DOI: 10.1070/RCR4750

Synthesis of oligosaccharides related to cell wall polysaccharides of the fungi *Candida* and *Aspergillus*

Alexander A. Karelin, Yury E. Tsvetkov, Nikolay E. Nifantiev

N.D.Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences
Leninsky prosp. 47, 119991 Moscow, Russian Federation

The cell wall of opportunistic pathogenic yeast fungi *Candida* and mould fungi *Aspergillus* is highly important for the pathogenesis of fungal infections, as it is the first to interact with the cells of the host organism, is responsible for pathogen adhesion and intra- and intercellular communications and bears important antigenic determinants. Fungal cell walls are composed mainly of polysaccharides. Methods that are currently used to study biological functions of cell wall polysaccharides require samples that are structurally characterized and have sufficient homogeneity and purity. However, the isolation of such samples from fungal cultures is often poorly feasible. Therefore, synthetic oligosaccharides of strictly specified structure corresponding to polysaccharide fragments of the cell wall of pathogenic fungi are indispensable tools for investigating the biological functions of such compounds. The review surveys studies devoted to the synthesis of oligosaccharides corresponding to fragments of major polysaccharide components of the fungal cell wall of *Candida* and *Aspergillus*: mannan, α- and β-(1→3)-glucans, chitin, galactosaminogalactan and galactomannan.
The bibliography includes 140 references.

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I. Introduction

Yeast fungi of the genus *Candida* and mould fungi of the genus *Aspergillus* are opportunistic pathogenic microorganisms. In healthy people with a normal immune system (immunocompetent individuals), the fungi *Candida* exist as part of the normal microflora of skin, the gastrointestinal tract and mucosa. The *Candida* population is kept under control by friendly bacterial microflora and the immune system of the host organism. Hence, infections caused by *Candida*, even if they are developed in immunocompetent individuals, are restricted to superficial tissues.[1] *Aspergillus* spores (conidia) are present in suspended dust all around us, both indoors and outside. The human airways are under constant exposure to conidia with daily inhalation of several hundred spores. Nevertheless, immunocompetent individuals are not generally considered at risk since conidia are eliminated efficiently by innate immune mechanisms.[2]

The situation changes dramatically for persons with a weakened immune system, particularly for HIV-infected patients, cancer patients after radiotherapy or chemotherapy, patients treated with immunosuppressive drugs after solid organ or bone marrow transplantation and patients treated with long-term courses of antibiotics or corticosteroids. In this case, there is a possibility of uncontrolled multiplication of fungi and their spread through the bloodstream to invade other organs in the body, producing finally serious invasive mycoses associated with high mortality rates.[3] The number of these high-risk patients at hospitals

A.A.Karelin. Researcher at the Laboratory of Glycoconjugate Chemistry at the ZIOC RAS.
Telephone: +7(499)135 – 6433, e-mail: karelin_alex@inbox.ru
Current research interests: carbohydrate chemistry, organic chemistry.
Yu.E.Tsvetkov. PhD (Chemical Sciences), Senior Researcher at the same Laboratory.
Telephone: +7(499)135 – 6433, e-mail: tsvetkov@ioc.ac.ru
Current research interests: carbohydrate chemistry and biochemistry, organic chemistry.
N.E.Nifantiev. Corresponding Member of the RAS, Doctor of Chemical Sciences, Professor, Head of the same Laboratory.
Telephone: +7(499)135 – 8784, e-mail: nen@ioc.ac.ru
Current research interests: carbohydrate chemistry and biochemistry, glycotechnology, organic chemistry, molecular biology, immunology.

Received 25 April 2017
Translation: T.N.Safonova

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has steadily increased over the past decades, resulting in an increase in the percentage of fungal infections among nosocomial infections.[2,4–6] The fungi of the genera *Candida* (primarily *C. albicans*) and *Aspergillus* (primarily *A. fumigatus*) are the two most frequently isolated causative agents of nosocomial fungal infections.[5,7]

The fungal cell wall plays a key role in the pathogenesis of fungal infections since it is the first to interact with host cells,[8–11] bears important antigenic determinants and is responsible for pathogen adhesion, as well as for intra- and intercellular communications.[12] The detection of cell wall polysaccharides and related antibodies in the serum of patients is employed in the diagnosis of fungal infections.[13–15] Structurally characterized samples of sufficient homogeneity and purity are required for studying biological functions and the role of individual polysaccharide components of the cell wall in the above-mentioned processes. However, the isolation of such samples from fungal cultures is often poorly feasible. Therefore, synthetic oligosaccharides of a strictly specified structure corresponding to polysaccharide fragments of the cell wall of pathogenic fungi are indispensable tools for studying the biological role, biosynthesis[16] and antigenic properties, generating specific antibodies, developing rapid methods for the diagnosis of fungal infections[13] and designing antifungal vaccines.[17] The review surveys studies devoted to the synthesis of oligosaccharides related to cell wall polysaccharides of the fungal pathogens *Candida* and *Aspergillus*.

II. Structure of the cell wall of the fungi *Candida* and *Aspergillus*

In the yeast form, the fungus *C. albicans* has the following composition[18] of cell wall polysaccharides (in mass percent): chitin, 1%–2%; β-(1→3)-glucan, 40%; β-(1→6)-glucan, 20%; mannoproteins, 35%–40%. The cell wall structure[19,20] of this pathogen is schematically shown in Fig. 1. The layer adjacent to the endoplasmic membrane consists of chitin — a polysaccharide composed of β-(1→4)-linked *N*-acetyl-D-glucosamine. The inner skeletal layer of the cell wall is a three-dimensional network of branched β-(1→3)-glucan molecules that are kept together by hydrogen bonding. About half of chitin chains are linked through their reducing end to glucose residues at the non-reducing end of β-(1→3)-glucan chains. A smaller portion of chitin molecules are connected *via* glycosidic linkages to terminal glucose residues of branched β-(1→6)-glucan, and the latter, in turn, glycosylates branched β-(1→3)-glucan. Chitin and glucans create a rigid three-dimensional network, which protects the cell against unfavourable environmental conditions. The outer part of the cell wall is enriched in glycoproteins covalently attached to the polysaccharide backbone. A part of glycoproteins are linked to β-(1→6)-glucan by glycosidic bonds *via* ethanolamine phosphate and oligomannoside, which have been previously involved in the glycosylphosphatidylinositol anchor.[20,21] Another part is linked to β-(1→3)-glucan chains apparently through acylation of hydroxyl groups of glucose with glutamic carboxyl groups of the polypeptide chain. Glycoproteins of the first group are highly glycosylated proteins (carbohydrates can compose up to 90% of their molecular mass), which have polysaccharide chains consisting of mannose residues (mannans). The mannan chains of these glycoproteins are largely responsible for antigenic specificity of the fungi *Candida*. The structure of *Candida* mannan will be considered in more detail in Section III.

The cell wall polysaccharide component of *A. fumigatus* consists of β-(1→3)-glucan (20%–35%), which can contain β-(1→6)-branching points (about 4%), α-(1→3)-glucan

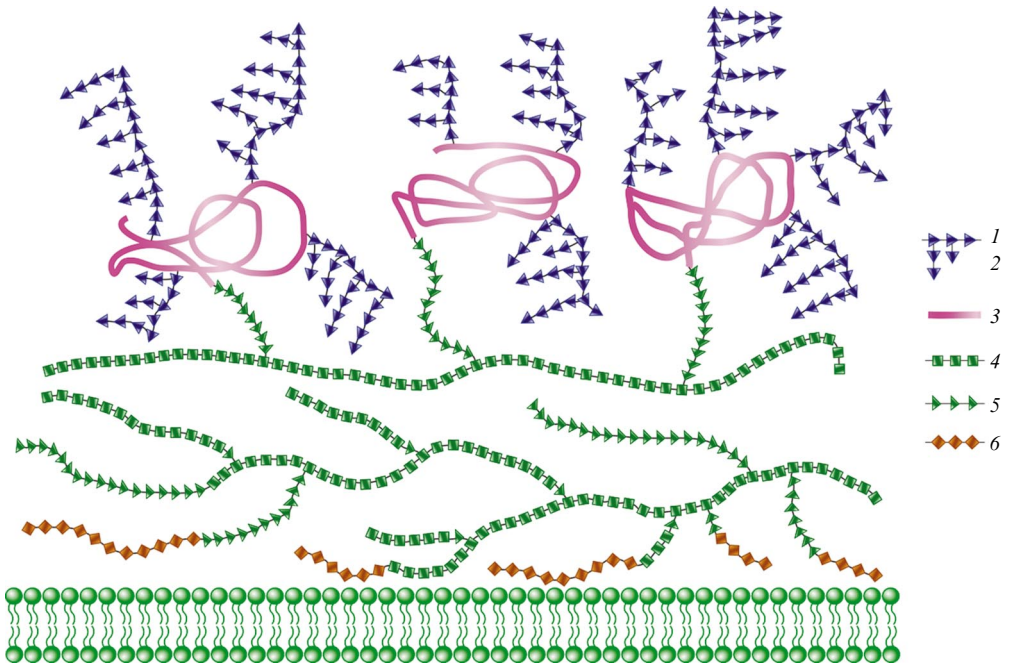


Figure 1. Schematic representation of the cell wall structure of the fungi *Candida*.
(*1*) Backbone; (*2*) mannan side chains; (*3*) polypeptide chain; (*4*) β-(1→3)-glucan; (*5*) β-(1→6)-glucan; (*6*) chitin.

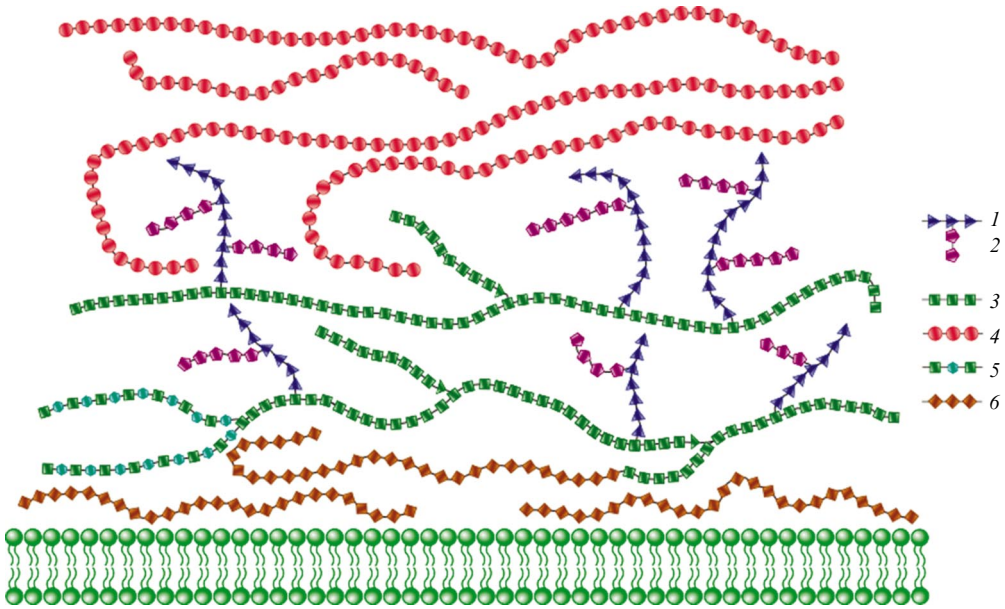


Figure 2. Schematic representation of the cell wall structure of the fungi *A. fumigatus*.
(*1*) Mannose chain galactomannan; (*2*) galactofuranose chain of galactomannan; (*3*) β-(1→3)-glucan; (*4*) α-(1→3)-glucan; (*5*) β-(1→3)(1→4)-glucan; (*6*) chitin.

(35% – 46%), galactomannan (20% – 25%) and chitin (7% – 15%).[22, 23] As in the case of *Candida*, β-(1→3)-glucan is the major structural component of the cell wall and is involved, together with the attached polysaccharides of other types, in the formation of a fibrillar network structure responsible for mechanical strength of the cell wall (Fig. 2). Chitin chains can be covalently linked to terminal glucose residues at the non-reducing ends of β-(1→3)-glucan by β-(1→4)-glycosidic bonds. β-(1→3,1→4)-Glucan is also attached at the non-reducing ends of branched β-(1→3)-glucan, the amount of the former being ~10% of the total content of β-(1→3)-glucan. Galactomannan is composed of the α-(1→2)-linked mannose backbone to which short β-(1→5)-oligogalactofuranoside side chains are attached.[24] Galactomannan chains are connected through α-(1→6)-glycosidic bonds to glucose residues at the non-reducing ends of branched β-(1→3)-glucan. The outer cell wall layer is composed of α-(1→3)-glucan. The data on the presence of a covalent bond between this polysaccharide and the β-(1→3)-glucan backbone are lacking. Apparently, this bond is cleaved in the course of the isolation of α-(1→3)-glucan, which involves the alkaline treatment,[25] or the polysaccharide is held in the cell wall through noncovalent interactions.

Relatively recently, another carbohydrate polymer — galactosaminogalactan — was found in *A. fumigatus*.[26] Galactosaminogalactan is not a covalently linked component of the cell wall. Details of its structure are not well understood,[27] which is to a certain extent due to non-stoichiometric N-acetylation of galactosamine units that are present in this polysaccharide product. Nevertheless, its structures can be schematically represented as follows:

α-Gal-(1→4)-[α-GalNAc/NH_2-(1→4)]$_{1-10}$-[α-GalNAc/NH_2-(1→4)-α-Gal-(1→4)]$_n$-[α-Gal-(1→4)]$_{1-10}$-α-GalNAc/NH_2

Before proceeding to the consideration of synthetic methods, let us note that polysaccharides structurally related to cell wall polysaccharides from *Candida* and *Aspergillus* were found in other natural sources as well. Hence, in some studies, the synthesis of oligosaccharides with structural motifs typical of cell wall polysaccharides of these fungi was described, although the synthesis of oligosaccharide fragments of polysaccharides from *Candida* and *Aspergillus* was not among the main goals of these works. These studies are also considered in the present review.

III. Synthesis of oligosaccharides corresponding to fragments of mannan from *Candida*

The structure of cell wall mannan from fungi of the genus *Candida* is schematically represented in Fig. 3. The synthesis of oligosaccharides corresponding to fragments of yeast cell wall mannan is described in a special chapter of the monograph [28] published in 2009. Hence, in the present review we consider only the works published afterwards. It is convenient to divide the methods for the synthesis of oligomannosides into three groups according to their structure: synthesis of oligosaccharides containing only α-mannosidic linkages, only β-mannosidic linkages or mannosidic linkages of both types.

Modern methods for the synthesis of oligosaccharides structurally related to fragments of the fungal cell wall are largely associated with further immunological and other studies aimed to elucidate the biological role of these polysaccharides and examine the possibility of using these compounds for the design of appropriate vaccines and diagnostics. This is also the goal of the majority of studies on the synthesis of oligomannosides, which not only reflect the structure of fragments of *Candida* cell wall mannan but also correspond to the so-called antigenic factors (selected

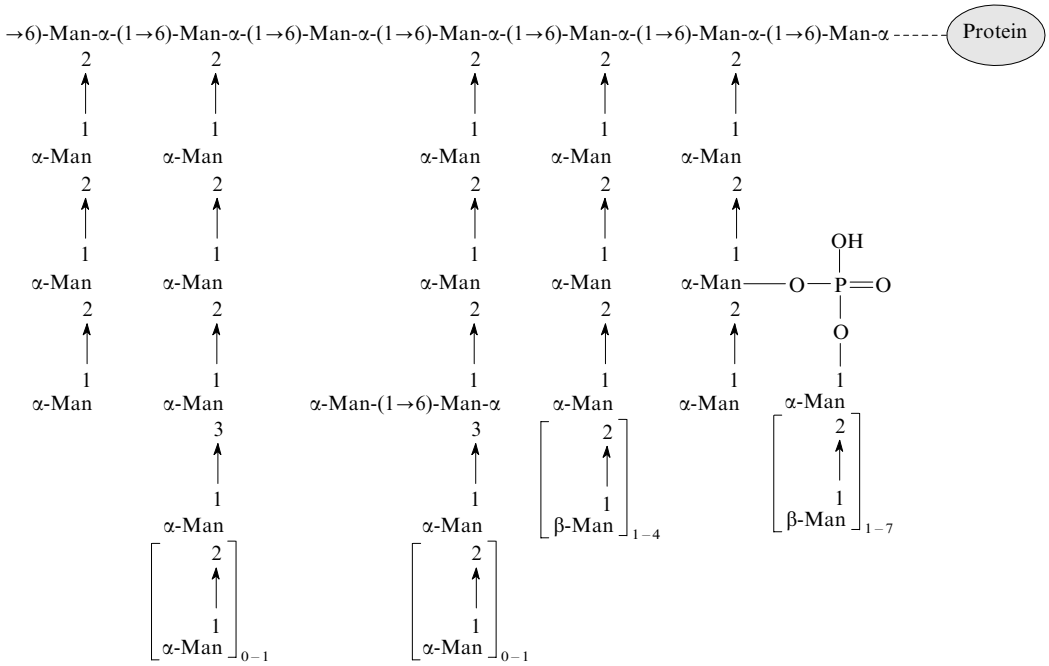


Figure 3. Structure of cell wall mannan from the fungi of the genus *Candida*.

factors are shown in Fig. 4) responsible for immunological characteristics of particular serotypes of *Candida*.

III.1. Synthesis of oligomannosides containing only α-glycosidic bonds

The methods considered in this subsection are divided into the following three groups: the synthesis of linear α-oligomannosides containing a single type of glycosidic bonds, the synthesis of linear α-oligomannosides containing two types of glycosidic bonds and the synthesis of branched α-oligomannosides.

III.1.a. Synthesis of linear α-oligomannosides containing a single type of glycosidic bonds

The synthesis of α-(1→2)- and α-(1→6)-linked trisaccharides performed by Tanifum and Chang [29] is unusual primarily in that the glycosylation is assisted by sonication. It is

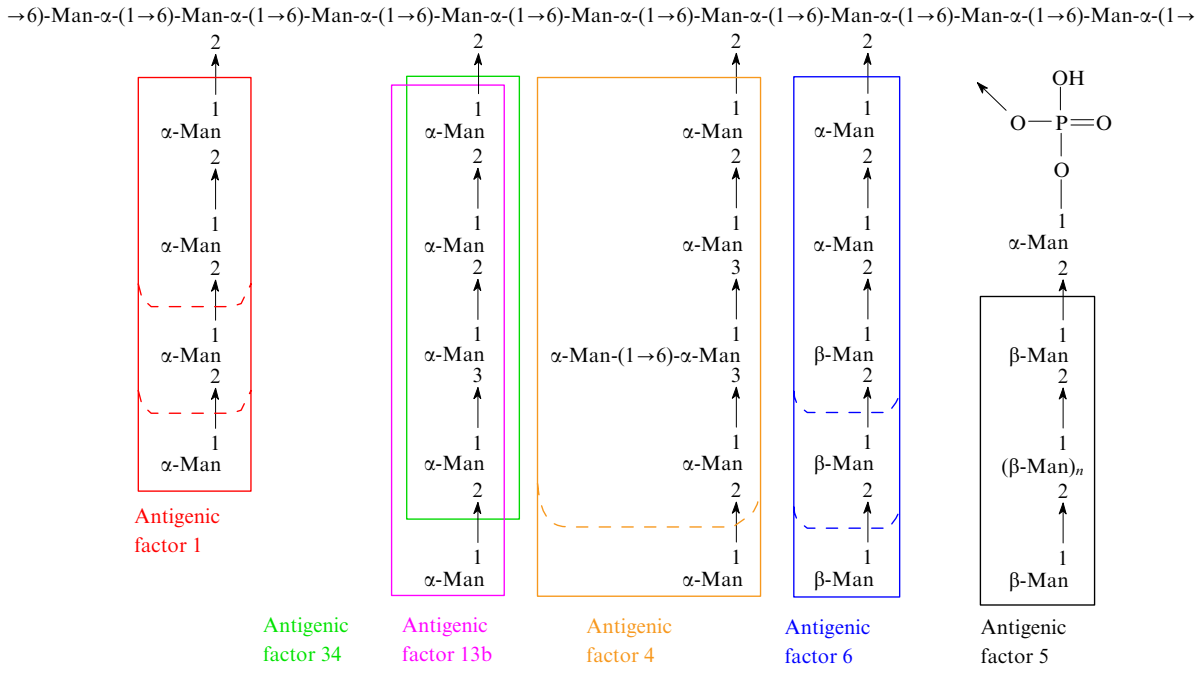


Figure 4. Distribution of antigenic factors in the structure of cell wall mannan from the fungi of the genus *Candida*.

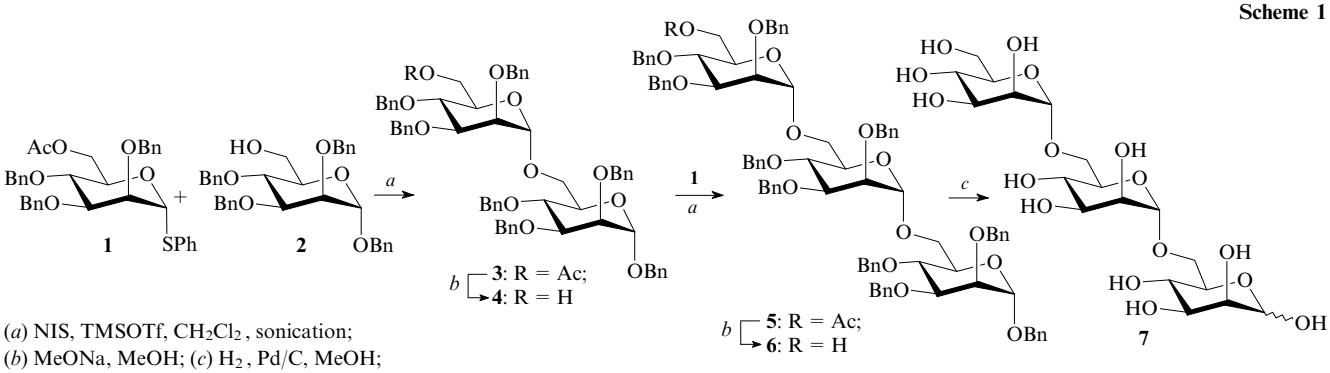
also noteworthy that the synthesis of α-(1→6)-linked trimannoside **7** was accomplished using thiogylcoside donor **1** that contained the non-participating benzyl group at the oxygen atom in the 2 position [O(C2)] (Scheme 1).† Nevertheless, the glycosylation of acceptors **2** and **4** with this donor was α-stereospecific and afforded disaccharide **3** and trisaccharide **5** in 95% yield, whereas the glycosylation of 6-azidohexanol **1** performed under the same conditions produced a mixture of α- and β-(6-azidohexyl)mannosides in a ratio of 3 : 2. The deacetylation of protected trimannoside **5** giving oligosaccharide **6** and debenzylation of the latter produced free trimannoside **7**.

The cited authors also described the synthesis of α-(1→2)-trimannosides **15** and **16** (structurally related to *Candida* antigenic factor 1, see Fig. 4) starting from acceptors **9** and **10** and donor **8** with the participating acetyl group at O(C2) (Scheme 2). In the first steps, disaccharide acceptors **11** and **12** were prepared by glycosylation and deacetylation (the yields in the glycosylation step were 80% and 75%, respectively). Then the acceptors were converted into trimannosides **13** and **14** in 65% and 60% yields, respectively. The debenzylation of the latter gave final products **15** (85% yield) and **16** (75%).

A simple approach to the synthesis of fully acetylated short α-(1→2)-linked oligomannosides was proposed by Chen and Tan.[30] Dimannoside **20** was synthesized by the coupling of mannosyl bromide **17** with acceptor **19**, which was, in turn, synthesized from compound **17** in two steps involving the transformation into orthoester **18a** and the cleavage of the latter under acidic conditions (Scheme 3). It was found that the portionwise addition of the acceptor to the reaction mixture leads to a considerable increase in the efficiency of the process (the product ratio **20** : **21**) and the yield of the target disaccharide (10 : 1 and 99% *versus* 2 : 1 and 45%).

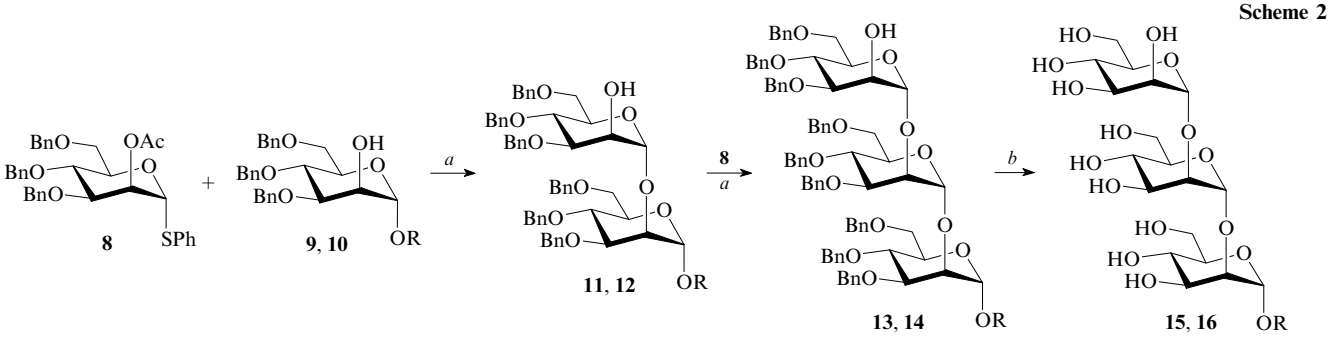
† In this review, the compounds are numbered according to their representation in the schemes — from the substrate to the product.

Scheme 1



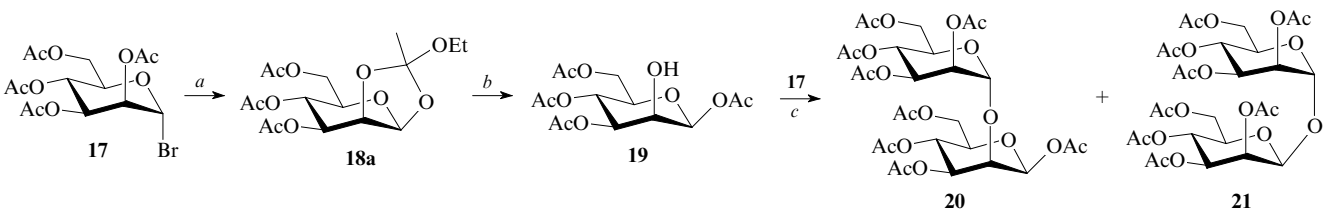
(*a*) NIS, TMSOTf, CH_2Cl_2, sonication; (*b*) MeONa, MeOH; (*c*) H_2, Pd/C, MeOH; NIS is *N*-iodosuccinimide, TMS is trimethylsilyl, OTf is trifluoromethanesulfonate (triflate)

Scheme 2



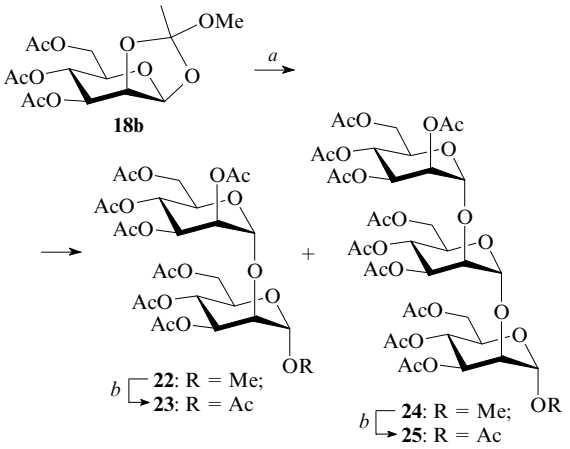
(*a*) 1) NIS, TMSOTf, CH_2Cl_2, sonication; 2) MeONa, MeOH; (*b*) H_2, Pd/C, MeOH; R = Bn (**9**, **11**, **13**), Me (**10**, **12**, **14**, **16**), H (**15**)

Scheme 3



(*a*) 2,4,6-collidine, EtOH, MeCN; (*b*) 1 M HCl, Me_2CO; (*c*) AgOTf, 2,4,6-collidine, MS 4 Å, CH_2Cl_2; MS are molecular sieves

Scheme 4



(*a*) TMSOTf, CH_2Cl_2, −30 °C; (*b*) Ac_2O, H_2SO_4, 0 °C

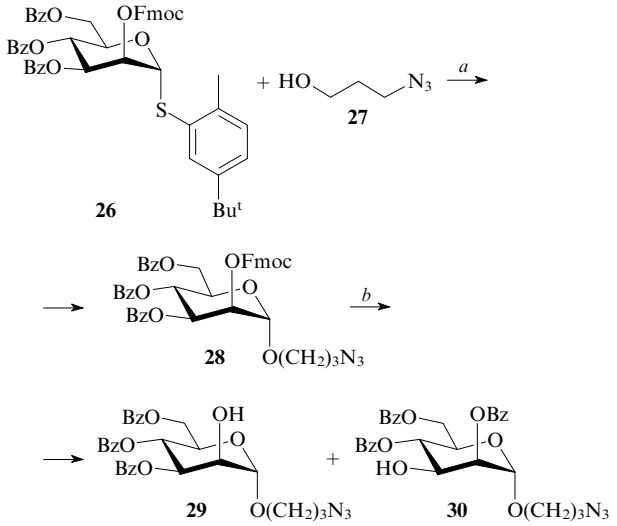
Disaccharide methyl glycoside **22** and trisaccharide methyl glycoside **24** were synthesized in 58% and 16% yields, respectively, by oligomerization of orthoester **18b** in the presence of TMSOTf (Scheme 4). The subsequent acetolysis of the methyl glycosides gave total acetates **23** and **25**, which were used for the O-glycosylation of serine and threonine derivatives. The resulting structures correspond to a carbohydrate – peptide linkage unit in O-linked mannose chains of yeast cell wall glycoproteins.

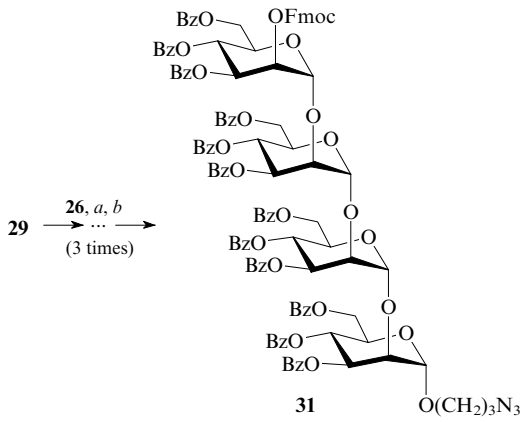
Pourcelot *et al.*[31] examined two mannosyl-containing donors, which differ in the set of protecting groups, in order to construct α-(1→2)-linked tetramannosides corresponding to antigenic factor 1 (see Fig. 4). In one donor (**26**), the 9-fluorenylmethyloxycarbonyl (Fmoc) group served as a temporary protecting group at the O(C2) atom, and benzoyl groups were permanent protecting groups in other positions (Scheme 5). In the second donor (**32**) (Scheme 6), a more traditional set of protecting groups was used, including the benzoyl function at the O(C2) atom and benzyl groups in other positions. In both cases, it was envisaged to build up the chain by the successive addition of single monosaccharide units.

Donor **26** proved to be efficient in the glycosylation step; however, the removal of temporary Fmoc protection was accompanied by the migration of the 3-O-benzoyl group. This situation was observed for all substrates regardless of the oligosaccharide chain length. Thus, the glycosylation of 3-azidopropanol **27** with donor **26** in the presence of NIS and HOTf gave glycoside **28** in 90% yield. The treatment of the latter with tetra-n-butylammonium fluoride afforded both target product **29** and compound **30** (in a 5 : 1 ratio), the latter being the product of 3→2-migration of the benzoyl group. Despite this complication, the authors continued the synthesis up to tetrasaccharide **31**, by performing chromatographic separation of isomeric 2- and 3-benzoates after each Fmoc deprotection step. However, it is evident that the set of protecting groups used in donor **26** does not provide the required overall efficiency of the synthesis.

