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Russ. Chem. Rev., 2021, **90** (2) 171 – 198

https://doi.org/10.1070/RCR4974

3-Amino-3-deoxy- and 4-amino-4-deoxyhexoses in the synthesis of natural carbohydrate compounds and their analogues

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The review considers general methods for the preparation of 3-amino-3-deoxy- and 4-amino-4-deoxyhexoses and their derivatives, including nitromethane condensation, reduction of 3- and 4-hexosulose oximes, epoxide opening with an azide ion, and nucleophilic substitution of sulfonates. The use of amino sugars of this type in the synthesis of natural carbohydrate-containing compounds and their analogues, including aminoglycoside antibiotics, glycosidase inhibitors, substrate analogues and inhibitors of glycan biosynthesis, galectin inhibitors, *etc*. is described.
The bibliography includes 89 references.

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1. Introduction

Amino sugars, *i.e*. derivatives of monosaccharides in which one or more hydroxyl groups are replaced by amino groups, are widespread and are parts of numerous carbohydrate-containing compounds belonging to various classes of natural biopolymers. For instance, polysaccharide chitin, composed of β-(1→4)-linked residues of *N*-acetylated 2-amino-2-deoxy-D-glucose (trivial name *N*-acetylglucosamine), is a structural component of exoskeletons of insects and crustaceans and also part of the cell wall of fungi and some types of algae.[1] Chitin, along with cellulose [a polymer of β-(1→4)-linked D-glucose], is the most abundant naturally occurring organic compound. In addition to chitin, *N*-acetylglucosamine forms a part of a variety of other biopolymers, such as glycoproteins, glycolipids, hexosaminoglycans, bacterial cell surface polysaccharides, *etc*. Homopolysaccharides of *N*-acetylated 2-amino-2-deoxy-D-galactose (*N*-acetylgalactosamine) have not been found in nature, however, this monosaccharide is also widespread, being a component of glycoproteins, glycolipids, hexosaminoglycans, and bacterial polysaccharides.[1]

Unlike 2-amino-2-deoxyhexoses, 3-amino-3-deoxy- and 4-amino-4-deoxyhexoses † are rare monosaccharides and are not detected in polysaccharides and other glycopolymers. The only class of natural carbohydrate-containing compounds comprising monosaccharides of this type are aminoglycoside antibiotics. To date, among them, three representatives of such monosaccharides have been identified, namely, 3-amino-3-deoxy-D-glucose (canosamine), 4-amino-4-deoxy-D-glucose, and 3-amino-3-deoxy-D-mannose. Examples of antibiotics in which these monosaccharides are detected are shown in Fig. 1.[2] Other 3-amino-3-deoxy- and 4-amino-4-deoxyhexoses known by now have been obtained synthetically and do not occur in nature.

Even though the monosaccharides under consideration are found only in a very narrow range of natural compounds, synthetic works aimed at obtaining structures that include 3-amino-3-deoxy- and 4-amino-4-deoxyhexoses and their derivatives are being carried out quite intensively. The purpose of such studies is the synthesis of novel antibiotics,

† The present review does not consider 3- and 4-amino sugars that have an additional modification, *e.g*., a 6-deoxy unit, as in 3-amino-3,6-dideoxyhexoses and 4-amino-4,6-dideoxyhexoses.

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Received 27 June 2020

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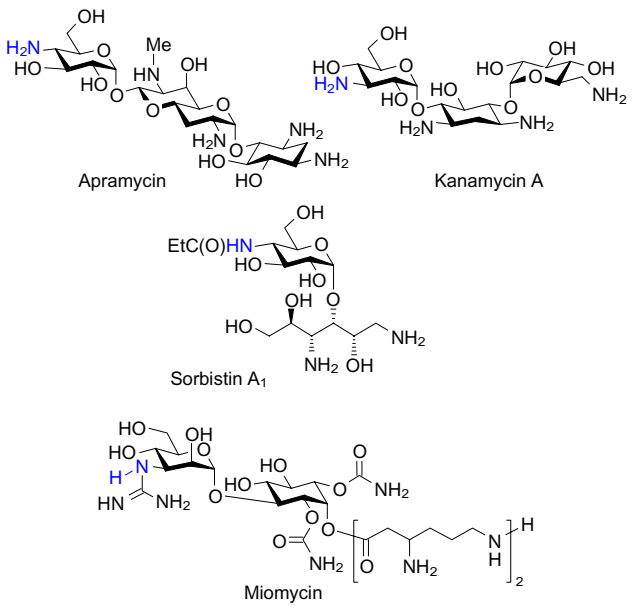


Figure 1. Certain aminoglycoside antibiotics containing 3-amino-3-deoxy- and 4-amino-4-deoxyhexoses.

model compounds for elucidating the substrate specificity of enzymes and carbohydrate specificity of antibodies, inhibitors of various types of enzymes and carbohydrate-binding proteins, as well as models for research in the field of carbohydrate chemistry. The results of such studies will be discussed in the present review. Our interest in the chemistry of 3-amino-3-deoxy- and 4-amino-4-deoxyhexoses is driven by the currently developed project for the synthesis of cyclic oligosaccharides[3] from monosaccharides bearing axial amino groups in positions 3 or 4.

The following abbreviations are used in the review:
All — allyl,
Bn — benzyl,
Boc — *tert*-butoxycarbonyl,
Bz — benzoyl,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DCC — dicyclohexylcarbodiimide,
DMAP — 4-dimethylaminopyridine,
dTDP — deoxythymidine diphosphate,
Fmoc — 9-fluorenylmethoxycarbonyl,
HMPA — hexamethylphosphoramide,
IC_{50} — half maximal inhibitory concentration,
MBn — *p*-methoxybenzyl,
MP — *p*-methoxyphenyl,
Ms — methylsulfonyl (mesyl),
NDPS — nucleoside diphosphate sugar,
NIS — *N*-iodosuccinimide,
Oct — n-octyl,
Phth — phthaloyl,
Py — pyridine,
TBS — *tert*-butyldimethylsilyl,
TEMPO — 2,2,6,6-tetramethylpiperidine-1-oxyl,
Tf — trifluoromethylsulfonyl,
TFA — trifluoroacetic acid,
TMS — trimethylsilyl,
Tr — triphenylmethyl (trityl),
Ts — *p*-tolylsulfonyl (tosyl),
Z — benzyloxycarbonyl.

2. General methods for the preparation of derivatives of 3-amino-3-deoxy- and 4-amino-4-deoxyhexoses

In this Section, without claiming to be exhaustive, we briefly consider the general methods for introducing an amino group (or its synthetic precursors) into positions 3 and 4 of monosaccharides of various configurations.

2.1. Nitromethane condensation

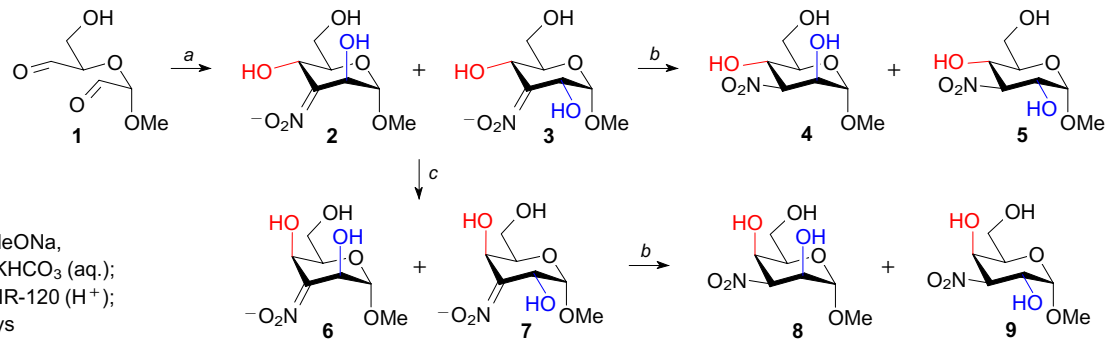
Nitromethane condensation is the condensation of dialdehydes produced by periodate oxidation of unprotected hexose glycosides with nitromethane in an alkaline medium. This reaction was actively studied in the middle of the 20th century.

Thus, the condensation of dialdehyde **1**, derived from α-methylglucoside, with nitromethane affords a mixture of nitronates **2** and **3** differing in the configuration of the C(2) atom (Scheme 1).[4,5] Upon acidification of the reaction mixture, 3-deoxy-3-nitro derivatives of mannose **4** and glucose **5** are produced. However, when the mixture of **2** and **3** is kept in an aqueous solution for 4 days, epimerization at C(4) results in the formation of a mixture, with nitronates **6** and **7** dominating. Acidification of this mixture gives 3-deoxy-3-nitro derivatives of talose **8** and galactose **9**. By catalytic hydrogenation, compounds **4**, **5**, **8**, and **9** were then converted into the corresponding 3-deoxy-3-amino sugars.

Although the nitromethane condensation furnishes a mixture of diastereomeric 3-nitrosugars,‡ this reaction is still used in synthetic practice,[6–9] since moderate yields of the products (30–40%) are partially compensated by the

‡ According to the Rules for Carbohydrate Nomenclature, the correct name for such compounds is 3-nitro-3-deoxy sugars. However, here and hereinafter, the prefix deoxy will be often omitted for the sake of brevity. The same applies to aminodeoxy- and azidodeoxy sugars.

Scheme 1

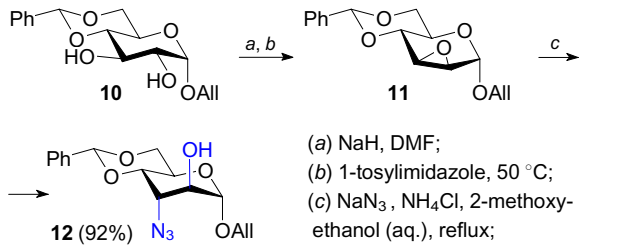


availability of the starting compounds and the ease of synthesis.

2.2. Ring opening of 2,3- and 3,4-epoxides

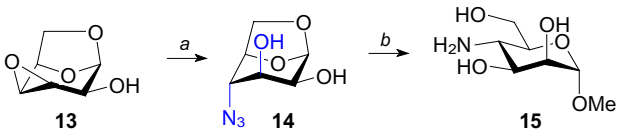
The ring opening of bicyclic epoxides with nucleophiles occurs in such a way that the incoming nucleophile and the resulting hydroxyl group have a *trans*-diaxial orientation in the product molecule. If the conformation of the starting epoxide is fixed due to the presence of the third ring in the molecule, as, *e.g.*, in 4,6-*O*-benzylidene derivative **11** (Scheme 2), then the rule of *trans*-diaxial ring opening provides high regioselectivity of the reaction.

Scheme 2



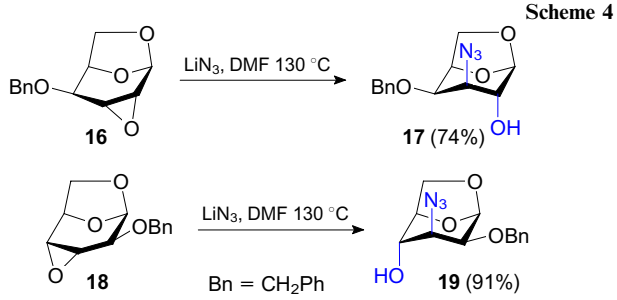
Indeed, *manno*-epoxide **11**, obtained from diol **10**, readily gives 3-azidoaltroside **12** upon treatment with sodium azide in an aqueous solution of 2-metoxyethanol (conditions *c*) (see Scheme 2).[10] The conformational rigidity of the starting epoxide is also achieved in 1,6-anhydro derivatives. The reaction between 3,4-*talo*-epoxide **13** and sodium azide in DMF smoothly leads to the product of *trans*-diaxial opening, namely, 1,6-anhydro-4-azidomannose **14**. Further opening of the 1,6-anhydro ring, proceeding under acid methanolysis, and reduction of the azido group afford 4-aminomannoside **15** (Scheme 3).[11]

Scheme 3



Other examples of ring opening of 2,3- and 3,4-epoxides of various configuration are shown in Scheme 4. The reaction of compounds **16** and **18** with lithium azide in DMF affords 1,6-anhydro-3-azidogalacose **17** and 1,6-anhydro-3-azidomannose **19** in high yields.[12]

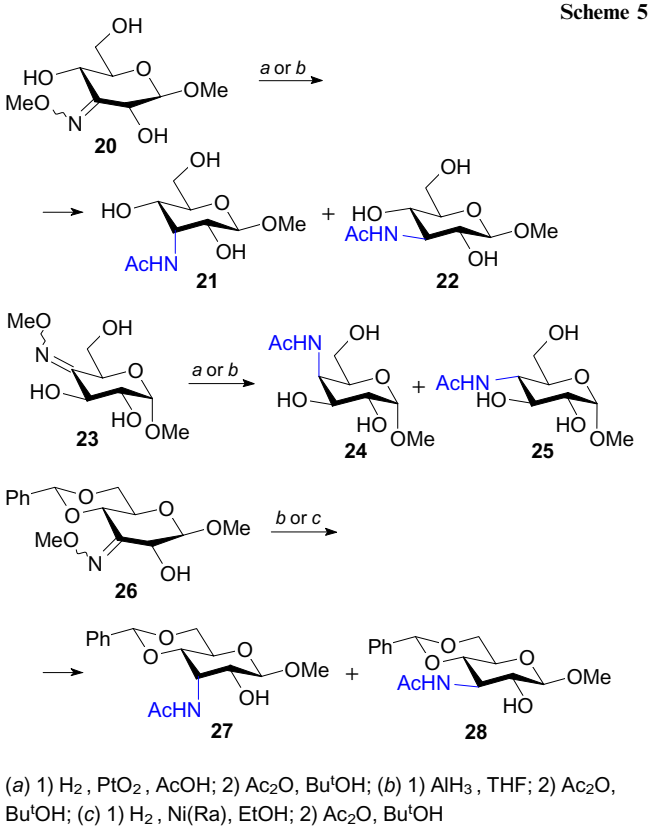
Scheme 4



2.3. Reduction of hexopyranozide-3- and -4-ulose oximes

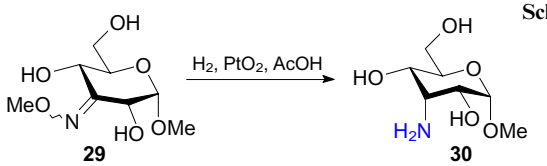
Oxidation of one of the positions in a free or partially protected hexoside to obtain the corresponding oxo derivative, conversion of the latter to oxime, and its reduction is a common method for introducing an amino group into sugars. Stereochemical configurations of resulting amines are governed by the structure of the starting oxime and the reaction conditions. Using an example of several oximes obtained from pentose and hexose methyl glycosides, the effect of reduction conditions on the stereochemical outcome of the reaction was studied.[13] It was shown that catalytic hydrogenation generates mostly the products with an axial amino group, whereas, in the case of reduction with aluminium hydride, the predominance of axial amines is not so pronounced (Scheme 5).

Scheme 5

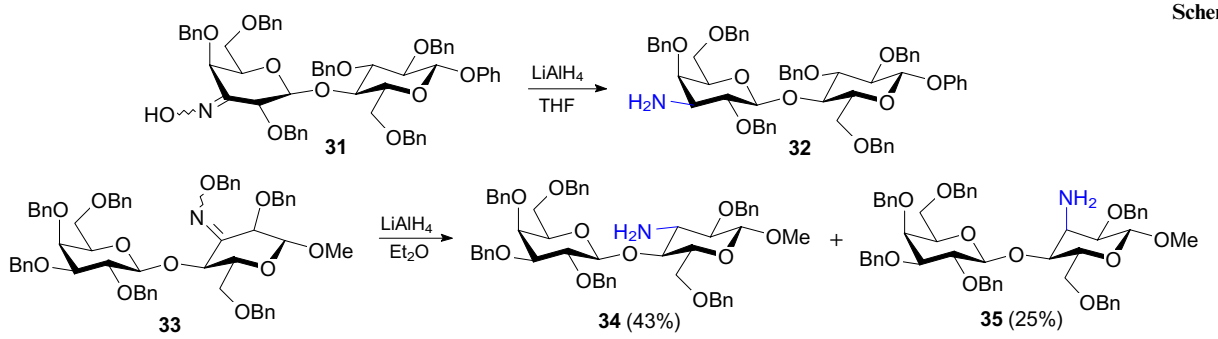


Thus, catalytic hydrogenation of 3-oxime **20** over PtO_2 followed by *N*-acetylation of the products leads to a mixture of *allo*- and *gluco*-products **21** and **22** in a ratio of 7 : 1, whereas upon reduction with AlH_3 the ratio changes in favour of the glucose derivative **22** (2 : 1). In the reduction of 4-oxime **23**, the ratio of the formed derivatives of galactose **24** and glucose **25** was 6 : 1 and 2 : 1 in the case of catalytic hydrogenation or hydride reduction, respectively. The presence of 4,6-*O*-benzylidene group in the starting oxime **26** promotes the formation of a product with an axial amino group: the catalytic hydrogenation gives exclusively *allo*

Scheme 6



Scheme 7



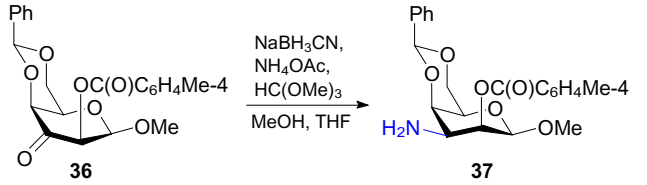
derivative **27**, and in the case of reduction with AlH_3, a mixture of **27** and **28** in a ratio of 4 : 1 is obtained.

The preparation of α-methyl glycoside of 3-aminoallose **30** *via* hydrogenation of oxime **29** is described (Scheme 6).[14]

The results of the reduction of two oximes — lactose derivatives — clearly show the effect of the structure of the starting oxime on the stereochemical outcome of the reaction (Scheme 7). In the case of compound **31**, in which one of the substituents adjacent to the oximine group is axial, product **32** with an equatorial amino group is exclusively formed,[15] whilst the reduction of oxime **33**, in which both adjacent substituents are equatorial, affords a mixture of amines **34** and **35** in moderate yields.[16]

A method related to the reduction of oximes, the reductive amination of ketones, has also been used to prepare amino sugars. Thus, the reductive amination of oxo derivative **36** was used to obtain a 3-aminotalose derivative **37** (Scheme 8).[17]

Scheme 8

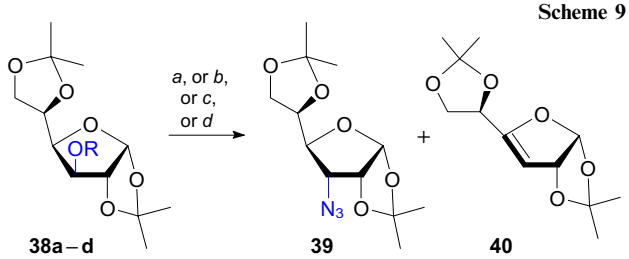


2.4. Nucleophilic substitution of sulfonates

When an azide ion is used as a nucleophile, the reaction products are azido sugars, which can be easily reduced to the corresponding amino sugars. Substitution of sulfonates is the most common approach towards the introduction of an azide group into the positions 3 and 4 of monosaccharides of various configurations, the undoubted advantage of which is the certainty of the stereochemical configuration of the resulting products, since the replacement of a sulfonate group by an azide one proceeds by the S_N2 mechanism. The efficiency of reactions of this type has significantly increased due to the introduction of trifluoromethanesulfonates (triflates) into synthetic practice, since they are more active leaving groups compared to the traditionally used mesylates and tosylates. Later, as a much cheaper alternative to triflates, 1-imidazolylsulfonates (imidazylates)[18] were proposed, which are comparable in their reactivity to triflates.

Comparison of the reactivity of four diacetone glucose sulfonates **38a – d** in the reaction of nucleophilic substitution with an azide has been carried out in a recent work.[19] According to the results, triflate **38a** reacts with azide under the mildest conditions, however, the yield of substitution product **39** is relatively low (59%) and is comparable to that of the elimination product **40** (36%) (Scheme 9). Substitution in mesylate **38b** and tosylate **38c** requires much more harsh conditions, while the yields of azide **39** are slightly lower than for triflate **38a**. The maximum yield of product **39** (72%) was achieved using imidazylate **38d**.

