** (Scheme 20) undergoes[60] (2 + 3)-cycloaddition reactions under Pd(0) catalysis giving a

SCHEME 19. Reaction of **12** with H-Phosphonate as Nucleophile



SCHEME 20. (2 + 3)-Cycloaddition of 2-Nitroglucal **11**

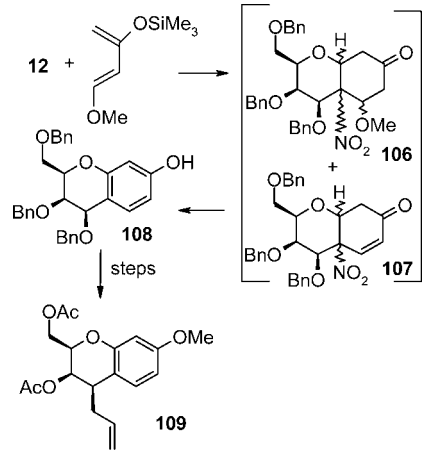


mixture of inseparable isomers **103** and separable isomers **104** and **105** in 1.6:1 ratio.

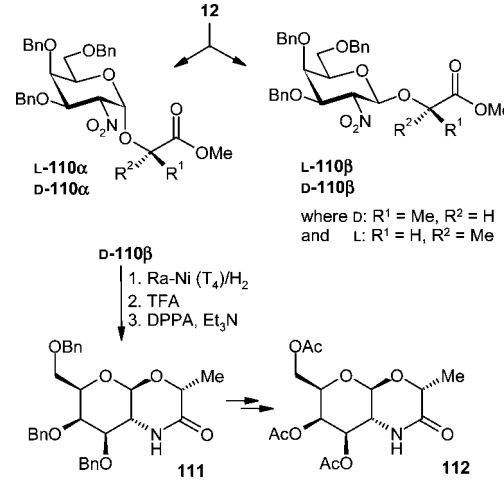
Likewise, 2-nitrogalactal **12** undergoes[61] (2 + 4) cycloaddition with Danishefsky diene to give the bicyclic intermediates **106** and **107** (Scheme 21) whose treatment with NaOMe furnished **108**; following a few reactions, the benzannellated derivative **109** was obtained.

Lactates have also been added[62] to 2-nitroglycals in the presence of *t*-BuOK forming the corresponding *O*-glycosyl lactates in good α/β selectivity, particularly with D-lactates. Thus, 2-nitrogalactal **12** reacted with methyl D-lactate (Scheme 22) to produce **D-110α** along with **D-110*β*** (α/β = 9:2) in 59% yield. However, with L-lactate the α/β ratio was found to be 1.2:1 of **L-110α** and **L-110*β***. Separation of these isomers, followed by their conversion to pyrano[2.3-*b*][1,4]-oxazines, is demonstrated by employing standard reactions on **D-110*β***.

SCHEME 21. (2 + 4)-Cycloaddition of **12** with an Electron-Rich Diene



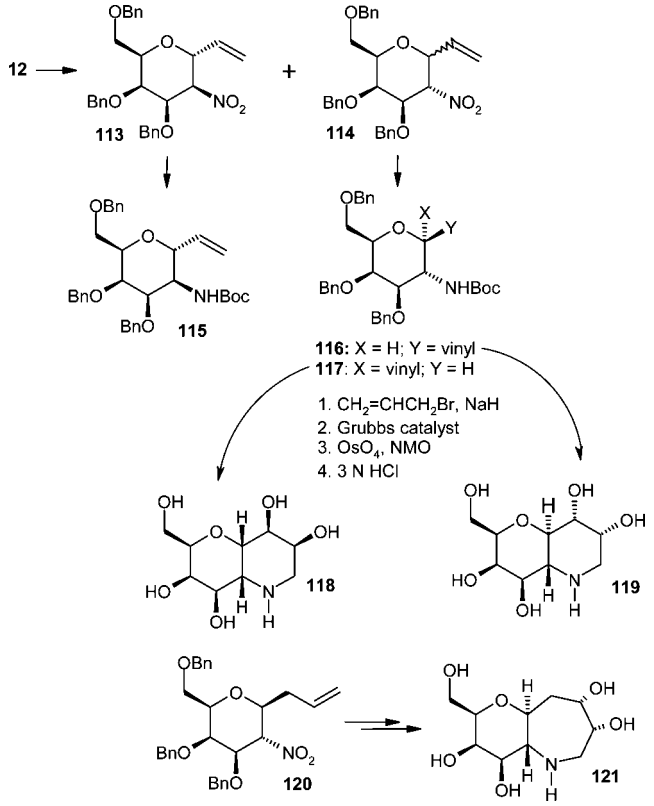
SCHEME 22. Addition of α-Hydroxy Acids and Ring Closure after Nitro Group Reduction