The employment of thioglycoside **32** containing benzyl groups as permanent protection proved to be much more successful. Otherwise, the synthesis of tetrasaccharide **34**

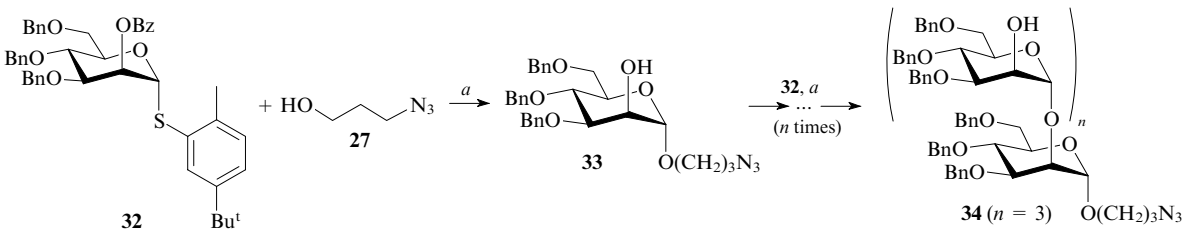
Scheme 5





(*a*) NIS, HOTf, MS 4 Å, CH_2Cl_2, 0 °C;
(*b*) TBAF, AcOH; TBA is tetra-n-butylammonium

Scheme 6



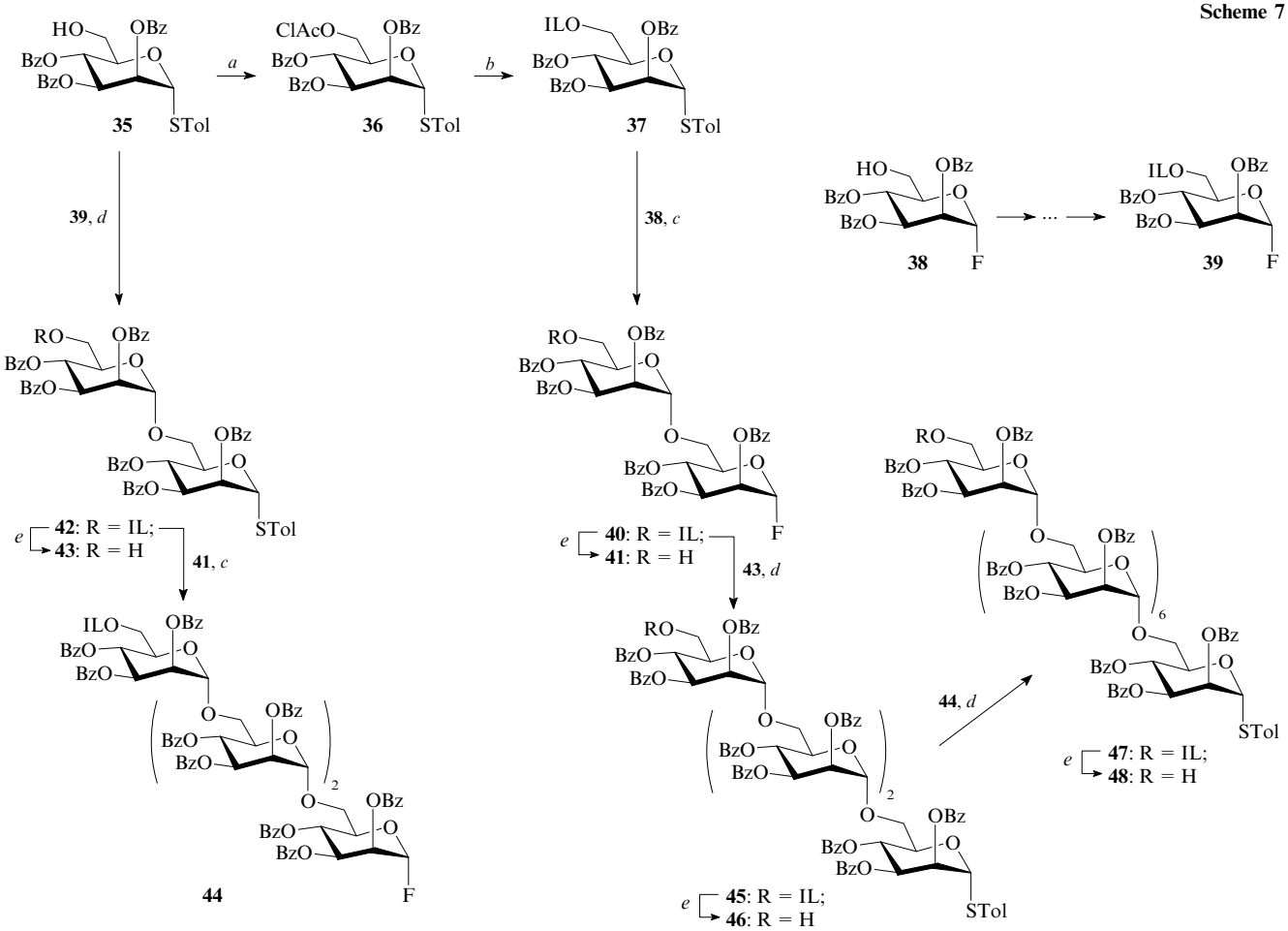
(*a*) 1) NIS, HOTf, MS 4 Å, CH_2Cl_2, 0 °C; 2) MeONa, MeOH

was similar to the previous method and included the repeated glycosylation and subsequent removal of the 2-O-benzoyl group (see Scheme 6). Here, the authors did not face any difficulties. Thus, the yields in the glycosylation steps were 80%, 72%, 74% and 70% for mono-, di-, tri- and tetramannosides, respectively, and the removal of the benzoyl group always proceeded with quantitative yield.

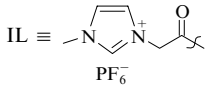
A convergent approach to the synthesis of α-(1→6)-linked octamannoside was described by Yerneni *et al.*[32] (Scheme 7). The oligosaccharide chain was assembled using glycosyl fluorides and thioglycosides as both donors and acceptors since, depending on the activation conditions, they can glycosylate one another. In each assembly step, the chain length was doubled, thioglycoside and fluoride of the appropriate length being synthesized in pairs. Another specific feature of this method is the employment of glycosyl donors containing the temporary *N*-methylimidazolium cation-tagged acetyl protecting group at the O(C6) atom, thus making them similar to ionic liquids (IL). Compounds containing an ionic substituent are poorly soluble in weakly polar solvents, such as diethyl ether, which allows the separation of non-tagged by-products by simply washing the reaction mixtures with weakly polar solvents without resorting to chromatography.

The first step of the synthesis involved the conversion of thiomannoside **35** through intermediate chloroacetate **36** to ionic derivative **37**. Then the orthogonal glycosylation of fluoride **38** with thioglycoside **37** in the presence of NIS and HOTf gave disaccharide fluoride **40** in 80% yield. Disaccharide thioglycoside **42** was prepared in 92% yield by orthogonal glycosylation of thioglycoside acceptor **35** with fluoride donor **39** in the presence of Cp_2HfCl_2 and $AgClO_4$. In order to obtain two donor – acceptor disaccharide pairs, the ionic protecting groups were selectively removed from the products using a saturated $NaHCO_3$ solution in the presence of TBAI in a diethyl ether – water two-phase system. Acceptors **41** and **43** thus synthesized were subjected to cross-glycosylation with donors **42** and **40** giving tetramannoside products — fluoride **44** and thioglycoside **45** — in 82% and 92% yields, respectively. Then the temporary protecting group was removed from thioglycoside **45** to form acceptor **46**. The final coupling of the latter with fluoride **44** produced octamannoside **47** in 78% yield. The removal of the ionic group from compound **47** gave target product **48** in 83% yield.

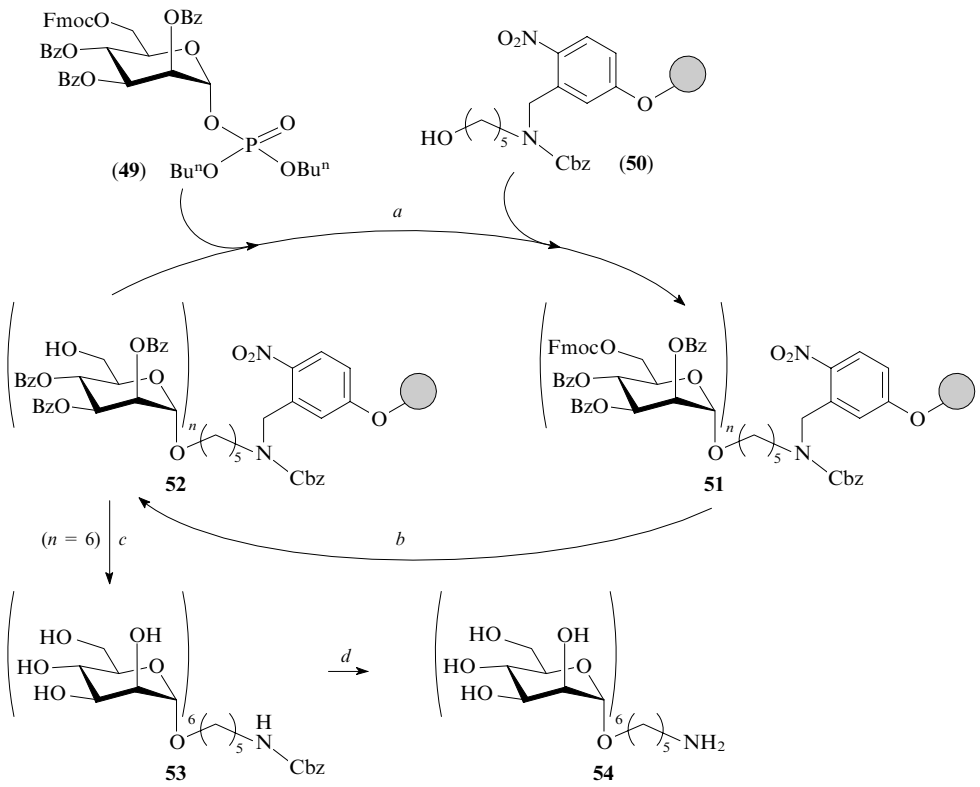
Scheme 7



(*a*) ClAcCl, Py, CH_2Cl_2, 0 °C → rt; (*b*) 1) *N*-methylimidazole, MeCN, Δ; 2) KPF_6, MeCN, Δ; (*c*) NIS, HOTf, MS 4 Å, CH_2Cl_2, 0 °C → rt; (*d*) Cp_2HfCl_2, $AgClO_4$, MS 4 Å, CH_2Cl_2; (*e*) $NaHCO_3$ (satur.), TBAI, Et_2O, H_2O; Tol is *p*-tolyl, ClAc is chloroacetyl, Py is pyridine, Cp is cyclopentadienyl;

IL ≡ 

Scheme 8



(*a*) TMSOTf, CH_2Cl_2, −15→0 °C; (*b*) piperidine, DMF, 25 °C; (*c*) 1) *hv* (UV), CH_2Cl_2; 2) NaOMe, MeOH; (*d*) H_2, Pd/C, H_2O; ◯ is a polymeric support, Cbz is benzyloxycarbonyl

Besides, the synthesis of α-(1→6)-mannooligosaccharides was accomplished by means of conventional approaches. For instance, Cao *et al.*[33] described the synthesis of α-(1→6)-trimannoside 8-azidooctyl glycoside through successive glycosylation with benzoylated *p*-tolyl thioglycosides. The first glycosylation was performed using a donor containing the temporary 6-O-*tert*-butyl(diphenyl)-silyl protecting group at the 6 position; the second glycosylation was carried out using *p*-tolyl thiomannoside tetrabenzoate.

The automated solid-phase synthesis of α-(1→6)-oligomannosides was performed by Calin *et al.*[34] In each step, the oligosaccharide chain was elongated by one monosaccharide unit using dibutyl phosphate **49**, which contained the temporary 6-O-Fmoc group and benzoate moieties in other positions, as the mannosyl donor (Scheme 8).

In the initial step of the assembly of oligomannoside, the first monosaccharide was immobilized on Merrifield resin (**50**) equipped with a photolabile linker to form glycoside **51** ($n = 1$). Then the Fmoc deprotection with piperidine followed by glycosylation of the resulting acceptor **52** with donor **49** in the presence of TMSOTf was repeated a specified number of times. The oligosaccharide was cleaved from the resin by exposure to UV light. Free hexasaccharide **54** was synthesized in an overall yield of 25%, intermediate protected hexasaccharide being isolated by traditional column chromatography. However, the column chromatographic isolation of protected oligomers longer than 12 mer was more challenging because of problems with solubility. Owing to the development of a special isolation strategy, the authors succeeded in preparing 12- and 30-mer oligomannosides — analogues of derivative **53** — in an overall yield of 13% and 1%, respectively (96% yield per step).

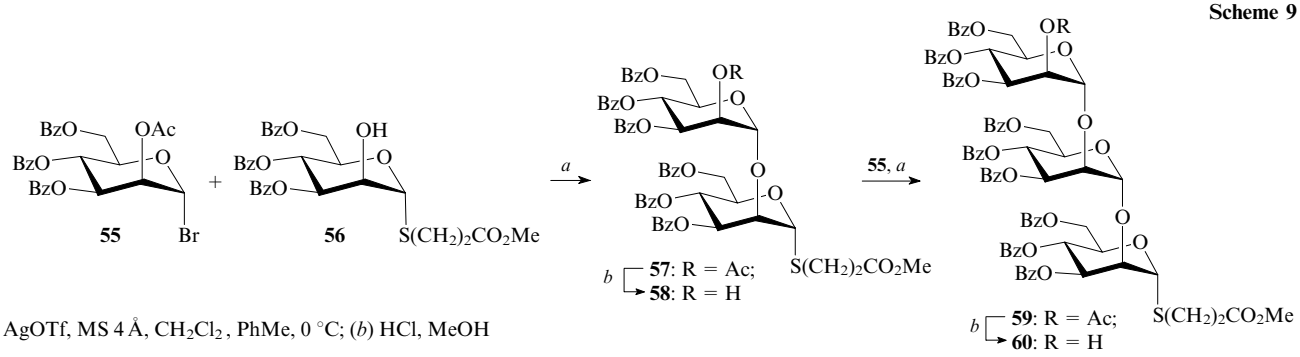
III.1.b. Synthesis of linear α-oligomannosides containing two types of glycosidic bonds

Abronina *et al.*[35] described the synthesis of pentamannoside containing a α-(1→2)-tetramannoside chain terminated by α-(1→3)-linked mannose (corresponds to *Candida* antigenic factor 34, see Fig. 4). Target product **67** was prepared through the [2 + 3] coupling of the (1→3)-linked dimannoside donor and the (1→2)-trimannoside acceptor (Schemes 9 and 10). The trisaccharide building block was prepared using benzoylated acceptor **56** and bromide **55** with a temporary acetyl group at the O(C2) atom. Their coupling in the presence of AgOTf gave disaccharide **57** in 66% yield (see Scheme 9). The acetyl deprotection *via* acidic methanolysis proceeded with difficulty, and disaccharide acceptor **58** was isolated in moderate yield (44% based on consumed dimannoside **57**). The glycosylation of acceptor **58** with bromide **55** afforded trisaccharide **59** in 82% yield. The acetyl deprotection of the latter gave target acceptor **60**.

(1→3)-Linked disaccharide donor **66** was synthesized by glycosylation of acceptor **62** with benzobromomannose (**61**) followed by the transformation of product **63** into bromide **66** through the formation of hemiacetal **64** and acetate **65** (see Scheme 10). In the final step, the coupling of bromide **66** with trisaccharide acceptor **60** in the presence of AgOTf produced target pentamannoside **67** in 43% yield. The deprotection of the product was not performed.

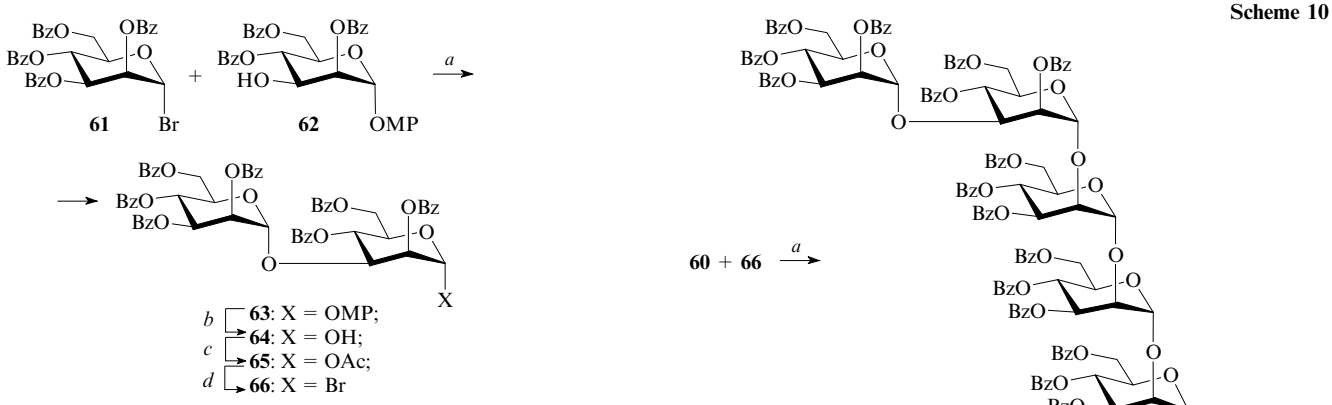
In 2012, Maity and Ghosh[36] reported the synthesis of structurally similar oligomannoside **70** by means of one-pot consecutive glycosylation reactions. In the preliminary step,

Scheme 9



(*a*) AgOTf, MS 4 Å, CH_2Cl_2, PhMe, 0 °C; (*b*) HCl, MeOH

Scheme 10

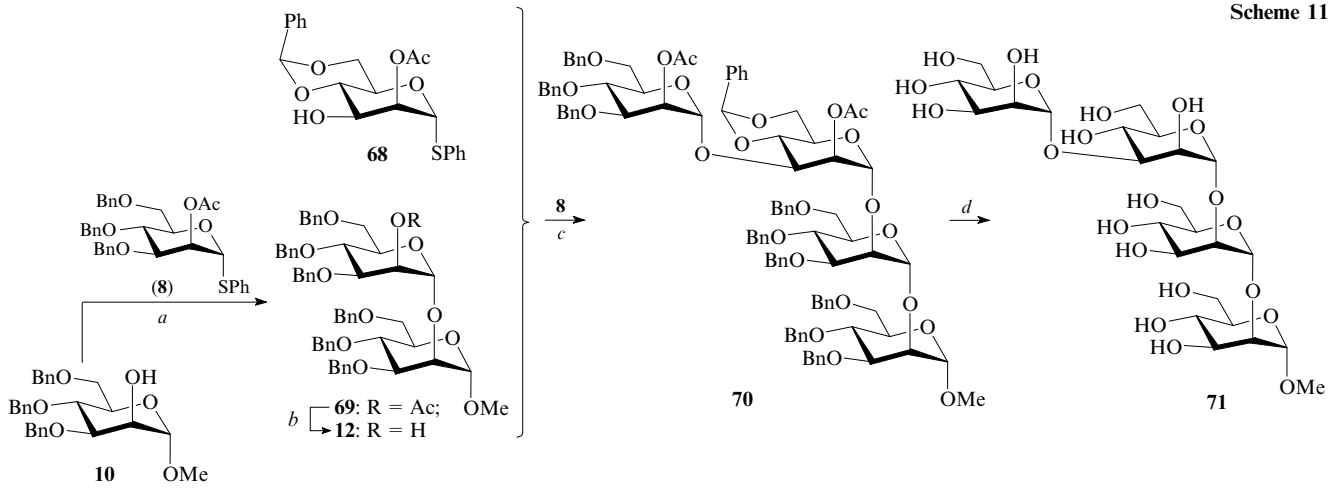


(*a*) AgOTf, MS 4 Å, CH_2Cl_2, PhMe, 0 °C; (*b*) $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O; (*c*) Ac_2O, Py; (*d*) HBr, AcOH, CH_2Cl_2;
MP is *p*-methoxyphenyl

dimannoside **69** was prepared in 92% yield by glycosylation of methyl mannoside **10** with donor **8** in the presence of *N*-(*p*-methylphenylthio)-ε-caprolactam (NMPTC) and TMSOTf. The subsequent acetyl deprotection afforded acceptor **12** (Scheme 11). This is followed by the one-pot consecutive glycosylation of thioglycoside **68** with donor **8** and coupling of the resulting disaccharide thioglycoside with acceptor **12**. Protected tetrasaccharide **70** was isolated in 54% yield. Free tetramannoside **71** was prepared as methyl glycoside in 88% yield by the Zemplén deacetylation followed by hydrogenolysis.

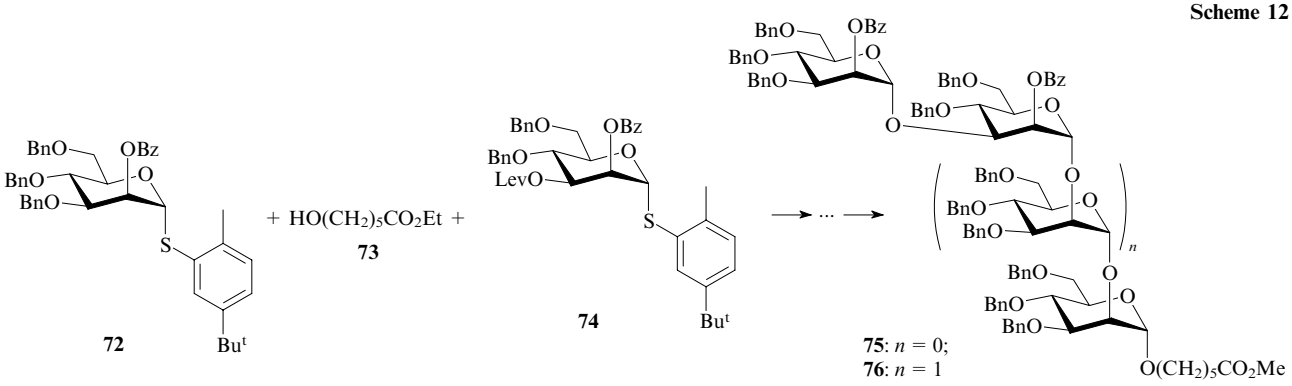
The synthesis of structurally similar oligomannosides **75** and **76**, which contain terminal (1→3)-linked mannose residues attached to the (1→2)-oligomannoside chain, was described by Despras *et al.*[37] In this synthesis, thioglycosides **72** and **74** containing the temporary 2-O-benzoyl and 3-O-levulinoyl protecting groups, respectively, served as mannosyl donors — precursors of 2- and 3-substituted

Scheme 11



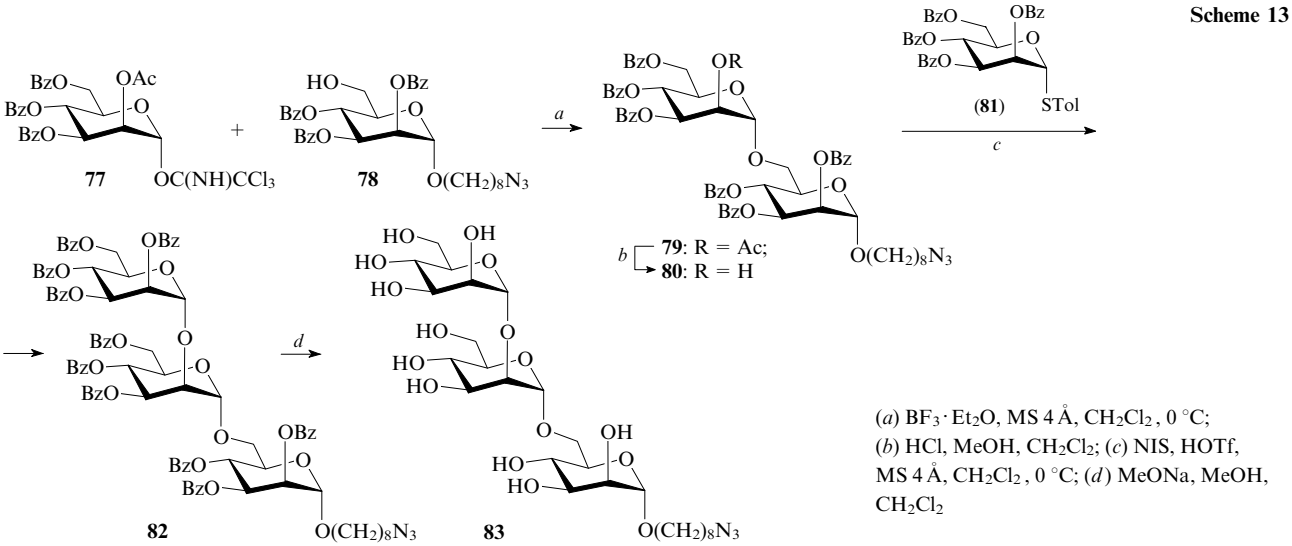
(*a*) NMPTC, TMSOTf, CH_2Cl_2, −10 °C → rt; (*b*) NaOMe, MeOH; (*c*) NMPTC, TMSOTf, CH_2Cl_2, −45 → −10 °C; (*d*) 1) NaOMe, MeOH; 2) H_2, Pd/C, AcOH, MeOH, EtOAc

Scheme 12



LevO is levulinate

Scheme 13

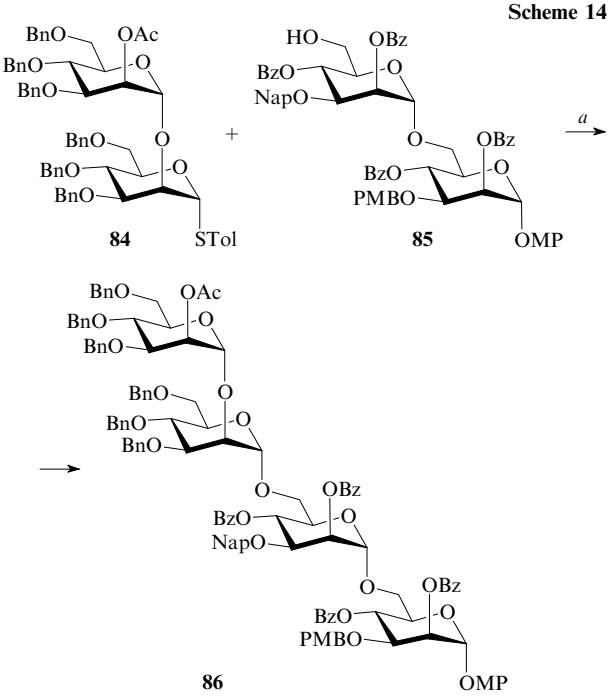


mannose (Scheme 12). Initially, the assembly of (1→2)-oligomannoside was accomplished, the terminal residue being introduced with the assistance of thioglycoside **74**. After the removal of the levulinoyl group, the final 3-*O*-glycosylation gave target products **75** and **76**. Unprotected oligomannosides were isolated as conjugates with biotin derivatives.

Trisaccharide **83** with α-(1→2)- and α-(1→6)-linkages was constructed [33] from synthetic building blocks bearing permanent benzoyl protecting groups and the temporary acetyl protecting group in diimidate **77**. In the first step, the glycosylation of primary acceptor **78** with donor **77** afforded disaccharide **79** in 76% yield. The removal of the only acetyl group from **79** *via* acidic methanolysis produced acceptor **80** (Scheme 13). The glycosylation of the latter with thiomannoside **81** in the presence of NIS and HOTf gave target protected trisaccharide **82** in 61% yield. The removal of all protecting groups *via* alkaline methanolysis afforded free trisaccharide **83**.

Similar protected oligomannoside **86** was synthesized [38] in 61% yield by the coupling of (1→2)-linked donor **84** and (1→6)-linked acceptor **85** in the presence of NIS and TMSOTf (Scheme 14).

Scheme 14



(*a*) NIS, TMSOTf, MS 4 Å, CH$_2$Cl$_2$, 0 °C; PMB is *p*-methoxybenzyl; Nap is 2-naphthylmethyl

III.1.c. Synthesis of branched α-oligomannosides

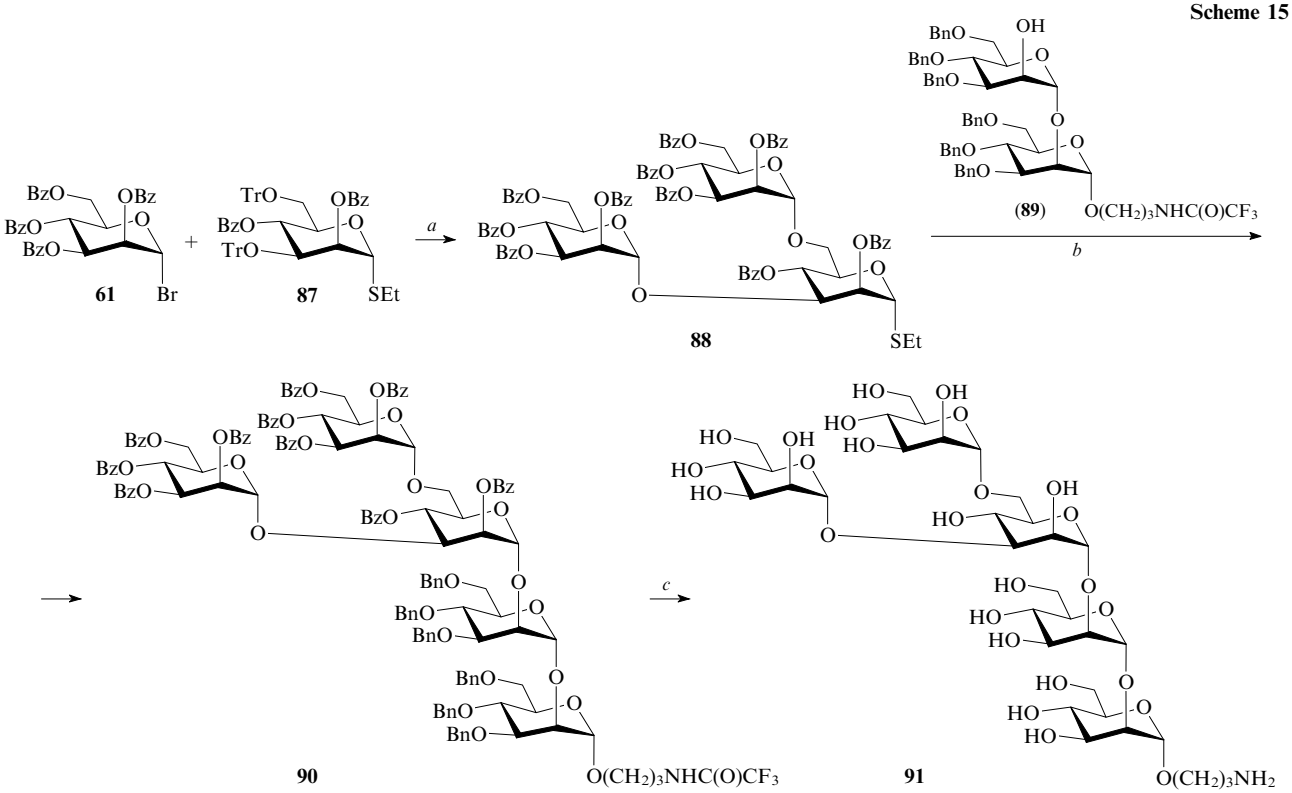
3,6-Branched oligosaccharides. Two oligosaccharides (**91** and **101**) containing the 3,6-branching point in the terminal

residue of the (1→2)-oligomannoside chain (correspond to *Candida* antigenic factor 4, see Fig. 4) were synthesized at the Laboratory of Glycoconjugate Chemistry of the ZIOC RAS.[39] The synthesis of symmetrical pentamannoside **91** was accomplished *via* the [3 + 2] scheme. For this purpose, thiomannoside 3,6-ditrityl ether **87** was glycosylated with benzobromomannose **61** according to a procedure first described by Bredereck to produce target trisaccharide building block **88** in 61% yield (Scheme 15). Protected pentasaccharide **90** was prepared in 57% yield by the coupling of donor **88** with (1→2)-linked acceptor **89**. The subsequent complete deprotection of compound **90** gave unprotected pentamannoside **91** as aminopropyl glycoside.

Hexamannoside **101**, in which the O(C3) and O(C6) atoms at the branching point bear different carbohydrate substituents, was synthesized by employing thioglycoside **92**. The character of protecting groups in the latter made it possible to perform the successive glycosylation of these positions. The assembly of the oligosaccharide chain was accomplished *via* the [2 + 2 + 2] scheme (Scheme 16). (1→6)-Linked disaccharide **93** was synthesized in 73% yield by the coupling of thioglycoside **92** with benzobromomannose **61** in the presence of AgOTf. This disaccharide was used to glycosylate acceptor **89** in the presence of NIS and HOTf, resulting in the formation of tetramannoside **94** with the (1→6)-linkage at the non-reducing end in 70% yield. After the silyl deprotection, tetrasaccharide acceptor **95** was employed in glycosylation with disaccharide thioglycoside **98**, which was produced from 2-OH-thioglycoside **97** and benzoylated trichloroacetamide **96**. Since thioglycoside **98** contained the non-participating mannosyl substituent at the O(C2) atom, the final glycosylation step afforded two products: target branched α-linked hexamannoside **99** (44% yield) and side β-(1→3)-mannosylation product **100** (14%). The deprotection of α-coupling product **99** gave target free hexamannoside **101**.

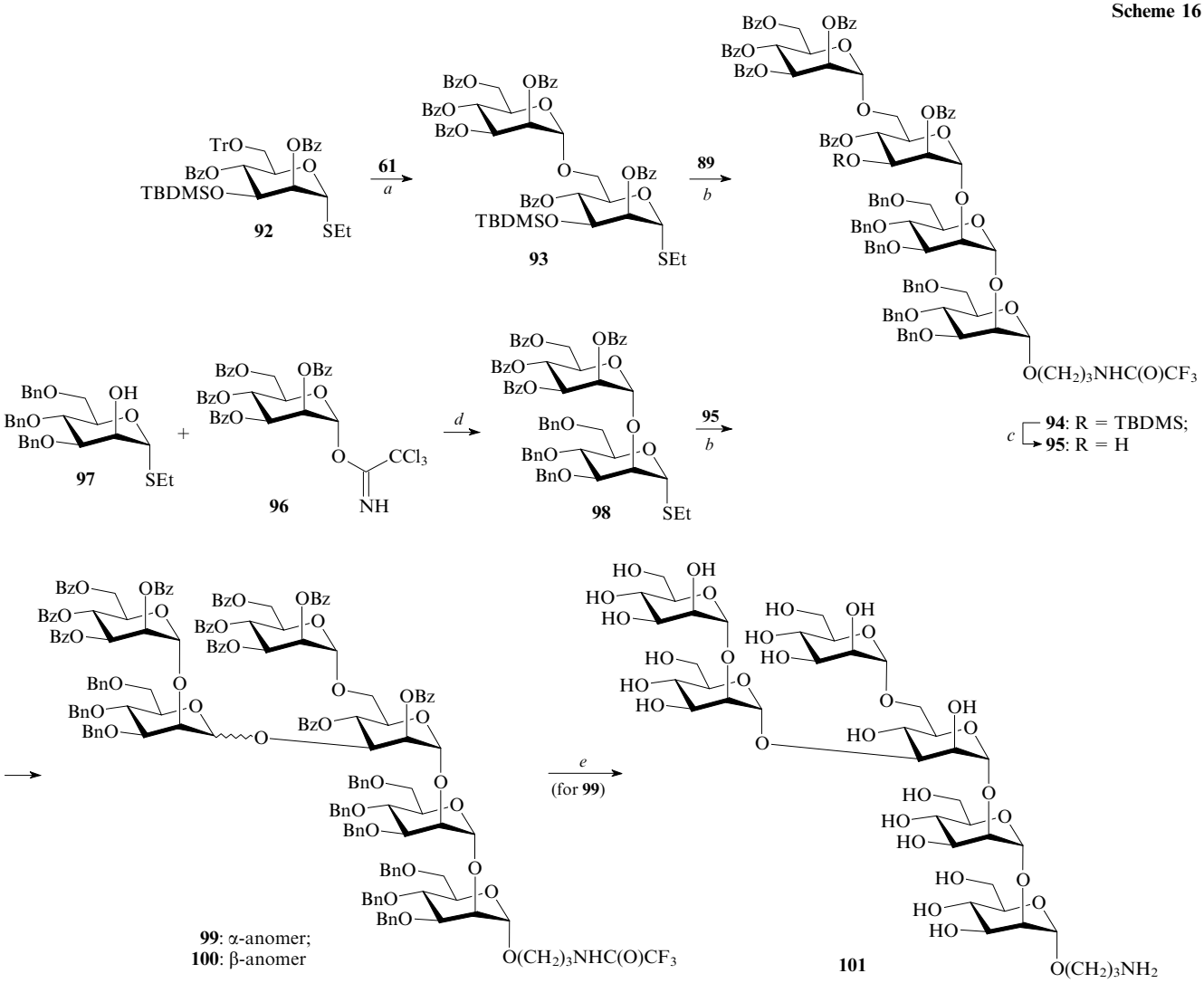
An alternative approach to the synthesis of hexasaccharide **101** has been proposed.[40] It was assumed that the formation of the β-linked product through the coupling of dimannoside **98** with tetrasaccharide acceptor **95** (see cheme 16) is favoured by the presence of a bulky carbohydrate substituent at the O(C6) atom of the mannose residue subjected to glycosylation. Therefore, another synthetic scheme was examined. In this scheme, the 3 and 6 positions of the mannose residue at the branching point are glycosylated in the reverse order compared to the scheme described above. For this purpose, thioglycoside **102** containing orthogonal protecting groups (silyl and chloroacetyl) at the 3 and 6 positions was synthesized and employed for glycosylation of acceptor **89** in the presence of NIS and HOTf, giving rise to trisaccharide **103** in 96% yield (Scheme 17). Then the silyl protection at the O(C3) atom was removed on treatment with aqueous trifluoroacetic acid to form acceptor **104**. The coupling of the latter with disaccharide donor **98** also gave a mixture of α- and β-products **105**; however, their total yield (70%) and the α : β ratio (6 : 1) were substantially higher compared to those achieved in the coupling of disaccharide **98** with tetrasaccharide **95**. An anomeric mixture of pentasaccharides **105** was converted into a mixture of **106** by removing the chloroacetyl group, and the latter mixture was glycosylated, without the separation, with benzobromomannose **61** in the presence of AgOTf. This process gave target hexasaccharide **99** in 75% yield and β-linked side product **100** in 11% yield.