Scheme 9



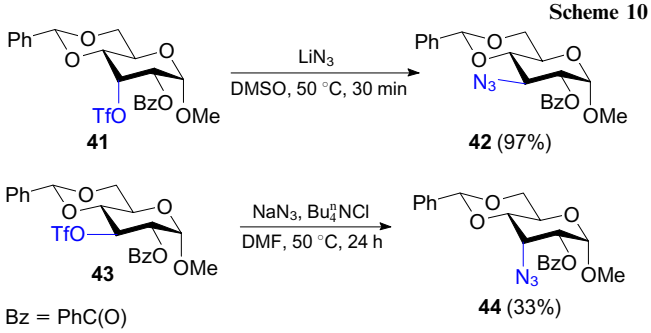
(*a*) NaN_3, DMF, 20 °C, 16 h; (*b*) NaN_3, DMSO, 140 – 145 °C, 180 h; (*c*) NaN_3, DMSO, 140 – 145 °C, 54 h; (*d*) NaN_3, DMSO, Bu^n_4NBr, 80 °C, 10 h

Compound **38**	R	Yield **39**, (%)	Yield **40** (%)
a	Tf	59	36
b	Ms	54	–
c	Ts	45	8
d	Imz	72	20

Tf = SO_2CF_3; Ms = SO_2Me; Ts = $SO_2C_6H_4Me$-4; Imz = 

Further, it will be shown on several examples that the replacement of the sulfonate group by an azide group at the C(3) or C(4) atoms is possible for most hexoses, with varying degrees of efficiency. Thus, the conversion of alloside **41** into 3-azidoglucoside **42** proceeds rapidly and virtually quantitatively under rather mild conditions,[20] whereas the 'reverse' transformation of *gluco*-triflate **43** into *allo*-azide **44** occurs much more slowly and in a much

Scheme 10

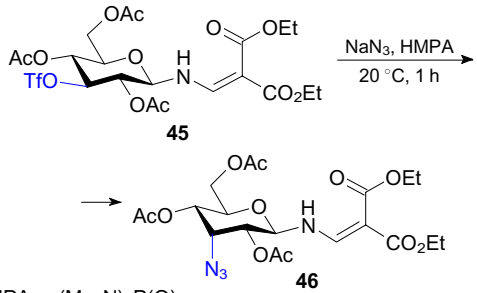


Bz = PhC(O)

lower yield (33%) (Scheme 10).[21] This is apparently due to steric hindrance caused by the substituents at the C(1), C(2), and C(4) atoms in *gluco*-triflate **43**, which are absent in the *allo*-isomer **41**.

Interestingly, monocyclic *gluco*-triflate **45** with the equatorial orientation of the substituent at the anomeric centre undergoes substitution with an azide under mild conditions, giving the 3-azidoallose **46** in almost quantitative yield (Scheme 11).[22]

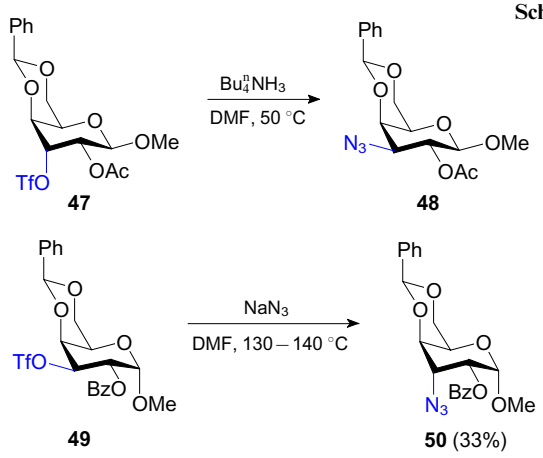
Scheme 11



HMPA = $(Me_2N)_3P(O)$

A similar relationship was observed in the galactose – gulose pair. The reaction of *gulo*-triflate **47** affords *galacto*-azide **48** in good yield (72% over two steps including the step of obtaining **47** from the corresponding OH derivative),[23] while the conversion of *galacto*-triflate **49** to 3-azidoguloside **50** proceeds in moderate yield (Scheme 12).[24]

Scheme 12

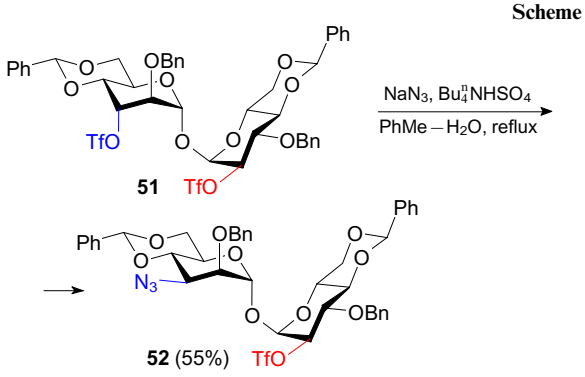


When disaccharide ditriflate **51** obtained from α,α-trehalose reacts with an azide under phase transfer catalysis conditions, the 3-triflate group in the altrose residue is selectively replaced to afford product **52** (Scheme 13).[25]

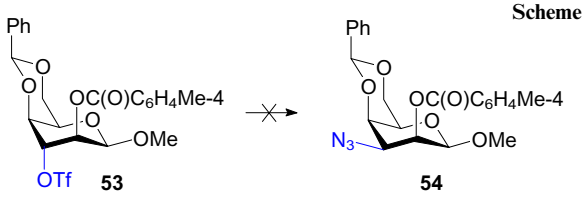
As an example of 3-triflate that does not form the substitution product in the reaction with an azide, idoside **53** can be mentioned (Scheme 14). Probably, the C(2)- and C(4)-axial substituents completely block the approach of a nucleophile to C(3), thus hampering the formation of the S_N2 substitution product **54**.[17] To circumvent this, reductive amination of the corresponding ketone was used to obtain a 3-amino derivative of talose (see Scheme 8).

Substitution at C(4) in glucose and galactose takes place generally without complications and furnishes *galacto*- and *gluco*-azides respectively. Scheme 15 gives examples of such transformations. Thus, galactose tetrabenzoate **55** was converted to 4-azidoglucose tetraacetate **56** in good yield.

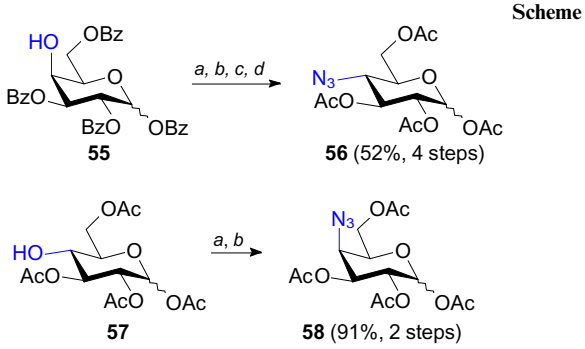
Scheme 13



Scheme 14



Scheme 15

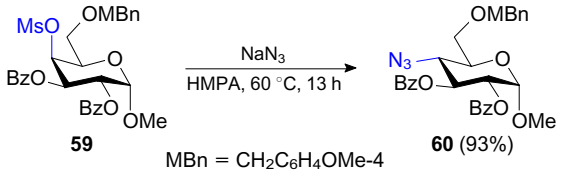


(*a*) Tf_2O, Py, CH_2Cl_2, 0 °C; (*b*) NaN_3, DMF, 20 °C; (*c*) NaOMe, MeOH; (*d*) Ac_2O, Py; Py is pyridine

Transformation of glucose tetraacetate **57** to 4-azidogalactose tetraacetate **58** proceeds even more readily.[26]

To achieve high results in the substitution reaction at C(4), there is no need to use reactive triflates. Accordingly, *galacto*-mesylate **59** was converted into 4-azido derivative of α-methyl glucoside in high yield (Scheme 16).[22]

Scheme 16

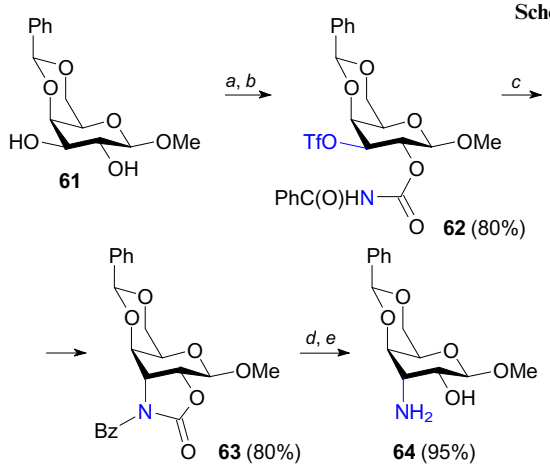


MBn = $CH_2C_6H_4OMe$-4

In the conclusion of this Section, let us consider examples of intramolecular nucleophilic substitution of sulfonates in which the nucleophile is a nitrogen-containing group present in the molecule. This approach makes it possible to synthesize amino derivatives that are difficult to obtain *via* intermolecular substitution reactions.

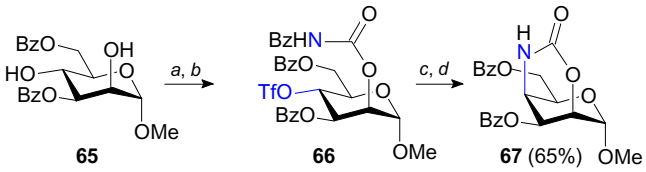
Thus, selective 3-*O*-trifluoromethylsulfonylation of galactoside **61** followed by the reaction with benzoyl isocya-

Scheme 17



(*a*) Tf_2O, Py, CH_2Cl_2, −20 °C; (*b*) BzNCO, CCl_4, 20 °C;
(*c*) NaH, THF, HMPA, 0 °C; (*d*) LiOH, THF (aq.);
(*e*) NaOH (aq.), reflux

Scheme 18



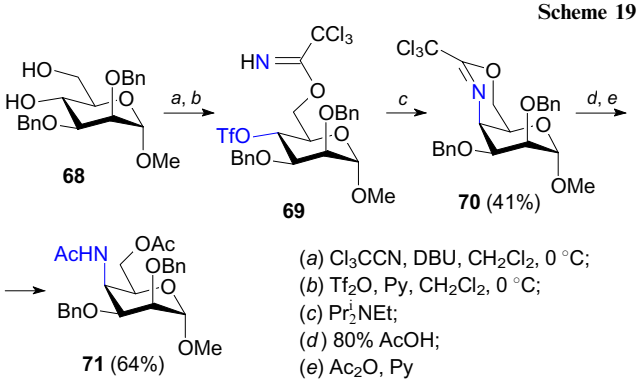
(*a*) Tf_2O, Py, CH_2Cl_2, −20 °C; (*b*) BzNCO, CCl_4, 20 °C;
(*c*) NaH, THF, HMPA, 0 °C; (*d*) LiOH, THF (aq.)

nate gives product **62** (Scheme 17). When the latter is treated with sodium hydride, the intramolecular substitution of sulfonate occurs affording guloside **63**. After removing acyl protecting groups, the derivative of 3-aminogulose **64** is formed.[27] In a similar way, mannoside **65** was converted *via* intermediate triflate **66**, to the derivative of 4-aminotalose **67** in a good yield (Scheme 18).[27]

6-Trichloroacetimidate was used as a functional group serving as an intramolecular nucleophile.[28]

When mannose diol **68** reacts with trichloroacetonitrile in the presence of DBU, the selective imidoylation of the primary hydroxyl occurs, then the secondary hydroxyl is sulfonylated, and the resulting intermediate **69** is treated with a base (Scheme 19). The intramolecular displacement of triflate gives oxasine **70**, which is subjected to hydrolysis and acetylation to furnish 4-acetamidotaloside **71**.

Scheme 19



(*a*) Cl_3CCN, DBU, CH_2Cl_2, 0 °C;
(*b*) Tf_2O, Py, CH_2Cl_2, 0 °C;
(*c*) Pr^i_2NEt;
(*d*) 80% AcOH;
(*e*) Ac_2O, Py

Some other examples of obtaining amino sugars of this type will be presented in the following Sections devoted to the use of 3- and 4-aminohexoses in the synthesis of natural compounds and their analogues.

3. The use of derivatives of 3-amino-3-deoxy- and 4-amino-4-deoxyhexoses in the synthesis of natural compounds and their analogues

3.1. Aminoglycoside antibiotics and their analogues

In studies [29, 30] addressing the synthesis of antibiotic sorbistin A_1 **81** and some of its analogues, the use was made of 4-azidoglucose derivatives (Scheme 20). Ogawa *et al.*[29] obtained both fragments of the antibiotic molecule, namely, derivatives of 4-azidoglucose and 1,4-diazidoglucitol, from methyl-4,6-*O*-benzylidene-α-D-galactopyranoside, which was transformed into mesylates **72** and **75** over a few simple steps.

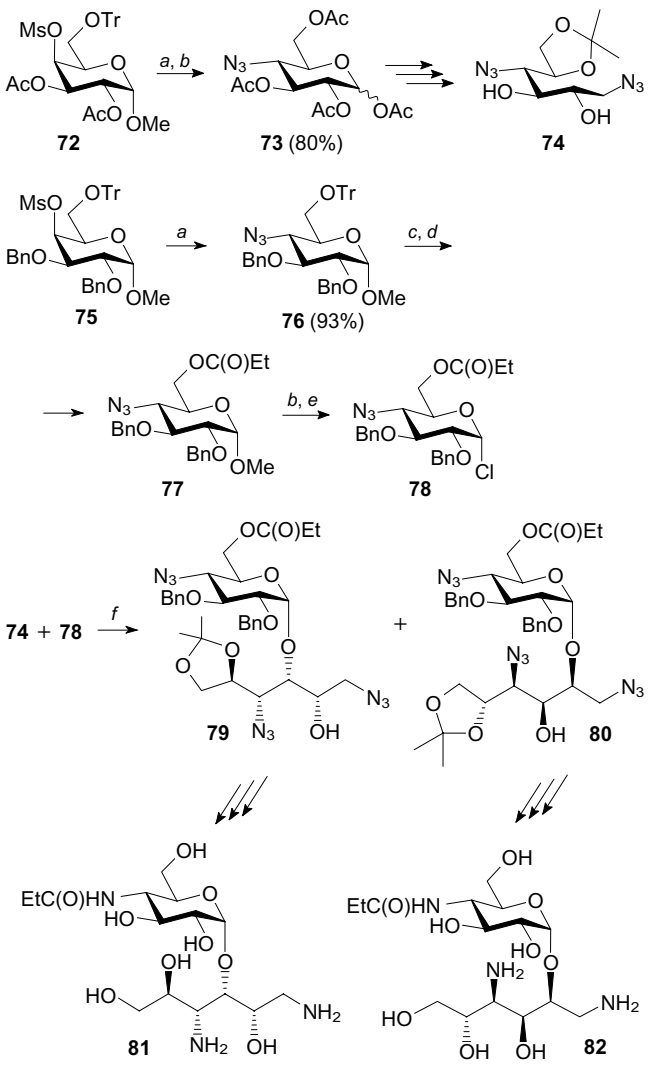
Compounds **72** and **75** reacted with sodium azide to produce 4-azidoglucose derivatives **73** and **76** in high yields. Further, tetraacetate **73** was converted into diol **74**, which acted as a nucleophile in the glycosylation reaction. The replacement of 6-*O*-trityl group in compound **76** with propionyl one, acetolysis of the resulting methyl glycoside **77**, and the reaction of the formed 1-acetate with HCl furnished glycosyl chloride **78**. As a result of the Lemieux condensation of **74** with **78**, glycosylation products **79** and **80** were obtained in a ratio of 1 : 1.6. Deprotection of **79** and **80**, reduction of azides, and acylation of the amino group in the glucose residue carried out by the directed migration of the propionyl group from O(6) to N(4), led to sorbistin A_1 **81** and its regioisomer **82**, respectively.

The synthesis of sorbistin analogue is reported using 4-azidothioglucoside **84**, obtained from tosylate **83** in high yield, as a glycosyl donor (Scheme 21).[30] Thioglycoside **84** appeared to be a much more effective glycosylating agent than the aforementioned chloride **78**. The reaction of **84** with 1,3-diazidogulitol derivative **85** provided the high yield of product **86**, which was then converted into an analogue of sorbistin A_1 **87**.

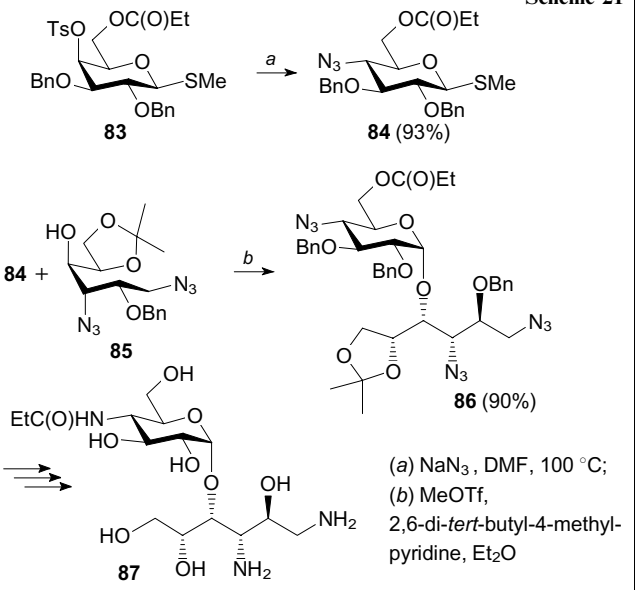
Derivatives of 3-amino- and 4-aminoglucose served as starting compounds in the synthesis of neamine analogues, which were subsequently used to study the structure – activity relationship.[31] Deprotection of acetal groups in 3-azidoglucofuranose **88** followed by acetylation provided tetraacetate **89**, which reacted with thiophenol to give thioglycoside **90** (Scheme 22). Replacement of acetyl groups by non-participating benzyl ones afforded glycosyl donor **91**. The derivative of phenyl thiogalactoside **92** was converted into mesylate **93**, which reacted with sodium azide to be converted to 4-azidothioglucoside **94**. Then, thioglycosides **91** and **94** were introduced into glycosylation reaction with 2-deoxystreptamine derivative **95** to obtain α-pseudodisaccharides **96** and **97**. Deprotection and reduction of azide groups in **96** and **97** provided the target neamine analogues **98** and **99**. These compounds, as well as their isomers bearing an amino group at positions 2 and 6, were evaluated for binding to the *Escherichia coli* ribosomal RNA sites in comparison with the naturally occurring neamine by surface plasmon resonance (SPR) technique.

Later, the same research team [32] synthesized a representative (61 compounds) library of tobramycin analogues, which included, among other amino- and diaminohexoses, 3-amino- and 4-aminoglucoses. Further, using the example of 3-azido- and 4-azido derivatives of glucose, we will