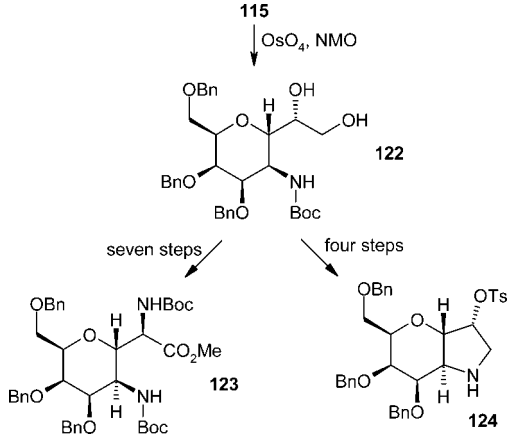
The importance of 1-deoxynojirimycin and its analogues as glycosidase inhibitors[63] and reports on improved or modified properties of hybrid molecules are well-known.[64] In this connection, carbohydrate-based hybrid molecules have been synthesized and found[65] to act as glycosidase inhibitors. Thus, 2-nitrogalactal **12** upon reaction with vinyl magnesium bromide followed by a sequence of reactions is converted into two hybrid molecules of D-galactose: 1-deoxygulonojirimycin **118** and 1-deoxymannonojirimycin **119** (Scheme 23). On the other hand, allyl zinc bromide addition to **12** followed by a similar strategy led to a hybrid of D-galactosamine and 1-deoxymannohomonojirimycin **121**. These hybrids were found to be selective inhibitors of different glycosidases.

Direct functionalization of the CC double bonds leads to the formation of 2-amino *C*-glycosyl amino acids and also to the formation of some hybrid molecules.[66] This is shown for the

SCHEME 23. Addition of Vinyl and Allyl Magnesium Bromide and Subsequent Ring Closure



SCHEME 24. Transformations of Vinyl *C*-Glycoside **115**



stereoselective dihydroxylation of **115** to give **122** and subsequent transformation into amino acid derivative **123** or into bicyclic molecule **124** (Scheme 24).

5. Outlook

2-Nitroglycals are readily obtained via direct nitration of glycals. Though they possess an electron-donating substituent at the β-position of the nitroolefin moiety, they are excellent Michael-type acceptors that readily react with various nucleophiles as shown for *O*-, *N*-, *S*-, *P*-, and *C*-nucleophiles. With *t*-BuOK as base and toluene as solvent, the equilibrium is shifted almost totally toward the addition product. Substrate-based stereocontrol in 2-nitrogalactals leads to preferential or even exclusive formation of one diastereomer (out of the four possible diastereomers) having α-galacto configuration or, alternatively, depending on the base, β-galacto configuration. Thus, two new stereogenic centers are stereoselectively generated under substrate stereocontrol. With nucleophiles having a configurationally labile stereocenter (aldoses, α-substituted acetates, etc.) even up to three new stereogenic centers can be created selectively in one step. Also for the equally important 2-nitroglucal derivatives, good results in terms of yield and stereoselectivity could be obtained. Particularly versatile proved to be the reaction with serine and threonine derivatives as nucleophiles, which led to efficient syntheses of the T_N and ST_N antigens and the eight mucin core structures. The value of these building blocks was demonstrated in the synthesis of a MUC 1 glycopeptide fragment containing the ST_N antigen and the synthesis of antifreeze glycoprotein fragments. The highly functionalized Michael-type addition products can be also successfully employed in various annellation reactions, and besides nitro group reduction, conversions into other functional groups are available. Hence, the versatility of 2-nitroglycals as synthons in glycoconjugate as well as in natural products synthesis is evident, and many more applications can be based on this readily available highly functionalized skeleton.

We thank our collaborators, whose names appear in the references, for their dedicated efforts leading to the fruitful outcome of 2-nitroglycal based chemistry. R.R.S. thanks the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie, Germany, and Y.D.V. thanks the Department of Science and Technology, New Delhi, for financial support of the research work and for a Ramanna Fellowship. Y.D.V. also thanks the Alexander von Humboldt Foundation for a fellowship to visit Germany for writing this Account in collaboration with R.R.S. Y.D.V. thanks Professor Gautam R. Desiraju for encouragement.

BIOGRAPHICAL INFORMATION

Richard R. Schmidt received his Ph.D. at the University of Stuttgart in 1962 under the guidance of Professor Gommper on push−pull stabilized quinone methides. From 1965 to 1966, he held a postdoctoral fellowship with Professor Frank M. Huennekens at the Scripps Research Foundation in La Jolla, CA, on coenzyme B12 metabolism. Since 1975, he has been full professor at the University of Konstanz; he denied calls to other universities.

In recent years, his work has mainly been dedicated to glycoconjugate chemistry and its biological relevance.

Yashwant D. Vankar received his Ph.D. in 1976 from the National Chemical Laboratory, Pune, India (Professor B. D. Tilak). After his postdoctoral work at King's College, London (Professor D. I. Davies); University of Southern California, Los Angeles (Professor G. A. Olah); and Rice University, Houston (Professor E. Wenkert), he joined IIT Kanpur as Lecturer in 1981 and became full Professor in 1991. In between, he spent a year (1990−1991) as an Alexander von Humboldt fellow in the research group of Professor Richard R. Schmidt. He was Head of the Chemistry Department for the period January 2005 to January 2008. His research interests are in the area of synthetic carbohydrate chemistry.

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