Scheme 15



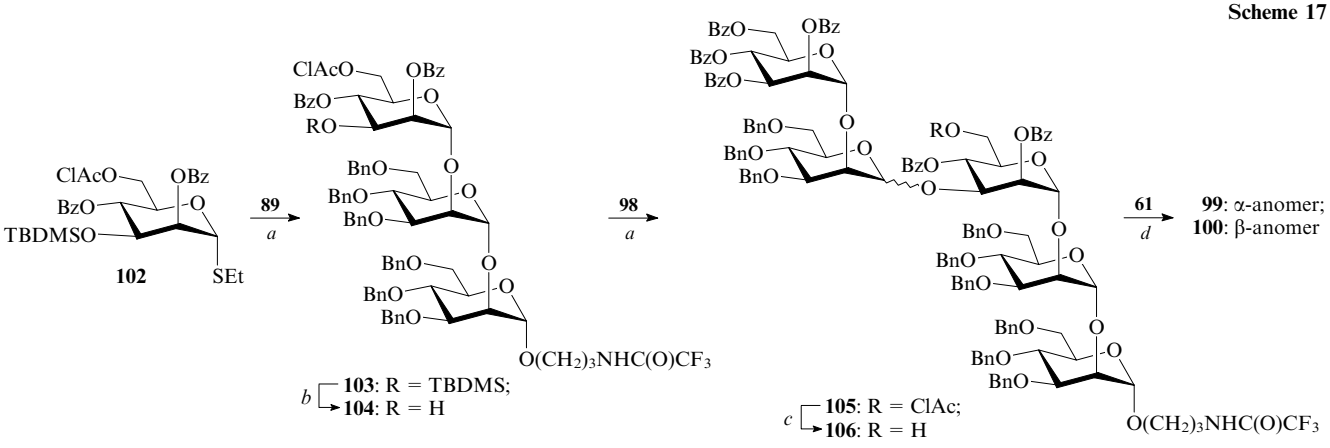
(*a*) AgOTf, MS 4 Å, CH_2Cl_2, −10 °C; (*b*) NIS, HOTf, MS 4 Å, CH_2Cl_2, −30 → −20 °C; (*c*) 1) H_2, Pd/C, MeOH; 2) MeONa, MeOH; 3) NaOH, MeOH, H_2O; Tr is trityl (triphenylmethyl)

Scheme 16



(*a*) AgOTf, MS 4 Å, CH_2Cl_2, −10 °C; (*b*) NIS, HOTf, MS 4 Å, CH_2Cl_2, −30 → −20 °C; *c* — TFA, $CHCl_3$; (*d*) TMSOTf, MS 4 Å, CH_2Cl_2, −20 °C; (*e*) 1) H_2, Pd/C, MeOH; 2) MeONa, MeOH; 3) NaOH, MeOH, H_2O; TBDMS is *tert*-butyldimethylsilyl, TFA is trifluoroacetic acid

Scheme 17



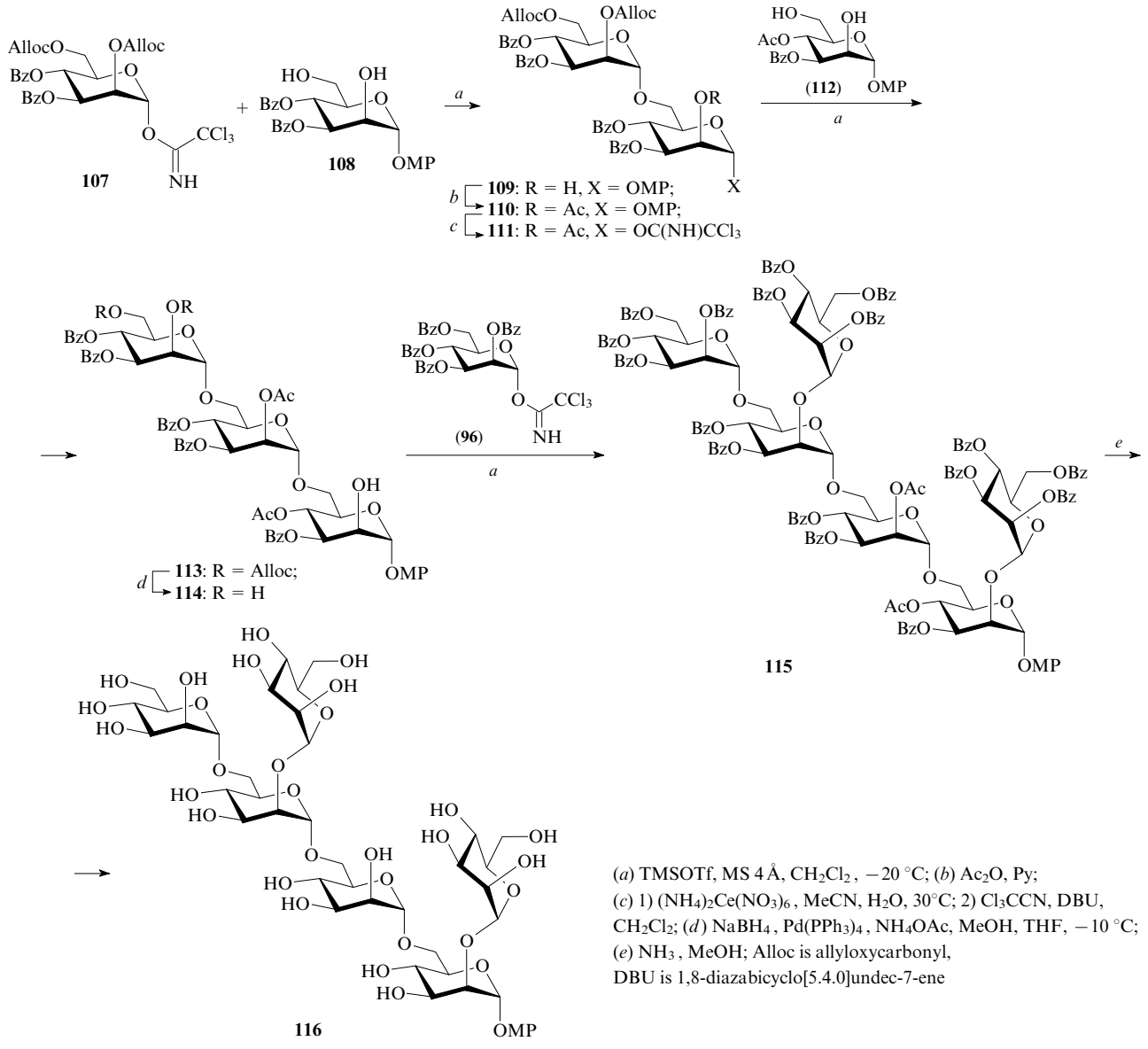
(*a*) NIS, HOTf, MS 4 Å, CH_2Cl_2, −25 → −15 °C; (*b*) 90% TFA (aq.); (*c*) $(NH_2)_2C(S)$, 2,4,6-collidine, MeOH, Δ; (*d*) AgOTf, CH_2Cl_2, −20 °C

2,6-Branched oligosaccharides. The approach employed by Zong *et al.*[41] for the synthesis of hexamannoside **116** involved the initial construction of a linear α-(1→6)-linked trisaccharide acceptor containing two free hydroxyl groups

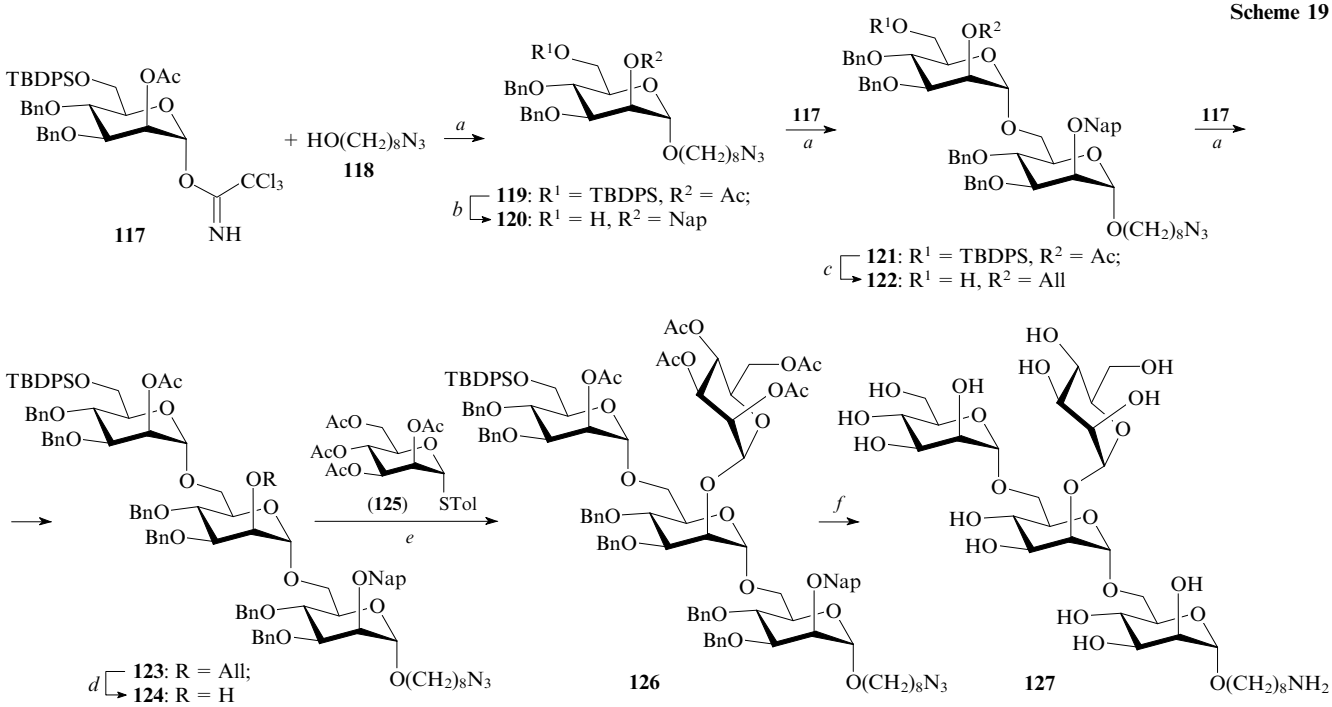
at the C(2) atoms and one hydroxyl group at the C(6) atom followed by the one-step glycosylation of this triol (Scheme 18). The linear α-(1→6)-linked trisaccharide was synthesized by the chain elongation reaction starting from the non-reducing end. In the first step, acceptor **108** containing two free hydroxyl groups at the 2 and 6 positions was selectively glycosylated at the O(C6) atom with imidate **107** containing temporary allyloxycarbonyl protecting groups at the O(C2) and O(C6) atoms. This procedure gave rise to (1→6)-linked disaccharide **109** in 87% yield. In this case, the products of β-glycosylation or glycosylation products at the O(C2) atom were not detected. The acetylation of the free hydroxyl group of dimannoside **109**, the removal of the *p*-methoxyphenyl protection from the anomeric position in compound **110** and the reaction with trichloroacetonitrile produced disaccharide donor **111**. The latter was, in turn, involved glycosylation with acceptor **112** structurally similar to acceptor **108**, which has been employed in the previous step. This procedure afforded trisaccharide **113**. The removal of the allyloxycarbonyl protecting groups from the latter gave trisaccharide triol **114**, which was glycosylated with imidate **96** in the presence of TMSOTf to form target protected hexamannoside **115** in 91% yield. The removal of all acyl protecting groups resulted in the formation of free hexasaccharide **116** as *p*-methoxyphenyl glycoside.

A similar approach was applied by Sahloul and Lowary,[42] who described the synthesis of branched tetramannoside **127** and branched pentamannoside **136** (Schemes 19 and 20). As opposed to the above-considered work, the α-(1→6)-chain was assembled starting from the reducing end with the participation of imidate donor **117** containing temporary orthogonal protecting groups at the O(C2) and O(C6) atom. The first step involved the glycosylation of 8-azidooctanol with this donor giving spacer-containing monosaccharide **119** in 75% yield. The replacement of the acetyl group in the latter with the naphthylmethyl group and the removal of the silyl group afforded acceptor **120**. The coupling of monosaccharides **117** and **120** in the presence of TMSOTf gave disaccharide **121** in 83% yield. In disaccharide **121**, the acetyl group was replaced by the allyl moiety and the silyl protection at the O(C6) atom was

Scheme 18

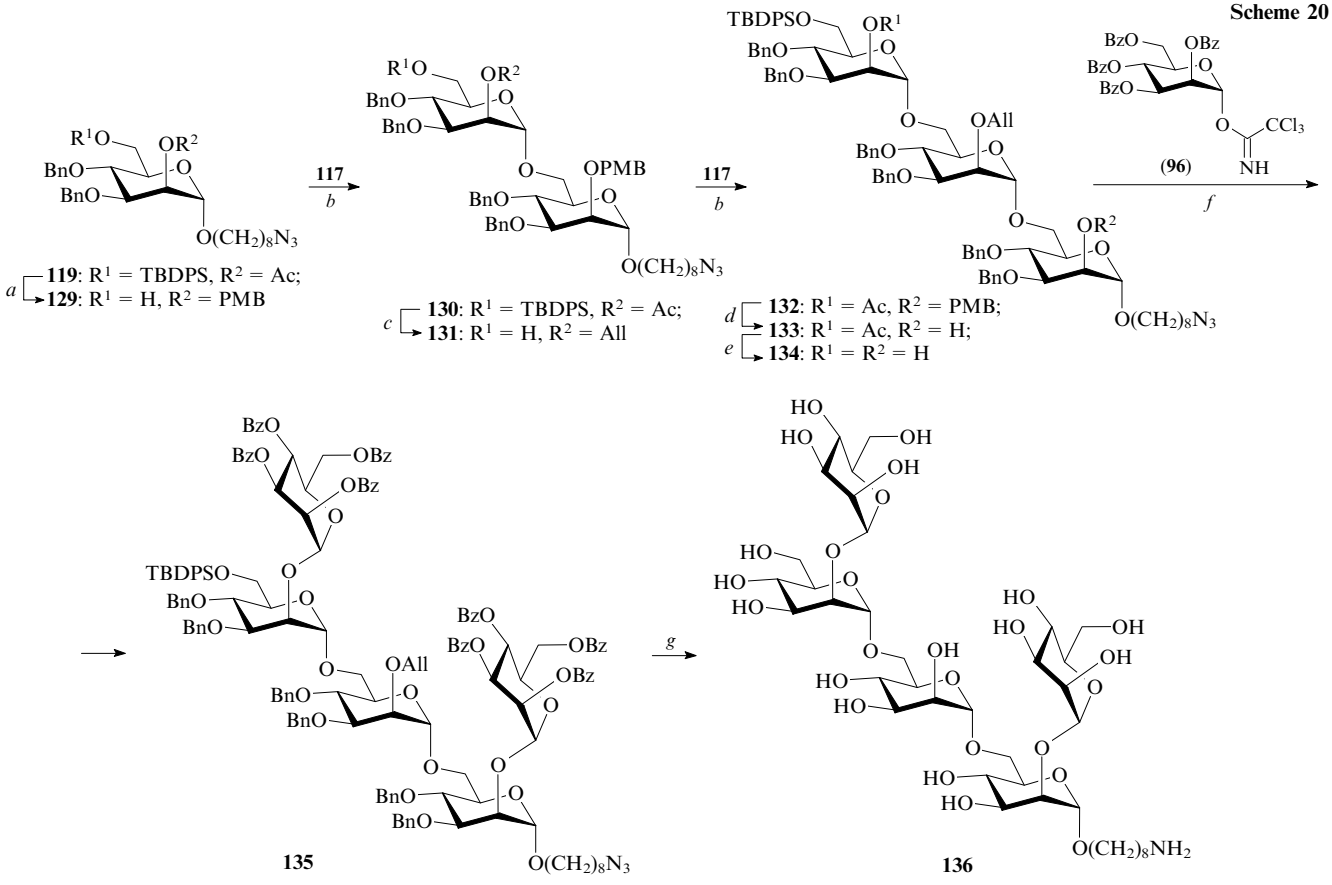


Scheme 19



(*a*) TMSOTf, MS 4 Å, CH_2Cl_2, −20 °C; (*b*) 1) MeONa, MeOH; 2) NapBr, NaH, DMF; 3) TBAF, THF; (*c*) 1) MeONa, MeOH; 2) AllBr, NaH, DMF; 3) TBAF, THF; (*d*) 1) $[Ir(COD)(MePh_2P)_2]PF_6$, THF; 2) HgO, $HgCl_2$, Me_2CO; (*e*) NIS, AgOTf, CH_2Cl_2, 0 °C; (*f*) 1) HF·Py, Py, THF; 2) MeONa, MeOH, Et_2O; 3) H_2, $Pd(OH)_2/C$, MeOH, H_2O; TBDPS is *tert*-butyl(diphenyl)silyl, All is allyl, COD is cycloocta-1,5-diene

Scheme 20



(*a*) 1) MeONa, MeOH; 2) PMBBr (**128**), NaH, DMF; 3) TBAF, THF; (*b*) TMSOTf, MS 4 Å, CH_2Cl_2, −20 °C; (*c*) 1) MeONa, MeOH; 2) AllBr, NaH, DMF; 3) TBAF, THF; (*d*) $(NH_4)_2Ce(NO_3)_6$, MeCN, Et_2O; (*e*) MeONa, MeOH, Et_2O; (*f*) TMSOTf, MS 4 Å, Et_2O, −15 °C; (*g*) 1) $[Ir(COD)(MePh_2P)_2]PF_6$, THF; 2) HgO, $HgCl_2$, Me_2CO; 3) HF·Py, Py, THF; 4) MeONa, MeOH, Et_2O; 5) H_2, $Pd(OH)_2/C$, MeOH, H_2O

removed. The resulting disaccharide acceptor **122** was, in turn, glycosylated with donor **117** giving trisaccharide **123** in 69% yield. The removal of the allyl group from the central fragment of mannose produced acceptor **124**, and the reaction of the latter with thiomannoside **125** in the presence of NIS and AgOTf afforded target protected tetramannoside **126** in 67% yield. After the complete deprotection and reduction of azide, free branched tetrasaccharide **127** was isolated (see Scheme 19).

Pentamannoside **136** was synthesized as follows. The acetyl group in derivative **119** that was prepared previously was replaced with the *p*-methoxybenzyl moiety followed by the removal of the 6-O-silyl protection. The subsequent steps of the construction of the (1→6)-linked trisaccharide chain were similar to those described above for trimannoside **123**. The glycosylation of acceptor **129** with donor **117** produced disaccharide **130**, which was converted to acceptor **131** by the replacement of the acetyl group with the allyl moiety and silyl deprotection. The coupling of **131** with donor **117** produced trimannosides **132** with different substituents at the O(C2) atoms of mannose residues. Two substituents (*p*-methoxybenzyl and acetyl) were successively removed, resulting in the isolation of trisaccharide diol **134** through the formation of intermediate **133**. The glycosylation of this diol with donor **96** afforded protected pentamannoside **135** in 67% yield. The target free pentasaccharide **136** was obtained after the complete deprotection and reduction of azide.

III.2. Synthesis of oligosaccharides containing β-(1→2)-mannosidic linkages

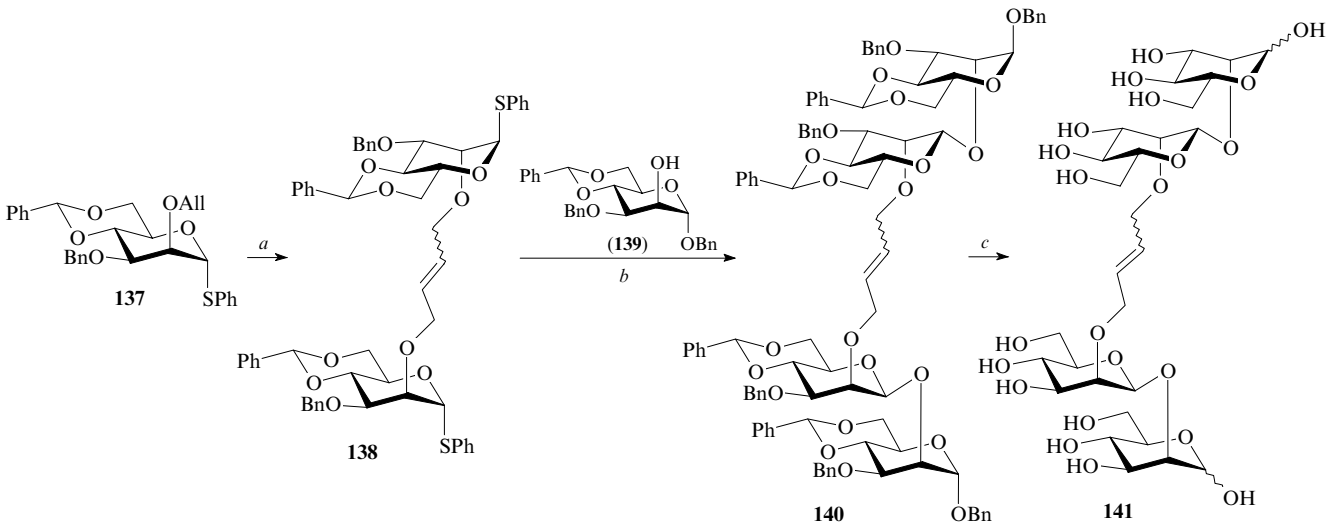
This Section deals with the synthesis of (1→2)-oligomannosides, in which either all mannose residues adopt a β configuration or the only α-linked mannose residue (or the mannose residue with an anomeric configuration that is not fixed) is present at the reducing end of the chain (corresponding to *Candida* antigenic factor 5, see Fig. 4). The strategy for the synthesis of oligosaccharides containing β-mannoside building blocks requires the application of methods other than those used for α-mannosylation in order to provide the desired stereoselectivity of glycosylation.

There are two rather general approaches to the construction of a β-mannosidic linkage: the use of conformationally restricted donors, *e.g.*, compound **137** (Scheme 21), bearing a non-participating group at the O(C2) atom and the 4,6-O-benzylidene protection or employment of β-glycosylation with a glucose donor followed by the inversion of configuration at the C(2) atom in the resulting β-glucoside.[43] It should be noted that the former approach has found wider use in recent years. Nevertheless, we give examples of application of both approaches. β-Mannosides can also be synthesized by glycosylation through intramolecular aglycon delivery,[44] but the application of this method to the preparation of β-(1→2)-oligomannosides was described only in one publication (see below).

Ekholm *et al.*[45] synthesized unusual compounds, in which two disaccharides are connected through a hydrocarbon bridge attached to the O(C2) atom of mannose residues, the bridge being introduced at the step of formation of the mannosyl donor and, therefore, serves, as a non-participating protecting group at the O(C2) atom in the β-mannosylation reaction (see Scheme 21). For instance, the metathesis of 2-O-allylated thioglycoside **137** gave dimer **138**. The glycosylation of benzyl mannoside **139** with this dimer produced a dimer of β-(1→2)-linked dimannosides (**140**) in 70% yield. Thioglycoside was activated using a mixture of reagents consisting of 2,4,6-tri-*tert*-butylpyrimidine, 1-benzylsulfinylpiperidine, and Tf_2O. This or similar promotion systems are widely employed in the synthesis of β-linked mannosides. Compound **140** was subjected to hydrogenolysis giving a dimer of free β-linked disaccharides (**141**) in 50% yield.

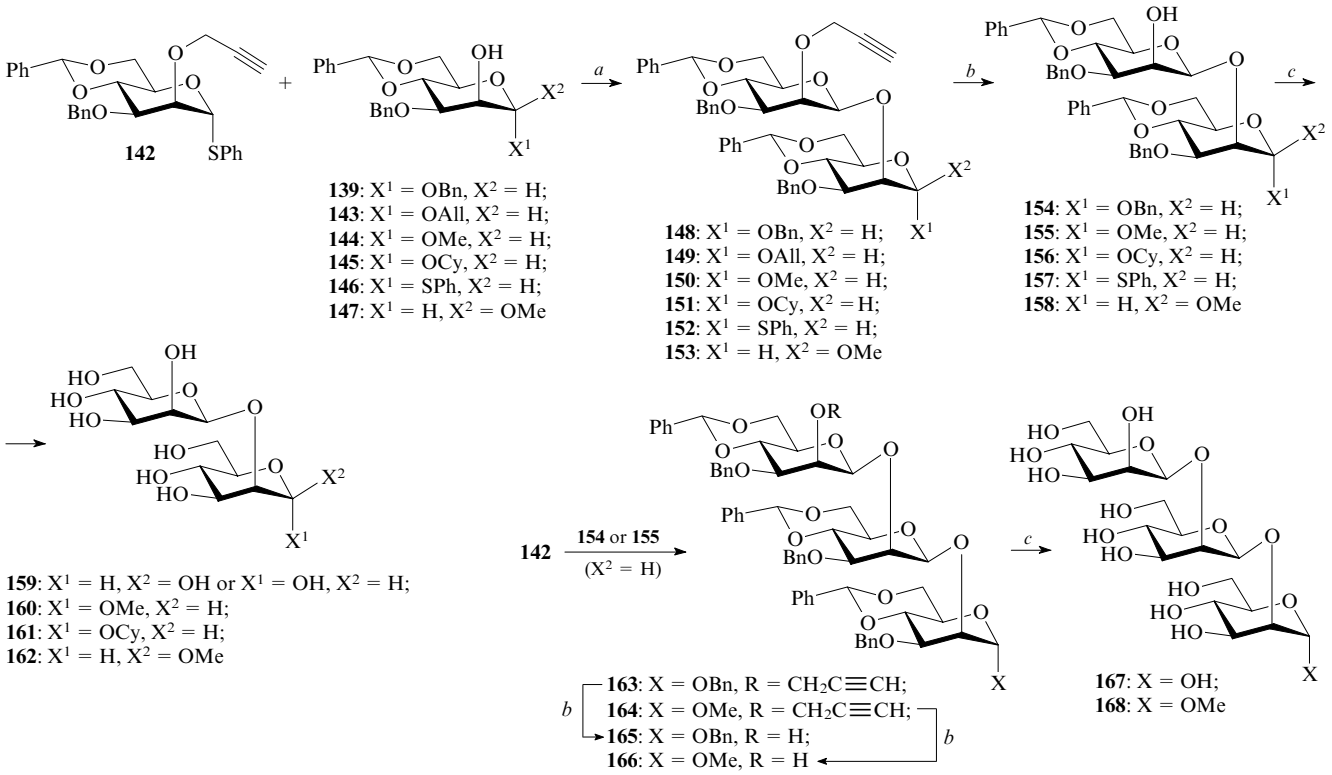
In the subsequent work, the same authors[46] investigated the β-glycosylation of different acceptors with donor **142** (Scheme 22). The non-participating propargyl group at the O(C2) atom was examined as an alternative to the benzyl group because it produces less steric hindrance to the access of a nucleophile in β-mannosylation reactions. The authors synthesized a series of β-linked disaccharides and two

Scheme 21



(*a*) Grubbs catalyst, CH_2Cl_2, 40 °C; (*b*) 1) TTBP, BSP, Tf_2O, MS 4 Å, CH_2Cl_2, −60 °C; 2) acceptor, −78 °C; (*c*) H_2, Pd/C, MeOH, EtOAc; TTBP is 2,4,6-tri-*tert*-butylpyrimidine, BSP is 1-benzylsulfinylpiperidine

Scheme 22



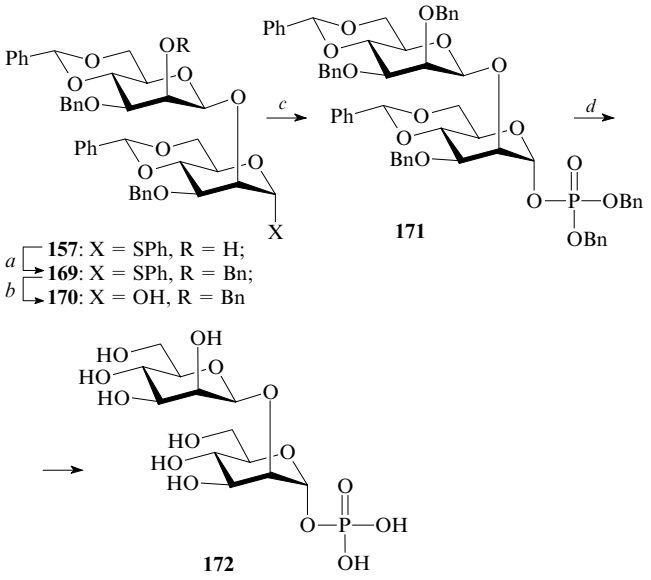
(*a*) 1) TTBP, BSP, Tf_2O, MS 4 Å, CH_2Cl_2, — 60 °C; 2) appropriate acceptor, −78 °C; (*b*) 1) Bu^{t}OK, THF; 2) OsO_4, *N*-methylmorpholine *N*-oxide, Me_2CO, H_2O; (*c*) H_2, Pd/C, MeOH; Cy is cyclohexyl

trisaccharides with different aglycons. In the first step, the coupling of six acceptors (**139**–**147**), which contain a free hydroxyl group at the C(2) atom and which differ only in the nature of the aglycon, with donor **142** in the presence of TTBP, BSP and Tf_2O produced six dimannosides (**148**–**153**) in yields from 72% to 87%. The propargyl protecting group was removed from five of these compounds (except allyl glycoside **149**). Four of the reaction products **154**–**158** (except thioglycoside **157**) were hydrogenated to free disaccharides **159**–**162**. Among potential acceptors **154**–**158**, α-benzyl glycoside **154** and α-methyl glycoside **155** were chosen for subsequent chain elongation reactions. The reaction of the latter two compounds with donor **142** produced trimannosides **163** and **164** in 72% and 74% yields, respectively. The removal of the propargyl group (compounds **165** and **166**) followed by hydrogenation gave free trimannosides **167** and **168**.

The same authors [46] synthesized phosphorylated derivative of dimannoside **172** (Scheme 23). For this purpose, the free OH group at the C(2′) atom in disaccharide **157** was benzylated giving rise to thioglycoside **169**, which was hydrolyzed to hemiacetal **170** by the treatment with *N*-bromosuccinimide in aqueous acetone. The reaction of compound **170** with $(BnO)_2PNPr^i_2$ in the presence of tetrazole followed by oxidation to phosphate produced protected phosphate **171**. Hydrogenolysis of the latter afforded free phosphate **172** in 70% yield.