Scheme 20

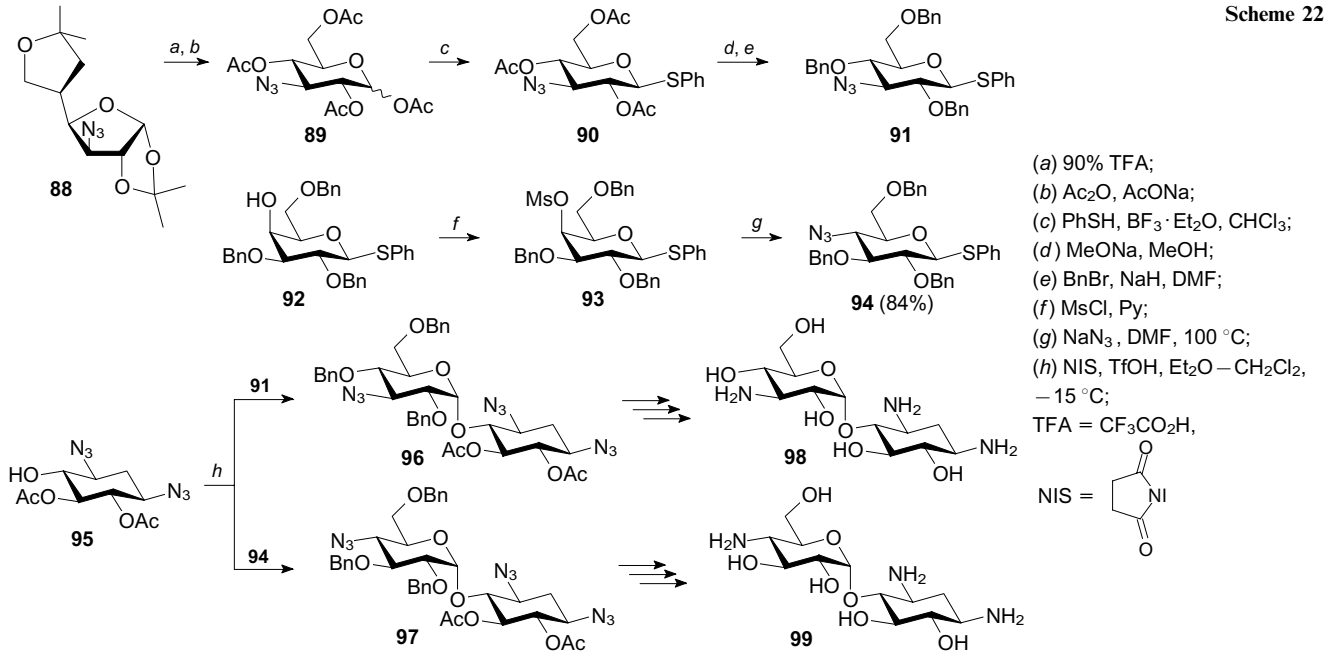


Scheme 21

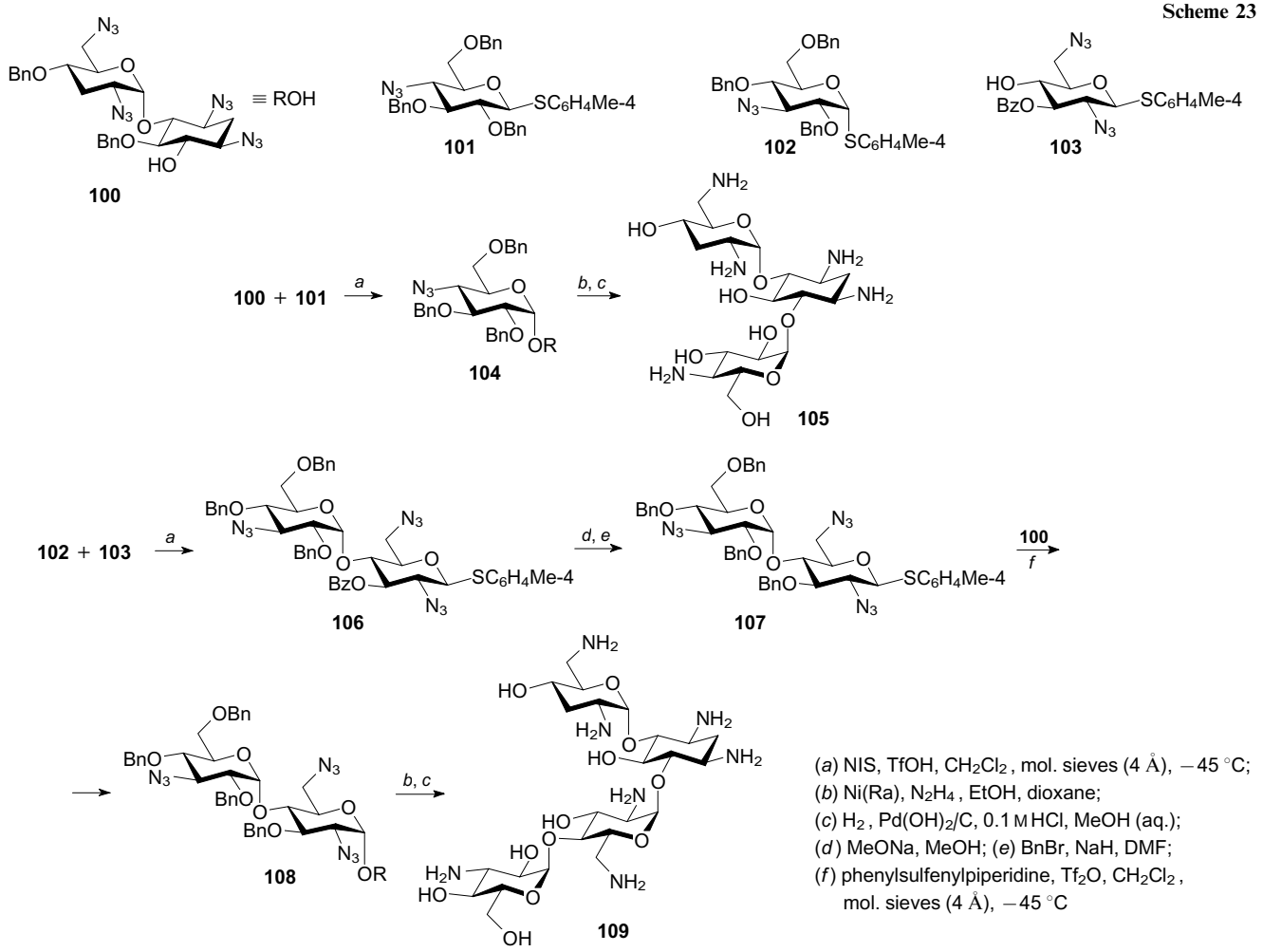


briefly consider the techniques used in the synthesis of this library (Scheme 23). Derivative **100**, obtained by modification of naturally occurring tobramycin, acted as a glycosyl acceptor in all reactions. Thioglycosyls **101** and **102** (along with nine other thioglycosides differing in configuration, number, and arrangement of the azide groups) were used as 'primary' glycosyl donors, which were reacted either directly with acceptor **100** or with the 'secondary' donor **103** (and with other eleven donors of this type). In the former case, the product was pseudo-trisaccharide **104**, which was then converted into the final product **105**. In the latter case, due to the difference in reactivity of the thiotolyl group in thioglycosydes **102** and **103**, selective activation of **102** occurred, leading to disaccharide thioglycoside **106**. With a view to improving the reactivity of the disaccharide donor, 3-*O*-benzoyl group in **106** was replaced with a benzyl one, and the resulting donor **107** was reacted with acceptor **100**. Deprotection and reduction of the azide

Scheme 22



Scheme 23

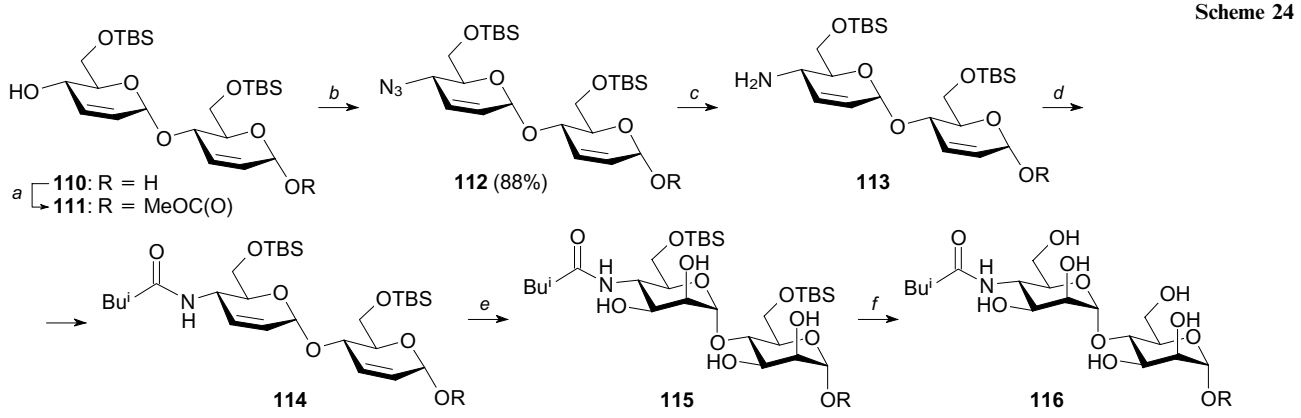


groups in product **108** provided the target tobramycin analogue **109**.

Compounds from the obtained library of tobramycin analogues were tested in the binding reaction with several RNA fragments by surface plasmon resonance since the degree of binding correlates with antibiotic activity. Some of the obtained compounds, including **109**, have a high affinity for oligonucleotides.

A similar approach to obtain the library of tobramycin analogues is described by Yao *et al.*[33] Having in hand a wide range of primary and secondary thioglycoside donors differing in configuration, number, and arrangement of azide groups, 25 trisaccharide analogues were obtained, including compound **105** (see Scheme 23) and its β-anomer, as well as 14 tetrasaccharide analogues, and the antibacterial activity of the resulting products was studied.

Scheme 24



Guppi and O'Doherty[34] reported the synthesis of a modified fragment of antibiotic mannopeptimycin E containing a 4-amino-4-deoxymannose residue. The peptide core of mannopeptimycin E glycopeptide antibiotic[35] comprises an L-tyrosine residue, which is glycosylated with 4-*O*-isovaleroyl-α-D-mannopyranosyl-(1→4)-α-D-mannopyranose disaccharide. Since *O*-acyl groups are unstable under physiological conditions and can be hydrolyzed or migrate to the adjacent hydroxyl groups, in the cited work dimannoside was synthesized, in which the ester functionality was replaced with a more stable amide one.

As a starting material, disaccharide **110** was used. An azide group was introduced into **110** using an unconventional method of allylic substitution catalyzed by an allyl palladium complex.[36] Acylation of **110** with methyl chloroformate gave carbonate **111**, which was converted into 4′-azide **112** in high yield *via* the reaction with trimethylsilyl azide (Scheme 24). Reduction of the azide group and subsequent acylation of amine **113** with isovaleric acid afforded amide **114** whose double bonds were hydroxylated to obtain dimannoside **115**. Desilylation of **115** gave the target free dimannoside **116** (Scheme 24).

3.2. Glycosidase inhibitors and their analogues

Acarbose and adiposin (Fig. 2), produced by some Actinomycetes bacteria, are potent α-glucosidase inhibitors.[37] Acarbose is widely used in clinical practice for the treatment of type 2 diabetes. Acarbose and adiposin have similar structures, the distinctive feature of which is the presence of 4-amino-4,6-dideoxy- and 4-amino-4-deoxyglucose, tethered *via* an amino group to an unsaturated cyclitol. Synthesis of analogues of these compounds with the purpose to study their inhibition mechanism and search for structures characterized by an enhanced inhibitory activity or ability to inhibit other types of glycosidases became the subject of numerous studies. Results related to the preparation of compounds in which the cyclitol is linked to a monosaccharide *via* nitrogen, oxygen, or sulfur atoms are summarized in review,[38] published in 2009. In this Section, we will consider the studies not included in the cited review, as well as works whose purpose was to obtain other types of derivatives of 3- and 4-aminohexoses — glycosidase inhibitors.

A number of publications dealt with the synthesis of potential inhibitors simulating the oxocarbenium ion in the transition state for glycoside hydrolysis at the glycosidase active site. In particular, the preparation of 4-aminoglucose derivatives in which an amino group forms an amidine functionality was described.[39]

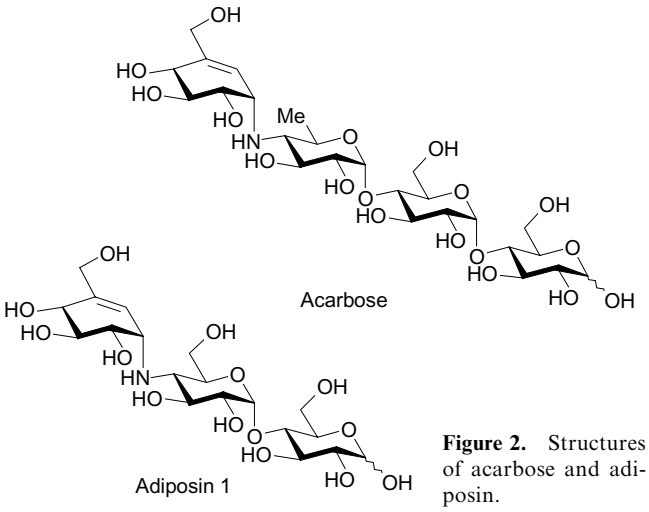
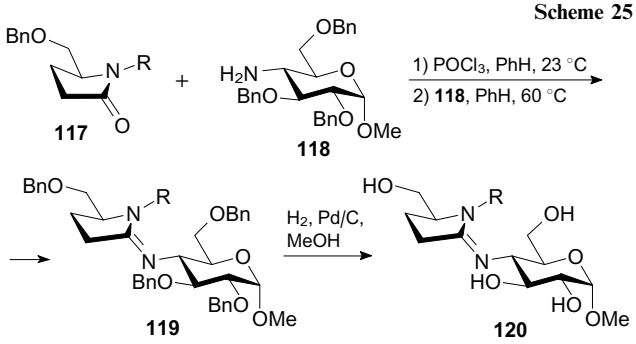


Figure 2. Structures of acarbose and adiposin.

By the reaction between lactams **117** and phosphorus oxychloride the corresponding Vilsmeier complexes were obtained, which were then reacted with 4-aminoglucose **118** to yield protected amidines **119** (Scheme 25). The debenzylation *via* the hydrogenation provided free amidines **120**.

Scheme 25



R = Me, Bn (**117**, **119**); Me, H (**120**)

Structurally related compounds, in which 4-aminoglucose forms a part of the guanidine group, are described by Lehmann *et al.*[40] Isothiocyanate **121**, obtained from the corresponding 4-aminoglucose and carbon disulfide, was reacted with diamines **122** and **123** mimicking the C(4)−C(6) moieties of glucose and galactose, to give thioureas **124** and **125** (Scheme 26). The latter were treated with lead oxide to afford guanidines **126** and **127**, from which free guanidines **128** and **129** were synthesized by deprotection *via* hydrogenation and acid hydrolysis of methyl glycosides.

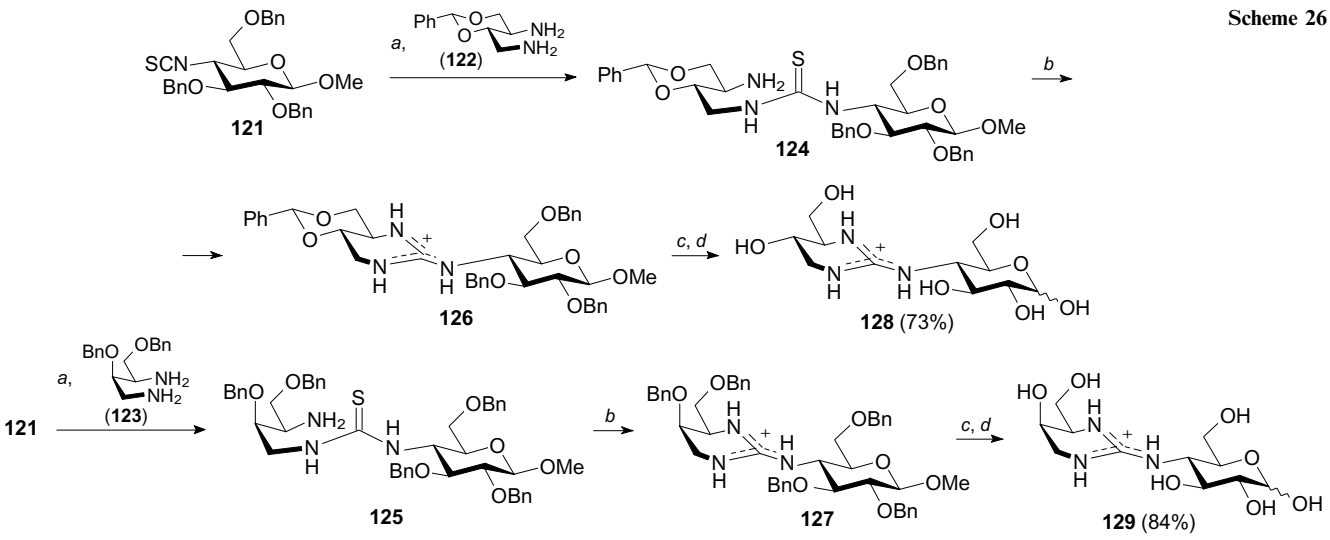
Compounds **128** and **129** did not show high inhibitory activity against various glycosidases, which the authors consider to be probably due to differences in conformation, the number of hydroxyl groups, and the degree of the positive charge delocalization in tetrahydro pyrimidine rings **128** and **129** and the pyranose ring in the transition state for the glycoside hydrolysis.

The synthesis of analogues of trehasoline, which is a potent inhibitor of trehalases — enzymes catalyzing the hydrolysis of α,α-trehalose, is described.[41] Isothiocyanate **130** derived from 4-aminoglucose **118** was used as a starting compound. The reaction of **130** with aminocyclitol **131**, being a degradation product of trehasoline, yields thiourea **132** (Scheme 27). The reaction of **132** with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate **133** led to oxazoline **134**, debenzylation of which provided the target trehasoline analogue **135**.

Based on isothiocyanates obtained from 4-amino derivatives of β-benzyl glucoside and α-methyl galactoside, analogues **135**, containing the residues of glucose and α-methyl galactoside, respectively, were synthesized. The obtained compounds showed no significant inhibitory activity against several studied glycosidases.

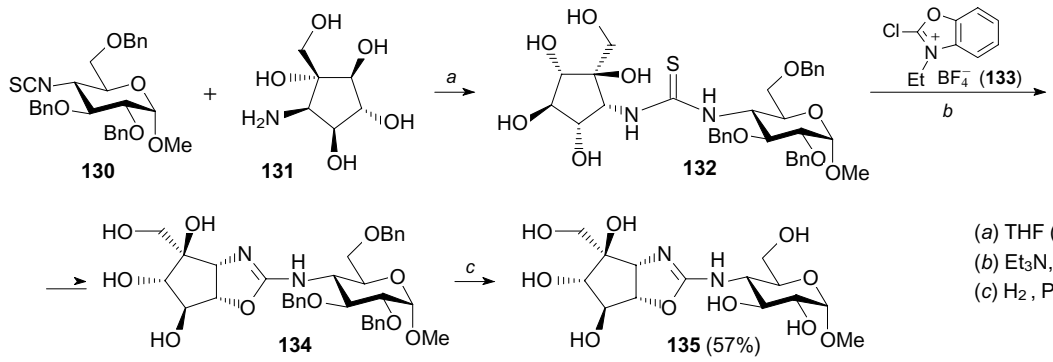
4-Aminoglucose **118** was also used in the synthesis of pseudo-disaccharide **139** bearing an amidine functionality (Scheme 28).[42] The amino group in **118** was acylated with 5-amino-D-arabinonic acid derivative **136** to obtain amide **137**, whose carbonyl group was converted into thiocarbonyl

Scheme 26



(*a*) CH_2Cl_2, 0 °C; (*b*) PbO, EtOH, reflux; (*c*) H_2, Pd/C, MeOH – 1 M HCl; (*d*) 2 M HCl, 90 °C

Scheme 27



(*a*) THF (aq.);
(*b*) Et_3N, MeCN, 0 °C;
(*c*) H_2, $Pd(OH)_2$/C, MeOH, 60 °C

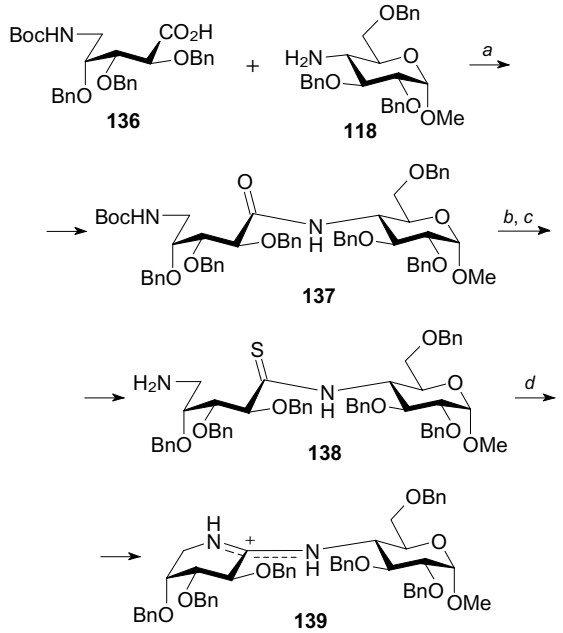
one, which was then *N*-Boc deprotected. Further, amine **138** was treated with mercury chloride resulting in cyclization to form amidine **139**.

The synthesis of a glycosidase substrate analogue in which the *O*-glycosidic linkage was replaced with the *N*-glycosidic one has been reported.[43] To improve the hydrolytic stability of the product, the synthesis was carried out using the 5-thio analogue of glucose **140** instead of glucose (Scheme 29). The acetic acid-catalyzed reaction of **140** with 4-aminoglucoside **141** produced *N*-linked disaccharide **142** as a mixture of α- and β-anomers.

Compound **142** appeared to be a competitive inhibitor of maltose binding to glucoamylase (K_i = 0.3 mol L^{-1}), being superior to 1-deoxynojimirimycin, but still far from acarbose in this regard.

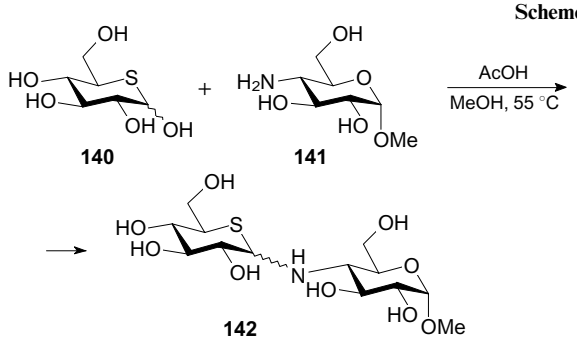
The synthesis of simple mimetics of the transition state for hydrolysis of glycosides, in which the sugar residue was replaced by the pyridine one, is described.[44] Arylation of 4-aminoglucose **118** with pyridinium halides in the presence of a palladium catalyst made it possible to obtain the corresponding 2-pyridyl amines, which were converted to derivatives **143** and **144** *via* catalytic debenzylation (Scheme 30). The resulting compounds were tested in the reaction of glucoamylase inhibition. Compound **144** exhibited moderate activity (K_i = 0.22 mmol L^{-1}), whereas the hydroxylated derivative **143**, whose substituents in the pyridine ring mimicked the C(4) – C(6) moiety of glucose, turned out to be two orders of magnitude more active

Scheme 28

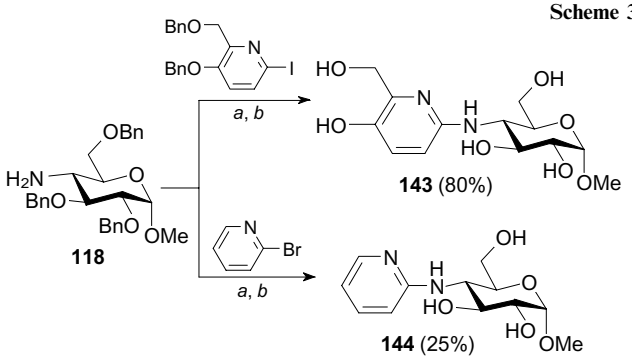


(*a*) *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide, 1-hydroxybenzotriazole, CH_2Cl_2; (*b*) Lawesson's reagent, PhMe; (*c*) TFA, CH_2Cl_2; (*d*) $HgCl_2$, Et_3N, DMF; Boc = $Bu^tOC(O)$

Scheme 29



Scheme 30



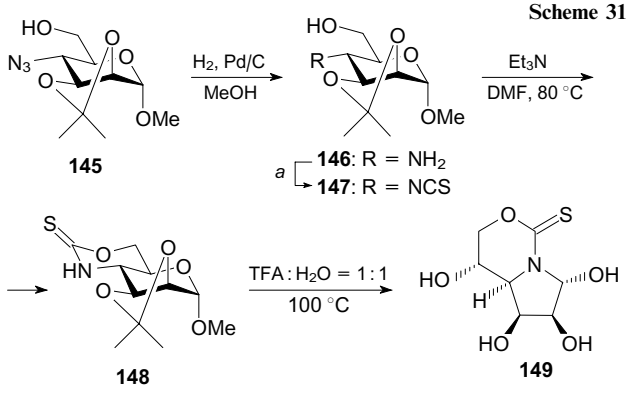
(*a*) 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, Bu^{t}ONa, PhMe, 100 °C;
(*b*) cyclohexene, Pd, EtOH, reflux

(K_i = 1.8 μmol L^{-1}) and comparable in its activity with acarviosin, a pseudo-disaccharide being a part of acarbose.