This research team also synthesized [47] β-(1→2)-linked tetramannoside **174** (Scheme 24). Initially, the coupling of dimannosides **154** and **169** gave protected tetramannoside **173** (the ratio of the anomers β : α = 10 : 1), which was fully

Scheme 23

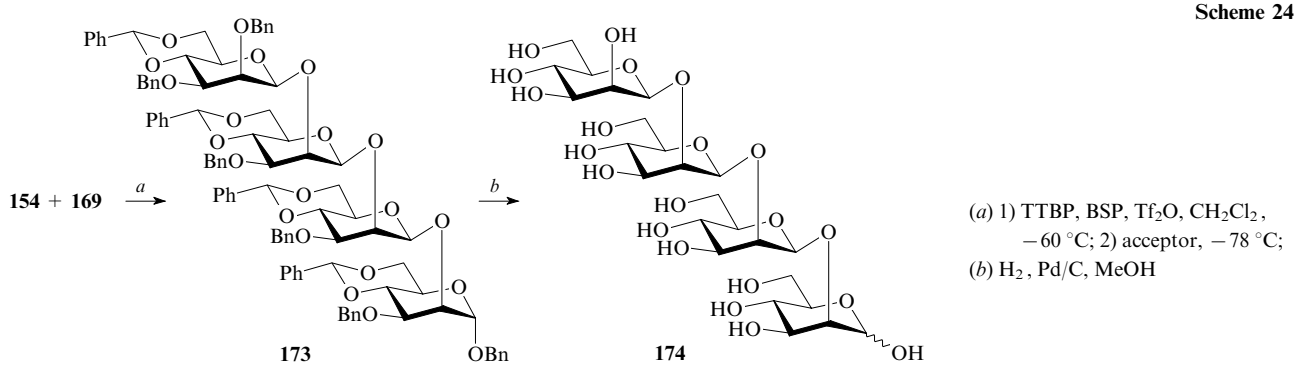


(*a*) BnBr, NaH, DMF; (*b*) NBS, Me_2CO, H_2O; (*c*) 1) tetrazole, $(BnO)_2PNPr^i_2$, CH_2Cl_2, — 40 °C; 2) m-CPBA, −40 °C; (*d*) H_2, Pd/C, MeOH; NBS is *N*-bromosuccinimide, m-CPBA is *m*-chloroperoxybenzoic acid

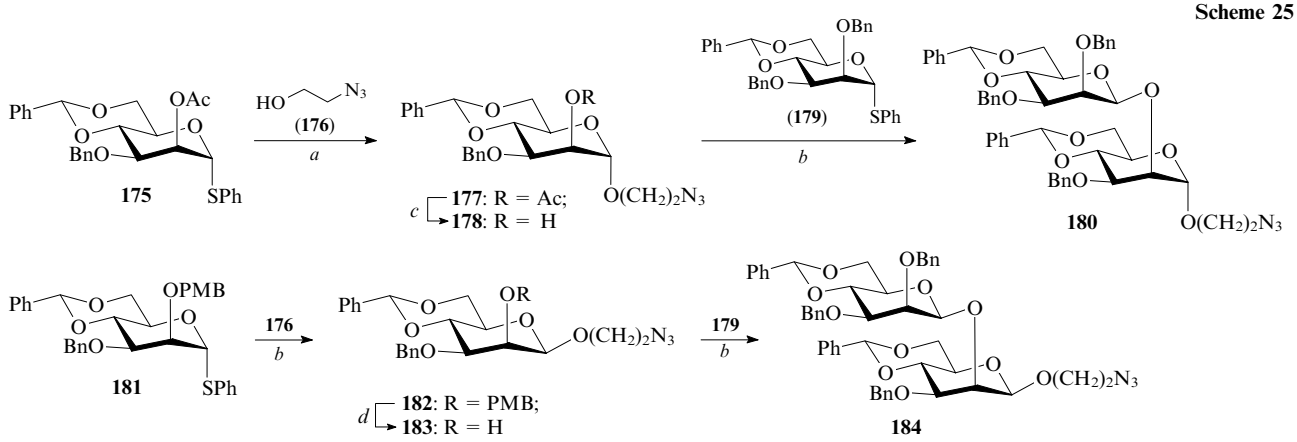
deprotected by hydrogenation to form free tetrasaccharide **174**.

A series of β-(1→2)-disaccharides, which differ in the configuration of the bond with the aglycon, has been

Scheme 24



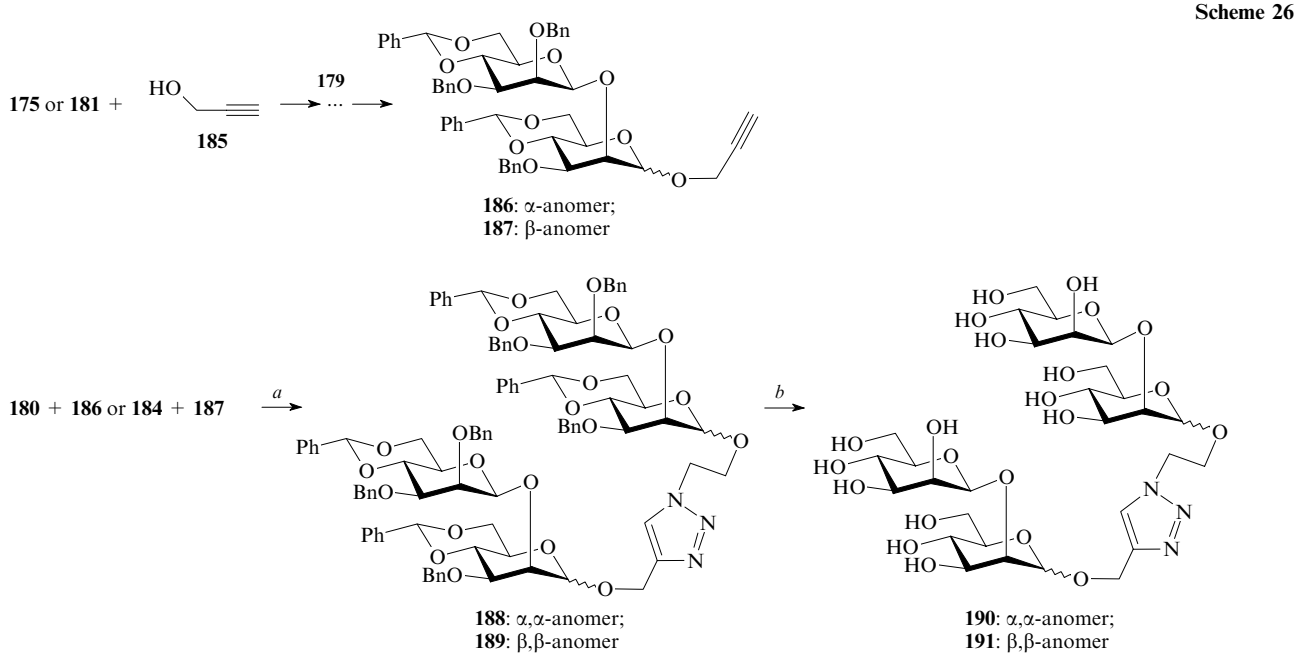
Scheme 25



(*a*) NIS, TMSOTf, MS 4 Å, CH_2Cl_2, −20 °C; (*b*) 1) TTBP, BSP, Tf_2O, MS 4 Å, CH_2Cl_2, −60 °C; 2) appropriate acceptor, −78 °C; (*c*) MeONa, MeOH; (*d*) DDQ, H_2O, CH_2Cl_2; DDQ is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

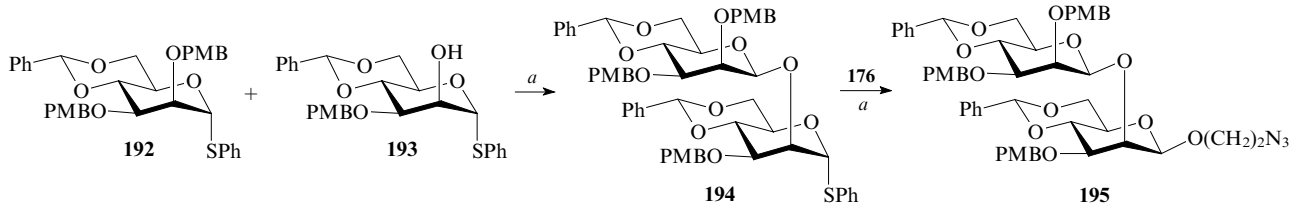
reported.[48] The first step involved the synthesis of α- and β-2-azidoethyl mannosides. In order to prepare the α-anomer, the reaction of thioglycoside **175** containing the acetyl group at the O(C2) atom with 2-azidoethanol (**176**) in the presence of NIS and TMSOTf was accomplished, resulting in the formation of α-mannoside **177** in 86%

Scheme 26



(*a*) $CuSO_4$, sodium ascorbate, Bu^tOH, H_2O, CH_2Cl_2; (*b*) H_2, Pd/C, MeOH, EtOAc

Scheme 27



(*a*) 1) TTBP, BSP, Tf_2O, MS 4 Å, CH_2Cl_2, −60 °C; 2) appropriate acceptor, −78 °C

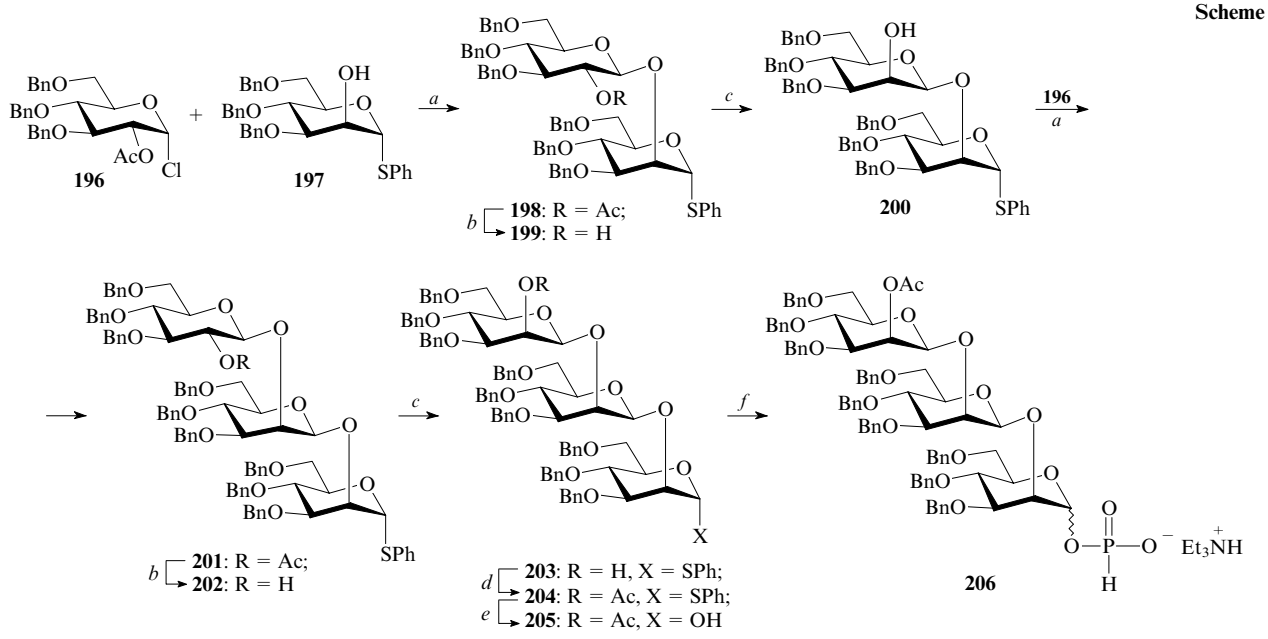
yield (Scheme 25). An analogue of compound **177**, in which the mannose residue and aglycon were connected by a β-linkage, was synthesized by employing donor **181** with the non-participating *p*-methoxybenzyl group at the O(C2) atom (see Scheme 25). The coupling of this donor with 2-azidoethanol in the presence of TTBP, BSP and Tf_2O gave β-mannoside **182** in a much lower yield (48%). In both mannosides, the protecting groups at the O(C2) atom were removed to prepare acceptors **178** and **183**. The coupling of the latter with donor **179** was performed under the same conditions. β-Mannosylation products **180** and **184** were isolated in 88% and 92% yields, respectively.

Two propargyl mannosides **186** and **187** were synthesized according to a similar scheme. The yields after the β-mannosylation step were 64% and 90%, respectively (Scheme 26). The cycloaddition of dimannoside 2-azidoethyl and 2-propargyl glycosides with the same anomeric configuration afforded dimers **188** and **189** connected *via* the triazole moiety. The subsequent hydrogenation afforded free dimers **190** and **191** with the α- and β-bond configurations between the dimannoside fragments and aglycon.

Another approach was employed for the synthesis of β,β-disaccharide **195**, which differs from compound **184** described above only by the presence of *p*-methoxybenzyl groups instead of benzyl moieties (Scheme 27).[49] The first step involved the coupling of thioglycosides **192** and **193** giving disaccharide **194** (76% yield). Donor **192** was preactivated with TTBP, BSP and Tf_2O followed by the addition of acceptor **193**. These conditions allow the activation of thioglycoside in the donor building block, with this function in the acceptor building block remaining intact. The glycosylation of 2-azidoethanol **176** with disaccharide **194** under the same conditions afforded disaccharide **195** in 34% yield.

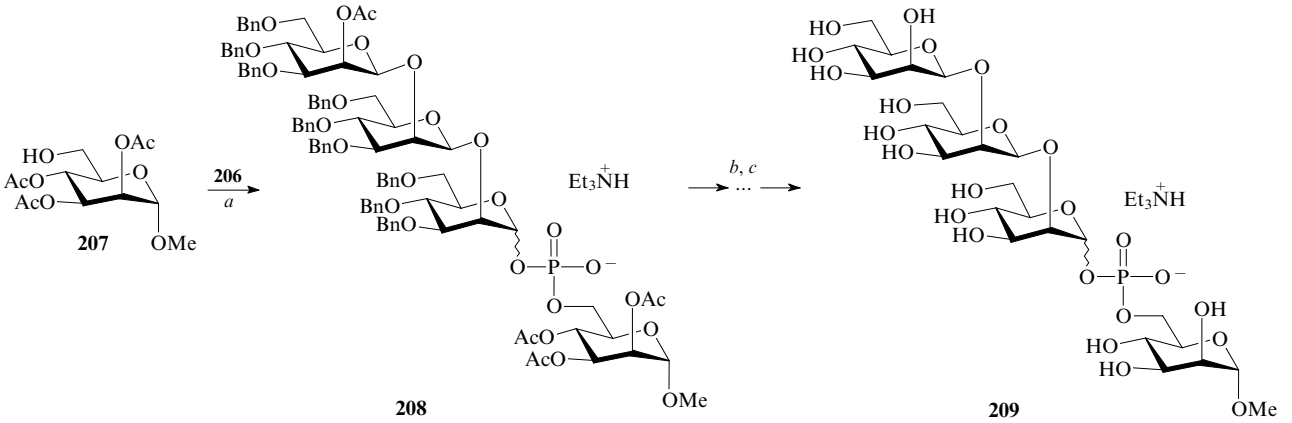
This Section includes only one work,[50] in which β-mannosides were prepared through the epimerization at the C(2) atom of β-glucosides. This study dealt with the synthesis of a phosphomannan fragment of *C. albicans*. Thiomannoside **197** and glucosyl chloride **196** containing benzyl groups as permanent protection served as the starting building blocks in the iterative assembly of the chain (Scheme 28). The β-mannoside chain was constructed by the successive addition of the glucose residue followed by C(2) epimerization. Thus, the coupling of thiomannoside **197** with chloride **196** in the presence of AgOTf afforded disaccharide **198** in 74% yield. The acetyl deprotection of the latter disaccharide gave compound **199**. The Swern oxidation of the latter produced ketone, which was reduced with L-selectride to form β-linked dimannoside acceptor **200** in 74% yield.

Scheme 28



(*a*) AgOTf, MS 4 Å, CH_2Cl_2, PhMe, −40 °C; (*b*) MeONa, MeOH; (*c*) 1) $(COCl)_2$, Et_3N, DMSO, CH_2Cl_2, −78 → 0 °C; 2) L-selectride, THF; (*d*) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (*e*) NIS, H_2O, Me_2CO; (*f*) PCl_3, imidazole, Et_3N, MeCN; 2) $Et_3NH^+HCO_3^-$, H_2O;
DMAP is 4-dimethylaminopyridine

Scheme 29



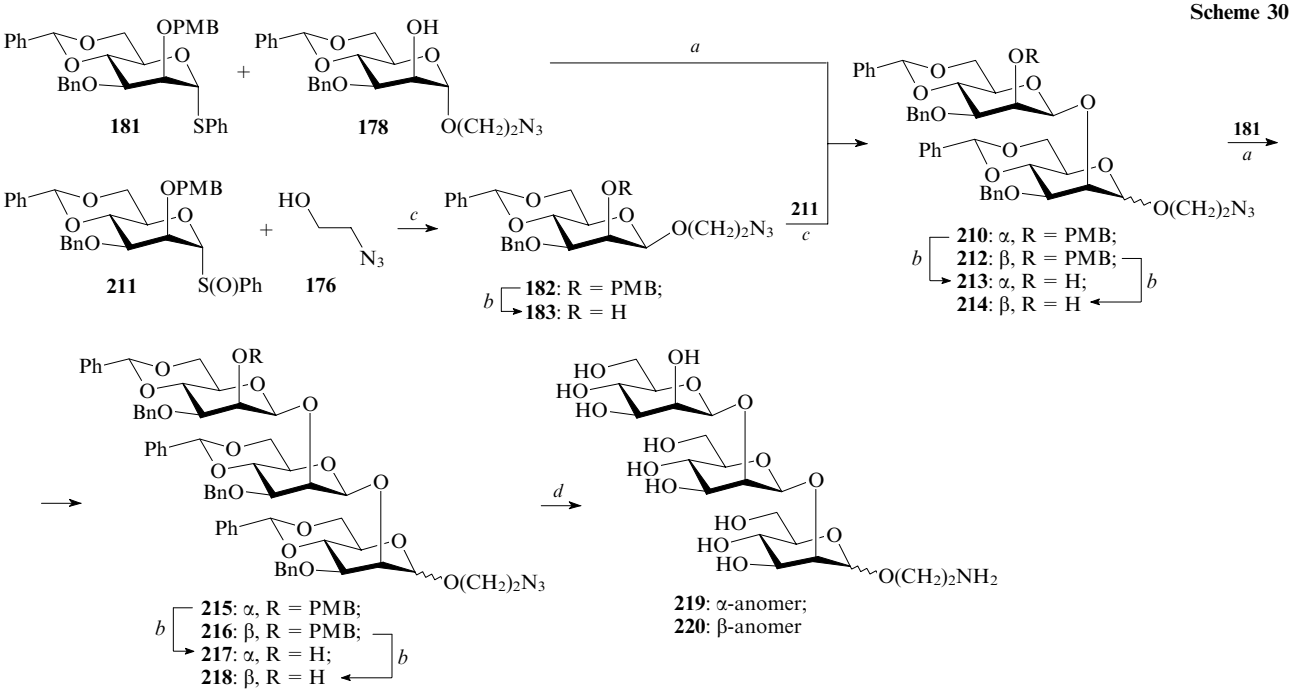
(*a*) 1) PivCl, Py; 2) I_2, Py, −40 °C; (*b*) MeONa, MeOH; (*c*) H_2, $Pd(OH)_2$/C, MeOH, CH_2Cl_2, H_2O; Piv is pivaloyl

The iterative process involving glycosylation (71% product yield), acetyl deprotection of trisaccharide **201** giving compound **202** and inversion of configuration in the latter produced trimannoside **203** (65%). The free hydroxyl group in **203** was acetylated. The anomeric thiophenyl group in intermediate oligosaccharide **204** was hydrolyzed to form hemiacetal **205**; its reaction with PCl_3 afforded hydrogen phosphonate **206**. Depending on the reaction conditions, the yield of compound **206** and the ratio of α- to β-anomers varied from 68% and 6 : 1 to 38% and 100 : 0. Mixtures with the ratios α : β = 6 : 1 and 33 : 1 were used in subsequent transformations.

Trimannoside hydrogen phosphonate **206** thus synthesized was employed in the synthesis of tetramannoside product **209** containing an inter-unit phosphate linkage. Thus, the condensation of compound **206** involving the 6-OH group of methyl mannoside **207** followed by oxidation of the phosphorus atom gave target protected phosphodiester **208** in 73% and 67% yields for mixtures with 6 : 1 and 33 : 1 ratios, respectively (Scheme 29). After the two-step deprotection, free phosphomannoside **209** was obtained in a total yield of 36% and an α- to β-anomer ratio of 20 : 1 when using the former mixture or the free α-anomer was prepared in 37% yield when using the latter mixture. A decrease in the fraction of the β-anomer was attributed to its losses during chromatography.

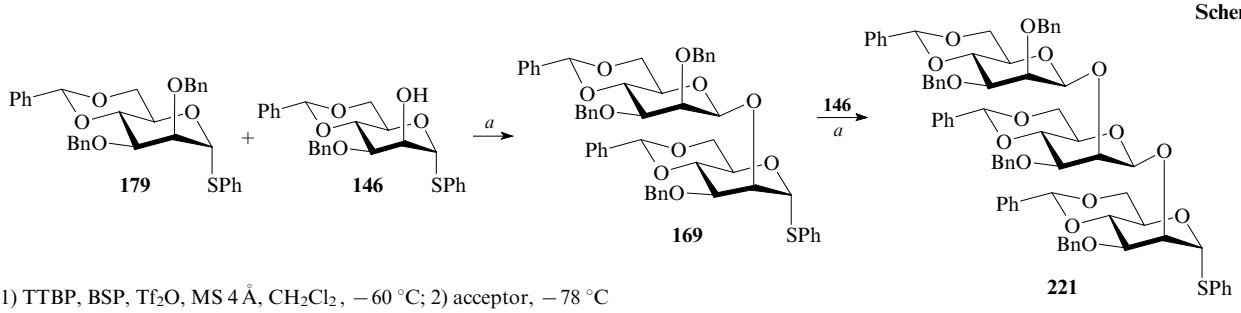
The synthesis of spacer-containing trimannosides, which differ in the anomeric configuration of the aglycon-bearing monosaccharide, like those in the disaccharide series described above, was reported by Bundle *et al.*[51] Target products were prepared by the chain elongation reaction starting from the non-reducing end using donor **181** with the temporary *p*-methoxybenzyl protecting group at the O(C2), as well as sulfoxide **211** derived from **181**

Scheme 30



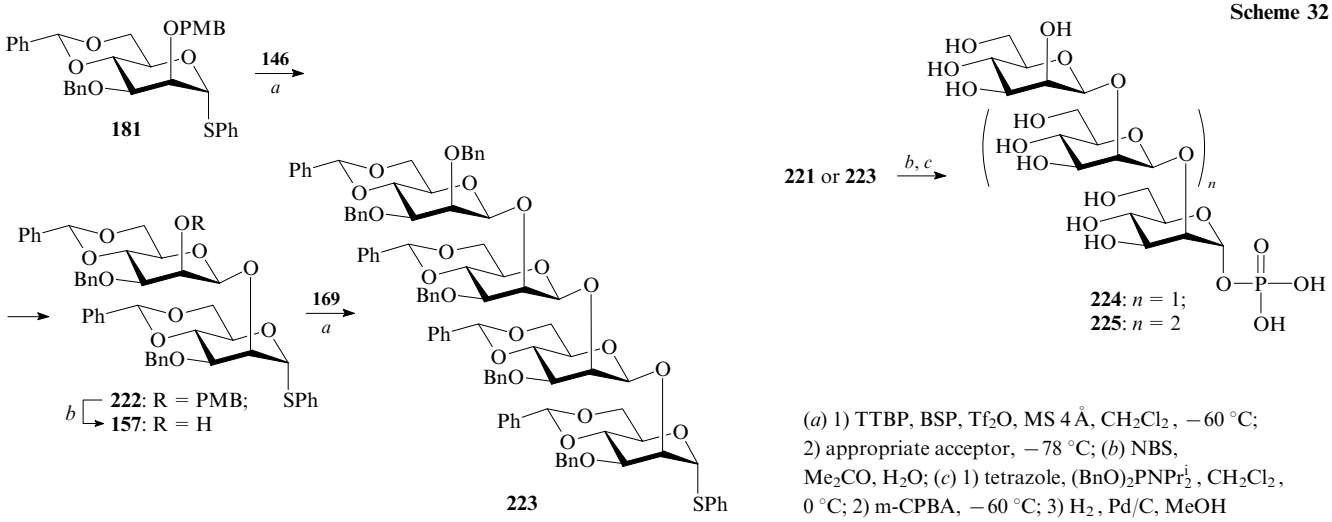
(*a*) 1) TTBP, BSP, Tf_2O, MS 4 Å, CH_2Cl_2, −60 °C; 2) appropriate acceptor, −78 °C; (*b*) DDQ, H_2O, CH_2Cl_2; (*c*) 1) TTBP, Tf_2O, MS 4 Å, CH_2Cl_2, −78 °C; 2) appropriate acceptor, −78 °C; (*d*) 1) H_2, Pd/C, Py; 2) H_2, $Pd(OH)_2$, AcOH, H_2O

Scheme 31



(*a*) 1) TTBP, BSP, Tf_2O, MS 4 Å, CH_2Cl_2, −60 °C; 2) acceptor, −78 °C

Scheme 32



(*a*) 1) TTBP, BSP, Tf_2O, MS 4 Å, CH_2Cl_2, −60 °C; 2) appropriate acceptor, −78 °C; (*b*) NBS, Me_2CO, H_2O; (*c*) 1) tetrazole, $(BnO)_2PNPr^i_2$, CH_2Cl_2, 0 °C; 2) m-CPBA, −60 °C; 3) H_2, Pd/C, MeOH

(Scheme 30). First, trisaccharide **219** with the α-linked aglycon was produced from α-mannoside **178**. The glycosylation of the latter with donor **181** gave disaccharide **210** in 78% yield. The deprotection of the O(2) position (compound **213**) and the repeated glycosylation with donor **181** afforded trisaccharide **215** in 49% yield. The removal of the *p*-methoxybenzyl group and subsequent hydrogenolysis of compound **217** yielded free trimannoside **219**.

The assembly of trisaccharide **220** bearing a β-linked aglycon was accomplished employing sulfoxide **211** as the mannosyl donor. The glycosylation of 2-azidoethanol **176** with sulfoxide **211** gave β-mannoside **182** (68% yield). After the deprotection of the O(C2) position and glycosylation of acceptor **183** thus obtained with sulfoxide **211**, disaccharide **212** was isolated in 69% yield. The conversion of this disaccharide into acceptor **214** followed by glycosylation with thioglycoside **181** and the removal of the *p*-methoxybenzyl protecting group, without the isolation of glycosylation product **216**, gave trisaccharide **218** in an overall yield of 45%. Compound **218** was converted into final β-linked trimannoside **220** through hydrogenation in the presence of a Pd catalyst.

Phosphorylated tri- (**224**) and tetramannosides (**225**) were synthesized [52] starting from β-(1→2)-linked dimannoside thioglycoside **169** and mono- (**146**) and disaccharide acceptors (**157**) (Schemes 31 and 32). The former was prepared in 75% yield by the coupling of thioglycosides **179** and **146** upon preactivation of donor **179**. Similar glycosylation of acceptor **146** with thioglycoside **169** produced trimannoside thioglycoside **221** in 62% yield.

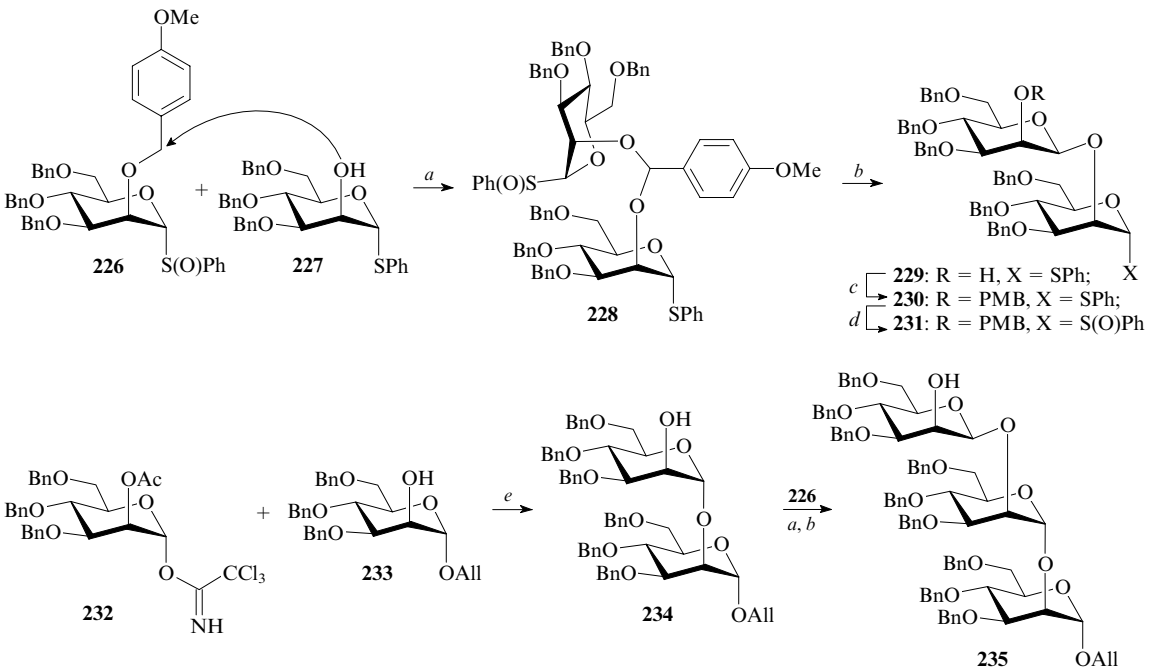
Donor **181** was employed in the synthesis of the above-mentioned disaccharide **157**. The preactivation-based coupling of donor **181** with acceptor **146** gave dimannoside **222** in 57% yield. The latter was converted to acceptor **157** by the deprotection of the O(C2) position (Scheme 32). The subsequent [2 + 2]-glycosylation of disaccharide **157** with donor **169** (see Scheme 32) afforded tetramannoside thioglycoside **223** in 35% yield. The phosphorylation of the anomeric position and deprotection were performed in the same way as in the synthesis of disaccharide phosphate **172** (see Scheme 23).

III.3. Synthesis of mixed β- and α-(1→2)-oligomannosides

This Section deals with the synthesis of oligomannosides containing at least one β-mannose residue attached through a (1→2)-glycosidic bond to α-(1→2)-oligomannoside, which is composed of at least two mannose residues (correspond to *Candida* antigenic factor 6, see Fig. 4).

For instance, Gannedi *et al.*[53] employed the intramolecular aglycon delivery approach in the synthesis of β-mannosides. The essence of this method is the use of a donor and an acceptor for the initial formation of an intermediate, in which the mutual arrangement of the anomeric centre of the donor and the hydroxyl group of the acceptor unambiguously determines the stereochemical outcome of subsequent intramolecular glycosylation. This method is illustratively shown in Scheme 33. The reaction of a mixture of sulfoxide **226** and thioglycoside **227** with DDQ produces mixed acetal **228** *via* the oxidation of the *p*-methoxybenzyl group. The attack at the anomeric centre of mannosyl sulfoxide can occur only from the β-side. Actually, when using

Scheme 33



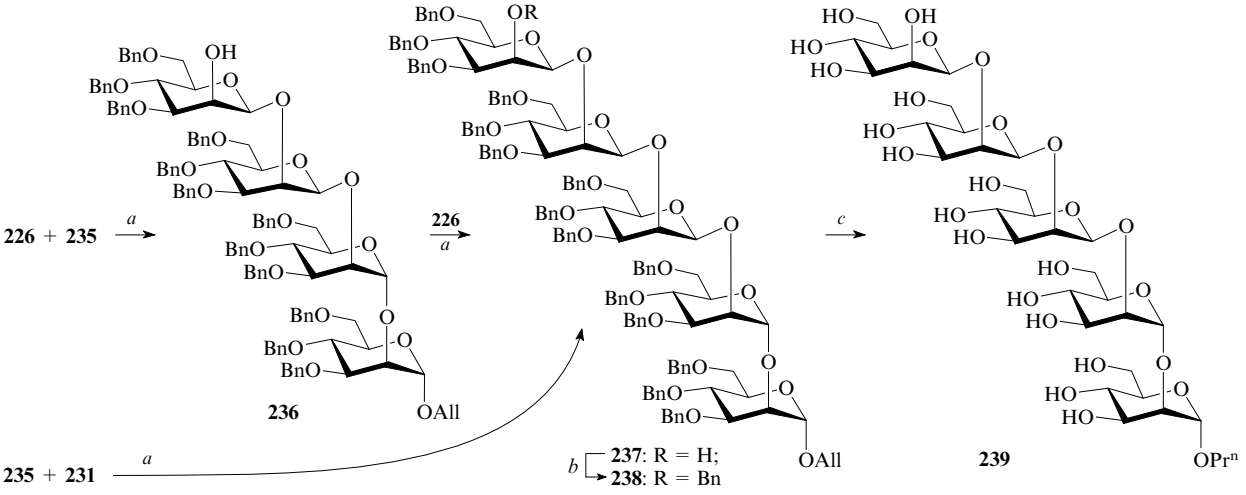
(*a*) DDQ, MS 4 Å, CH_2Cl_2, 0 °C; (*b*) DTBMP, Tf_2O, MS 4 Å, CH_2Cl_2, −78 °C; (*c*) PMBCl, NaH, DMF; (*d*) m-CPBA, CH_2Cl_2; (*e*) 1) TMSOTf, MS 4 Å, CH_2Cl_2; 2) MeONa, MeOH; DTBMP is 2,6-di-*tert*-butyl-4-methylpyridine

Tf_2O/DTBMP-activated glycosyl sulfoxides, acetal **228** easily forms β-dimannoside **229** (84% yield) without the α-anomer as a by-product.

It should also be noted that the *p*-methoxybenzyl protecting group is removed during the reaction. Therefore, the product can be immediately used as an acceptor for the further chain elongation. This approach was applied to the synthesis of pentamannoside with three β-linkages. Thus, disaccharide building block **231** was synthesized from compound **229** by the successive *p*-methoxybenzylation of the hydroxyl group and oxidation of thioglycoside to sulfoxide. Disaccharide acceptor **234**, which was prepared in two steps from trichloroacetimidate **232** and allyl mannoside **233**, was also subjected to coupling with donor **226** using the above-described approach. This procedure afforded trisaccharide acceptor **235** in 86% yield over two steps.

Then pentamannoside was synthesized by the coupling of trimannoside acceptor **235** and dimannoside donor **231**. However, the product was obtained in only 18% yield, which did not satisfy Gannedi *et al.*[53] Therefore, the authors performed the chain elongation by means of an iterative strategy using donor **226**, which allowed them to prepare condensation products in substantially higher yields. Thus, two successive glycosylation reactions gave first tetramannoside acceptor **236** and then pentamannoside **237** in 84% and 75% yields, respectively. Compound **237** was converted into fully benzylated pentasaccharide **238**. All benzyl groups were removed by hydrogenolysis with the simultaneous

Scheme 34



(*a*) 1) DDQ, MS 4 Å, CH_2Cl_2; 2) DTBMP, Tf_2O, MS 4 Å, CH_2Cl_2, −78 °C → rt; (*b*) BnBr, NaH, DMF; (*c*) H_2, Pd/C, THF, MeOH

reduction of the anomeric allyl group to the propyl moiety giving free oligosaccharide **239** (Scheme 34).