Swainsonine, hydroxylated perhydroindolizine of the fungal origin, is a potent α-mannosidase inhibitor. Díaz-Pérez *et al.*[45] reported the synthesis of the swainsonine analogue, containing an additional α-hydroxyl group, which, according to the authors' opinion, can promote its binding at the enzyme active site.

As a starting material, 4-azido-α-methylmannoside **145** was used, which was reduced to 4-amino-α-methylmannoside **146** and then reacted with thiophosgen to yield isothiocyanate **147** (Scheme 31). When the latter was treated with triethylamine, the ring closure occurred producing thiocarbamate **148**. The acid hydrolysis of isopropylidene protecting groups and methyl glycoside in **148** led to 4,6-*N*,*O*-thiocarbonyl-4-aminomannose, which underwent

Scheme 31

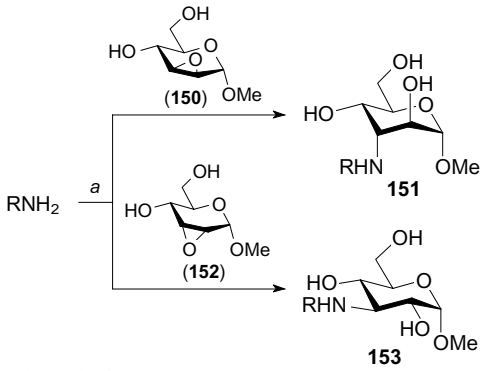


(*a*) $CSCl_2$, $CaCO_3$, acetone (aq.)

a spontaneous pyrrolidine ring closure involving the thiocarbamate nitrogen atom to yield the target product **149**.

A representative series of simple *N*-alkyl derivatives of 3-aminoaltrose **151** and 3-aminoglucose **153** was synthesized by ring opening of epoxides **150** and **152** under the action of an excess of amine (Scheme 32).[46]

Scheme 32



(*a*) 100 – 120 °C, neat;
151, **153**: R = $H_2N(CH_2)_4$ (**a**), $Ph(CH_2)_3$ (**b**), Bn (**c**), $Ph(CH_2)_4$ (**d**), Bu^n (**e**)

A total of 25 amino altrosides **151** (certain substituents R are represented in Scheme 32) and 4 amino glucosides **153** have been synthesized. The study of the inhibitory activity of the obtained compounds showed that compounds **151a**,**b** inhibit bovine liver β-galactosidase at a micromolar concentration (IC_{50} 70 – 150 μmol L^{-1}), and compounds **151c** – **e** inhibit almond β-glucosidase.

α-Glucosidase II is involved in the biosynthesis of *N*-linked carbohydrate chains of glycoproteins, where it catalyzes the hydrolysis of the second and third glucose residues in the oligosaccharide $Glc_3Man_9GlcNAc_2$ (Glc is glucose, Man is mannose). α-Glucosidase II inhibitors, capable of blocking the biosynthesis of *N*-glycans, can be used as antiviral drugs.

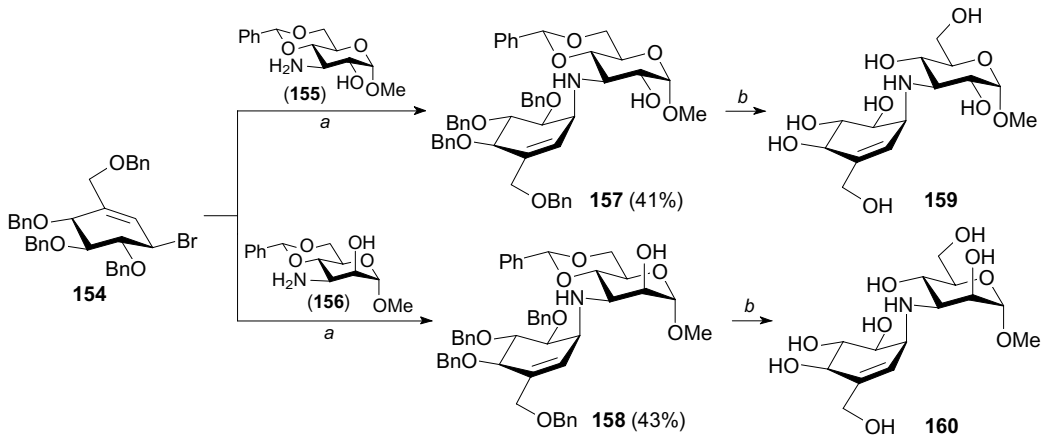
Cumpstey *et al.*[47] reported the synthesis of two pseudo-disaccharides **159** and **160**, which mimick α-Glc-(1→3)-α-Glc and α-Glc-(1→3)-α-Man disaccharide sites in *N*-glycan, hydrolysis of which is catalyzed by α-glucosidase II. Derivatives of 3-aminoglucose **155** and 3-aminomannose **156** were alkylated with bromide **154** to obtain protected pseudo-disaccharides **157** and **158**. The subsequent removal of benzyl and benzylidene protecting groups led to the target products **159** and **160**. Testing the inhibitory activity of the latter on the natural substrates showed that they inhibit α-glucosidase II at micromolar concentrations (Scheme 33).

3.3. Substrate analogues of glycan biosynthesis enzymes

Hexoses containing an amino group in position 3 or 4 were utilized in the synthesis of substrate analogues of other types of glycan biosynthesis enzymes to obtain model compounds to study their carbohydrate specificity and in search for inhibitors of such enzymes.

Nucleoside diphosphate sugars (NDPs) are substrates for a variety of enzymes involved in the biosynthesis of natural oligo- and polysaccharides, in particular, glycosyl transferases. Among other analogues of NDPs, derivatives of 3- and 4-amino sugars were also synthesized. Thus, the preparation of amino derivatives of deoxythymidine diphosphate glucoses (dTDP-glucoses), substrate analogues

Scheme 33



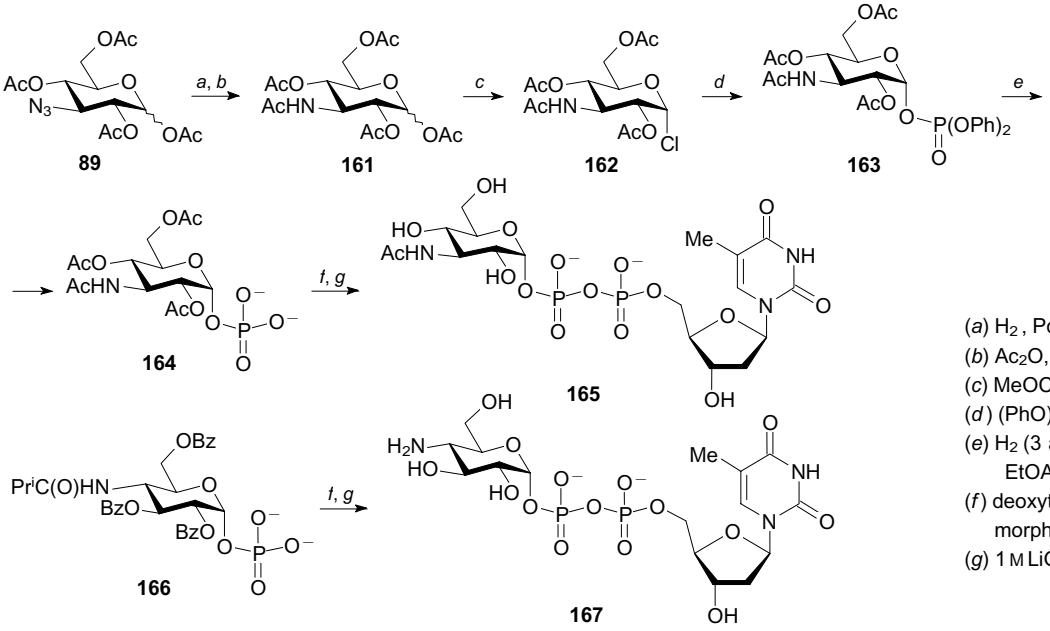
of dTDP-glucose 4,6-dehydratase has been described.[48] The starting 3-azidoglucose tetraacetate **89** was hydrogenated and then acetylated to give 3-acetamido derivative **161**, which gave rise to glycosyl chloride **162** (Scheme 34). The reaction of the latter with silver diphenyl phosphate afforded trisubstituted phosphate **163**, in which phenyl ester groups were cleaved to give mono-substituted phosphate **164**. Condensation of **164** with deoxythymidine monophosphate followed by the removal of acyl protecting groups produced the target dTDP-3-acetamido glucose **165**. Similarly, phosphate **166** was converted into dTDP-aminoglucose **167**.

The synthesis of α-glucosyl phosphate analogues and the study of their substrate specificity in reactions with deoxythymidine triphosphate catalyzed by α-D-glucopyranosyl phosphate thymidylyltransferase E_p from *Salmonella enterica* have been reported.[49] Starting from 3-azidoglucose tetraacetate **89**, thioglycoside **168** was obtained, in which the acetyl protection was replaced by the benzyl one, thereby affording tribenzyl derivative **169** (Scheme 35). Reduction of the azide group in **169** followed by acetylation afforded 3-acetamide **170**. Thiogalactazide **171** *via* the corresponding 4-triflate and its further reaction with the azide ion was converted into 4-azidoglucose derivative **172**, which after reduction of the azide and acetylation gave 4-acetamide **173**.

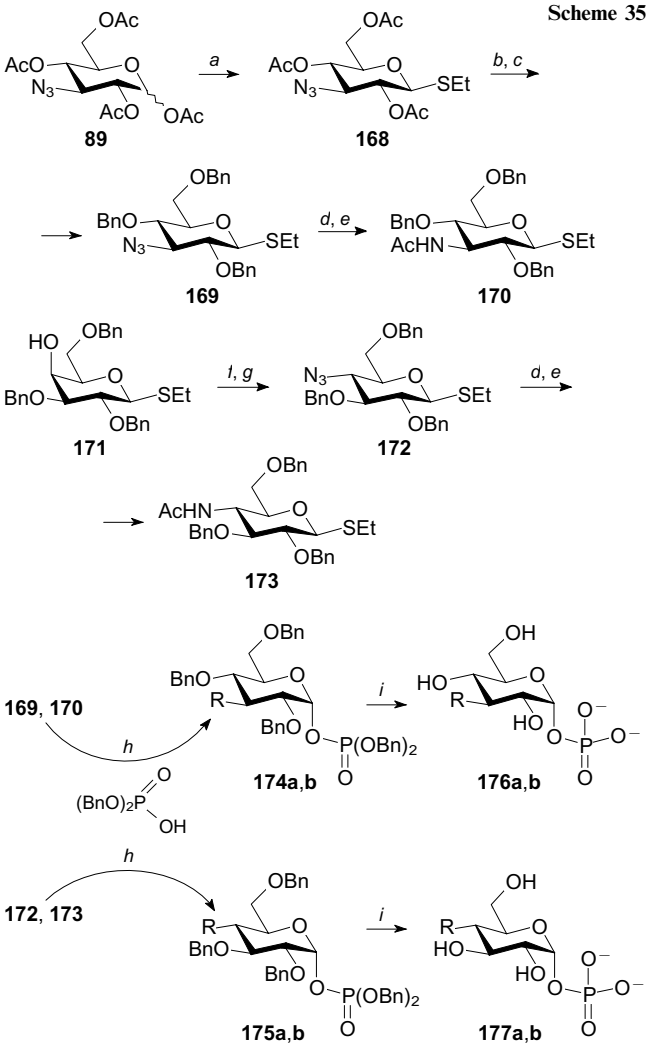
Glycosylation of dibenzyl phosphate with thioglucosides **169**, **170**, **172**, and **173** produced protected α-glucosyl phosphates **174a**,**b** and **175a**,**b**. Debenzylation *via* the catalytic hydrogenation (with simultaneous reduction of the azide group in the case of **174a** and **175a**) furnished free modified α-glucosyl phosphates **176a**,**b** and **177a**,**b**. The obtained compounds were then studied in the reaction with deoxythymidine triphosphate **178**, catalyzed by α-D-glucopyranosyl phosphate thymidylyltransferase E_p (Scheme 36).

The aim of this research was twofold: first, to study the substrate specificity of the enzyme and, second, to develop a method for the enzymatic synthesis of unnatural dTDP-sugars. It turned out that phosphates **176a** and **177a**, bearing free amino groups, do not differ in activity from the standard — α-D-glucopyranosyl phosphate — and form readily the corresponding NDPs **179a** and **167**. In the case of *N*-acetylated analogues, the activity of 3-acetamido phosphate **176b** was ~60% of the activity of the standard and, accordingly, NDPs **165** was formed in a lower yield, while 4-acetamidophosphate **177b** was not a substrate in this reaction and its utilization did not lead to NDPs **179b**.

Scheme 34



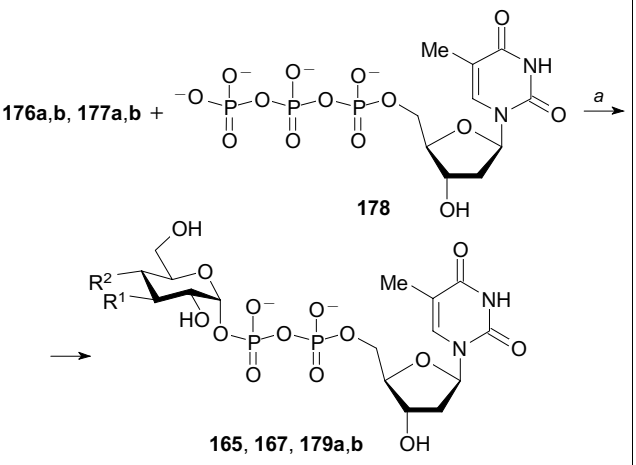
Scheme 35



(*a*) TMS-SEt, ZnI_2, CH_2Cl_2; (*b*) MeONa, MeOH; (*c*) BnBr, NaH, DMF; (*d*) $SnCl_2$, PhSH, Et_3N, MeCN; (*e*) Ac_2O, Py; (*f*) Tf_2O, Py, CH_2Cl_2; (*g*) NaN_3, DMF; (*h*) NIS, TfOH, CH_2Cl_2; (*i*) H_2, Pd/C, MeOH; **174**, **175**: R = N_3 (**a**), NHAc (**b**); **176**, **177**: R = NH_2 (**a**), NHAc (**b**)

Similar results were obtained when studying the substrate specificity of Cps2L thymidylyltransferase from *Streptococcus pneumoniae*.[50] The synthesis of 3-amino- and 3-azidoglucosyl phosphates, utilized as substrates, is illustrated in Scheme 37.

Scheme 36

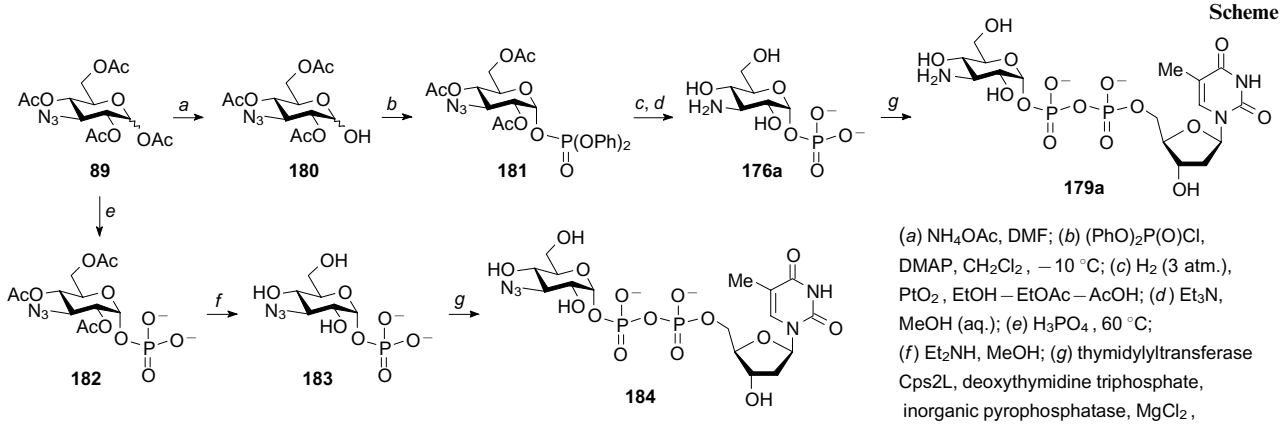


(*a*) α-D-glucopyranosyl phosphate thymidylyltransferase, Mg^{2+}, inorganic pyrophosphatase, 37 °C;
R^2 = OH: R^1 = NHAc (**165**), NH_2 (**179a**);
R^1 = OH: R^2 = NH_2 (**167**), NHAc (**179b**)

As a starting material for the preparation of both phosphates, tetraacetate **89** was used, which was subjected to anomeric deacetylation and phosphorylation of the resulting hemiacetal **180** with diphenyl phosphochloridate to give phosphate **181**. Then phenyl and acetyl protecting groups in **181** were sequentially removed to afford 3-aminoglucosyl phosphate **176a**. To obtain 3-azidoglucosyl phosphate, compound **89** was phosphorylated with anhydrous phosphoric acid and then deacetylated to produce the target product **183**. Phosphates **176a** and **183** served as substrates in the thymidylyltransferase Cps2L-catalyzed reaction with deoxythymidine triphosphate, with **176a** appearing to be more active: in preparative experiments, the yields of NDPs **179a** and **184** were 86% and 33%, respectively. Compounds **176a** and **183** were also utilized as the reaction substrates when uridine triphosphate was employed as a source of nucleoside monophosphate.

Attempts were made to use the modified NDPs as inhibitors of some polysaccharide biosynthesis by introducing a monosaccharide incapable of further glycosylation into the growing chain. In particular, a series of uridine diphosphate glucoses was synthesized in which the hydroxyl group at C(3) was replaced by other functionalities including azide and acetamide ones, with the purpose to inhibit

Scheme 37



(*a*) NH_4OAc, DMF; (*b*) $(PhO)_2P(O)Cl$, DMAP, CH_2Cl_2, −10 °C; (*c*) H_2 (3 atm.), PtO_2, EtOH – EtOAc – AcOH; (*d*) Et_3N, MeOH (aq.); (*e*) H_3PO_4, 60 °C; (*f*) Et_2NH, MeOH; (*g*) thymidylyltransferase Cps2L, deoxythymidine triphosphate, inorganic pyrophosphatase, $MgCl_2$, Tris·HCl buffer, pH 7.4

the biosynthesis of β-(1→3)-glucan, vital for the normal functioning of the fungal cells.[51]

The synthesis of uridine diphosphate-3-acetamido glucose from 3-azidoglucose tetraacetate **89** is shown in Scheme 38. By removing the anomeric acetyl group, **89** was converted into hemiacetal **180**, which was phosphorylated with tetrabenzyl pyrophosphate in the presence of lithium diisopropylamide to give the phosphate **185**. Removal of the benzyl protecting groups by catalytic hydrogenation with the simultaneous reduction of azide followed by acetylation led to 3-acetamido phosphate **164**, deacetylation of which afforded the free phosphate **186**. In the final step, the coupling of **186** with uridine monophosphate morpholidate provided NDPs **187**. Also, analogue **187** bearing the azide group at the C(3) atom was synthesized *via* intermediate 3-azidoglucosyl phosphate **183**. Here, *o*-phenylene phosphochloridate was utilized to phosphorylate hemiacetal **180**, and deprotection of the formed glucosyl phosphate was accomplished by oxidation with lead tetraacetate (not shown in Scheme 38). The test for inhibitory activity towards spore germination on the fungus *Trichophyton rubrum* revealed the absence of antifungal activity in the obtained NDPs.