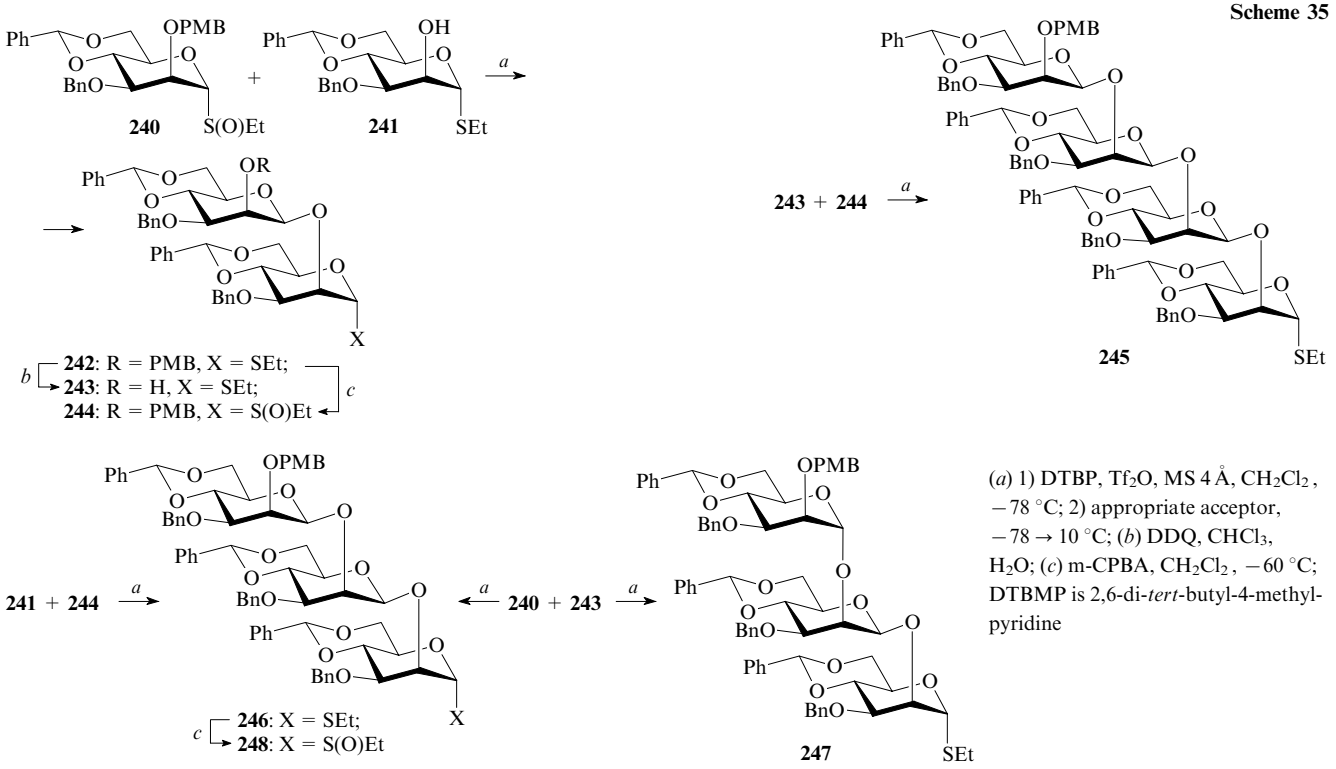
A series of oligomannosides of this type were synthesized at the Laboratory of Glycoconjugate Chemistry of the ZIOC RAS.[54, 55] The method was based on a convergent approach, which involved the preparation of an individual oligomannoside donor building block containing only β-linked mannose residues followed by its coupling with α-linked oligomannoside. The synthesis of β-(1→2)-linked donor building blocks is shown in Scheme 35. Thus, preactivation-based glycosylation of thioglycoside **241** with sulfoxide **240** gave β-linked dimannoside **242** in 59% yield. Then dimannoside **242** was converted into acceptor **243** by the treatment with DDQ to remove the *p*-methoxybenzyl protecting group from the 2 position, while the oxidation of the thioethyl group of **242** with *m*-chloromethoxybenzoic acid resulted in the conversion of **242** into donor **244**. The subsequent coupling of the acceptor and the donor, with preactivation of glycosyl sulfoxide, gave tetramannoside **245** (75% yield), which was used as a glycosyl donor without any modifications. Trisaccharide **246** was synthesized using two approaches — [2 + 1]- and [1 + 2]-coupling reactions. The coupling of monosaccharide donor **240** with disaccharide acceptor **243** afforded two products — target β-anomer **246** (40% yield) and α-linked by-product **247** (16%), whereas the use of disaccharide donor **244** and monosaccharide acceptor **241** resulted in the formation of exclusively target product **246** (52% yield), which was then oxidized to sulfoxide **248**.

A series of target oligomannosides were synthesized by glycosylation of α-linked trisaccharide acceptor **250** with mono-, di- and trisaccharide donors, each being a thioglycoside – glycosyl sulfoxide pair. The glycosylation with thioglycosides was performed without preactivation, *i.e.*, by the addition of a catalytic amount of HOTf to a mixture of a donor, an acceptor and NIS, whereas when using sulfoxides as donors, the latter were preactivated with Tf_2O and the glycosylation was performed in the presence of 2,6-di-*tert*-butylpyridine. The application of a set of donors made it possible to examine the influence of their nature and conditions of their activation on the efficiency of β-mannosylation. The glycosylation with monosaccharide donors **240** and **249** gave mixtures of target β-linked product **251** and α-tetramannoside by-product **252** in 37% and 22% yields (in the case of thioglycoside **249**) and in 17% and 8% yields (in the case of sulfoxide **240**) (Scheme 36). The reaction of acceptor **250** with disaccharide donors **242** and **244** produced β-pentamannoside **253** in 65% and 37% yields, respectively. The glycosylation with trimannoside donors **246** and **248** proved to be most problematic. Thus, the glycosylation with the sulfoxide produced hexasaccharide **254** in 27% yield, while product **254** was not detected at all when using the thioglycoside. Therefore, the structure of the reaction counterparts has apparently a more considerable effect on the efficiency of β-mannosylation with mono- and oligosaccharide mannosyl donors compared to the influence of the type of the donor and glycosylation conditions.

The reactions of trisaccharide thioglycoside (**246**) and tetrasaccharide thioglycoside (**245**) with α-linked disaccharide acceptor **89** gave pentamannoside **258** and hexamannoside **259** (41% and 53% yields, respectively) (Scheme 37). Protected oligomannosides **251**, **253**, **254**, **258** and **259** were converted into free oligomannosides **255** – **257**, **260** and **261** by successive hydrogenation over $Pd(OH)_2/C$ and alkaline hydrolysis.

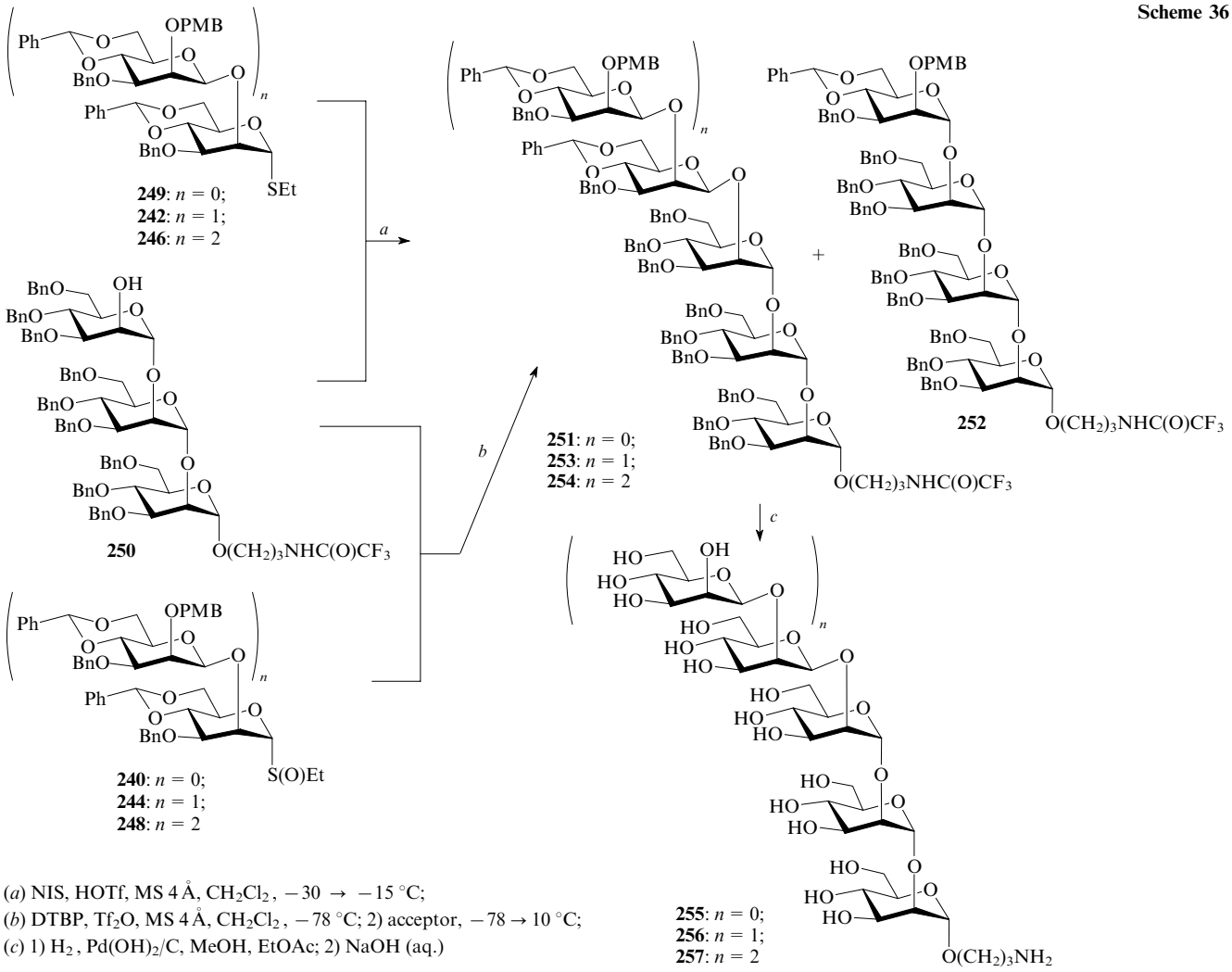
The approach utilizing the inversion of configuration at the C(2) atom in β-glucosides was also employed[56] to synthesize mixed (1→2)-linked mannoside chains. For instance, the assembly of α-trimannoside **263** was accomplished using mannosyl donor **262**. Then the coupling of trisaccharide **263** with glucosyl donor **264** gave tetrasac-

Scheme 35



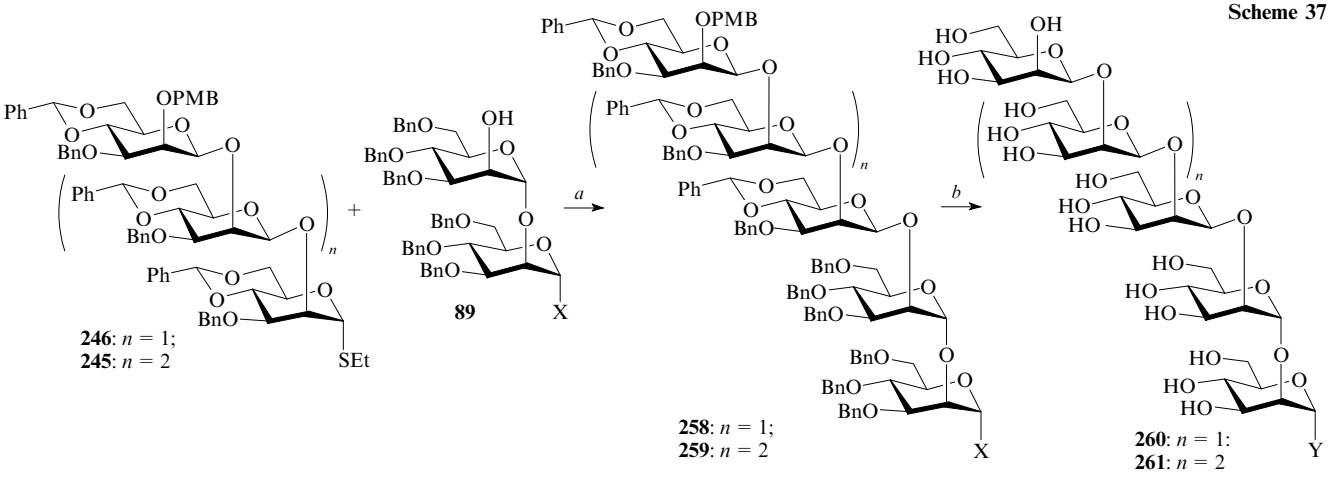
(*a*) 1) DTBP, Tf_2O, MS 4 Å, CH_2Cl_2, −78 °C; 2) appropriate acceptor, −78 → 10 °C; (*b*) DDQ, $CHCl_3$, H_2O; (*c*) m-CPBA, CH_2Cl_2, −60 °C; DTBMP is 2,6-di-*tert*-butyl-4-methylpyridine

Scheme 36



(*a*) NIS, HOTf, MS 4 Å, CH_2Cl_2, −30 → −15 °C;
(*b*) DTBP, Tf_2O, MS 4 Å, CH_2Cl_2, −78 °C; 2) acceptor, −78 → 10 °C;
(*c*) 1) H_2, $Pd(OH)_2$/C, MeOH, EtOAc; 2) NaOH (aq.)

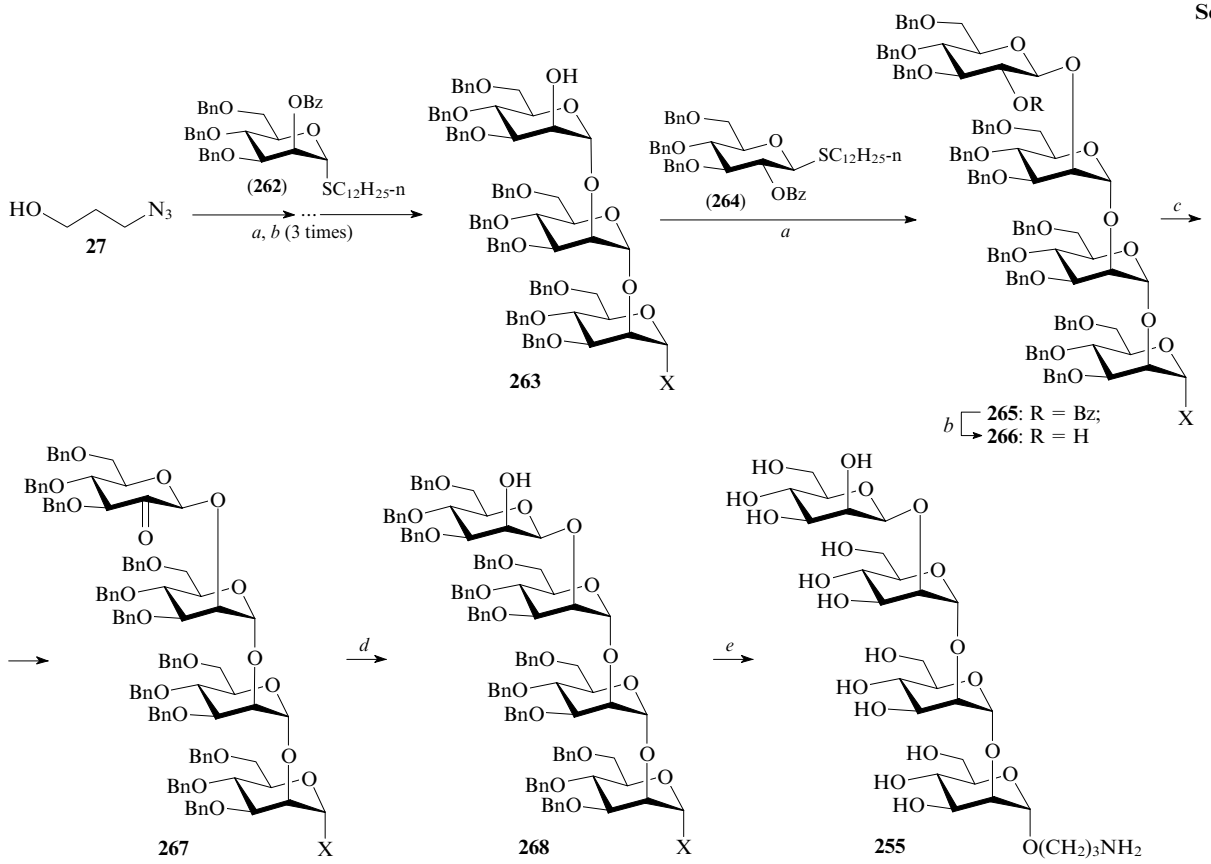
Scheme 37



(*a*) NIS, HOTf, MS 4 Å, CH_2Cl_2, −30 → −15 °C; (*b*) 1) H_2, $Pd(OH)_2$/C, MeOH, EtOAc; 2) NaOH (aq.); X = $O(CH_2)_3NHC(O)CF_3$, Y = $O(CH_2)_3NH_2$

charide **265** containing the terminal β-glucose residue. The removal of the benzoyl group and oxidation of compound **266** at the C(2) atom with Dess – Martin (DMP) periodinane followed by reduction of the keto group in oxidation product **267** with $NaBH_4$ afforded protected tetramannoside **268** in 67% yield over three steps. The final step involved the complete deprotection with the simultaneous reduction of the azido group to the amino group to form free tetrasaccharide **255** (Scheme 38).

Scheme 38



(*a*) NIS, HOTf, MS 4 Å, CH_2Cl_2, 0 °C; (*b*) MeONa, MeOH; (*c*) DMP, CH_2Cl_2; (*d*) $NaBH_4$, MeOH, CH_2Cl_2; (*e*) H_2, Pd/C, HCl (aq.), MeOH; X = $O(CH_2)_3N_3$

IV. Synthesis of linear oligosaccharides corresponding to fragments of β-(1→3)-glucan from *Candida* and *Aspergillus*

The previous review published in 2015[57] summarizes research on the synthesis of linear β-(1→3)-oligoglucosides reported up to 2014. The present review includes only works published later. In most studies devoted to the synthesis of such structures, the oligosaccharide chain elongation was performed using the following donors: monosaccharides (or longer homologues), *e.g.*, compound **271** (Scheme 39), which contain an orthogonal protecting group at the O(C3) atom and the acyl group at the O(C2) atom favourable for the formation of a β-linked product, as well as benzylidene groups at the 4 and 6 positions.

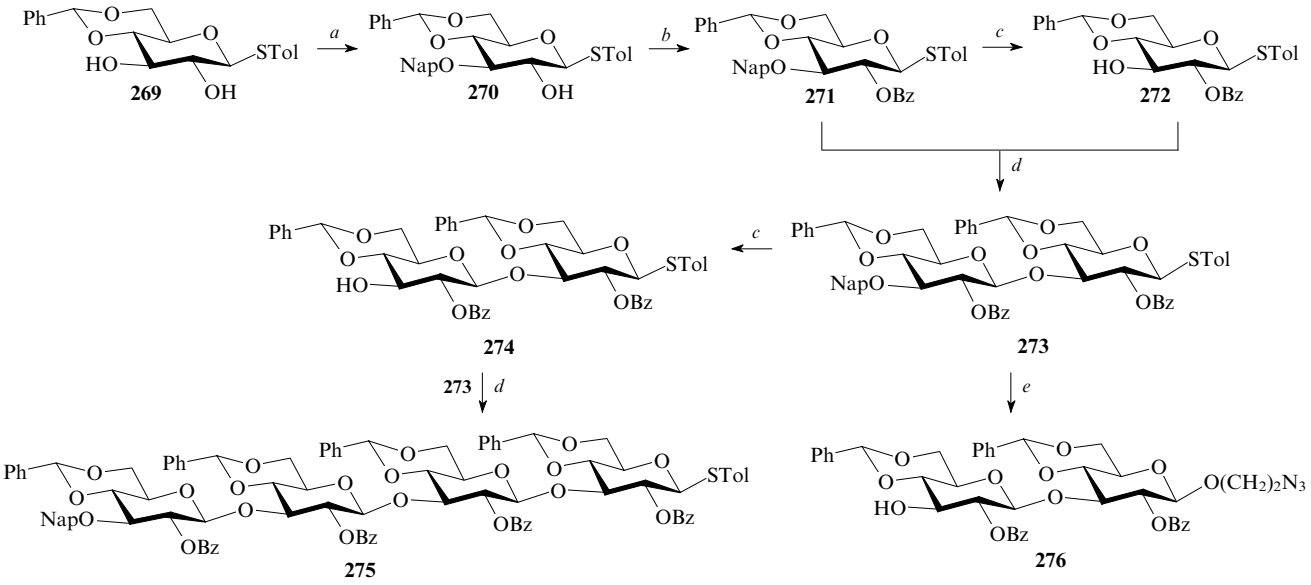
Liao *et al.*[58] described a synthetic building block containing the 2-naphthylmethyl substituent at the O(C3) atom and the participating benzoyl protecting group at the O(C2) atom. The preparation of this building block from partially protected thioglycoside **269** included the selective introduction of the 2-naphthylmethyl protecting group at the 3 position (compound **270**) followed by the benzoylation of the hydroxyl group that remained intact (see Scheme 39). Then disaccharide (**273**) and tetrasaccharide (**275**) donor building blocks were synthesized and used for the assembly of oligoglucosides composed of 6 to 12 monosaccharide units.

The disaccharide building block was prepared as follows. The Nap group of thioglycoside **271** was removed by the treatment with DDQ giving rise to acceptor **272**. The preactivation-based glycosylation of the latter with donor **271** produced disaccharide thioglycoside **273** in 90% yield. After the removal of the Nap group, acceptor **274** was condensed with disaccharide **273** under the same preactivation conditions to form a tetrasaccharide donor (85% yield). The reaction of thioglycoside **273** with azidoethanol followed by the removal of the Nap group afforded also the starting disaccharide building block **276** containing the 2-azidoethyl spacer.

The oligosaccharide chain elongation was accomplished in the same way by glycosylation of different acceptors with donors **273** or **275** followed by the Nap deprotection without the isolation of the glycosylation product (Scheme 40). For instance, the coupling of disaccharides **273** and **276** produced tetrasaccharide **277** (90% yield), which was then elongated by 2 and 4 glucose residues to form hexasaccharide **278** (87%) and octasaccharide **279** (81%). The latter was, in turn, glycosylated with donors **273** and **275**, resulting in the formation of oligosaccharides containing 10 (**280**, 80% yield) and 12 (**281**, 85% yield) glucoside units. The complete deprotection of these oligosaccharides with the simultaneous reduction of the azide group gave free glucosides **282** – **285**, which were then used for the design of an antifungal vaccine.

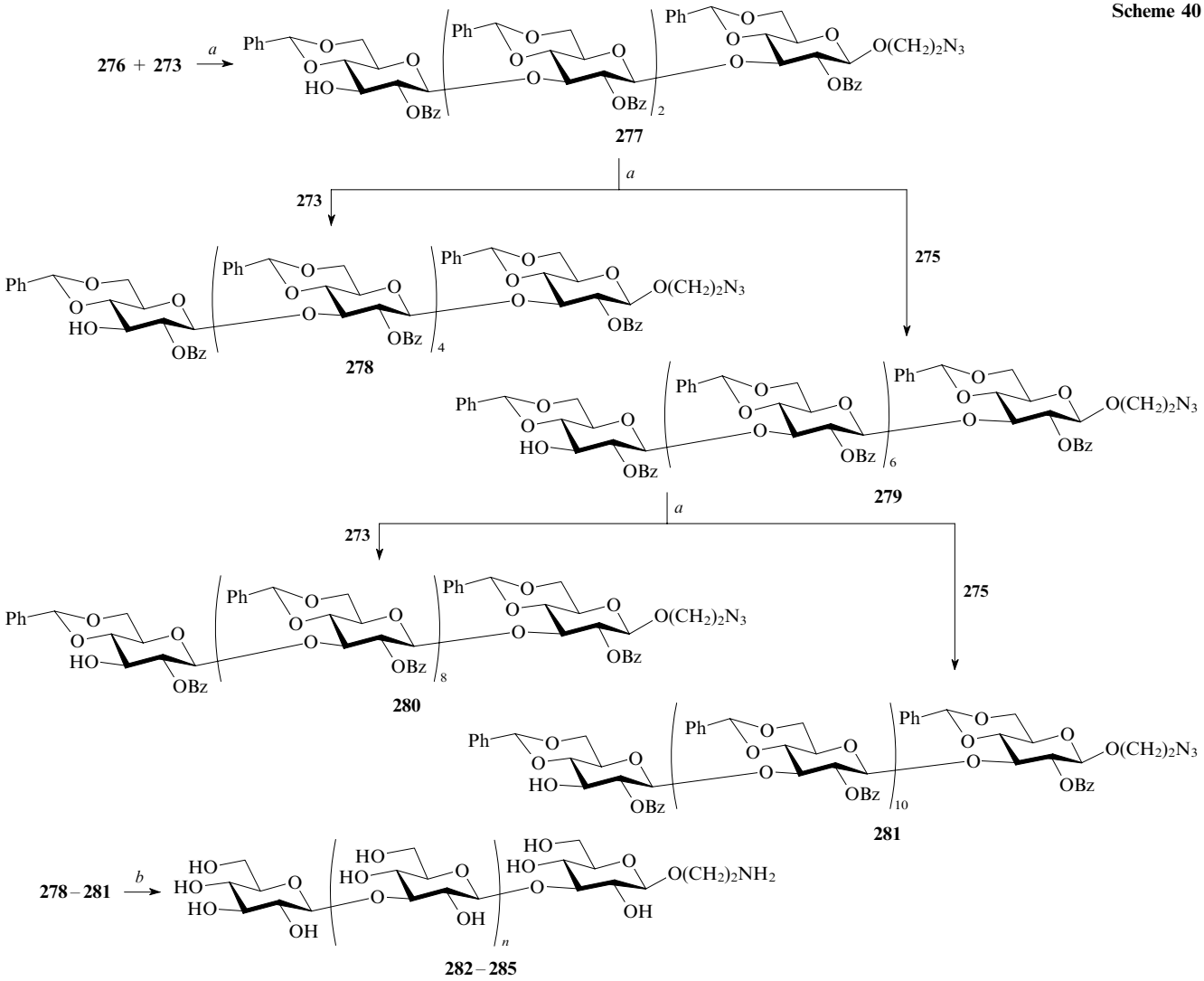
The publication[59] is notable for the attempt to develop an original approach to the synthesis of β-(1→3)-oligoglucosides. However, the authors had to return to the classical synthetic building blocks. Initially, diacetoneglucose **286**

Scheme 39



(*a*) 1) Bu^n_2SnO, PhMe, Δ; 2) NapBr, CsF, DMF, 70 °C; (*b*) BzCl, Et_3N, CH_2Cl_2; (*c*) DDQ, CH_2Cl_2, H_2O; (*d*) AgOTf, TTBP, TolSCl, MS 4 Å, CH_2Cl_2, −78 °C; (*e*) 1) $N_3(CH_2)_2OH$, AgOTf, TTBP, TolSCl, MS 4 Å, CH_2Cl_2, −78 °C; 2) DDQ, CH_2Cl_2, H_2O

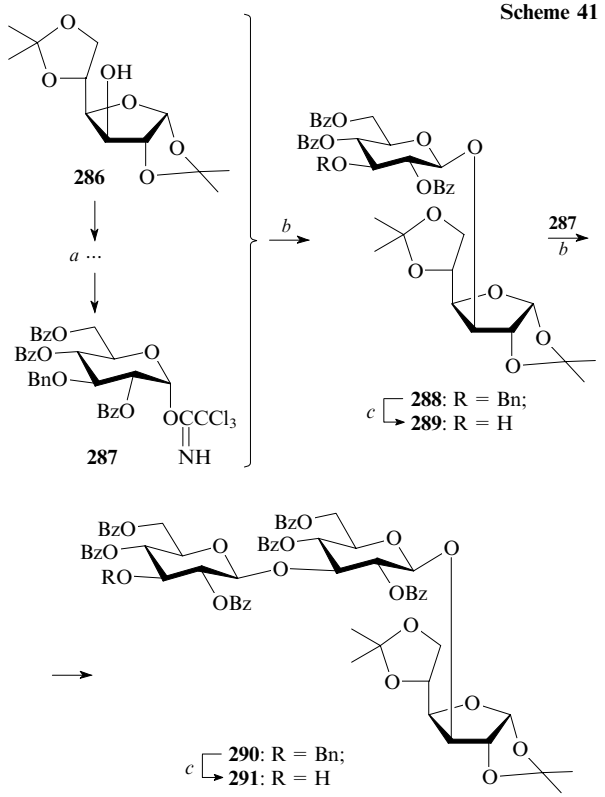
Scheme 40



(*a*) 1) AgOTf, TTBP, TolSCl, MS 4 Å, CH_2Cl_2, −78 °C; 2) DDQ, CH_2Cl_2, H_2O; (*b*) 1) Zn, AcOH, CH_2Cl_2; 2) AcOH, H_2O, 60 °C; 3) NaOH, Bu^tOH, H_2O; n = 4 (**282**), 6 (**283**), 8 (**284**), 10 (**285**)

was converted in five steps into imidate **287** containing the temporary benzyl protecting group at the O(C3) atom and benzoyl groups in other positions. Imidate **287** was used to glycosylate **286**. The removal of the benzyl group from

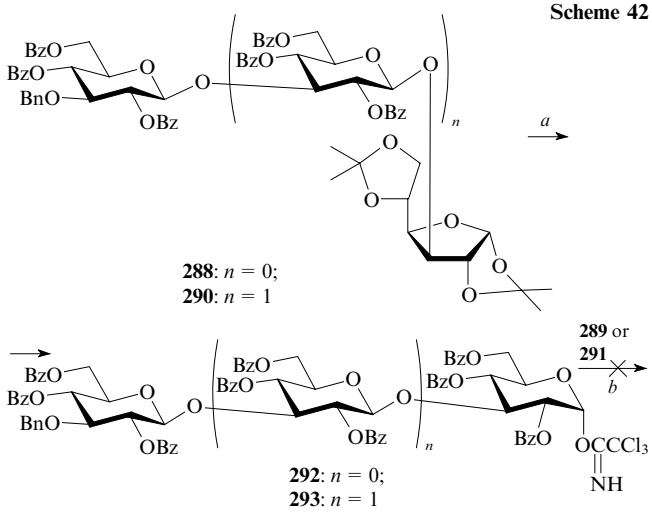
Scheme 41



(*a*) 1) BnCl, NaH, DMF; 2) 1 M HCl, dioxane; 3) BzCl, Py; 4) $MeNH_2$, CH_2Cl_2, THF; 5) CCl_3CN, DBU, CH_2Cl_2; (*b*) TMSOTf, MS 4 Å, CH_2Cl_2; (*c*) H_2, Pd/C, CH_2Cl_2, MeOH

reaction product **288** through hydrogenation (93% yield) gave acceptor **289**, which was repeatedly glycosylated with the same donor. After the benzyl deprotection of trisaccharide **290**, acceptor **291** was obtained (Scheme 41).

Scheme 42

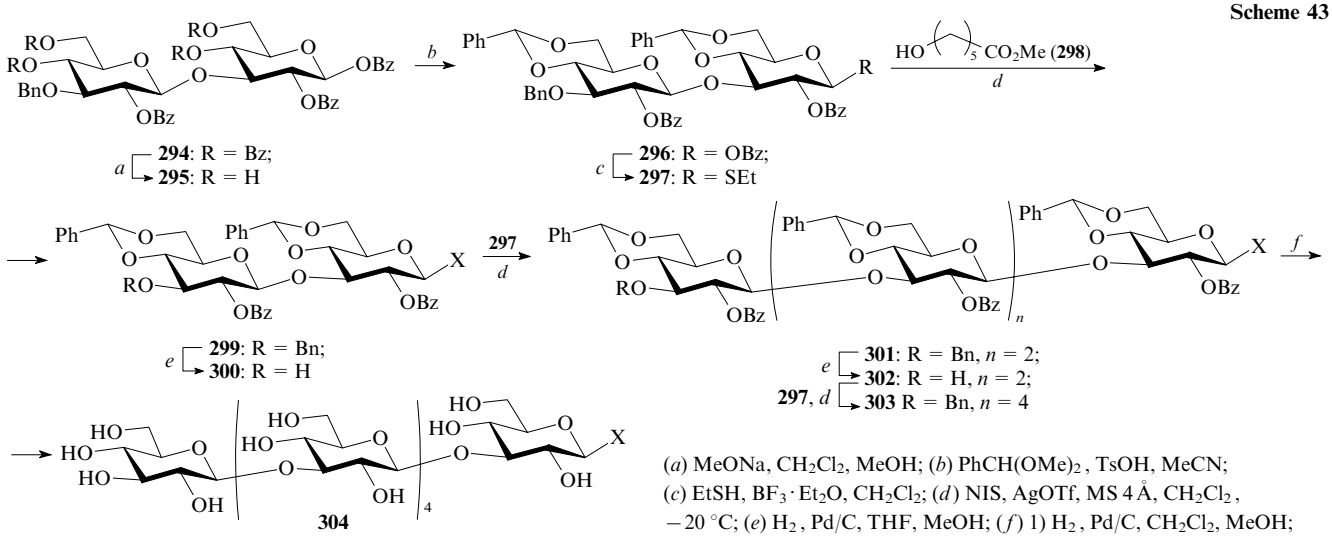


(*a*) 1) 1 M HCl, dioxane; 2) BzCl, Py; 3) $MeNH_2$, CH_2Cl_2, THF; 4) CCl_3CN, DBU, CH_2Cl_2; (*b*) TMSOTf, MS 4 Å, CH_2Cl_2

Since Elsaidi *et al.*[59] planned to synthesize hexaglucoside, trisaccharide **290** was converted in four steps, without the isolation of intermediates, into donor **293** in an overall yield of 78% (Scheme 42). However, an attempt to couple this donor with trisaccharide acceptor **291** failed despite variations in glycosylation conditions. Attempts to glycosylate disaccharide acceptor **289** with donor **293** were also unsuccessful. Besides, the authors failed to prepare glycosylation products of acceptors **289** and **291** using disaccharide imidate **292**; in the case of trisaccharide acceptor **291**, even the glycosylation with monosaccharide donor **287** was unsuccessful.