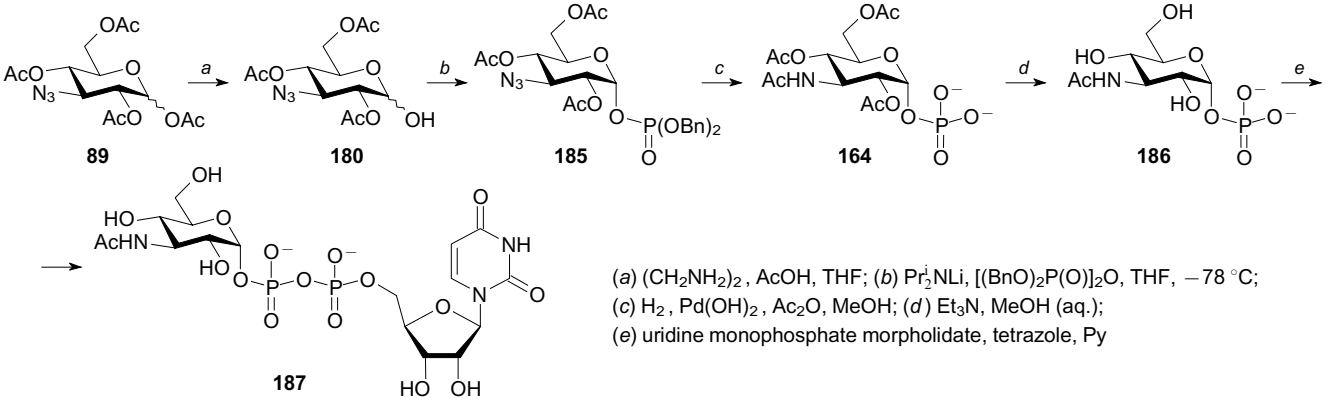
To study the substrate specificity of enzymes and in search for their inhibitors, modified substrates were synthesized acting as glycosyl acceptors in enzymatic glycosylation reactions including those involving 3- and 4-aminohexoses. In particular, the synthesis of a series of glycosyl acceptors of glycosylation reactions catalyzed by α-(1→3)-*N*-acetylgalactosaminyl- and α-(1→3)-galactosyltransferases has been described.[52] Scheme 39 illustrates the synthesis of disaccharide acceptor, in which a galactose residue was replaced with a 3-amino galactose residue.

The starting 3-azidogalactose tetraacetate **188** was converted into bromide **189**, which was then used to glycosylate 1-octanol providing octyl glycosyl **190**. Deacetylation of **190** and subsequent introduction of the 4,6-*O*-benzylidene group afforded 2-OH derivative **191**. Glycosylation of the latter with fucosyl bromide **192** under Lemieux conditions gave disaccharide **193**, which was deprotected and an azide was reduced to an amine by catalytic hydrogenation to yield the final product **194**.

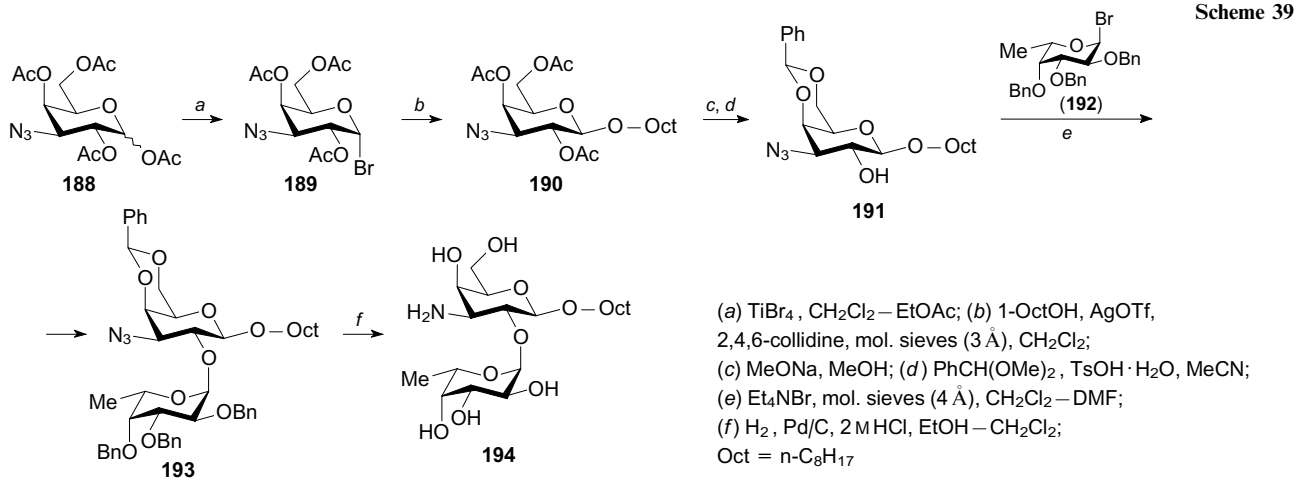
The starting material used to obtain disaccharide with an amino group at the galactose C(4) atom was octyl glucoside **195**, which was converted into 4-azidogalactoside **196** *via* the corresponding triflate. Then debenzylation by the catalytic hydrogenation and reduction of the azide group was accomplished. The amino group in **197** was trifluoroacetylated and the resulting **198** was selectively benzoylated *via* the intermediate dibutyl stannylene derivative affording 2-OH derivative **199**. Glycosylation of **199** with fucosyl bromide **192** and the subsequent deprotection of disaccharide **200** provided the target product **201**. 3-Amino derivative **194** displayed inhibitory activity against both transferases, whereas 4-amino derivative **201** was inactive (Scheme 40).

To study the substrate specificity of transferases involved in the biosynthesis of lactosamine chains of glycoproteins, a series of derivatives of β-D-Gal-(1→3)-β-D-GlcNAc-(1→2)-α-D-Man trisaccharide, modified on the

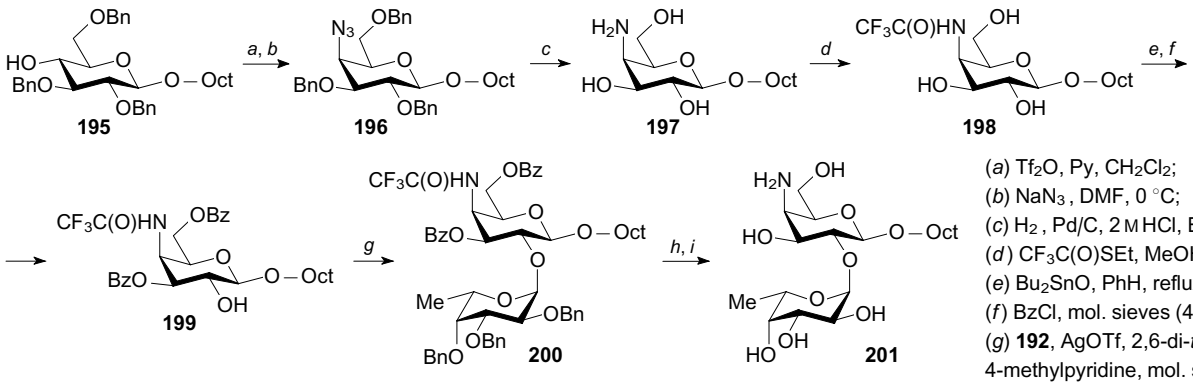
Scheme 38



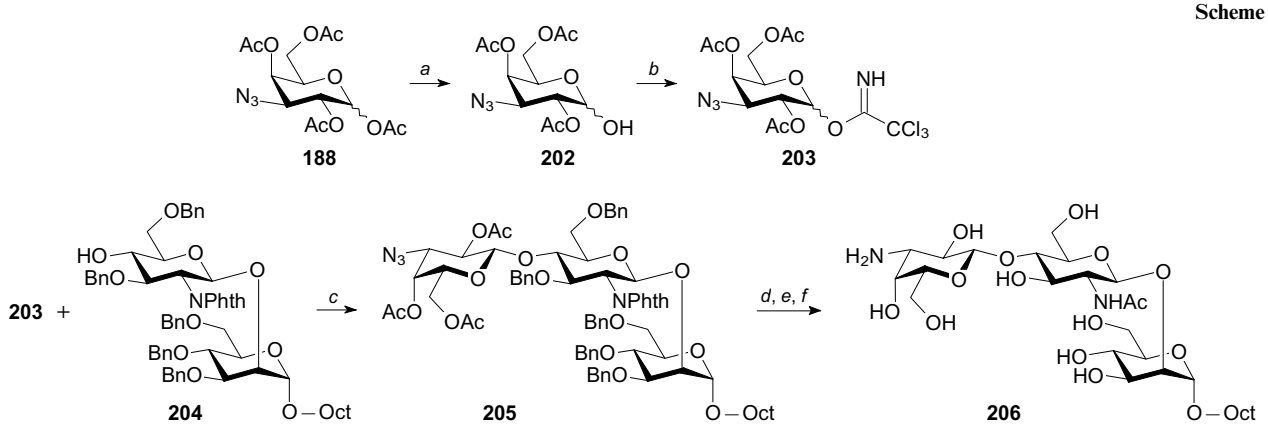
Scheme 39



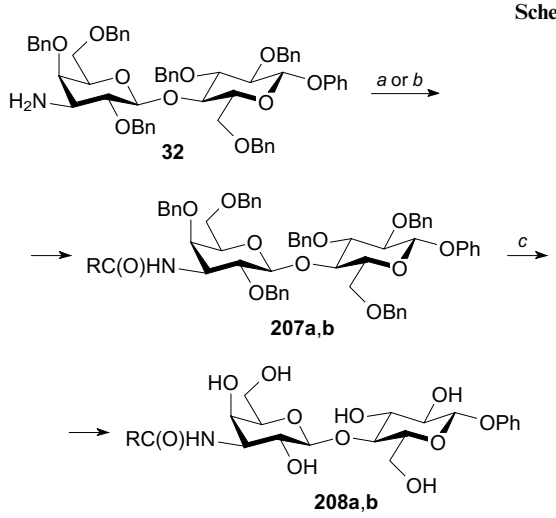
Scheme 40



Scheme 41



Scheme 42



galactose residue, was synthesized.[53] The preparation of 3-amino derivative is shown in Scheme 41. The anomeric deacetylation of tetraacetate **188** provided hemiacetal **202**, which was converted into trichloroacetimidate **203**. Glycosylation of acceptor **2** with imidate **203** gave trisaccharide **205**; subsequent deprotection and reduction of the azide group in **205** led to the target trisaccharide **206**.

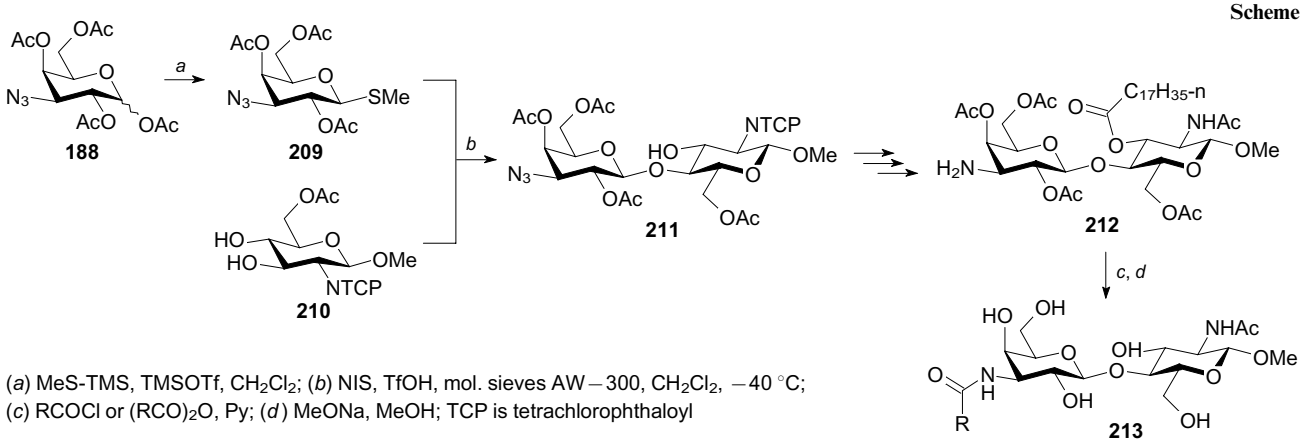
To study the substrate specificity of *N*-acetylglucosaminyltransferase from *Neisseria meningitidis*, a series of β-phenyllactoside derivatives modified on the galactose residue, including 3-acetamido- and 3-benzamido derivatives, was synthesized.[15]

The synthesis of the starting 3′-aminolactoside **32** was presented above (see Scheme 7). The amino group in **32** was acetylated or benzoylated and the resulting amides **207a**,**b** were converted into the target compounds **208a**,**b** by the catalytic hydrogenation (Scheme 42). Due to the absence of the 3′-OH group, these compounds were not glycosyl acceptors in the enzymatic glycosylation catalyzed by *N*-acetylglucosaminyltransferase. Inhibitory activity of **208a**,**b** was not investigated in this work.[15]

3.4. Inhibitors of galectins and other carbohydrate-binding proteins

Galectins are a family of carbohydrate-binding proteins (lectins) of animal origin that exhibit specificity for β-galactosides. To date,15 members of this family have been known; they all contain a conserved carbohydrate recognition domain. Galectins play a pivotal role in many physiological and pathological processes, such as the development of inflammation, angiogenesis, immune response, malignant growth, metastasis, regulation of apoptosis, and others.[54] Therefore, galectin inhibitors, the search for which has been

Scheme 43



(*a*) MeS-TMS, TMSOTf, CH_2Cl_2; (*b*) NIS, TfOH, mol. sieves AW – 300, CH_2Cl_2, –40 °C; (*c*) RCOCl or $(RCO)_2O$, Py; (*d*) MeONa, MeOH; TCP is tetrachlorophthaloyl

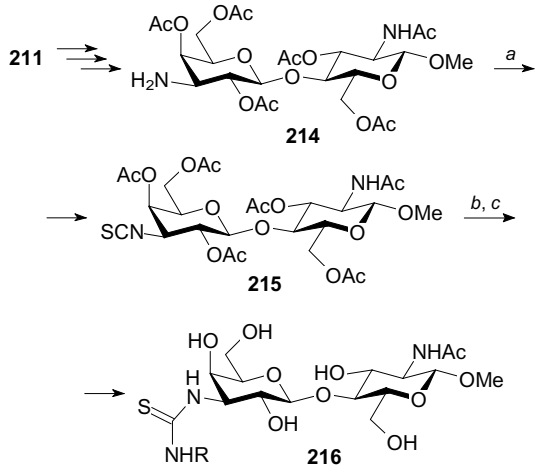
intensively conducted over the past 15 – 20 years, are considered as potential therapeutic agents against the pathologies mentioned above. One of the main focuses in the search for galectin inhibitors is the introduction of aromatic groups at the C(3) atom of the galactose residue since it was shown by X-ray diffraction analysis that such groups facilitate the binding of the carbohydrate ligand in the carbohydrate recognition domain due to the interaction of the aromatic π-system with a positive charge in the arginine-144 residue.[55] Most of the approaches used to obtain inhibitors of this type are based on the use of 3-aminogalactose and its derivatives. It is noteworthy that the C(3)-amino group itself does not contribute to the binding of the ligand to galectin, but is only a convenient functional group that allows the efficient and selective introduction of various substituents at the 3-position of galactose. Hereinafter, we consider examples of the synthesis of galectin inhibitors based on 3-aminogalactose that were developed by a team of Swedish researchers at the University of Lund.

Scheme 43 shows one of the first syntheses of this type of inhibitors.[56] The starting tetraacetate **188** was converted into thioglycoside **209**, which selectively glycosylated diol **210** at the 4-OH group to yield a lactosamine derivative **211**. Compound **211** was transformed into amine **212** over several steps, which we will not address here in detail (the stearyl group was introduced to isolate the products by solid-phase extraction). Acylation of the amine with carboxylic acid anhydrides or chlorides provided products **213**. The study of binding to galectin-3 showed that compounds **213** with aromatic substituents had the highest inhibitory activity: for R is phenyl, 2-carboxyphenyl, and 4-methoxy-2,3,5,6-tetrafluorophenyl, IC_{50} values were 14, 13, and 4.4 μmol L^{-1}, respectively. The synthesis of a representative library of potential inhibitors of galectins of type **213** (42 compounds) is described.[55]

The same research team[57] synthesized lactosamine derivatives containing a thioureide group at the C(3) atom of galactose (Scheme 44).

Disaccharide **211** (see Scheme 43) was converted into amine **214**, which reacted with thiophosgene to give isothiocyanate **215**. A series of thioureas **216** was obtained by the reaction of **215** with amines. The study of the binding of **216** to various galectins showed that cyclohexyl and 3-pyridylmethyl derivatives (R is cyclohexyl, 3-pyridylmethyl) have a high affinity for galectin-7, exceeding the unmodified β-methyl lactosaminide by more than an order of magnitude.

Scheme 44

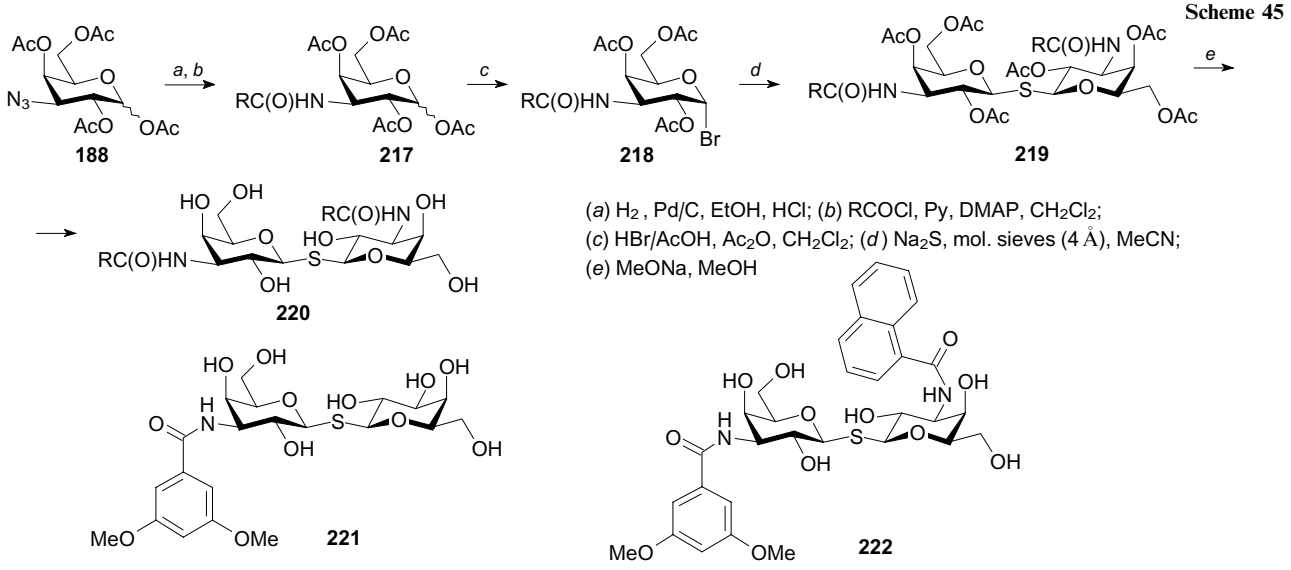


(*a*) Cl_2CS, Et_3N, CH_2Cl_2; (*b*) RNH_2, Py; (*c*) MeONa, MeOH

Based on the analysis of X-ray diffraction data for the complex of β-methyllactosaminide with galectin-3,[55] bis(3-amido)thiodigalactosides, novel galectin inhibitors, were proposed.[58, 59] The synthesis of such derivatives is illustrated in Scheme 45. Azidogalactose tetraacetate **188** was again used as a starting material, providing amides **217** *via* the azide reduction followed by acylation of the resulting amine with aromatic carboxylic acid chlorides. These amides were converted into galactosyl bromides **218**, which were reacted with sodium sulfide to afford thiodigalactosides **219**. The final deacetylation of **219** led to the target products **220**. Also, non-symmetrical derivatives were synthesized, *e.g.*, **221** and **222**.[59] The study of the inhibitory activity of thiogalactosides against galectins showed that disubstituted compounds **220** (R is 3-methoxyphenyl, 3,5-dimethoxyphenyl, 4-nitrophenyl) and **222** have a high affinity to galectin-3 ($K_d \sim 50$ nmol L^{-1}), being appreciably superior to monosubstituted **221** (K_d 1.1 μmol L^{-1}) and unmodified β-methyllactosaminide (K_d 59 μmol L^{-1}).[59]

It has been suggested that the anionic groups at the O(2) atom of galactose can increase the affinity of the ligand due to an ionic interaction with a positive charge on arginine-144 at the galectin binding site.[60, 61] The synthesis of one of the derivatives bearing an anionic substituent at O(2) is provided in Scheme 46.

Scheme 45



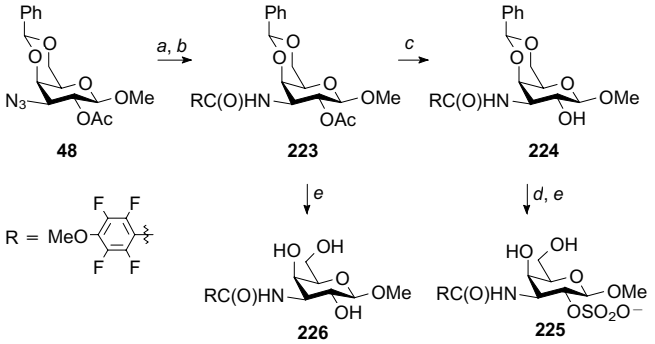
The azide group in galactosamine **48** was reduced by the catalytic hydrogenation, and the resulting amine was acylated to produce the amide **223**. Removal of the single acetyl group in **223** gave the 2-OH derivative **224**, the hydroxyl group in which was sulfated, and the benzylidene one was cleaved by mild acid hydrolysis. This led to sulfate **225**. Also, the removal of the benzylidene group in **223** provided an unsulfated analogue **226**. Comparing the activity of derivatives **225** and **226** in the reaction with galectin-3 showed that the affinity of sulfate **225** (K_d 65 μmol L^{-1}) exceeds that of **226** (K_d 1300 μmol L^{-1}) by a factor of 20.[61]

The same team from the University of Lund synthesized some other types of potential galectin inhibitors based on 3-amino sugars. Among them are *O*-galactosylated oximes, such as **227** and **228**,[62] derivatives of 3-aminotalose (for example, **229**) [17] and 3-aminogulose **230**.[63] Most of the types of compounds listed here did not demonstrate high activity in the binding reaction with galectins, although taloside **229** and similar talosides showed selectivity towards galectin-4 with a sufficiently high affinity($K_d \sim 100$ μmol L^{-1}).[17]

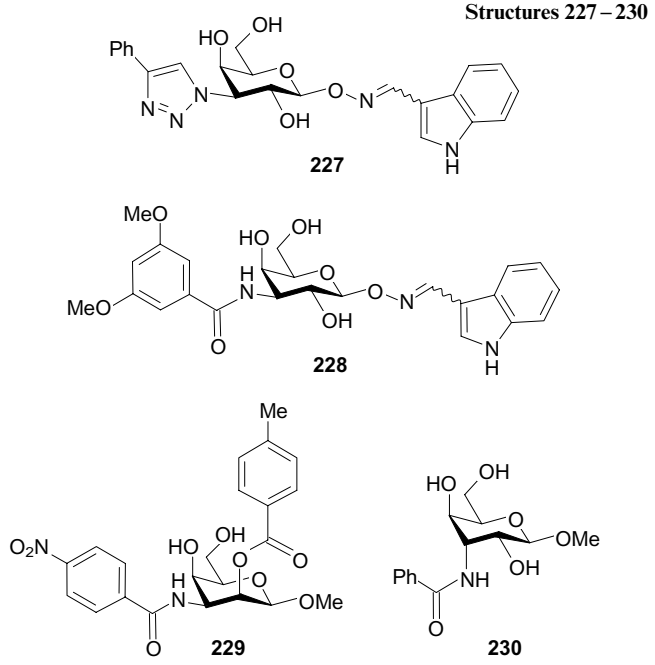
3-Aminogalactose derivatives were also utilized in the synthesis of inhibitors of other carbohydrate-binding proteins. Several potential inhibitors of bacterial adhesins have been synthesized from the disaccharide 3′-aminogalactobiose (Scheme 47).[64] Thiogalactoside triacetate **209** was converted into a tribenzyl derivative **231**, which was then used as a glycosyl donor in glycosylation of acceptor **232**. The resulting α-digalactoside **233** was debenzoylated and further, the benzyl groups in triol **234** were removed by the catalytic hydrogenation with the simultaneous reduction of the azide. In the final step, amine **235** was acylated with aliphatic and aromatic carboxylic acid anhydrides or chlorides or isocyanates to afford derivatives **236**. The binding of these compounds to adhesine PapG II from *Escherichia coli*, as well as P_N and P_O from *Streptococcus suis*, was studied. Compounds **236** showed no inhibitory activity towards PapG II, but proved to be potent inhibitors of aghesin P_N [the minimum IC_{50} 0.04 μmol L^{-1} was observed for **236** at R = PhNHC(O)] and less effective inhibitors of aghesin P_O (IC_{50} 31.3 – 62.5 μmol L^{-1}).

The synthesis of a representative library of 3-aminogalactose derivatives tested as selective binders to some

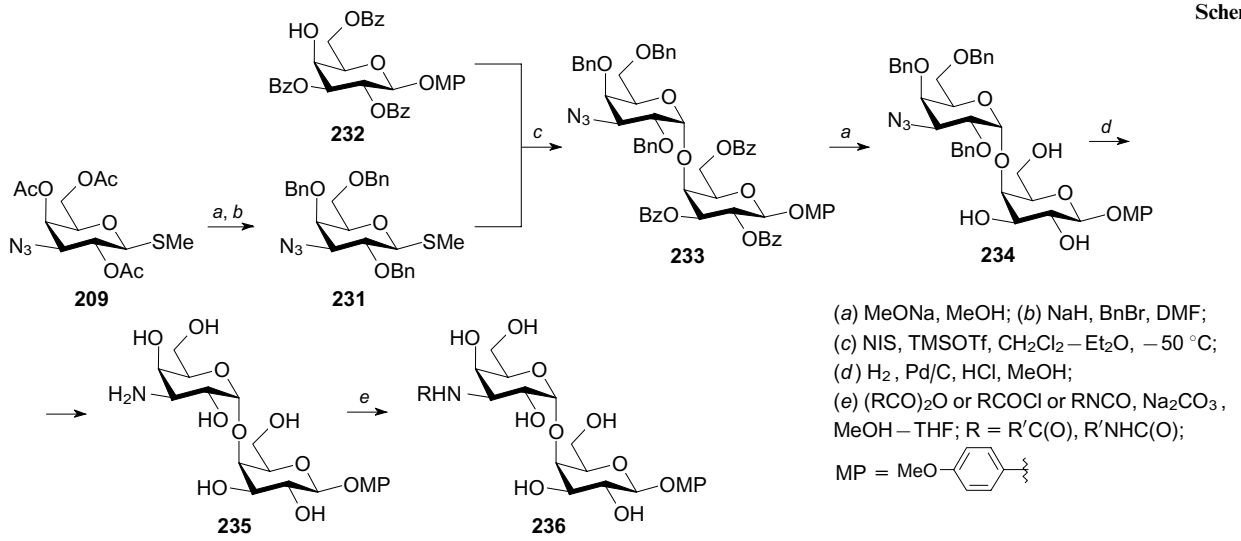
Scheme 46



Structures 227 – 230



Scheme 47



plant lectines has been described.[65] The synthesis of three types of monosaccharide derivatives is illustrated in Scheme 48.

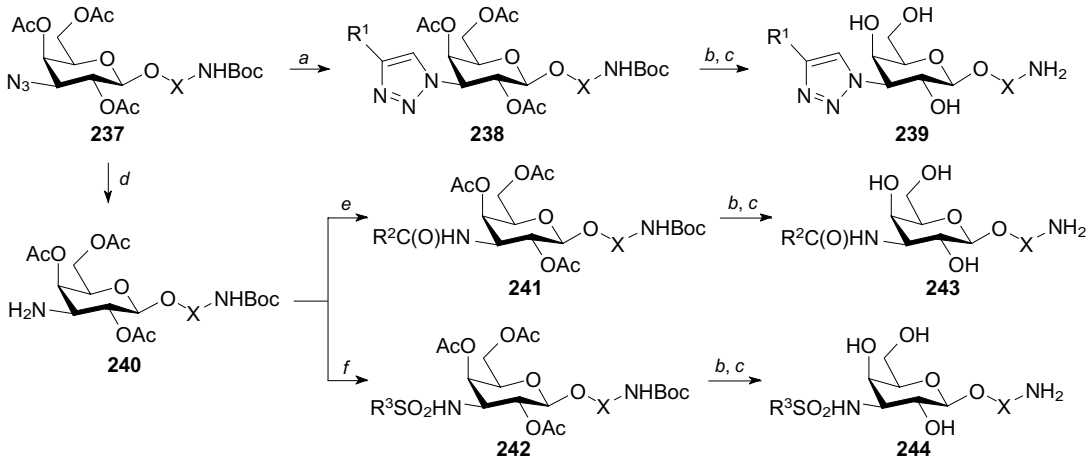
The derivative of 3-azidogalactose **237** bearing a terminal protected hydrazide group in the aglycone was used as a starting material. The copper-catalyzed cycloaddition of terminal alkynes to the azide group of **237** provided a series of triazoles **238**, the removal of acetyl and *N*-Boc protecting groups from which led to derivatives **239**. The reduction of azide **237** afforded amine **240**, which was then acylated or sulfonylated to give amides **241** or sulfonamides **242**, respectively. The final deprotection furnished derivatives **243** and **244**.

The synthesis of similar disaccharide derivatives is shown in Scheme 49.

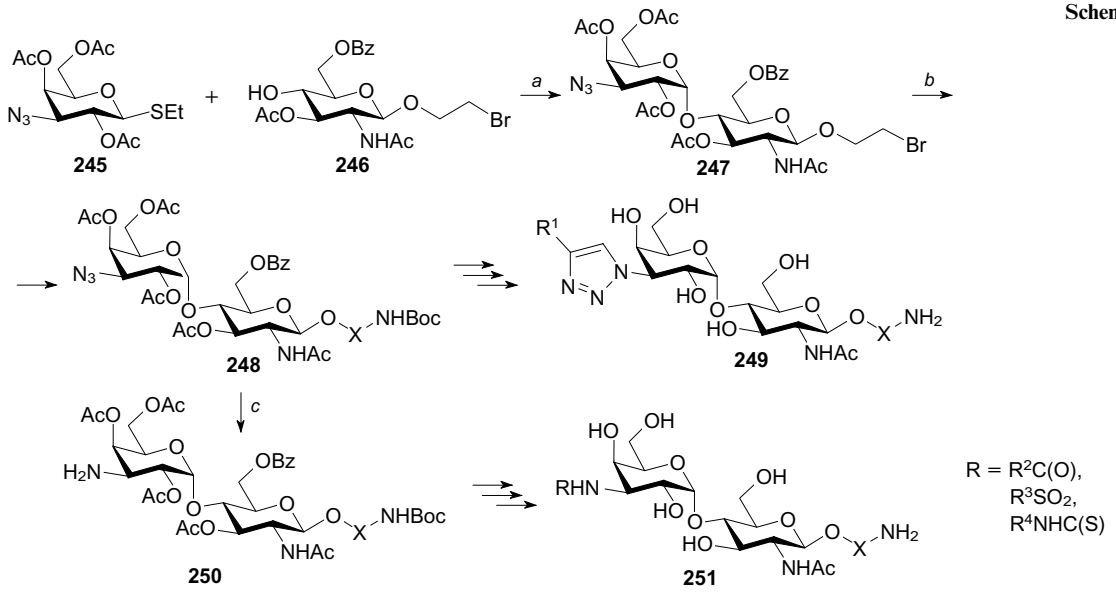
Glycosylation of acceptor **246** with thiogalactosides **245** results in disaccharide **247**. It should be noted that this reaction produces solely α-disaccharide, despite the presence of a participating acetyl group at the O(2) atom of the donor **245**. Then, a spacer group was introduced into 2-bromoethyl glycoside **247** (see Scheme 48) to give disaccharide **248**. Following the reaction sequence similar to that described for monosaccharide **237** (see Scheme 48), compound **248** was converted into a series of triazole derivatives **249**. Amine **250**, obtained *via* the reduction of the azide group in **248**, was reacted with acylating agents such as sulfonyl chloride or isothiocyanates, then the resulting products were deprotected (see Scheme 48), and a series of amides, sulfonamides and thioureas **251** was obtained. In total, 55 mono- and disaccharide ligands bearing various substituents at the C(3) atom of the galactose residue were synthesized. These ligands were immobilized onto the surface of epoxide-functionalized glass slides, and the resulting glycochips were used to study the interaction of ligands with 11 plant lectins. The ligands **252** and **253** were shown to be specific to potato lectin and wheat germ agglutinin, respectively, and have a fairly high affinity for them (K_d 179 and 844 nmol L^{-1}).

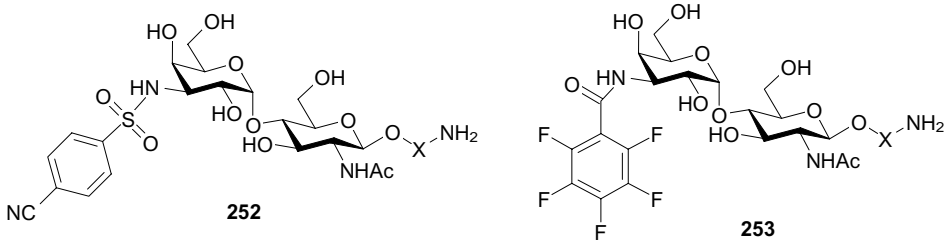
Verotoxin is a protein produced by *Escherichia coli* that specifically recognizes globotriosylceramide. With the purpose to study the carbohydrate specificity of verotoxin and in search for its inhibitors, several amine derivatives of

Scheme 48



Scheme 49

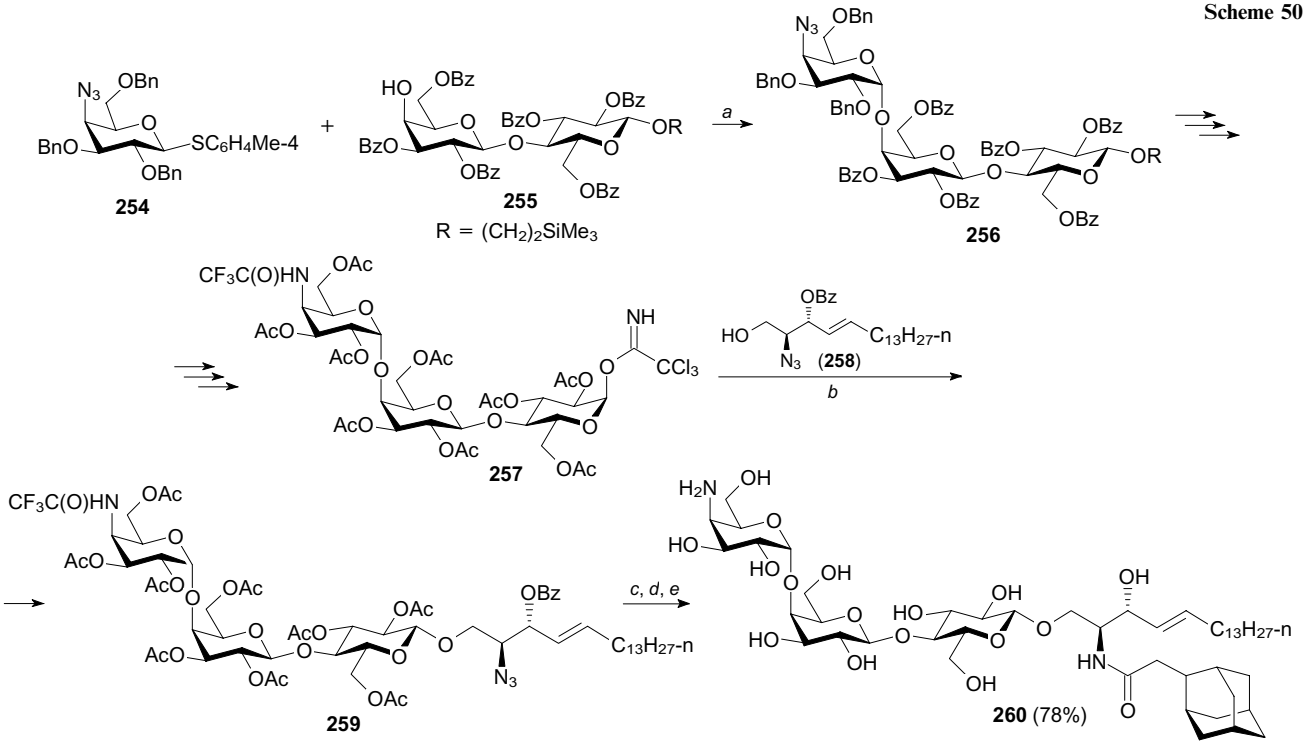




globotriosylceramide were synthesized, including those containing an amino group at position 4″ (Scheme 50).[66, 67]

Glycosylation of lactose glycosyl acceptor **255** with 4-azidothiogalactoside **254** afforded trisaccharide **256**, which was converted into a new glycosyl donor **257** through

Scheme 50



a number of standard manipulations with protecting groups, including debenzoylation, removal of benzyl groups with simultaneous reduction of the azide, *N*-trifluoroacetylation, *O*-acetylation, removal of the anomeric 2-trimethylsilylethyl group, and formation of trichloroacetimidate. Glycosylation of a sphingosine derivative **258** with donor **257** led to the formation of glycoside **259**, reduction of the azide group, *N*-acylation, and removal of all *N*- and *O*-acyl protecting groups in which provided the target globotriaosylceramide analogue **260**. Studying the reaction of globotriaosylceramide with verotoxin demonstrated that 4″-amino derivative **260** and the corresponding 6″-isomer did not bind to the protein, whereas 2″- and 6′-amino derivatives were fairly potent (IC_{50} 10 μmol L^{-1}) verotoxin inhibitors.[68]

3.5. Modified analogues of natural oligosaccharides

In this Section, we will discuss the synthesis of analogues of naturally occurring oligosaccharides in which one of hexose moieties is replaced with 3-amino-3-deoxy- or 4-amino-4-deoxyhexose. Such a replacement may have different objectives, *e.g.*, studying the structure – activity relationship, obtaining stable amide analogues of esters, identifying immunodominant regions of oligosaccharides, *etc*.

Lactams of certain gangliosides have been synthesized as hydrolysis-resistant analogues of ganglioside lactones, the formation of which involved the carboxyl group of sialic acid and hydroxyl groups at the C(2) or C(4) atoms of the adjacent galactosyl moiety.

The procedure to obtain sialyl Le^x-lactam tetrasaccharide was reported.[69] Glycosylation of glycosyl acceptor **262** with the 4-azidothiogalactoside **261** proceeded regioselectively at the 4-OH group and provided the disaccharide **263**, in which the tetrachlorophthaloyl amino-protecting group was replaced by the acetyl one (Scheme 51). The obtained disaccharide **264** was α-fucosylated with bromide **265** and the resulting trisaccharide **266** was deacetylated to give diol **267**. The latter was sialylated with thioglycoside **268** to yield tetrasaccharide **269**. Then, the auxiliary thiophenyl group in the sialic acid residue in compound **269** was removed using the Raney nickel, deacetylation, and debenzylation with simultaneous reduction of the azide group were carried out. The amine thus formed spontaneously reacted with carbomethoxy group of sialic acid providing the target lactam **270**.

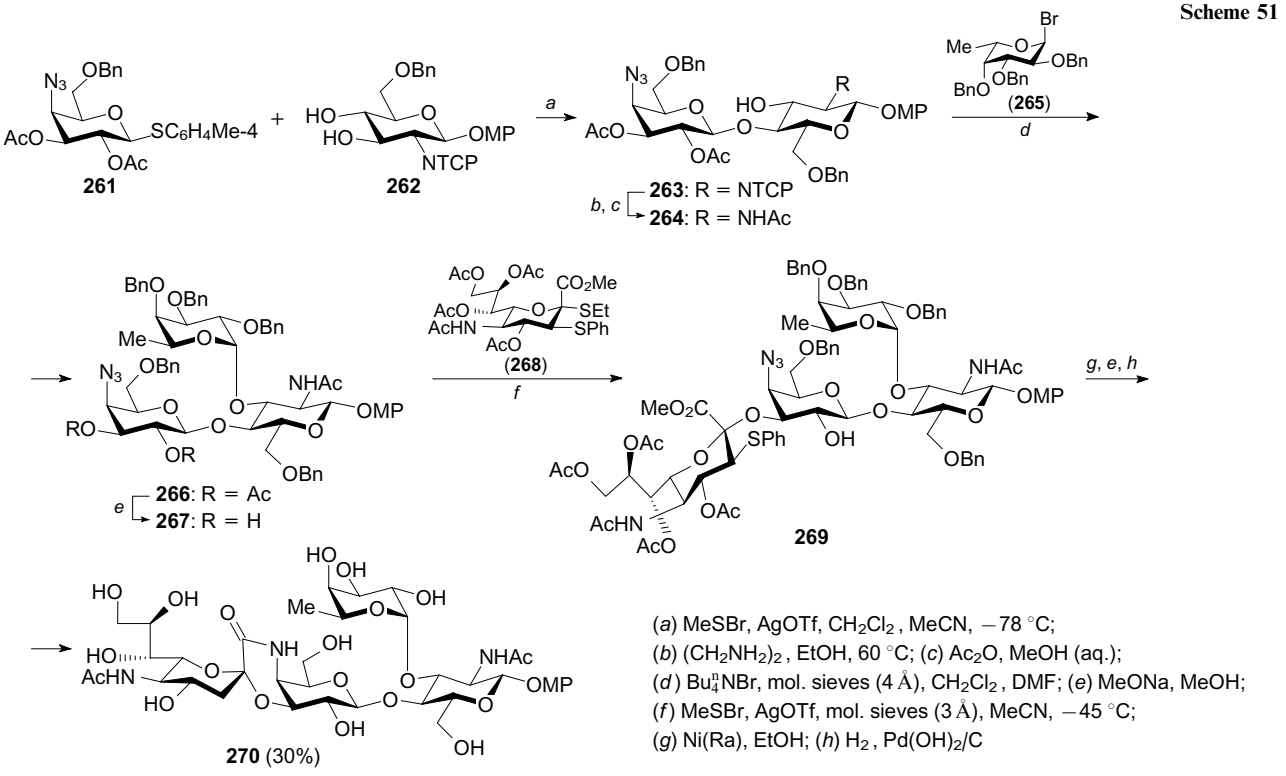
The synthesis of a bis-lactam of ganglioside GD_3 was also reported.[70]

Glycosylation of 4′-azidolactoside **272** with α-(2→8)-disialoside thioglycoside **271** produces tetrasaccharide **273**, which was subjected to the catalytic hydrogenation to remove benzyl groups and reduce the azide (Scheme 52). In the resulting amine, the second lactam ring underwent a spontaneous closure, after which the *O*-acetyl and *N*-trifluoroacetyl groups were removed. The final N-acetylation of amino groups in sialic acid residues led to the target bis-lactam **274**.