Hence, the authors returned to the classical strategy but employing the already available compounds. For this purpose, the benzoyl groups at the 4 and 6 positions in both glucose residues of disaccharide **294** derived from compound **288** were selectively removed to form compound **295**. The free hydroxyl groups in the latter were protected with benzylidene moieties. Disaccharide **296** was converted into thioglycoside **297** by the reaction with EtSH in the presence of $BF_3 \cdot Et_2O$. The condensation of compound **297** with methyl 6-hydroxyhexanoate (**298**) afforded spacer-

Scheme 43



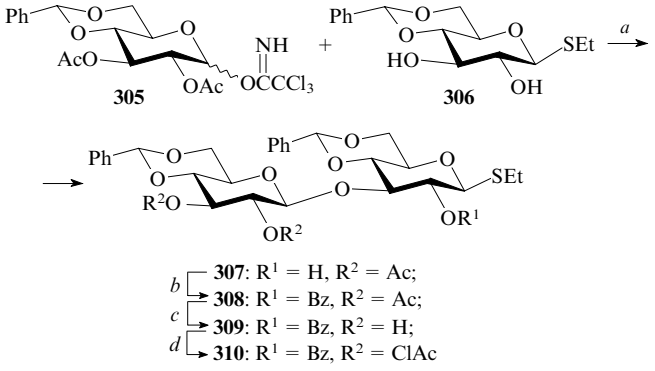
(*a*) MeONa, CH_2Cl_2, MeOH; (*b*) $PhCH(OMe)_2$, TsOH, MeCN; (*c*) EtSH, $BF_3 \cdot Et_2O$, CH_2Cl_2; (*d*) NIS, AgOTf, MS 4 Å, CH_2Cl_2, −20 °C; (*e*) H_2, Pd/C, THF, MeOH; (*f*) 1) H_2, Pd/C, CH_2Cl_2, MeOH; 2) MeONa, MeOH, 3) H_2, $Pd(OH)_2$/C, AcOH; Ts is *p*-toluenesulfonyl (tosyl); X = $O(CH_2)_5CO_2Me$

containing diglucoside **299** in 89% yield. The hydrogenation of **299** resulted in the removal of the benzyl protecting group to form acceptor **300**. The twofold repetition of the glycosylation with donor **297** (91% and 73% yields) through the intermediate benzyl deprotection of tetraglucoside **301** (compound **302**) gave target protected hexasaccharide **303**. In the step of deprotection, the authors again experienced difficulties and had to repeat the first reaction under more drastic conditions (in acetic acid) after the hydrogenation and methanolysis, with the result that product **304** was isolated in only 24% yield (Scheme 43).

A series of linear β-(1→3)-linked glucooligosaccharides were synthesized at the Laboratory of Glycoconjugate Chemistry of the ZIOC RAS.[60] The approach was based on the possibility of regioselective glycosylation of the 3-OH group in 4,6-O-benzylidene-protected β-glucopyranoside diols. This made it possible to avoid the need of differentiating protecting groups at the 2 and 3 positions and, consequently, to develop a more efficient synthetic scheme. A similar approach has been applied earlier in the study,[61] in which levulinic acid residues served as temporary protecting groups at the 2 and 3 positions of glycosyl donors. In the method developed by Yashunsky *et al.*,[60] chloroacetyl groups were chosen for protection. Since the goal was to synthesize a series of oligoglucosides that differ in the length by two monosaccharide residues the chain elongation reaction was performed with a disaccharide glycosyl donor, which was synthesized as follows. The regioselective glycosylation of diol **306** with imidate **305** gave β-(1→3)-linked disaccharide **307** (55% yield), and the corresponding β-(1→2)-regioisomer was isolated in 8% yield. The free 2-OH group in diglucoside **307** was benzoylated to form target donor building block **308** (Scheme 44).

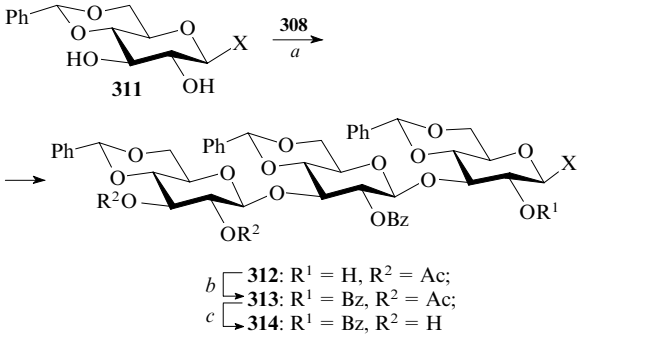
The glycosylation of spacer-containing glucoside **311** with disaccharide donor **308** also gave (1→3)-trisaccharide **312** as the major product (the overall yield was 54%; the

Scheme 44



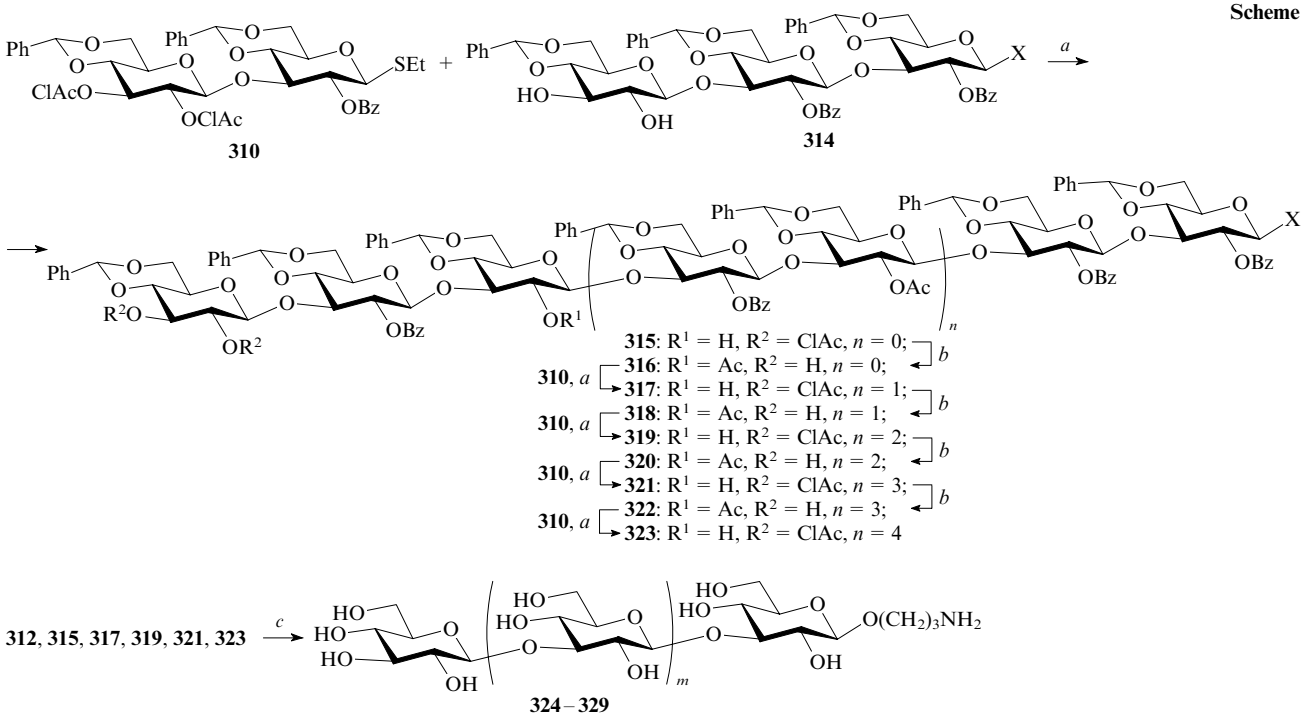
(*a*) TMSOTf, CH_2Cl_2, −30 °C; (*b*) 1) BzCl, Py; 2) $NH_2NH_2 \cdot AcOH$, DMF; (*c*) $NH_2NH_2 \cdot H_2O$, CH_2Cl_2, MeOH; (*d*) ClAcCl, 2,4,6-collidine, CH_2Cl_2

Scheme 45



(*a*) NIS, HOTf, MS AW-300, CH_2Cl_2, −30 °C; (*b*) BzCl, Py; (*c*) $NH_2NH_2 \cdot H_2O$, CH_2Cl_2, MeOH; X = $O(CH_2)_3NHCbz$

Scheme 46



(*a*) NIS, TfOH, MS AW-300, CH_2Cl_2, −30 °C; (*b*) 1) AcCl, Py; 2) $(NH_2)_2C(S)$, 2,4,6-collidine, EtOAc, EtOH; (*c*) 1) 1 M HCl, $CHCl_3$, MeOH, 40 – 45 °C; 2) MeONa, MeOH, then H_2O, 40 – 45 °C; 3) H_2, $Pd(OH)_2/C$, MeOH (aq.); *m* = 1 (**324**), 3 (**325**), 5 (**326**), 7 (**327**), 9 (**328**), 11 (**329**); X = $O(CH_2)_3NHCbz$

yield of the 2-O-glycosylation product was 10%). In compound **312**, the free hydroxyl group was benzoylated, and the acetyl groups in triglucoside **313** were selectively removed by the treatment with hydrazine hydrate. This procedure gave trisaccharide acceptor **314** in 79% yield (Scheme 45). However, the further chain elongation was performed by employing donor **310** bearing chloroacetyl groups because the authors were concerned about the decrease in selectivity of deacetylation with increasing number of benzoyl groups as the oligosaccharide chain length increases. Thus, disaccharide **308** was quantitatively deacetylated to form diol **309**, and the chloroacetylation of the latter produced compound **310** (see Scheme 44).

The oligosaccharide chain elongation was performed by the successive glycosylation of acceptors containing free OH groups at the 2 and 3 positions with donor **310**. Then the free 2-OH group of the glycosylated residue of the oligosaccharides was acetylated, and chloroacetyl groups were removed by the treatment with thiourea to form a new glycosyl acceptor (compounds **316**, **318**, **320** and **322** in Scheme 46). It should be noted that, as opposed to monosaccharide 2,3-diols **306** and **311**, the glycosylation of oligosaccharide 2,3-diols, which contain a bulky carbohydrate substituent in the anomeric position of the glycosylated residue of glucose, did no give 2-O-glycosylation products, while the yields of target products were much higher (80% – 95%). This approach enabled the successive synthesis of oligoglucosides **315**, **317**, **319**, **321** and **323**. The complete deprotection gave rise to a series of free oligomers **324** – **329** containing an odd number of monosaccharide units.

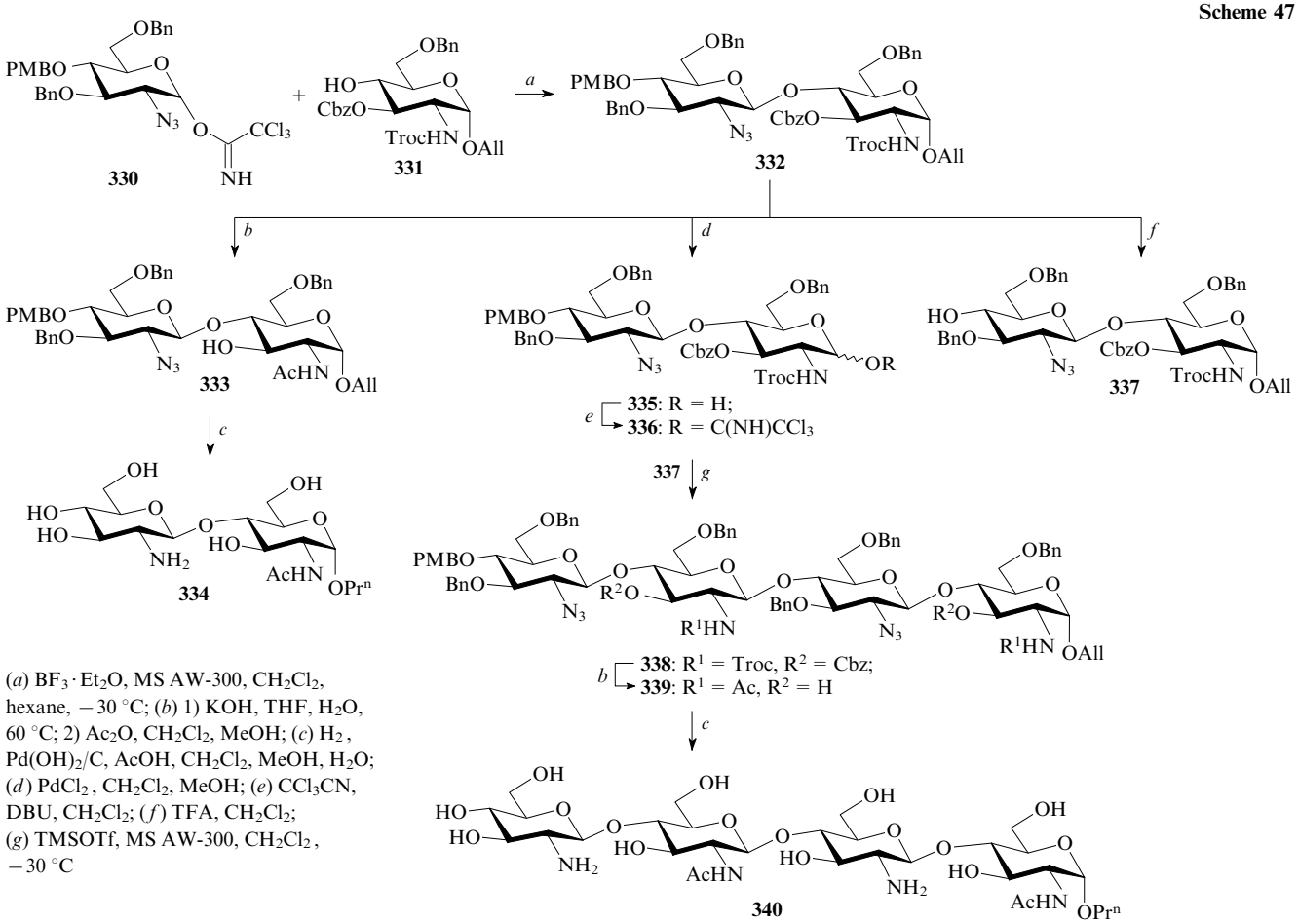
V. Synthesis of chitooligosaccharides

Major advances in the synthesis of chitooligosaccharides were summarized in the review published in 2014.[62] Therefore, the present review includes only studies published after that date.

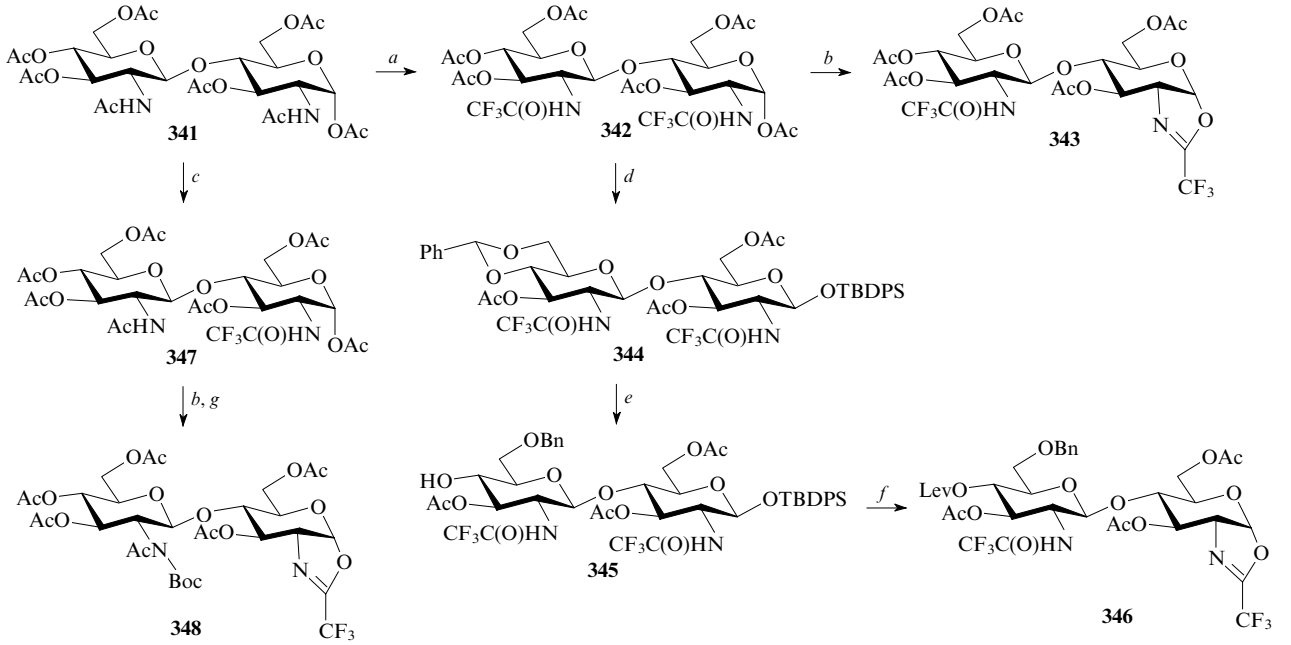
Bedini *et al.*[63] reported the synthesis of partially N-acetylated chitooligosaccharides composed of two or four glucosamine residues. In the starting synthetic building blocks, 2-azido derivatives were employed as precursors of nonacetylated glucosamine; the amino group in precursors of *N*-acetylglucosamine was protected with the *N*-trichloroethoxycarbonyl (Troc) group. Disaccharide **332** was prepared by glycosylation of allyl glycoside **331** with trichloroacetimidate **330** (71% yield) (Scheme 47). Then Troc and Cbz groups were removed by alkaline hydrolysis, and the free amino group was acetylated. Compound **333** was subjected to catalytic hydrogenation with the simultaneous reduction of the azido and allyl groups, resulting in the formation of disaccharide propyl glycoside **334**.

The donor and acceptor building blocks required for the construction of tetrasaccharide **340** were synthesized from disaccharide **332**. The removal of the allyl group from the anomeric position and the reaction of the resulting hemiacetal **335** with trichloroacetonitrile gave donor building block **336**; acceptor **337** was prepared by the removal of the *p*-methoxybenzyl group. The coupling of donor **336** with acceptor **337** produced protected tetrasaccharide **338** in 72% yield. The latter was converted into target free tetrasaccharide **340** through the intermediate formation of com-

Scheme 47

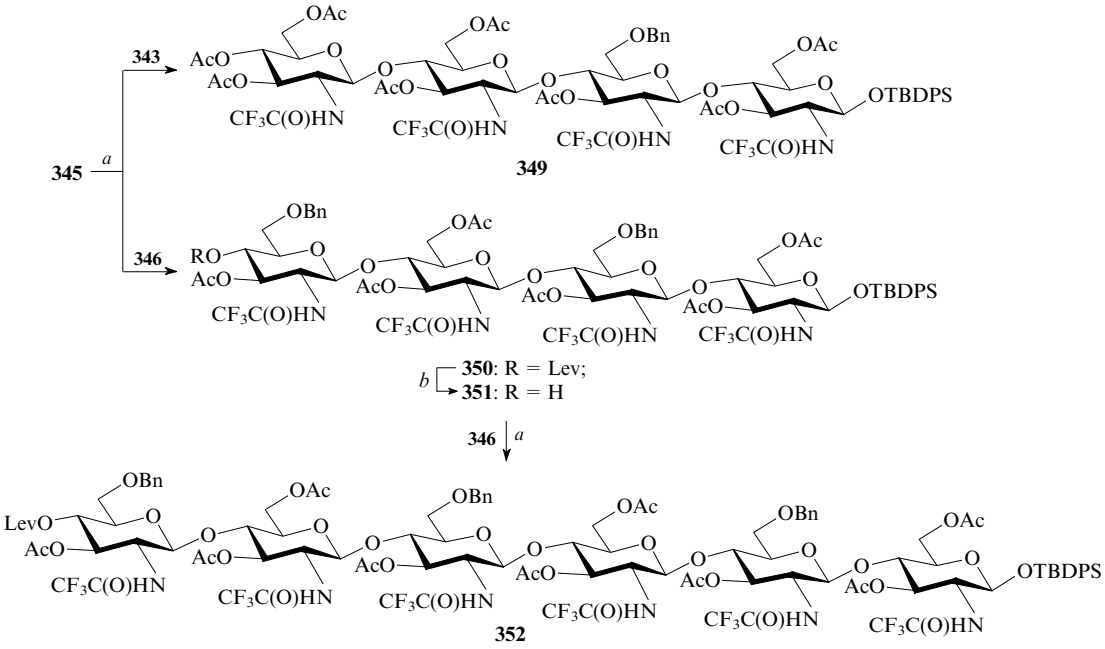


Scheme 48



(*a*) TFAA, Py, 135 °C; (*b*) 1) $NH_2NH_2 \cdot AcOH$, DMF, 55 °C; 2) Ms_2O, Et_3N, MeCN; (*c*) TFAA, MeCN, 135 °C; (*d*) 1) $NH_2NH_2 \cdot AcOH$, DMF, 55 °C, 2) TBDPSCl, imidazole, DMF; 3) MeONa, MeOH; 4) PhCHO, $ZnCl_2$; 5) Ac_2O, Py; (*e*) Et_3SiH, TFA, MS AW-300, 0 °C → rt; (*f*) 1) Lev_2O, DMAP, Py; 2) TBAF, AcOH, THF, 0 °C → rt; 3) Ms_2O, Et_3N, MeCN; (*g*) Boc_2O, DMAP, THF, Δ; TFFA is trifluoroacetic anhydride, Ms is methanesulfonyl (mesyl), Boc is *tert*-butoxycarbonyl

Scheme 49



(*a*) TMSOTf, CH_2Cl_2; (*b*) $NH_2NH_2 \cdot AcOH$, CH_2Cl_2, MeOH

pound **339** *via* a reaction sequence similar to that described for disaccharide **332**.

An original approach to the synthesis of chitooligosaccharides was proposed by Despras *et al.*[64] The method was based on the utilization of chitobiose and chitotriose peracetates, which were produced through acetolysis of chitosan, as building blocks for the construction of longer oligosaccharides. Chitosan acetolysis has long been known as a method for the preparation of lower chitooligosaccharide peracetates. However, these derivatives have not been commonly used because glycosyl donors — 1,2-(2-methyloxazolines) — synthesized from N-acetylated amino sugars are poorly reactive and are of little value for glycosylation of secondary hydroxyl groups in carbohydrates. The authors addressed these limitations by replacing all N-acetyl groups with N-trifluoroacetyl groups *via* the recently discovered transacylation reaction under mild conditions.[65]

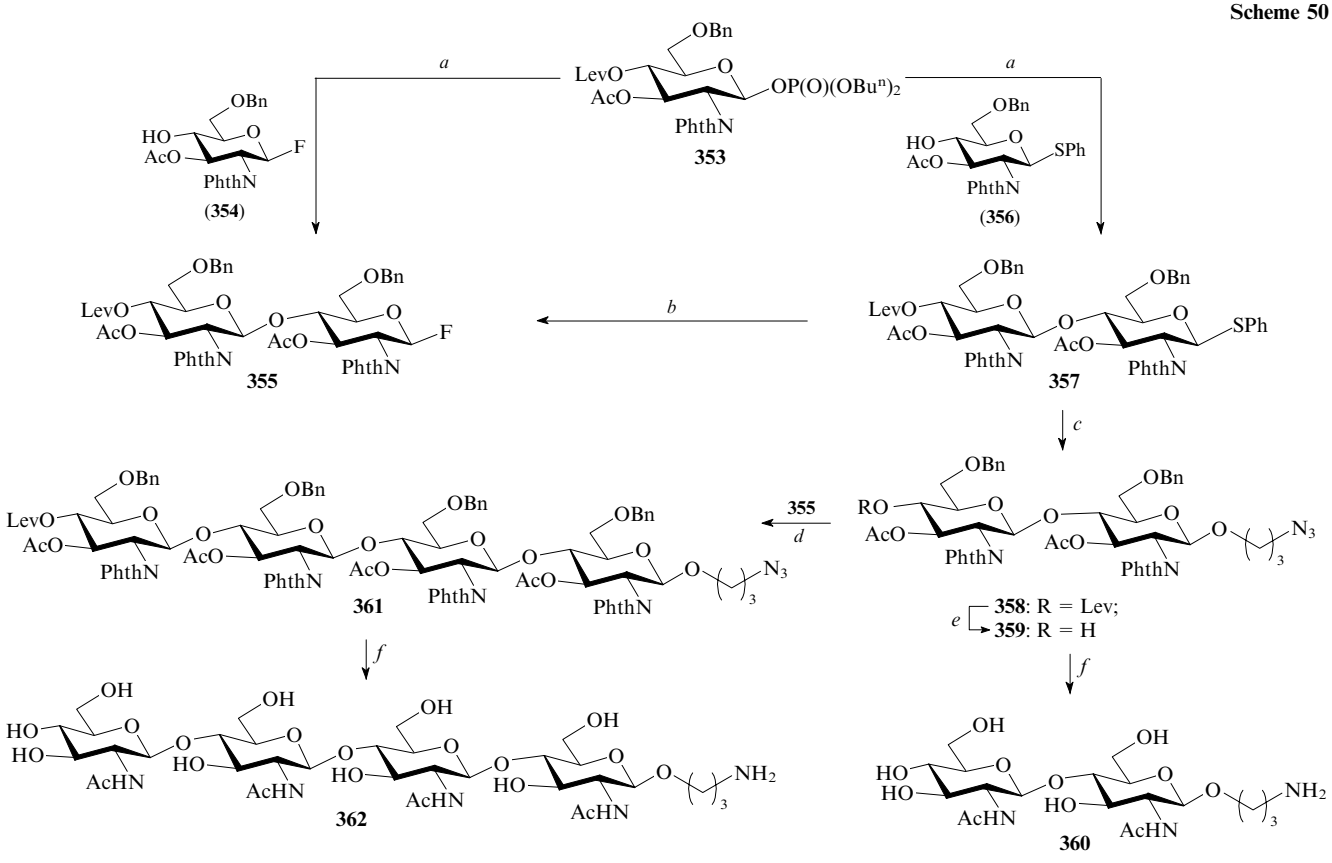
As an illustration of this approach, let us consider the construction of chitohexaose from chitobiose peracetate **341** (Schemes 48 and 49). The replacement of N-acetyl groups by trifluoroacetyl moieties giving derivative **342** (89% yield) was accomplished by the treatment of compound **341** with trifluoroacetic anhydride in pyridine at 135 °C for 15 – 30 min. It should be noted that the latter reaction in acetonitrile performed for 10 min resulted mainly in the replacement of the N-acetyl group only in the reducing glucosamine residue of **347** (69% yield). The removal of the anomeric acetyl group from disaccharide **342** followed by the treatment of intermediate hemiacetal with methanesulfonic anhydride and Et_3N gave 1,2-(2-trifluoromethyloxazoline) **343**. Compound **342** was converted into derivative **344** by the successive removal of the anomeric acetyl group, silylation of the free OH group, deacetylation, introduction of the 4,6-O-benzylidene moiety and acetylation. The reductive cleavage of the benzylidene ring in **344** gave glycosyl acceptor building block **345**. Derivative **345** was also used as the starting material for the synthesis of oxazoline **346** bearing the selectively removable levulinoyl protecting group at the O(C4′) atom. The latter compound served as the donor for chain elongation in the synthesis of hexasaccharide.

The authors demonstrated for the first time that, as opposed to 2-methyl analogues, 2-trifluoromethyloxazolines are highly reactive glycosyl donors, as illustrated by the synthesis of chitohexaose **352** (see Scheme 49). The model reaction of acetylated oxazoline **343** with acceptor **345** in the presence of TMSOTf smoothly produced tetrasaccharide **349** (78% yield). The glycosylation of compound **345** with selectively protected donor **346** gave tetrasaccharide **350**, which was converted into acceptor **351** by removing the levulinic acid moiety. The final glycosylation of tetrasaccharide **351** with donor **346** afforded target hexasaccharide **352**.

Disaccharide **347** containing different N-protecting groups was converted into oxazoline **348** (see Scheme 48), which was employed to glycosylate acceptor **345** and its trisaccharide analogue derived from chitotriose peracetate. Tetra- and pentasaccharides thus prepared were used in the synthesis enabling access to chitooligosaccharides containing a free amino group in the terminal glucosamine residue.

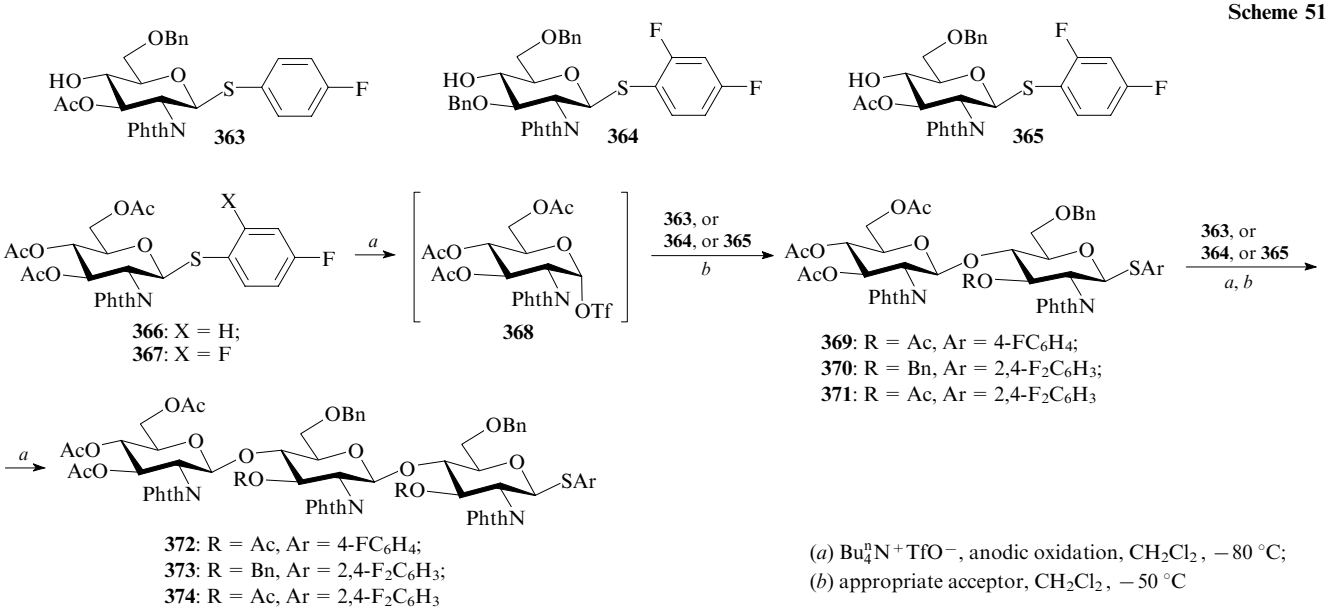
Nilo *et al.*[66] developed a method for the synthesis of spacer-containing chitotetraoside *via* the [2 + 2] scheme. The amino group was protected with a phthaloyl moiety, the hydroxyl groups at the 3 and 6 positions were protected with acetyl and benzyl groups, respectively, and the levulinic acid moiety served as temporary protection of the 4-OH group. Disaccharide donor building blocks **355** and **357** were prepared by orthogonal glycosylation of fluoride **354** and thioglycoside **356** with phosphate **353** in the presence of TMSOTf (85% and 93% yields, respectively). An alternative route to fluoride **355** was based on the reaction of thioglycoside **357** with DAST and *N*-bromosuccinimide (65% yield). The glycosylation of 3-azidopropanol with thioglycoside **357** in the presence of NIS and HOTf gave spacer-containing disaccharide **358**. The levulinoyl deprotection of compound **358** and glycosylation of the resulting acceptor **359** with fluoride **355** resulted in the isolation of target tetrasaccharide **361** in 55% yield. The authors did not comment on the reasons for using different

Scheme 50



(*a*) TMSOTf, MS 4 Å, CH_2Cl_2, −30 °C; (*b*) DAST, NBS, CH_2Cl_2, −10 °C → rt; (*c*) $N_3(CH_2)_3OH$, NIS, HOTf, MS 4 Å, CH_2Cl_2, −40 °C → rt; (*d*) Cp_2HfCl_2, AgOTf, MS 4 Å, CH_2Cl_2, −60 °C; (*e*) $NH_2NH_2 \cdot AcOH$, CH_2Cl_2; (*f*) 1) $NH_2(CH_2)_2NH_2$, EtOH, 60 °C; 2) Ac_2O, Py; 3) NH_3, MeOH; 4) H_2, Pd/C, MeOH; DAST = Et_2NSF_3, PhthN is phthalimido

Scheme 51



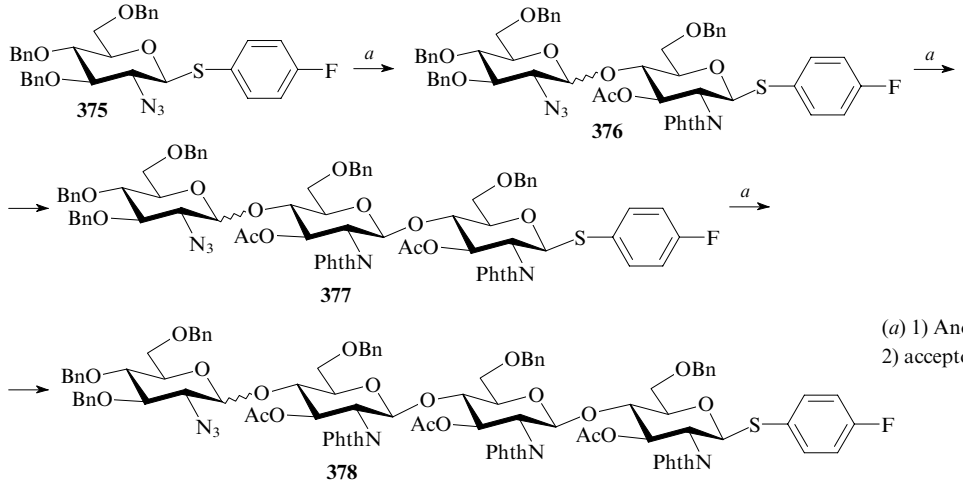
glycosyl donors in the first (**357**) and second (**355**) glycosylation reactions. Free chitooligosaccharide 3-aminopropyl glycosides **360** and **362** were synthesized from protected precursors **359** and **361** by the phthaloyl deprotection, N-acetylation, reduction of the azido group and debenzylation (Scheme 50).

Nokami *et al.*[67] reported an unusual electric current-mediated preactivation of thioglycosides, which makes it possible to perform the assembly of an oligosaccharide chain in an automated manner. Thioglycosides were used as acceptors, thus allowing chain extension starting at the non-reducing end, without deprotecting the O(C4) atom in intermediates. The process was performed as follows. According to the authors, after passage of electric current at −80 °C, the starting thioglycoside was converted into intermediate glycosyl triflate **368**. Then the acceptor was added and the temperature was raised to −50 °C. After the completion of the reaction, the process was repeated using a new glycosyl acceptor. Two acetylated thioglycosides (**366** and **367**) served as the starting terminal building blocks. Thioglycosides **363**, **364** and **365**, which differ in the nature of the protecting group at the O(C3) atom and the substituent in the aglycon, were used as acceptor building blocks. Two successive chain elongation reactions with each acceptor, which were performed according to the above algorithm, produced first disaccharides **369** – **371** and then trisaccharides **372**, **373** and **374** in 58%, 55% and 41% yields, respectively, over two steps (Scheme 51).

Tetrasaccharide **378** containing the 2-azido-2-deoxyglucose residue at the non-reducing end was synthesized in a similar manner, which allowed the differentiation of amino groups in the oligosaccharide. In the first step of this process, the reaction of benzylated donor **375** with thioglycoside **363** afforded a mixture of anomers **376** in 82% yield in the ratio $\alpha:\beta = 16:84$. This mixture was used, without separation, in a series of successive glycosylation reactions to prepare trisaccharide **377** and tetrasaccharide **378** (28% yield over three steps) as a mixture of α- and β-anomers in a 13 : 87 ratio (Scheme 52).

A series of chitooligosaccharide 2-aminoethyl glycosides composed of an odd number (3, 5, 7) of units were synthesized at the Laboratory of Glycoconjugate Chemistry of the ZIOC RAS.[68] The oligosaccharide chain elongation was accomplished starting at the reducing end with the

Scheme 52



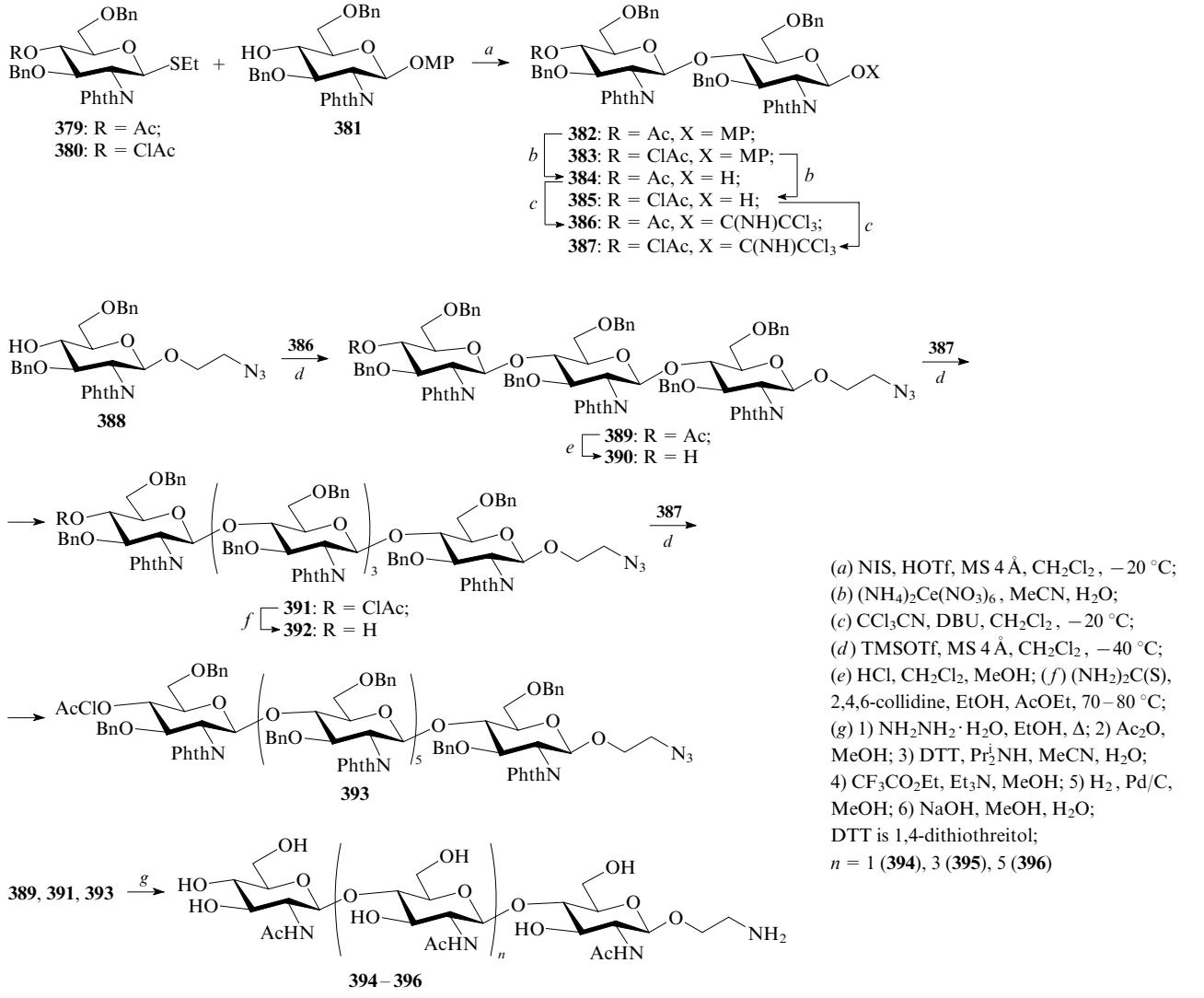
participation of disaccharide trichloroacetimidate donors containing phthaloyl-protected amino groups and permanent benzyl protecting groups at the oxygen atoms in the 3 and 6 positions. It was initially supposed to utilize an acetyl group as temporary protection at the O(C4) atom. Within the framework of this scheme, the coupling of thioglycoside **379** with acceptor **381** was employed to prepare disaccharide **382** in 90% yield. The replacement of the anomeric *p*-methoxyphenyl group in the latter by the trichloroacetimidoyl group afforded disaccharide donor **386**, with the reaction proceeding through the formation of hemiacetal **384** (Scheme 53).

The glycosylation of acceptor **388** with imidate **386** produced trisaccharide **389** in 76% yield. The subsequent acetyl deprotection by acidic methanolysis giving trisaccharide acceptor **390** proceeded slowly (5 – 6 days) and was not highly efficient (product yield was 70%). The acetyl deprotection of pentasaccharide, which was prepared by the coupling of compound **390** with donor **386**, was even less efficient (57% yield). Hence, the authors decided against using the acetyl group as temporary protection at the O(C4) atom. The chain elongation of compound **390** was performed using donor **387** bearing the chloroacetyl group. This donor was prepared from donor **380** and acceptor **381** by the following scheme: *p*-methoxyphenyl glycoside **383** → hemiacetal **385** → trichloroacetimidate **387** (similar to that for compound **386**). The reaction of donor **387** with trisaccharide **390** afforded pentasaccharide **391** (58% yield). The removal of the chloroacetyl group from the latter proceeded with 78% yield. Acceptor **392** thus synthesized was again glycosylated with donor **387** to form heptasaccharide **393** (68% yield).

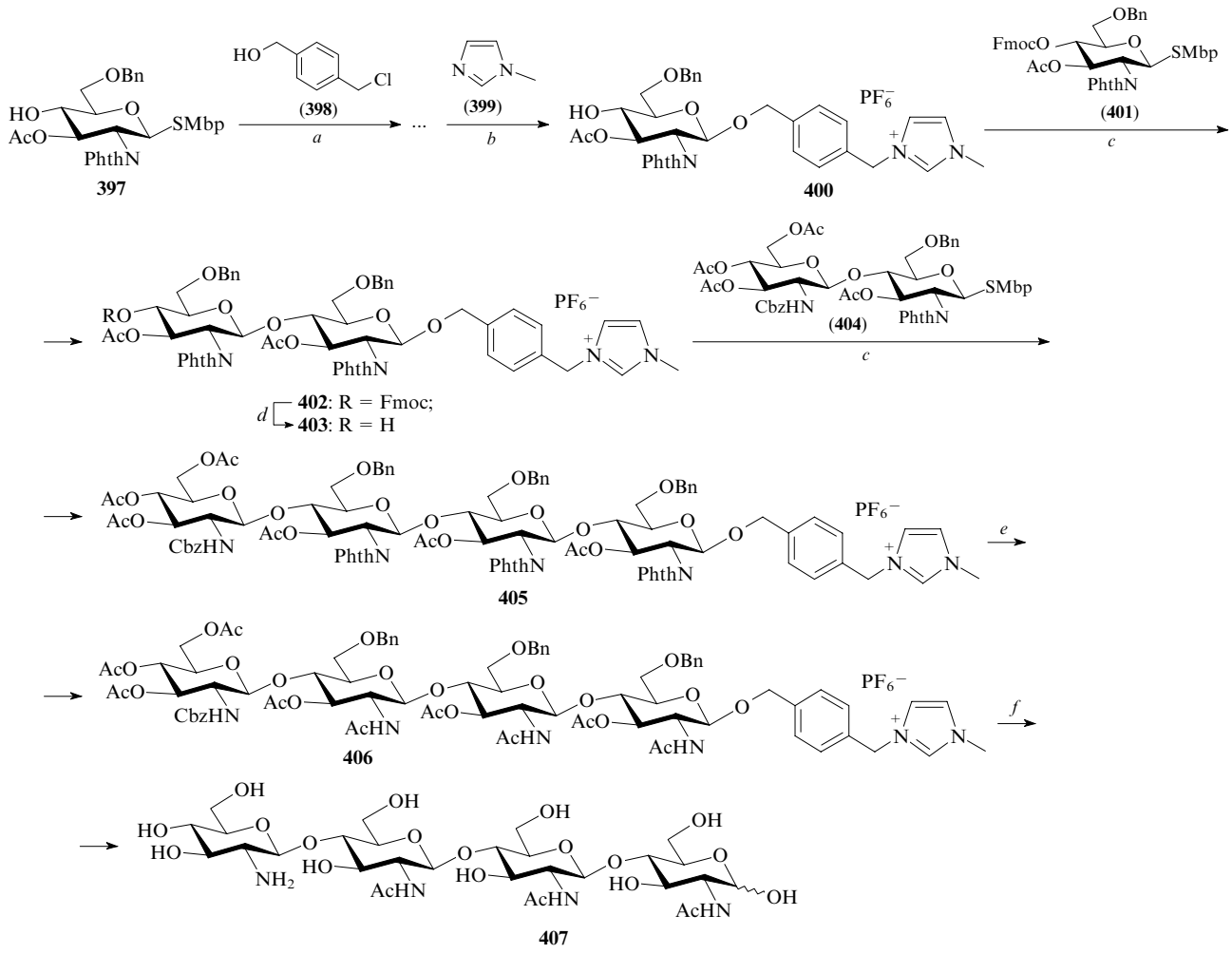
The removal of phthaloyl and acetyl (or chloroacetyl) protecting groups from oligosaccharides **389**, **391** and **393** with hydrazine hydrate, N-acetylation, reduction of the azido group, trifluoroacetylation of the resulting amine followed by hydrogenolysis of benzyl groups and alkaline hydrolysis gave the target free chitooligosaccharides in overall yields of 37%, 22% and 3.4% for products **394**, **395** and **396**, respectively. More recently, the authors found conditions for catalytic hydrogenation, under which the reduction of the azido group of the spacer can be performed simultaneously with debenzylation, resulting in a substantial increase in the overall efficiency of the conversion of protected precursors into oligosaccharides **394** – **396**.[69]

Gillard *et al.*[70] described the employment of glycosyl acceptors bearing an ionic tag in the synthesis of tetrasaccharide **407** containing the glucosamine residue with the nonacetylated amino group at the non-reducing end. The presence of an ionic tag facilitated the isolation of glycosylation products (see also Scheme 7). In the first step, an ionic tag was introduced into the glycosyl acceptor *via*

Scheme 53



Scheme 54



(*a*) NIS, HOTf, MS 4 Å, PhMe, −30 °C; (*b*) 1) MeCN, 85 °C; 2) KPF_6, MeCN, 85 °C; (*c*) NIS, HOTf, MS 4 Å, CH_2Cl_2; (*d*) Et_3N, CH_2Cl_2; (*e*) 1) $NH_2(CH_2)_2NH_2$, EtOH, MeCN, 60 °C; 2) Ac_2O, Py; (*f*) 1) supported ammonium formate, Pd/C, Pr^iOH, H_2O, microwave irradiation, 80 °C; 2) MeONa, MeOH; Mbp is 5-*tert*-butyl-2-methylphenyl

glycosylation of *p*-(chloromethyl)benzyl alcohol (**398**) with thioglycoside **397** followed by the reaction with *N*-methylimidazole (**399**) in the presence of KPF_6 (Scheme 54) to form acceptor **400** in 85% yield. The glycosylation of this acceptor with thioglycoside **401** bearing the Fmoc group at the 4 position gave disaccharide **402** (92% yield). The removal of Fmoc protection by the treatment with triethylamine and subsequent glycosylation of disaccharide acceptor **403** with the earlier synthesized [71] disaccharide donor **404** containing different protecting groups at the nitrogen atoms produced tetrasaccharide **405**. The removal of phthaloyl protecting groups, N-acetylation, hydrogenation of intermediate **406** and subsequent alkaline deacetylation produced target chitotetraoside **407**.

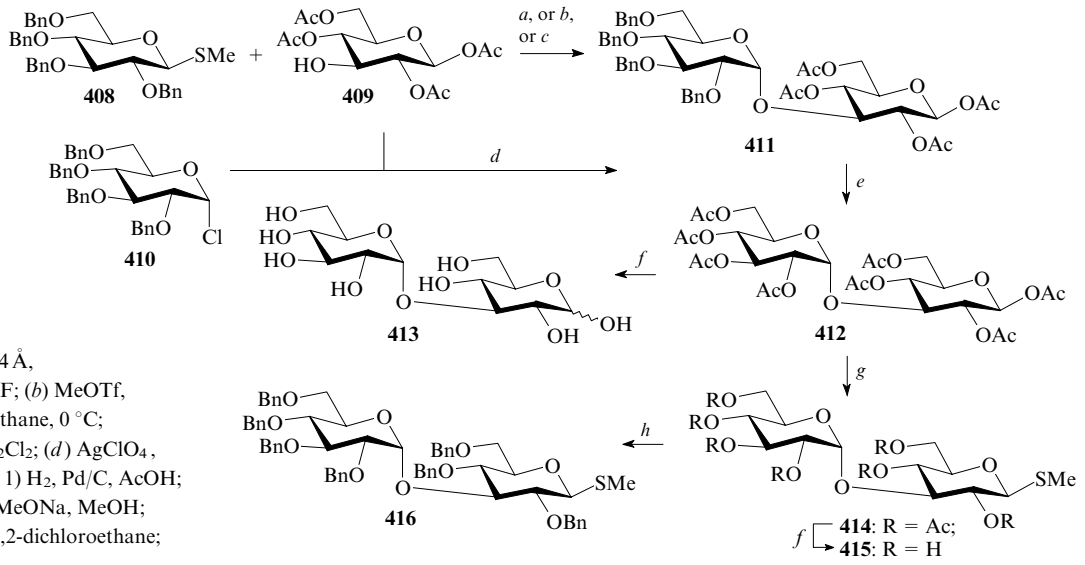
VI. Synthesis of oligosaccharides corresponding to fragments of α-(1→3)-glucan from *Aspergillus*

The targeted synthesis of α-(1→3)-oligoglucosides containing more than two glucose residues was considered only in two publications,[70,72] the earlier one [72] being published back in 1992. In some earlier publications on this issue, the corresponding disaccharide was described as the final product;[73–76] some other works described model glycosylation reactions, which gave the disaccharides in a mixture with numerous products.[77–80]

Takeo *et al.*[72] reported the synthesis of a series of oligoglucosides (from di- to pentasaccharides) *via* oligosaccharide chain elongation by successive attachment of one monosaccharide unit starting at the non-reducing end in the case of di- and trisaccharides and by means of a building block approach for longer oligomers. In order to prepare disaccharide **413** and synthetic building block **416**, the glycosylation of tetraacetate **409** with thioglucoside **408** and chloride **410** was examined under different conditions (Scheme 55). The best yield of disaccharide **411** (77%) was achieved with donor **408** in the presence of copper(II) bromide and tetra-n-butylammonium bromide. The hydrogenation of compound **411** and subsequent acetylation gave octaacetate **412**, which was converted, on the one hand, into free diglucoside **413** and, on the other hand, into thioglycoside **414**. All acetyl protecting groups in compound **414** were replaced, through the formation of intermediate free thioglycoside **415**, by non-participating benzyl groups (compound **416**).

Triglucoside **419** was synthesized in a similar manner as disaccharide **413** (Scheme 56). The glycosylation of acceptor **409** with disaccharide thioglycoside **416** in the

Scheme 55



(*a*) $CuBr_2$, TBABr, MS 4 Å, 1,2-dichloroethane, DMF; (*b*) MeOTf, MS 4 Å, 1,2-dimethoxyethane, 0 °C; (*c*) MeSBr, MS 4 Å, CH_2Cl_2; (*d*) $AgClO_4$, 2,4,6-collidine, Et_2O; (*e*) 1) H_2, Pd/C, AcOH; 2) Ac_2O, Py, 70 °C; (*f*) MeONa, MeOH; (*g*) $SnCl_4$, Bu^n_3SnSMe, 1,2-dichloroethane; (*h*) NaH, BnBr, DMF

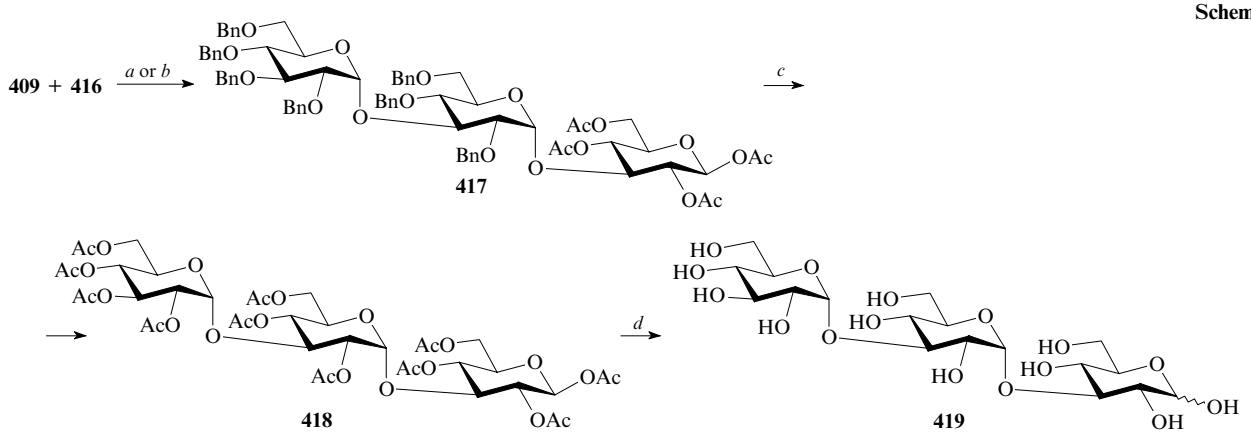
presence of $CuBr_2$ and TBABr or MeOTf gave trisaccharide **417** in a yield of about 60%. The successive hydrogenolysis of benzyl groups, acetylation (compound **418**) and deacetylation afforded target free trisaccharide **419**.

To synthesize α-(1→3)-tetra- and pentaglucosides, the authors utilized glycosyl donors containing a selectively removable temporary protecting group at the O(C3) atom. Thus, thioglycosides **421** and **422** bearing allyl and chloroacetyl groups, respectively, which were derived from tetraacetate **420** (Scheme 57), served as donors. The glycosylation of acceptor **409** with donor **421** in the presence of MeOTf gave disaccharide **423** in 61% yield, whereas donor **422** containing an electron-withdrawing chloroacetyl group did not form the corresponding disaccharide in the reaction with acceptor **409**. The removal of the allyl group from compound **423** afforded disaccharide acceptor **424**, the glycosylation of which with thioglycoside **416** gave protected tetraglucoside **425** in 64% yield. The hydrogenolysis, acetylation and subsequent saponification produced target α-(1→3)-linked tetraglucoside **427**.

Pentasaccharide **432** was synthesized in a similar manner but with additional elongation of acceptor **424** by one monosaccharide unit with the participation of donor **421** (Scheme 58). The allyl group was removed from triglucoside **428** and the subsequent reaction of resulting acceptor **429** with disaccharide thioglycoside **416** afforded protected pentaglucoside **430** in 59% yield. Like the oligoglucosides considered above, compound **430** was initially converted into total acetate **431** followed by its deacetylation to form target pentaglucoside **432**. It should be noted that most of the glycosylation reactions described in the cited study gave α-linked products in quite good yields (~60%). However, only the yields of the target products were reported, but nothing was said as to whether these reactions were α-stereoselective.

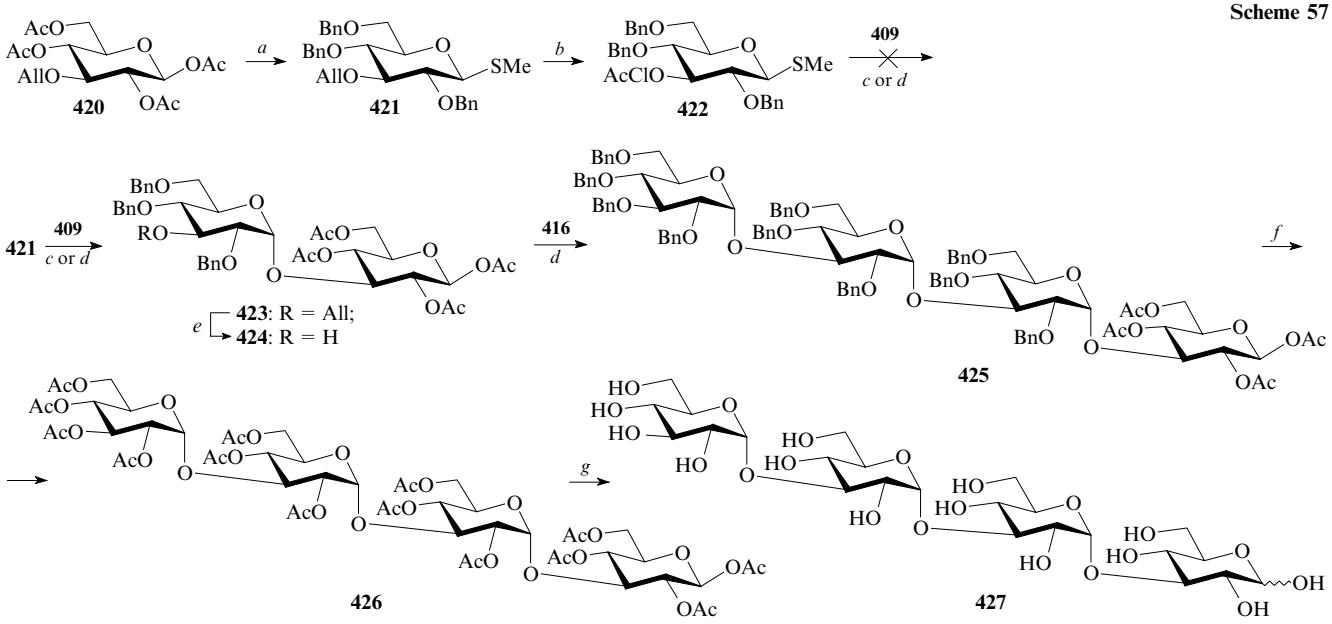
As opposed to the study[72] considered above, the synthesis of α-(1→3)-linked pentaglucoside performed at the Laboratory of Glycoconjugate Chemistry of the ZIOC RAS was designed so as to provide the maximum α-stereoselectivity in each glycosylation step. To achieve this goal, the the approach was relied on the remote anchimeric assistance of acyl groups.[81–83] Besides, the target pentasaccharide was synthesized as 3-aminopropyl glycoside, which made it possible to employ the latter for the construction of various biomolecular systems.[84, 85]

Scheme 56



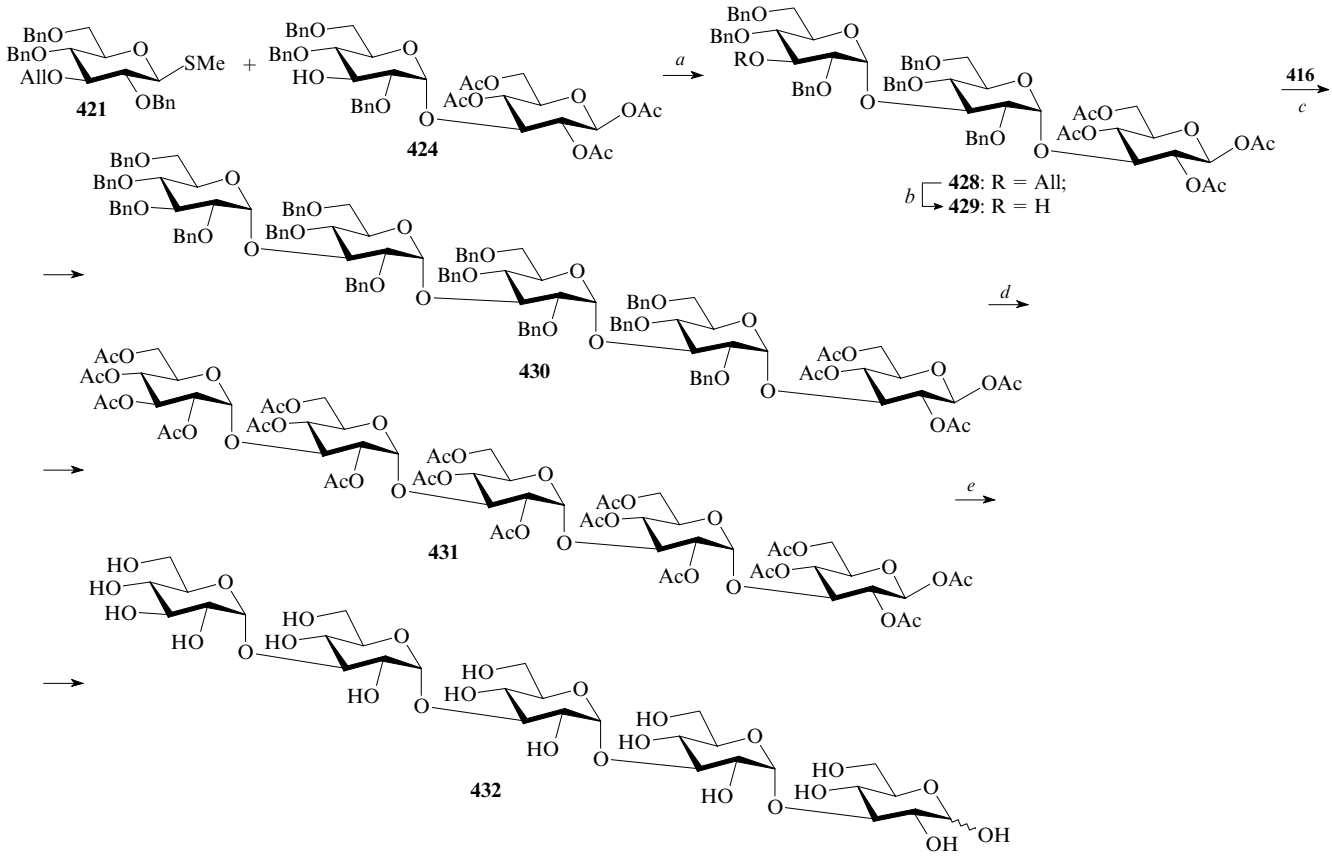
(*a*) $CuBr_2$, TBABr, MS 4 Å, 1,2-dichloroethane, DMF; (*b*) MeOTf, MS 4 Å, 1,2-dimethoxyethane, 0 °C; (*c*) 1) H_2, Pd/C, AcOH; 2) Ac_2O, Py, 70 °C; (*d*) MeONa, MeOH

Scheme 57



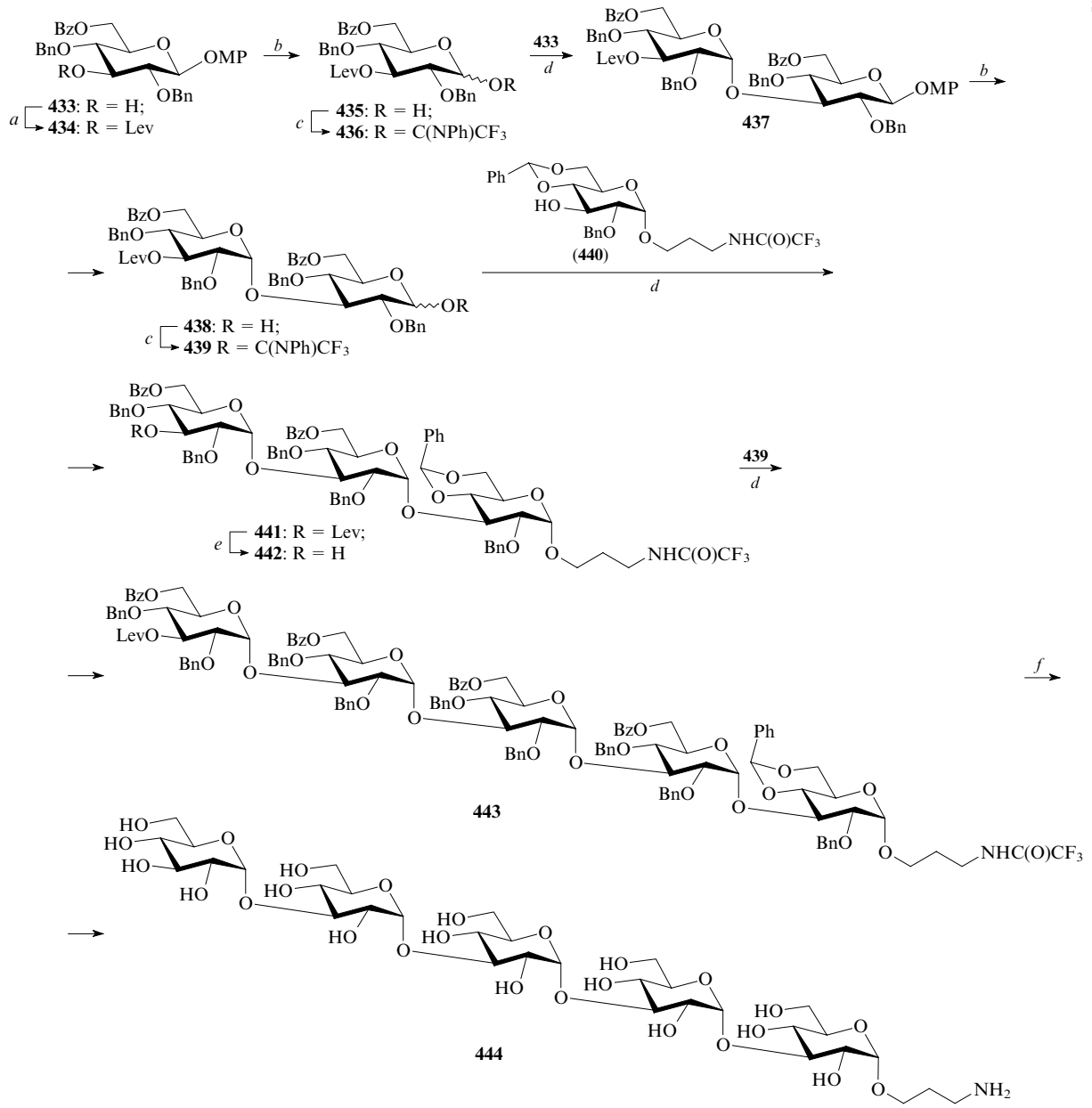
(*a*) 1) $SnCl_4$, Bu^n_3SnSMe, 1,2-dichloroethane; 2) MeONa, MeOH, Δ; 3) BnBr, NaH, DMF; (*b*) 1) Bu^tOK, DMF; 2) 1 M HCl; 3) $ClCH_2C(O)Cl$, Py, CH_2Cl_2; (*c*) MeOTf, MS 4 Å, 1,2-dimethoxyethane, 0 °C; (*d*) $CuBr_2$, TBABr, 1,2-dichloroethane, DMF; (*e*) $PdCl_2$, NaOAc, AcOH, H_2O; (*f*) 1) H_2, Pd/C, AcOH, 2) Ac_2O, Py, 70°C; (*g*) MeONa, MeOH

Scheme 58



(*a*) MeOTf, MS 4 Å, 1,2-dimethoxyethane, 0 °C; (*b*) $PdCl_2$, NaOAc, AcOH, H_2O; (*c*) $CuBr_2$, TBABr, MS 4 Å, 1,2-dichloroethane, DMF; (*d*) 1) H_2, Pd/C, AcOH; 2) Ac_2O, Py, 70 °C; (*e*) MeONa, MeOH

Scheme 59



(*a*) LevOH, DCC, DMAP, CH_2Cl_2; (*b*) $(NH_4)_2Ce(NO_3)_6$, MeCN (aq.); (*c*) $ClC(NPh)CF_3$, K_2CO_3, Me_2CO; (*d*) MeOTf, MS AW-300, CH_2Cl_2; $-35 \rightarrow -15$ °C; (*e*) $NH_2NH_2 \cdot H_2O$, AcOH, Py; (*f*) 1) $NH_2NH_2 \cdot H_2O$, AcOH, Py; 2) H_2, Pd/C; 3) NaOH, MeOH; 4) NaOH, H_2O;
DCC is dicyclohexylcarbodiimide

The route to the target structure involved the chain elongation by successive attachment of two monosaccharide units starting at the reducing end.[86] Based on the results of preliminary experiments,[82, 86] the following optimal protection pattern in glucose was found: benzyl groups at the oxygen atoms in the 2 and 4 positions and the benzoyl group at the O(C6) atom as permanent protection. The latter group provides high α-stereoselectivity *via* remote anchimeric assistance. Levulinoyl and *p*-methoxyphenyl moieties were used as temporary protection of the 3-OH group and the anomeric position, which allows the rapid and efficient interconversion of donor and acceptor building blocks. The *N*-phenyltrifluoroacetimidate group served as the leaving group in glycosyl donors. The oligosaccharide chain elongation was accomplished starting from 3-trifluoroacetamidopropyl glycoside **440** (Scheme 59).