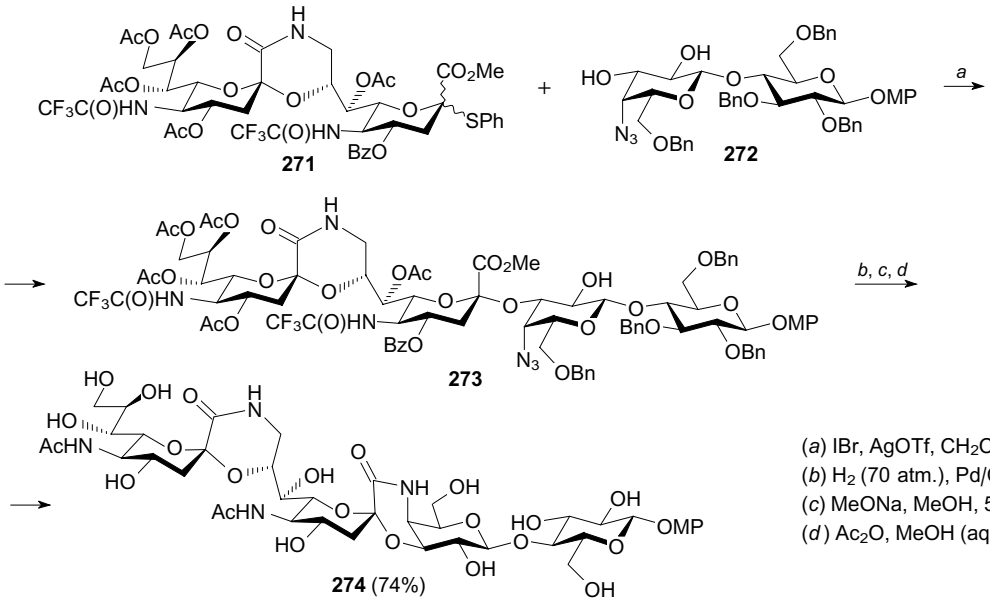
The amino derivatives were used to introduce a fluorescent label into the trehalose molecule.[71] 3-Azidotrehalose **275**[72] was reduced to amine **276**, which was converted into product **277** *via* the reaction with fluorescein isothiocyanate (Scheme 53). Similarly, 4-azide **278** was utilized to synthesize a fluorescently labeled derivative **279**. It turned out that compounds **277** and **279** can integrate into the mycobacterial cell membrane formed by trehalose mycolates, which was used to visualize and study the dynamics of the membrane by fluorescence microscopy.[71]

Saponin QS-21 isolated from the bark extracts of *Quillaja saponaria* is a potent adjuvant that can potentiate immune response during vaccination. However, putting it into clinical practice is hindered by a number of obstacles including its chemical instability under physiological conditions. One of the structural constituents of QS-21 is a linear tetrasaccharide with D-fucose at the reducing terminus, which glycosylates the C(28)-carboxyl group of the

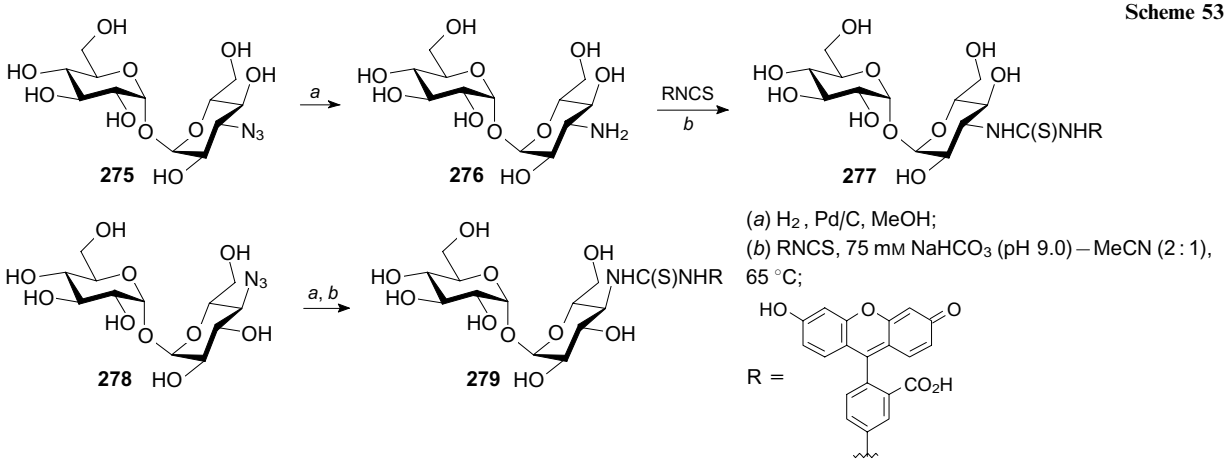
Scheme 51



Scheme 52



Scheme 53



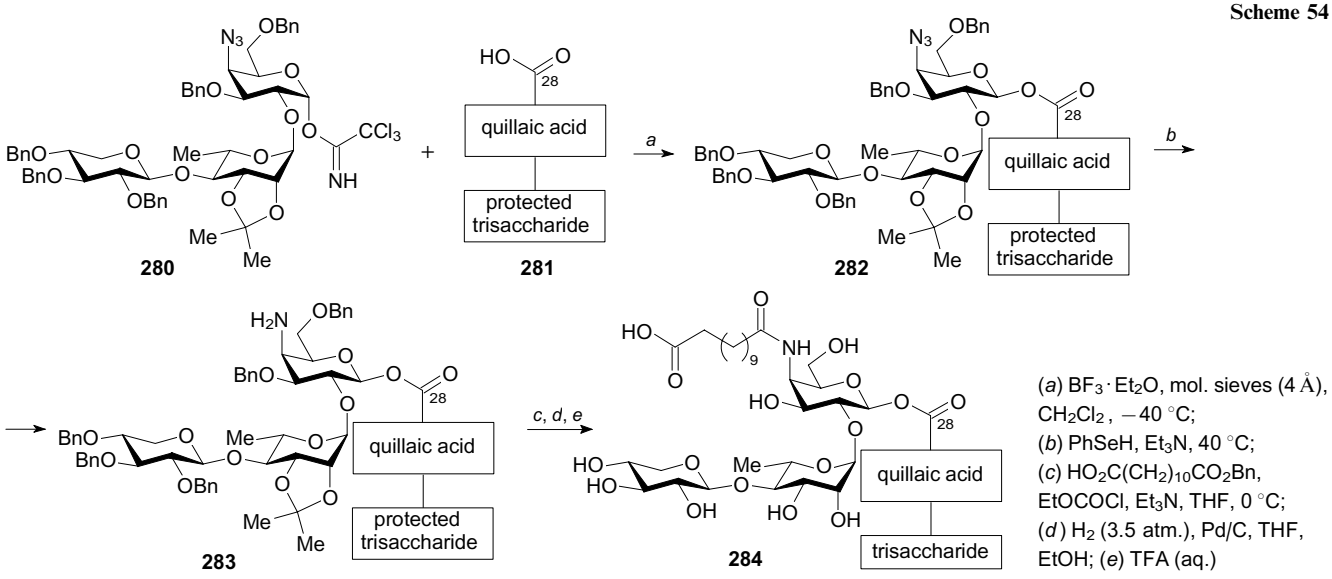
triterpene of quillaic acid. The C(4)-hydroxyl group of fucose is acylated with a complex carboxylic acid, which undergoes hydrolysis quite readily, thereby changing the biological activity profile. Therefore, in a series of works, analogues of QS-21 were synthesized, in which the labile ester group was replaced with a much more stable amide one.[73, 74] One of the syntheses of such compounds is exemplified in Scheme 54.

Synthetic trichloroacetimidate **280**, in which the fucose residue was replaced with 4-azidogalactose, was used to glycosylate the C(28)-carboxyl group of quillaic acid in protected prosapogenin **281** (the full structure of prosapogenin is not shown in the Scheme to save space,[73, 74]), obtained by a modification of natural QS-21. In product **282**, the azide group was reduced and the resulting amine **283** was acylated with dodecanedicarboxylic acid monobenzyl ester. Overall deprotection gave the target product **284** with a substituent resistant to hydrolysis at the C(4) atom of galactose.

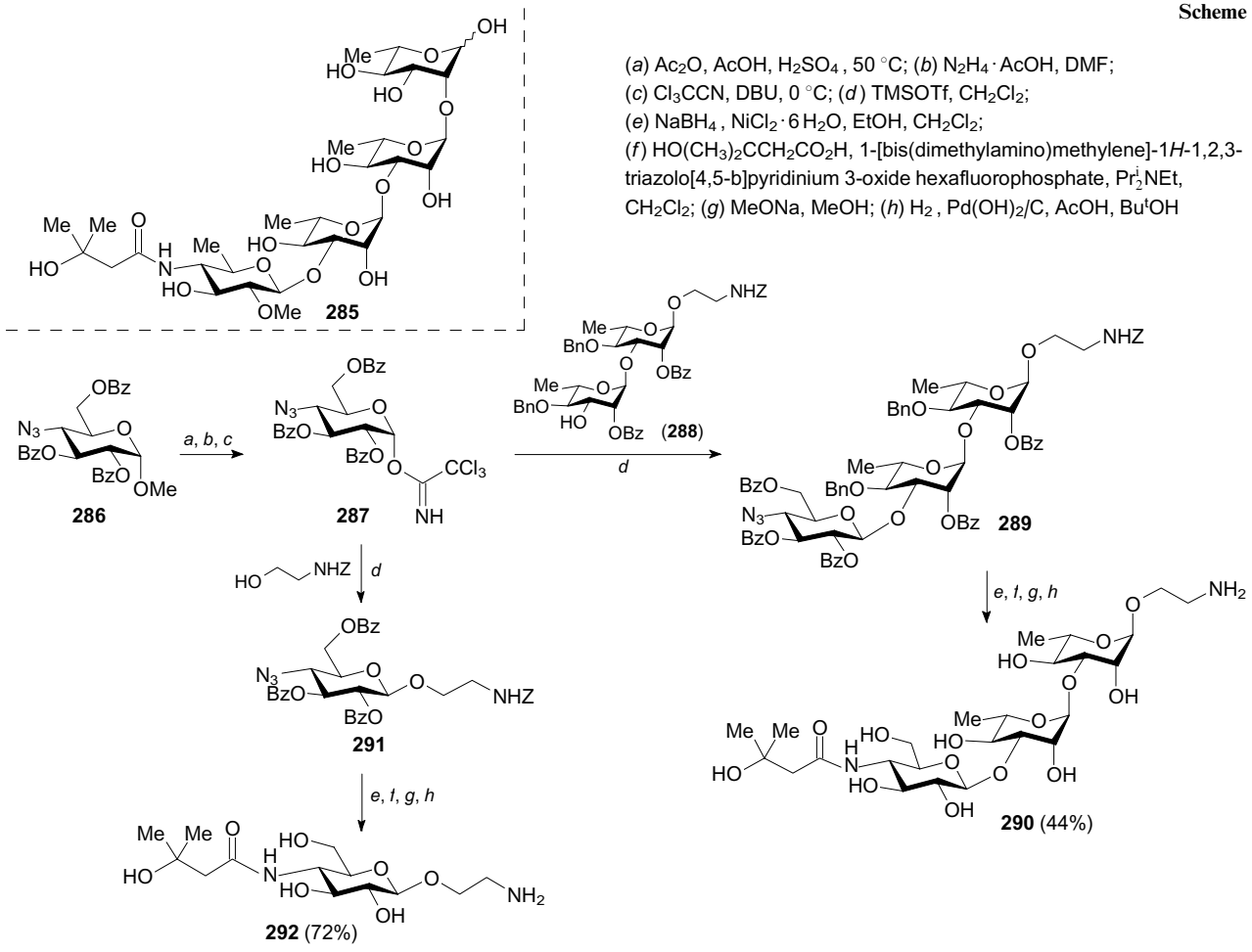
Tetrasaccharide **285** (Scheme 55) is a part of a surface glycoprotein Bc1A of *Bacillus anthracis* spores, which is the causative agent of anthrax. The terminal monosaccharide — 4,6-dideoxy-4-(3-hydroxy-3-methylbutyrylamido)-2-*O*-methyl-D-glucose (the trivial name is anthrose) — appears to be specific for *B. anthracis*, B, thus making tetrasaccharide **285** or shorter oligosaccharides of this type attractive ligands for the development of vaccines and immunological tools. To identify tetrasaccharide fragments responsible for the formation of specific antibodies, C(6)-hydroxylated analogues derived from 4-amino glucose were synthesized.[75]

Methyl 4-azidoglucoside **286** was converted into imidate **287** over three steps including acetolysis, anomeric deacetylation and the reaction with trichloroacetonitrile (see Scheme 55). Glycosylation of dirhamnoside acceptor **288** and *N*-protected ethanolamine provided trisaccharide **289** and glycoside **291**, respectively. Subsequent reduction of the azide, acylation of the resulting amines with 3-hydroxy-3-methylbutyric, and overall deprotection led to 2-aminoethyl glycosides of trisaccharide **290** and an analogue of 6-hydroxylated anthrose **292**. An immunochemical study of the compounds synthesized showed that **290** and **292** virtually do not bind to antibodies obtained by rabbit immunization with the conjugate of the trisaccharide β-D-anthrosyl-(1→3)-α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranose with the carrier protein KLH, and thus the C(5)-methyl group of the anthrose unit is immunodominant.

Scheme 54



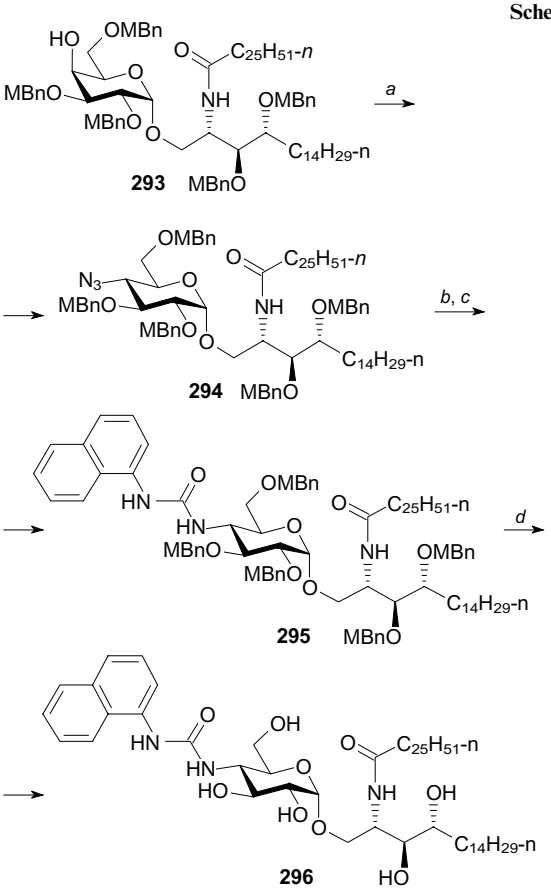
Scheme 55



A synthetic strategy for the generation of analogues of α-galactosylceramide immunostimulator including an 4-aminoglucose derivative is reported (Scheme 56).[76]

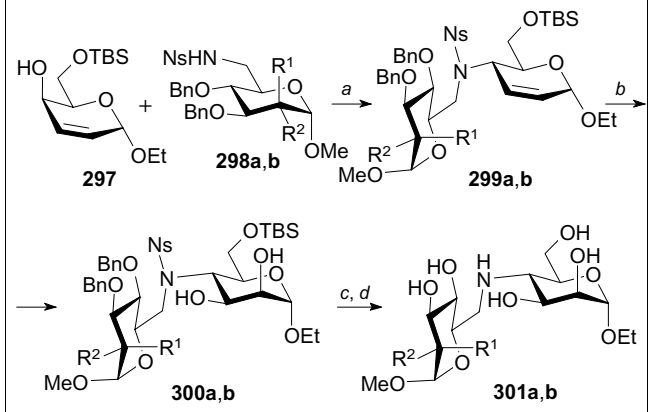
The protected α-galactosylceramide derivative **293** was converted into *gluco*-azide **294** *via* the Mitsunobu coupling. Reduction of the azide group and acylation of the resulting amine with naphthyl isocyanate led to the 4-ureido derivative **295**, the removal of *p*-methoxybenzyl protecting groups in which furnished the target analogue **296**. The study of the ability of the obtained analogues to stimulate *i*NKT cells demonstrated that compound **296** has activity comparable to that of the parent α-galactosylceramide.

Scheme 56

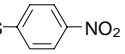


(*a*) $(PhO)_2P(O)N_3$, DEAD, PPh_3, THF, −20 °C;
(*b*) H_2S, Py (aq.); (*c*) 1-naphthyl isocyanate, DMF;
(*d*) HCl, PhOMe, 1,4-dioxane; DEAD = $EtO_2CN{=}NCO_2Et$

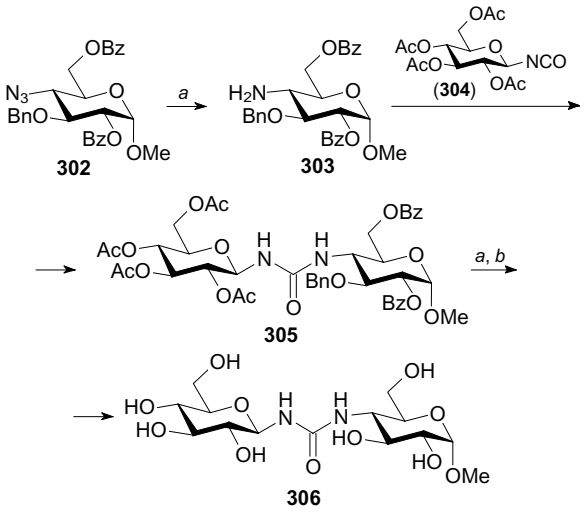
Scheme 57



(*a*) diisopropyl azodicarboxylate, PPh_3, THF, 0 °C;
(*b*) K_2OsO_4, *N*-methylmorpholine *N*-oxide, acetone (aq.));
(*c*) 1 M HCl, MeOH; (*d*) Na, liq. NH_3, −78 °C;
298–**300**: R^1 = H, R^2 = OBn (**a**), R^1 = OBn, R^2 = H (**b**);
301: R^1 = H, R^2 = OH (**a**), R^1 = OH, R^2 = H (**b**);

Ns = 

Scheme 58



(*a*) H_2, Pd/C, MeOH; (*b*) MeONa, MeOH

3.6. Other applications

This Section covers the studies that, according to the objectives set out therein, are beyond the scope of any of the Sections discussed above.

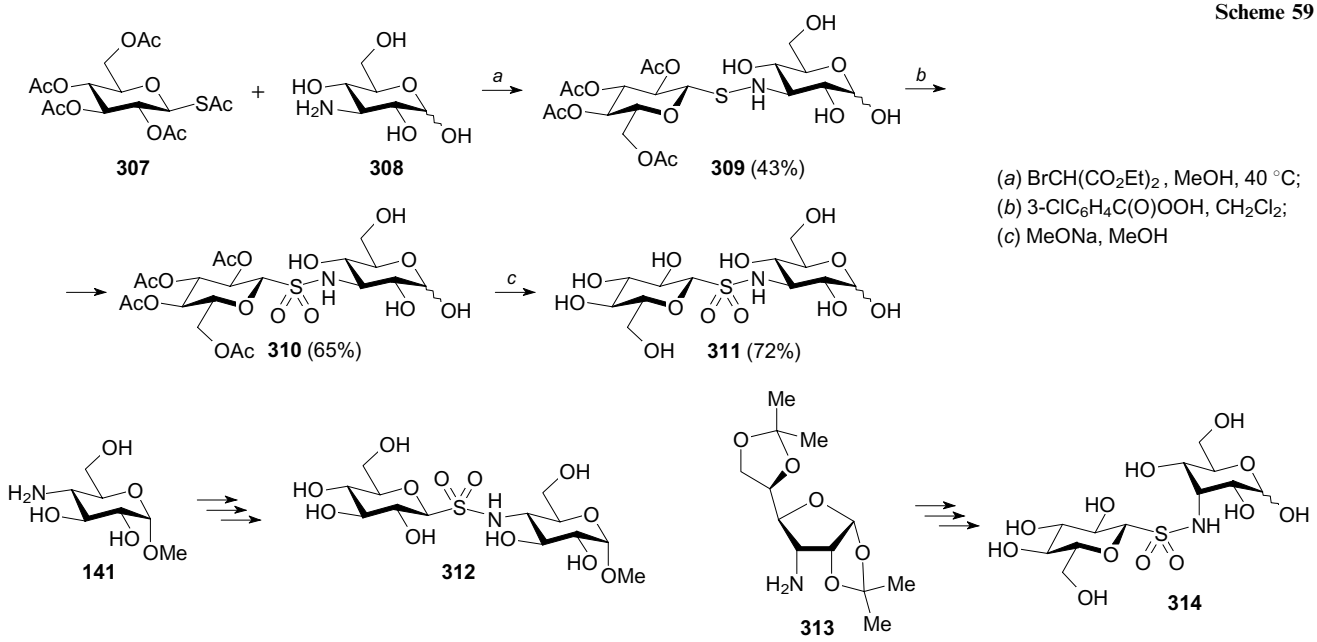
A few publications reported the use of 3- and 4-aminohexoses in the synthesis of glycosidase-resistant disaccharide mimics in which an intermonosaccharide glycosidic linkage is replaced with another functionality. Thus, Cumpstey *et al.*[77] synthesized structures composed of two carbohydrate residues linked by an amino group, with the anomeric carbon atoms being not involved. In the unsaturated compound **297**, the allyl hydroxyl group was replaced with 6-amino derivatives of α-methylgluco- and mannopyranosides **298a**,**b** under the Mitsunobu coupling conditions (Scheme 57). Hydroxylation of the double bond in the resulting disaccharides **299a**,**b** afforded compounds **300a**,**b**; the subsequent deprotection provided 4-amino mannose derivatives **301a**,**b**.

The preparation of pseudodisaccharides in which monosaccharide residues are linked by an ureide group is described.[78] In the synthesis of such derivatives, 4-amino-α-methyl glucoside, obtained by catalytic hydrogenation of azide **302**, was also used (Scheme 58). The reaction of **303** with glucosyl isocyanate **304** afforded urea **305**, the deprotection of which led to the target pseudodisaccharide **306**.

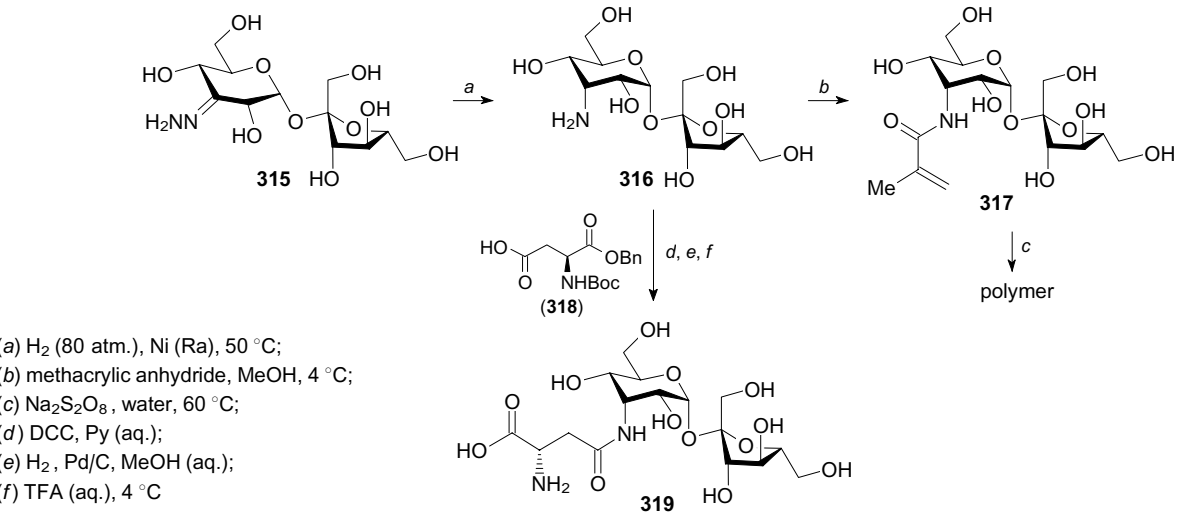
Glycomimetics in which monosaccharide residues were bridged by a sulfonamide were obtained.[79] 1-Thioglucose pentaacetate **307** reacts with 3-aminoglucose **308** in the presence of diethyl bromomalonate to give sulfenamide **309**, which was oxidized with *m*-chloroperbenzoic acid to provide sulfonamide **310** (Scheme 59). Deacetylation of **310** afforded the target pseudodisaccharide **311**. Similarly reactions of 4-amino-α-methyl glucoside **141** and 3-aminoallose derivative **313** gave rise to mimetics **312** and **314**, respectively.

3-Amino-allosucrose **316**, obtained *via* hydrogenation of hydrazone **315**, served as a reactant in the synthesis of a series of unusual derivatives of sucrose (Scheme 60).[80] Acylation of **316** with methacrylic anhydride led to methacrylamide **317**, which was subjected to radical polymerization to give the corresponding polymer. Acylation of **316** with the aspartic acid derivative **318** with subsequent deprotection provided the sucrose–asparagine conjugate **319**. Similarly, conjugates with glycine, phenylalanine, and tryptophane were obtained.

Scheme 59



Scheme 60

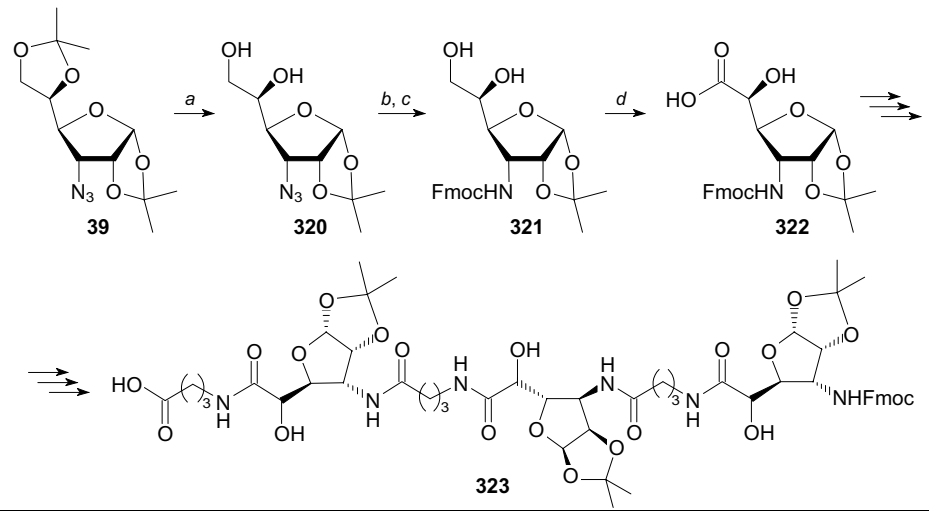


The synthesis of carbohydrate amino acids and peptidomimetics derived therefrom is described.[81] The derivative of 3-azidoallose **39** was used as a starting material, in which 5,6-*O*-isopropylidene group was selectively removed to afford diol **320** (Scheme 61). Reduction of the azide followed by protection of the amino group furnished compound **321**; oxidation of C(6)-OH-group in **321** gave amino acid **322**. The acid **322** was used to acylate γ-aminobutyric acid immobilized *via* the carboxyl group onto the polymer surface, then, *N*-Fmoc-γ-aminobutyric acid and **322** were sequentially introduced into peptide synthesis. This led to oligopeptide **323**. In a similar way, an oligopeptide was synthesized, consisting of 3-aminoribofuranuronic acid and β-alanine. The conformational behaviour of the synthesized peptidomimetics was studied using NMR spectroscopy, circular dichroism, and molecular modelling.

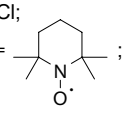
The synthesis of a polyamide derived from 3-aminoaltronic acid is reported.[82] Methyl 3-azidoaltroside **324** was subjected to exhaustive methylation, and the anomeric methyl group in the product **325** was removed by acid hydrolysis (Scheme 62). The azide group in hemiacetal **326** was reduced with thioacetic acid, with the simultaneous acetylation of the generated amino group. The resulting **327** was oxidized to lactone **328**, which was treated with methyl iodide and KOH to be converted into linear methyl ether **329**. Acid hydrolysis of **329** led to β-amino acid **330**; its subsequent cyclization provided β-lactam **331**. Anionic polymerization of **331** afforded polyamide **332**.

Derivatives of 3-amino- and 4-aminodeoxyhexoses were used as objects in some physicochemical studies. Thus, disaccharide **333** with 3-aminoaltrose located at its non-reducing terminus, was utilized as a model compound to study CH – π-interactions between carbohydrates and aromatic systems in an aqueous environment,[83] which is believed to contribute significantly to the processes of carbohydrate – protein recognition. Amine **333** reacts with aldehyde **334** to form an equilibrium mixture of the starting **333**, hemiaminal **335**, and imine **336** (Scheme 63). Once the equilibrium is established, sodium cyanoborohydride was added to the reaction mixture, which irreversibly led to the formation of a secondary amine **337**. The reaction was monitored using ^{1}H NMR. Based on the changes in che-

Scheme 61

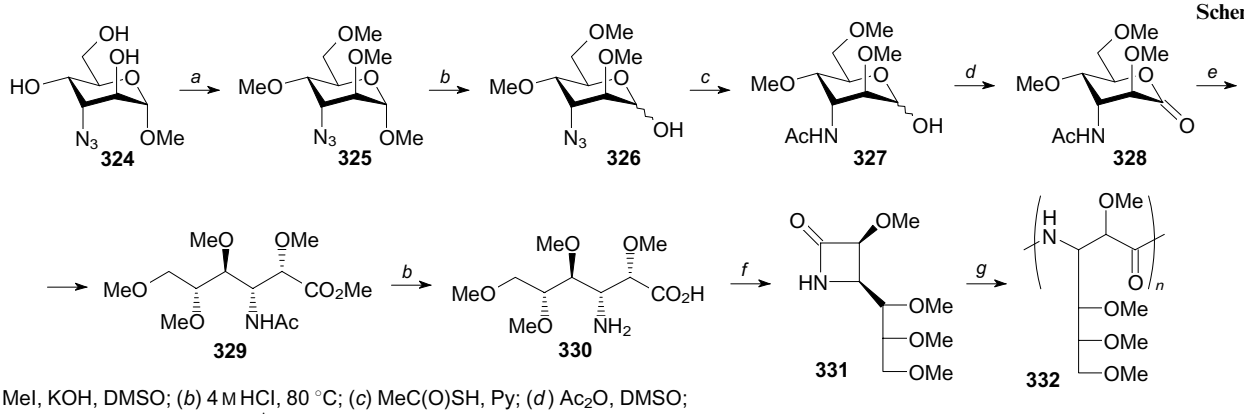


(*a*) 80% AcOH, 65 °C;
(*b*) H_2, Pd/C, MeOH;
(*c*) Fmoc-Cl, $NaHCO_3$, pH 8 – 9, THF, MeOH;
(*d*) NaOCl, TEMPO, KBr, CH_2Cl_2, $NaHCO_3$ (aq.), Bu^n_4NCl;



Fmoc is 9-fluorenylmethoxycarbonyl

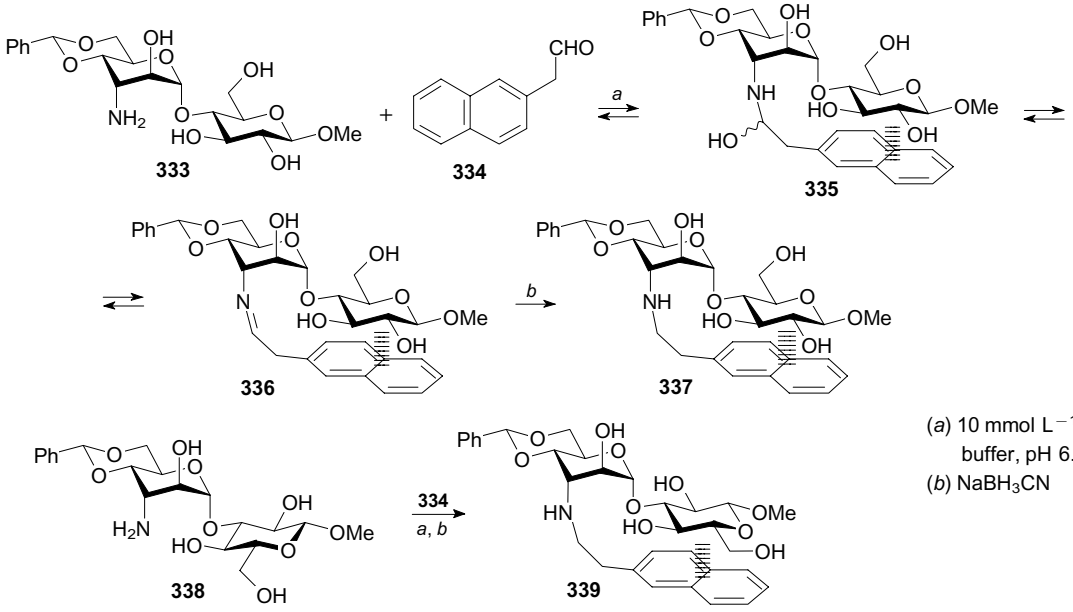
Scheme 62



(*a*) MeI, KOH, DMSO; (*b*) 4 M HCl, 80 °C; (*c*) MeC(O)SH, Py; (*d*) Ac_2O, DMSO;
(*e*) MeI, KOH, THF; (*f*) MsCl, Pr^i_2NEt, $NaHCO_3$, MeCN; (*g*) 1-*tert*-butoxycarbonyl-4-methyl-4-phenylazetidin-2-one, Bu^tOK, CH_2Cl_2

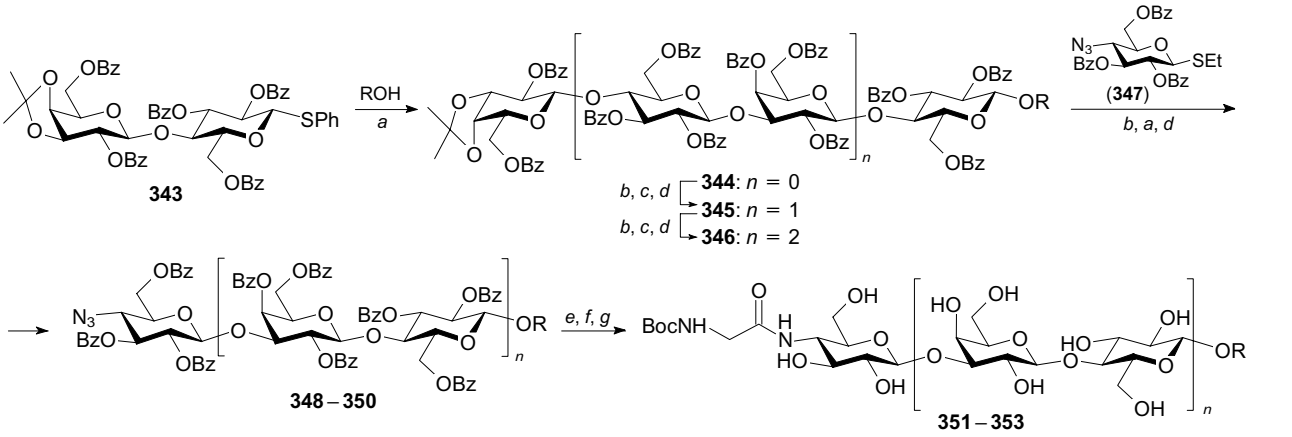
mical shifts of the protons of the glucose residue in the product **337** compared to those for the starting **333**, it was concluded which of the protons of the pyranose ring are involved in the CH – π-interaction. In the case of product **337**, H(1), H(3), and H(5) signals were significantly shifted upfield (up to 2.1 ppm), suggesting an interaction of the α-face of the glucopyranose ring in **337** with the aromatic π-system of the naphthyl moiety. With isomeric (1→3)-linked disaccharide **338**, the similar reaction afforded a secondary amine **339**, in which the glucopyranosyl ring interacted with the naphthyl group through its β-face.

Scheme 63



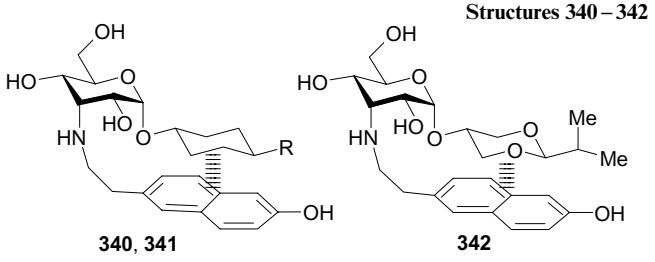
(*a*) 10 mmol L^{-1} phosphate buffer, pH 6.2;
(*b*) $NaBH_3CN$

Scheme 64



(*a*) NIS, AgOTf, mol. sieves (4 Å), CH_2Cl_2, 0 °C; (*b*) TFA (aq.), CH_2Cl_2; (*c*) **343**, NIS, AgOTf, mol. sieves (4 Å), CH_2Cl_2, 0 °C; (*d*) BzCl, Py; (*e*) MeONa, MeOH – CH_2Cl_2; (*f*) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH; (*g*) $BocNHCH_2CO_2H$, 1-hydroxy-7-aza-1,2,3-benzotriazole, *N*-methylmorpholine, *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide, MeOH; *n* = 1 (**348**, **351**), 2 (**349**, **352**), 3 (**350**, **353**); R = ZHN

Structures 340 – 342



R = H (**340**), OH (**341**)

The competitive reaction between equimolar amounts of amines **333** and **338** with a deficient amount of aldehyde **334** led to a mixture of products **337** and **339** in a ratio of 3.5 : 1. This value can be taken as an indicator of the CH – π-interaction efficiency in **337** and **339**.

The same research team[84] employed the method of competitive reactions, similar to those outlined in Scheme 63, to assess the efficiency of the CH – π-binding by the example of 3-aminoallose derivatives **340** – **342**, and revealed that the interaction energies decrease in the order **342** > **341** > **340**.

Pedersen *et al.*[11] measured the basicity of amino groups in 2-, 3-, 4-, and 6-aminodeoxyhexopyranosides of α- and β-*gluco*-, α-*galacto*-, and α-*manno*-configurations. It was shown that the basicity of amino groups decreases in the series 6-NH_2 > 3-NH_2 > 2-NH_2 > 4-NH_2. According to the authors, the value of the basicity of the amino group is a measure of the electron density at a certain position and reflects the total stereoelectronic effect of the pyranose ring at a given position. The obtained values of the basicity of amino groups in aminodeoxyhexopyranosides correlated well with the known data on the reactivity of the corresponding hydroxyl groups.

In the conclusion of this Section, let us consider the preparation of 2-aminoethyl glycosides of lactose oligomers containing a 4-aminoglucose residue at the non-reducing terminus, which the authors propose to use as heterobifunctional linkers in the synthesis of bioconjugates.[85] 2-Benzyloxycarbonylaminoethanol was glycosylated with thioglycoside of lactose **343** to give glycoside **344**, in which isopropylidene group was removed (Scheme 64). Glycosylation of the obtained 3′,4′-diol with thioglycoside **343** followed by benzoylation of the 4′-OH group of galactose provided tetrasaccharide **345**. Repetition of hydrolysis of isopropylidene group, glycosylation with donor **343**, and benzylation led to the synthesis of hexasaccharide **346**. Glycosyl acceptors obtained *via* removal of isopropylidene in **344** – **346**, were then glycosylated with 4-azidothioglycoside **347**, and after benzoylation, tri-, penta-, and heptasaccharides **348** – **350** were obtained. Sequential debenzoylation, reduction of the azide, and acylation of the amino group with *N*-Boc-glycine led to target products **351** – **353**, containing orthogonal protected amino groups in aglycon and non-reducing terminus of glucose. Examples of the use of trisaccharide **351** in the synthesis of bioconjugates are described.[86]

4. Conclusion

As can be seen from the data discussed above, 3-amino-3-deoxy- and 4-amino-4-deoxyhexoses are rare monosaccharides that are found in a single class of natural compounds — aminoglycoside antibiotics. Nevertheless, the studies describing the synthesis or applications of these monosaccharides and their derivatives go far beyond the chemistry of this class of antibiotics. Although in this review we virtually did not address the works published before 1980, it should be noted that the investigation of approaches towards 3-amino-3-deoxy- and 4-amino-4-deoxyhexoses began at an early stage in the development of carbohydrate chemistry (see, *e.g.*, Refs 87 – 89). Due to the previous efforts in this area, several fairly general and complementary approaches to the introduction of an amino group into positions 3 and 4 of monosaccharides have been developed to date, which made available such aminohexoses with almost any configuration. Structures including 3- and 4-aminodeoxyhexoses, the synthesis of which is considered in this review, can, with some conventions, be divided into two groups. The first group covers compounds in which the amino group plays a functional role, for example, aminoglycoside antibiotics and their analogues, glycosidase inhibitors, and substrate analogues of glycan biosynthesis enzymes. The second group com-

prises structures in which the amino group is used as a convenient 'anchor' to attach various functional substituents. These include galectin inhibitors based on 3-amino galactose, non-hydrolyzable amide analogues of natural esters, and a number of other types of compounds, the synthesis of which is described in Section 3.6. Thus, it can be assumed that in the future, 3- and 4-aminodeoxyhexoses will find very wide application in the synthesis of various natural compounds and their analogues, and if these amino sugars are found in new natural objects, a significant increase in interest in them among synthetic chemists could be expected.

The work was financially supported by the Russian Science Foundation, Project 19-43-02023.

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