Disaccharide donor building block **439** was prepared from precursor **433**. The protection of the 3 position of monosaccharide **433** with the levulinoyl group, the removal of the MP group from intermediate **434** and the reaction of hemiacetal **435** with *N*-phenyltrifluoroacetamidoyl chloride gave donor **436**, which was used to glycosylate acceptor **433** in the presence of MeOTf. α-Linked disaccharide **437** was isolated in 90% yield; the α : β ratio was 27 : 1. Disaccharide **437** was converted into disaccharide donor building block **439** through the formation of hemiacetal **438**. The reaction of **439** with acceptor **440** in the presence of MeOTf produced trisaccharide **441** in 72% yield (α : β = 14 : 1). The removal of levulinoyl protection from triglucoside **441** and glycosylation of trisaccharide acceptor **442** with donor **439** gave exclusively α-linked pentaglucoside **443** (68% yield). The complete deprotection afforded target oligosaccharide **444** in a total yield of 77% over four steps. This approach is

applicable to further glucan chain elongation, thus opening a route to longer α-(1→3)-oligoglucosides.

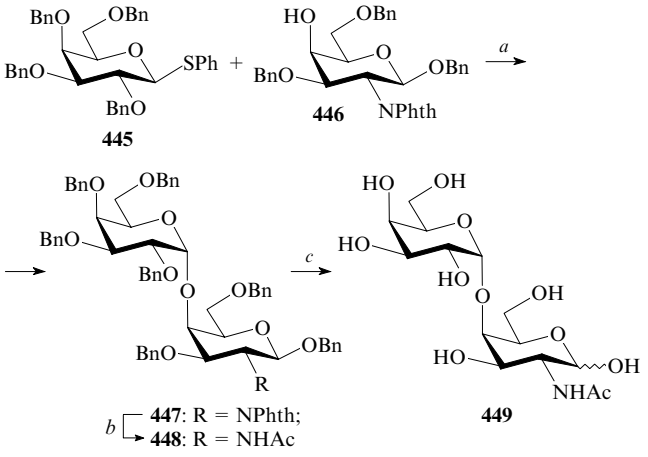
A conjugate of pentaglucoside **444** with bovine serum albumin was used to immunize mice in order to induce specific anti-α-(1→3)-glucan antibodies. The resulting polyclonal antibodies labelled with a fluorescent dye were employed to identify α-(1→3)-glucan-positive *A. fumigatus* morphotypes.

VII. Synthesis of oligosaccharides corresponding to fragments of galactosaminogalactan from *Aspergillus*

The literature offers a limited number of examples of the construction of oligogalactosides corresponding to fragments of galactosaminogalactan. Data on the synthesis of chains composed of alternating galactose and galactosamine units are not available in the literature. Only a few examples of the synthesis of protected disaccharides of this type are known. However, these publications are either focused on glycosylation reactions [87, 88] or describe disaccharides as intermediates [89, 90] for the preparation of longer-chain oligosaccharides.

Free disaccharide was synthesized as the final product in the only study.[91] The glycosylation of benzylated galactosamine acceptor **446** with fully benzylated donor **445** in the presence of dimethyl(thiomethyl)sulfonium triflate (DMTST) gave protected disaccharide **447** in 66% yield (Scheme 60). The replacement of the N-phthaloyl protecting group by the N-acetyl group (93% yield) and subsequent hydrogenolysis of benzyl groups in compound **448** opened a route to free disaccharide **449** (68% yield).

Scheme 60



(*a*) DMTST, MS 4 Å, CH_2Cl_2, Et_2O, PhMe; (*b*) 1) $NH_2NH_2 \cdot H_2O$, PhMe, EtOH; 2) Ac_2O, CH_2Cl_2, MeOH; (*c*) H_2, Pd/C, EtOH

VII.1. Synthesis of α-(1→4)-oligogalactosides

α-(1→4)-Linked digalactosides were described in more than a dozen publications. Some of these galactosides were obtained, among other porducts, in the course of studies of glycosylation reactions,[92, 93] some other were synthesized as the target products but without deprotection,[94 – 96] or they were considered as intermediates for the preparation of longer oligosaccharides, which do not belong to the class of compounds under consideration.[90, 97 – 103] Besides, free α-(1→4)-linked digalactosides have been isolated.[104 – 107]

Most publications devoted to this issue were focused on the synthesis of α-(1→4)-oligomers of galacturonic acid corresponding to pectin fragments; however, their syntheses involved α-(1→4)-oligogalactosides as intermediates, while the oxidation at the C(6) atom took place in the final steps of the synthesis. Therefore, we deem that these studies are important for the consideration of synthetic approaches to the class of compounds in question.

Nakahara and Ogawa [108 – 110] reported the synthesis of decagalactoside *via* chain elongation by successive attachment of two monosaccharide units starting at the reducing end of the growing chain with glycosyl fluorides as the donors. The required disaccharide donors were synthesized as follows (Scheme 61). The terminal building block corresponding to the non-reducing end of the oligosaccharide sequence was prepared by the coupling of the α-anomer of fluoride **450** with acceptor **451** in the presence of $SnCl_2$ and $AgClO_4$ giving α-digalactoside **453** in 87% yield along with an insignificant amount of the β-anomer (9% yield). A similar reaction of β-anomer **450** with acceptor **452** containing a silyl protecting group at the anomeric position gave α-digalactoside **454** in 78% yield (along with the β-anomer in 16% yield). The removal of the anomeirc protecting groups from α-linked disaccharides **453** and **454** resulted in the formation of hemiacetal **455**, which was converted into donor **456** by the treatment with DAST.

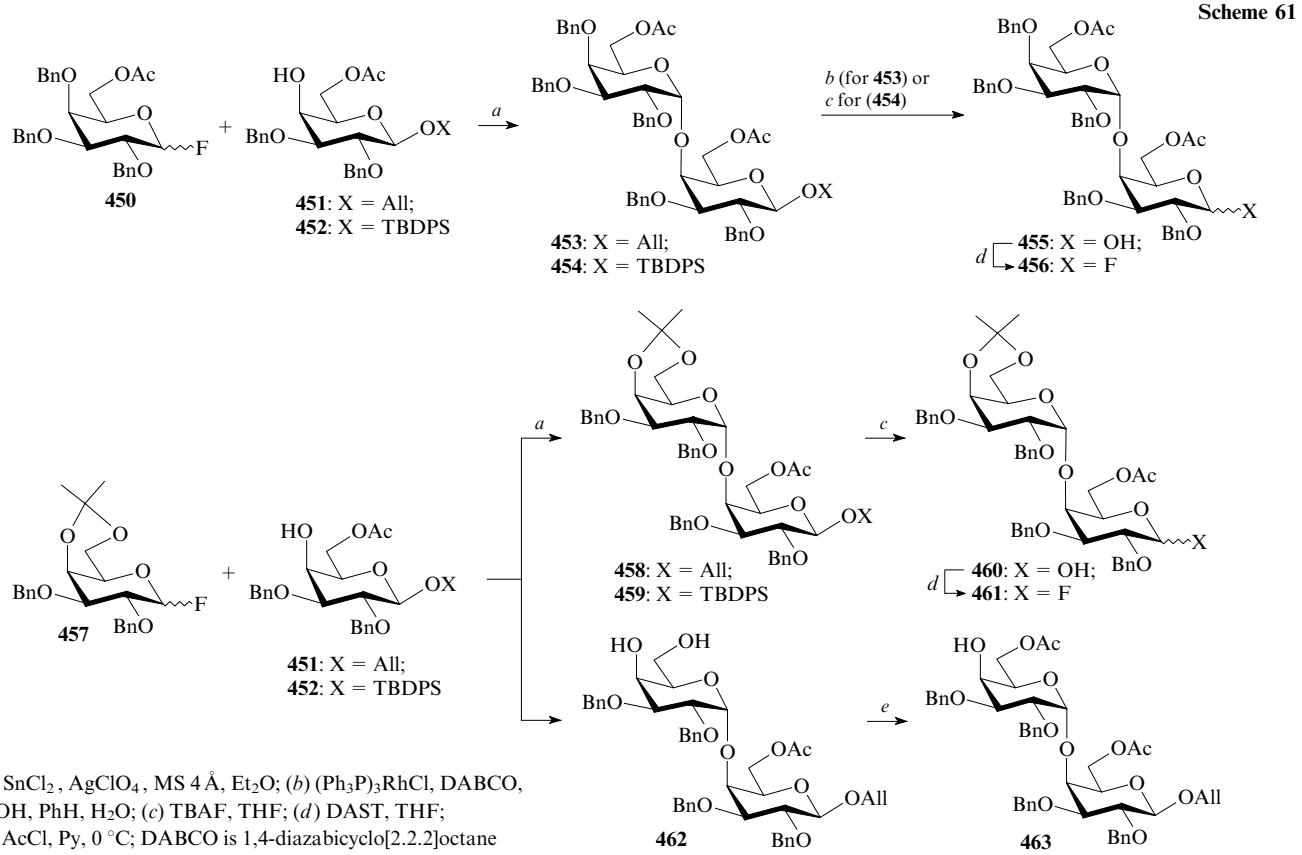
The building block corresponding to disaccharide fragments in the inner core region of the target decasaccharide were synthesized starting from acceptor **452** and galactosyl fluoride **457** containing the temporary 4,6-O-isopropylidene protecting group. The coupling of the substrates gave exclusively α-product **459** in 84% and 96% yields for the α- and β-fluorides, respectively. After the silyl deprotection with tetra-n-butylammonium fluoride (92% yield) and subsequent fluorination of hemiacetal **460**, target digalactoside building block **461** was isolated in 98% yield.

It should be noted that the glycosylation of allyl glycoside **451** with donor **457** was accompanied by the elimination of the isopropylidene group giving 4,6-diol **462** (74% yield), while expected product **458** was isolated in only 4% yield. Nevertheless, this has only helped the authors since the selective acetylation of the free hydroxyl group at the 6 position of diol **462** directly produced third synthetic building block **463** corresponding to the reducing end of the oligosaccharide chain.

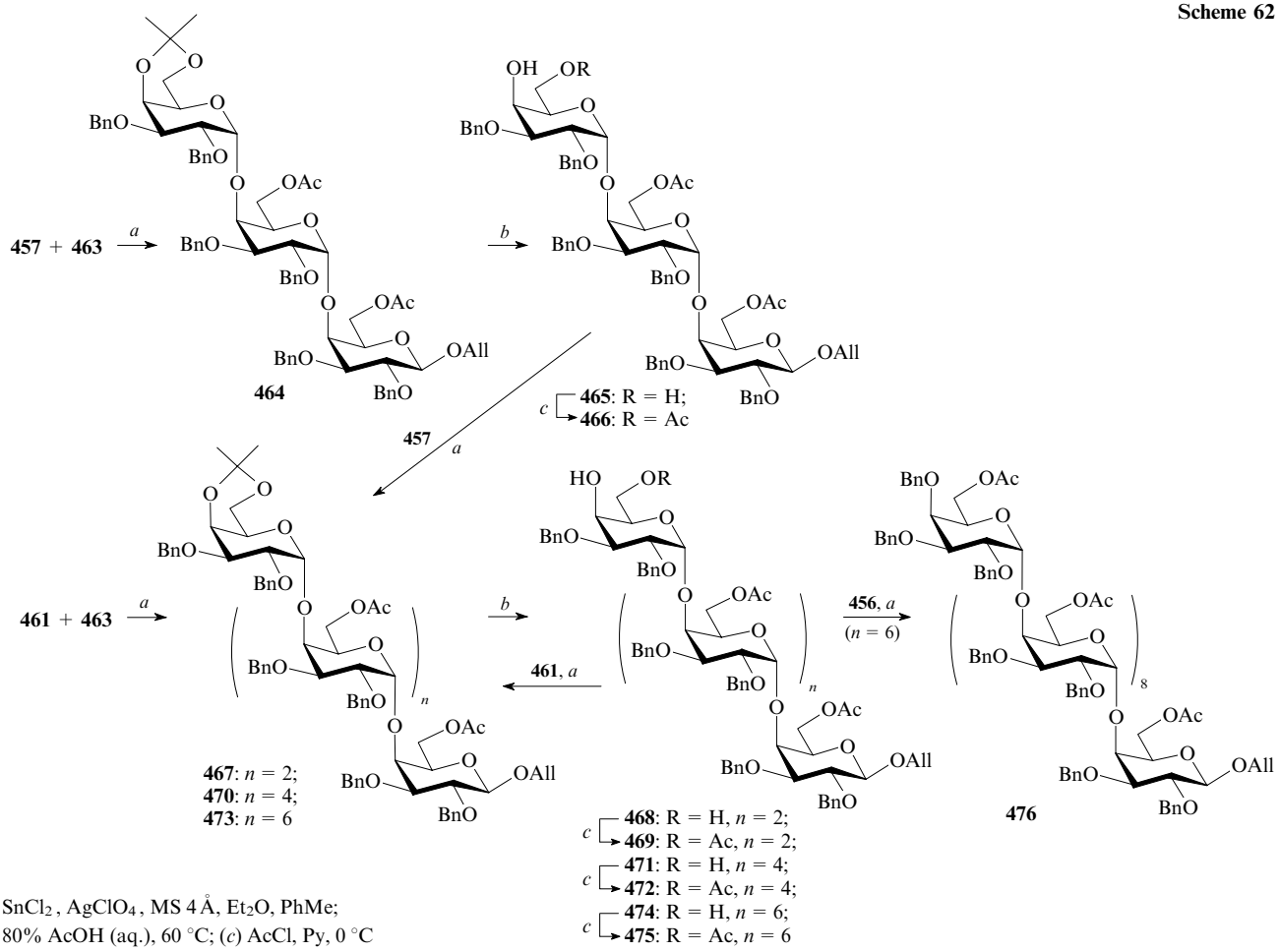
The condensation of disaccharide **463** with disaccharide fluoride **461** followed by the removal of the isopropylidene group from product **467** afforded diol **468** (Scheme 62). This product was also synthesized starting from acceptor **463** by twofold oligosaccharide chain elongation using galactosyl fluoride **457**, through the intermediate formation of trisaccharide **464**, diol **465** and trisaccharide acceptor **466**. However, this approach proved to be less efficient. The selective acetylation of the primary hydroxyl group in tetrasaccharide **468** gave acceptor **469**. The reaction cycle involving glycosylation with donor **461**, acid hydrolysis of the isopropylidene group in condensation products **470** and **473** and selective acetylation of the 6-OH group in diols **471** and **474** gave octasaccharide acceptor **475**; the yields of intermediate diols **471** and **474** were 77% and 82%, respectively. The terminal disaccharide unit was attached to octasaccharide **475** *via* glycosylation with fluoride **456** giving target decasaccharide **476** in 76% yield.

A structurally similar dodecagalactoside, which differs only in the protection of the anomeric position (*tert*-butyldiphenylsilyl group instead of the allyl moiety), was

Scheme 61



Scheme 62



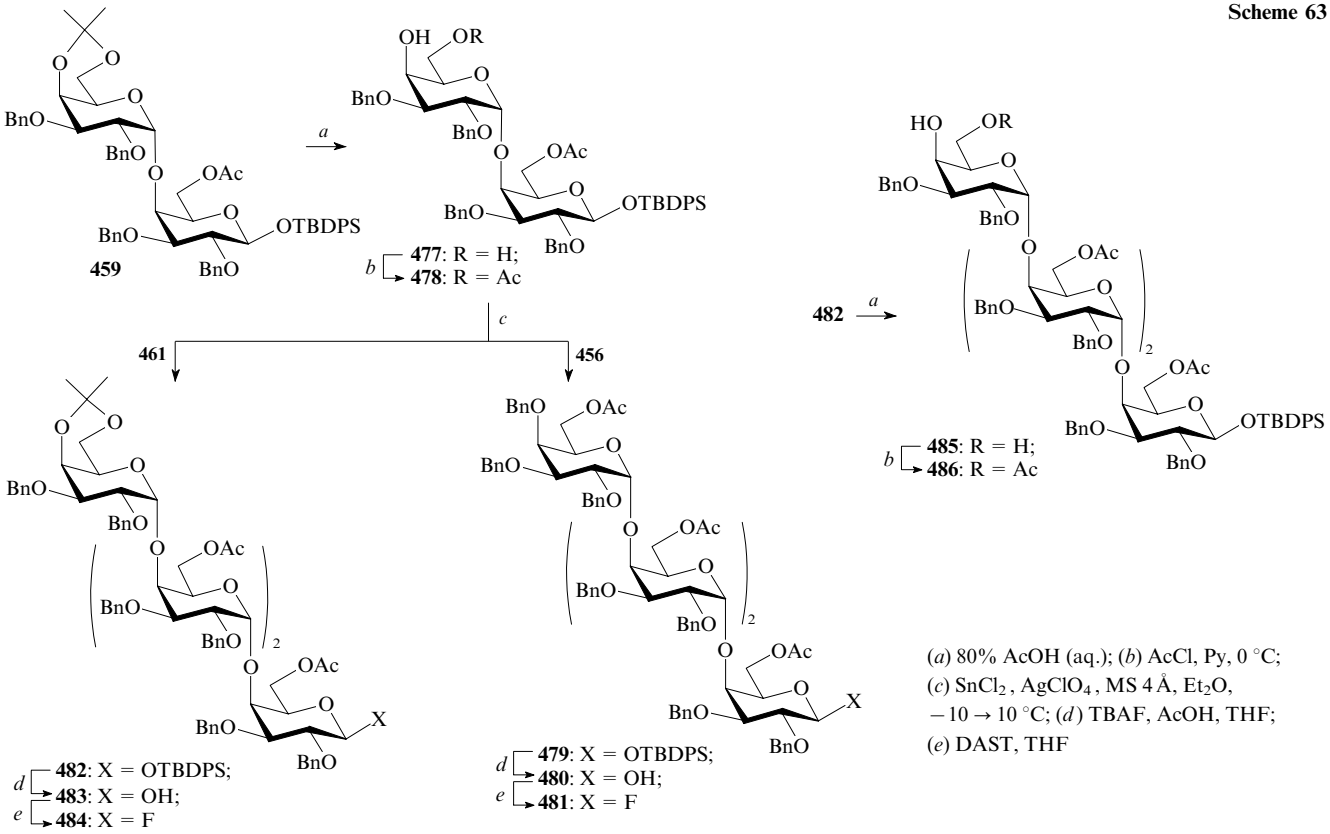
synthesized [111, 112] by the same research team but using the [4 + 4 + 4] scheme. In the initial step, tetrasaccharide building blocks were synthesized from known disaccharide precursors and then they were used for the assembly of the final product. Terminal building block **481** was constructed by the coupling of digalactoside acceptor **478** with donor **456**, the acceptor being synthesized from digalactoside **459** through the removal of isopropylidene protection (91% yield) and selective acetylation of the 6 position in disaccharide **477** (87%). Then the silyl group was removed from the anomeric position of tetrasaccharide **479** and the hydroxyl group of hemiacetal **480** was replaced by the fluorine atom (97% yield). The glycosylation of the same acceptor **478** with fluoride **461** gave tetrasaccharide **482** containing both the silyl group at the anomeric position and 4,6-O-isopropylidene protection in the terminal glucose residue (77% yield). This tetrasaccharide served as the starting component for the synthesis of two other tetrasaccharide building blocks: acceptor **486** was prepared by the removal of isopropylidene protection and selective 6-O-acetylation of diol **485**, and donor **484** required for the construction of the inner core fragment of the oligogalactoside chain was prepared by the removal of the anomeric silyl group and fluorination of hemiacetal **483** (Scheme 63).

The oligosaccharide chain was assembled in a manner similar to that described above for decasaccharide **476**. Thus, two synthetic approaches to the synthesis of octagalactoside diol **491** were tested: 1) [4 + 4]-coupling of donor **484** and acceptor **486** followed by the removal of the isopropylidene group from octasaccharide **487**; 2) chain elongation *via* the [4 + 2 + 2] scheme using disaccharide donor **461** (the sequence of compounds **488** → **489** → **490**). In the final step, acceptor **492**, which was prepared by selective 6-O-acetylation of compound **491**, was glycosylated with terminal donor **481** giving dodecasaccharide **493** (Scheme 64). It should be noted that the data on the stereoselectivity of glycosylation reactions was not reported.

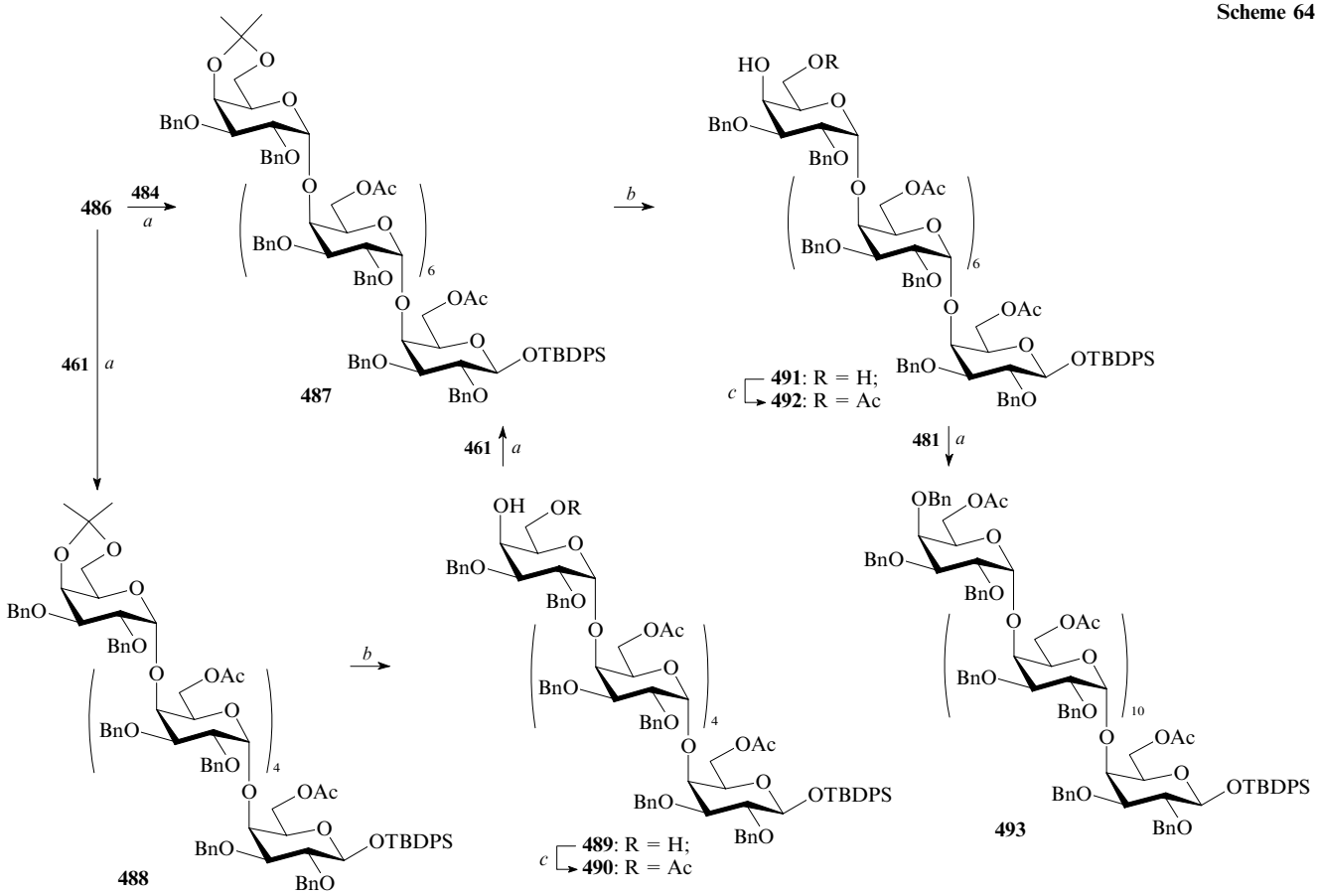
Clausen *et al.*[113 – 115] utilized pentenyl glycosides as glycosyl donors for the assembly of the oligogalactoside chain. As in the above-considered studies, α-(1→4)-galacturonosides were the target compounds. Therefore, the authors protected the 6 position of galactoside residues by protecting groups (acetyl or *p*-methoxyphenyl) orthogonal to benzyl groups at the 2 and 3 positions. In one of the publications,[113] three structurally similar α-(1→4)-trigalactosides were synthesized (Scheme 65). Since the ultimate aim of the synthesis was to prepare α-(1→4)-trigalacturonosides containing the esterified carboxyl group in the specified uronic acid residue, the trigalactosides used as precursors differ only in the arrangement of 6-O protecting groups along the chain. Therefore, we will restrict the consideration to oligosaccharide **498** since all other oligosaccharides were synthesized in a similar manner. In the first step, pentenyl donor **494** bearing the temporary 4-O-chloroacetyl group was used to glycosylate acceptor **495** in the presence of NIS and triethylsilyl triflate giving the corresponding digalactoside in 71% yield. The removal of chloroacetyl groups with thiourea and the subsequent coupling of the resulting acceptor **496** with donor **497a** produced trisaccharide **498** as a mixture of α- and β-anomers in a ratio of 3 : 1.

In the subsequent study, Clausen and Madsen [114] described the synthesis of three α-(1→4)-hexagalactosides, which differ in the number of monosaccharide residues bearing the *p*-methoxyphenyl group at the O(C6) atom. The first two hexagalactosides were constructed *via* chain elongation by successive attachment of one monosaccharide unit with the final [2 + 4] assembly; the third one was prepared *via* chain elongation by two monosaccharide

Scheme 63

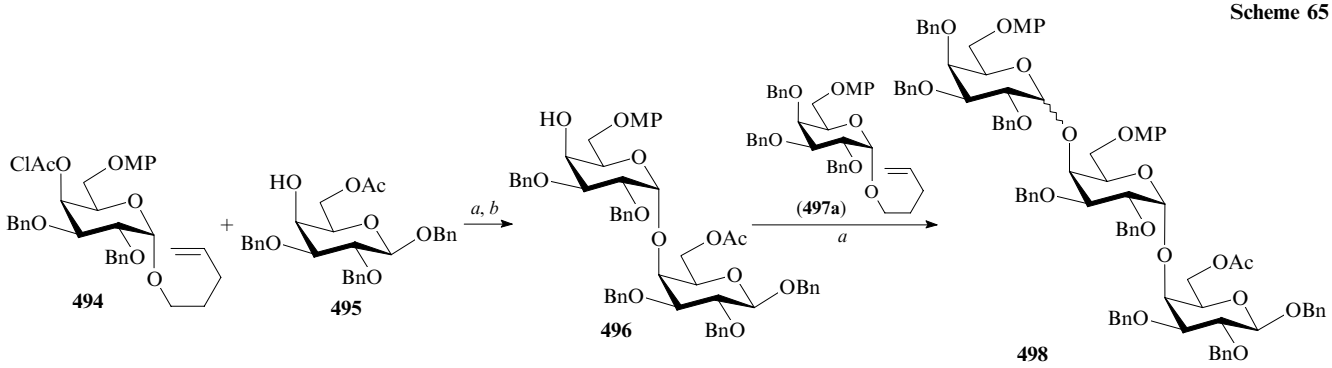


Scheme 64



(*a*) $SnCl_2$, $AgClO_4$, MS 4 Å, Et_2O, $-10 \rightarrow 10$ °C; (*b*) 80% AcOH (aq.); (*c*) AcCl, Py, 0 °C

Scheme 65

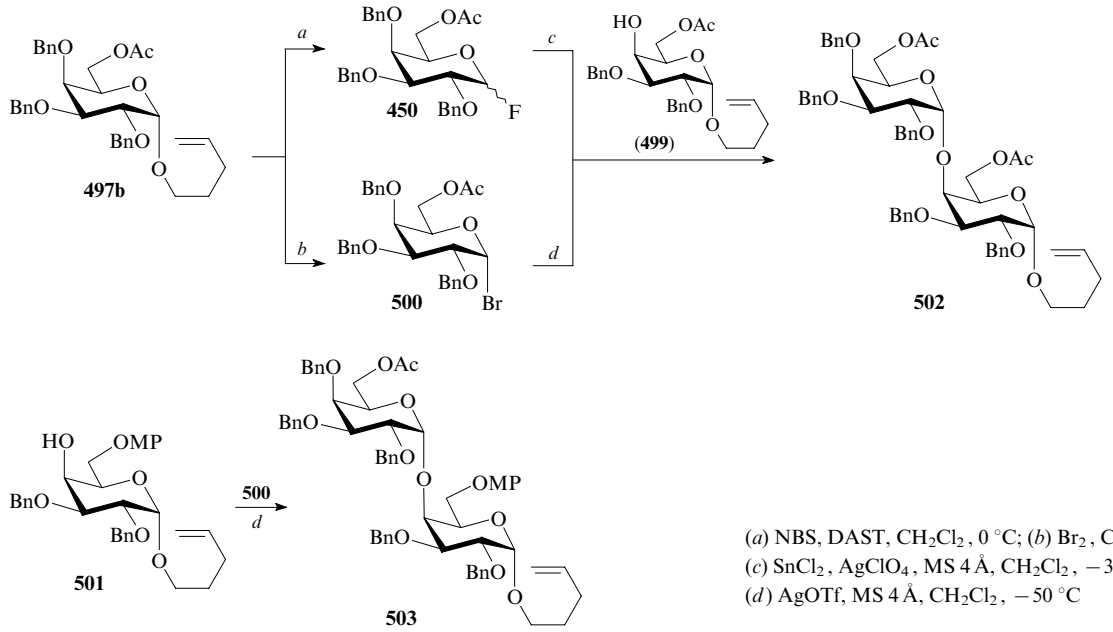


(*a*) NIS, TESOTf, CH_2Cl_2, -20 °C; (*b*) $(NH_2)_2C(S)$, $NaHCO_3$, MeOH, CH_2Cl_2; TES is triethylsilyl

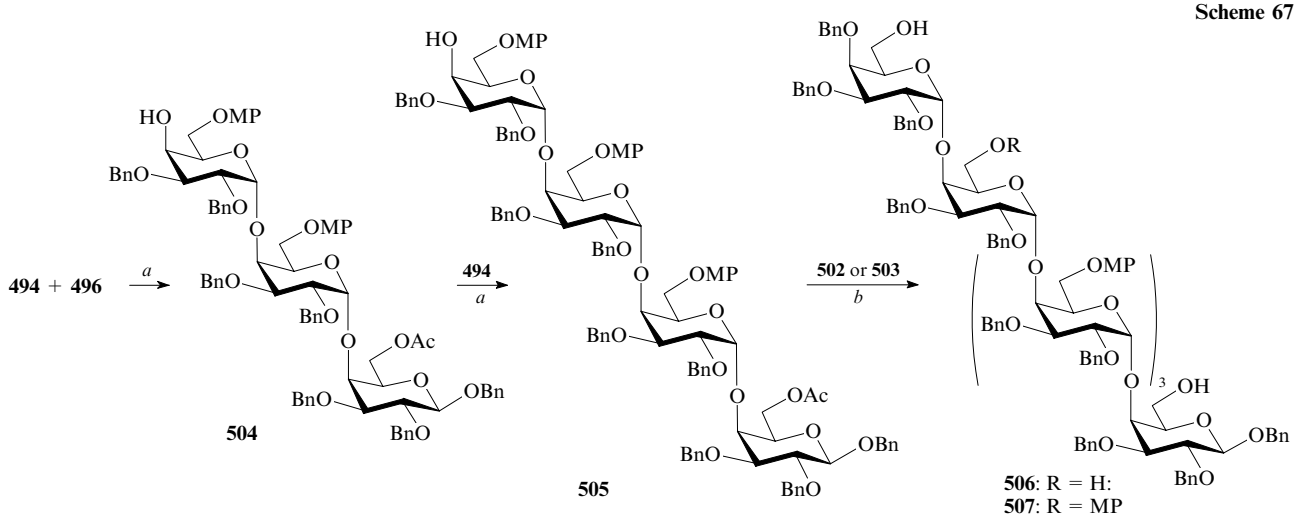
units. Terminal disaccharide donors **502** and **503**, which differ only in the nature of the substituent at the O(C6) atom of the reducing galactose residue, were synthesized as follows. Pentenyl galactoside **497b** was converted into fluoride **450** by the treatment with NBS and DAST (74% yield). The resulting mixture of α- and β-fluorides was used to glycosylate pentenyl 6-O-acetylated acceptor **499** giving target α-digalactoside **502** in 55% yield (along with the β-anomer in 15% yield). The reaction with bromide **500** (derived from galactoside **497b** by the treatment with bromine) as the donor produced digalactoside **502** in 40% yield. However, the authors considered this synthetic route as a method of choice because the β-anomer was produced only in trace amounts. Hence, digalactoside **503** containing the *p*-methoxyphenyl group at the O(C6) atom of the reducing residue was synthesized by the coupling of bromide **500** with acceptor **501** (61% yield) (Scheme 66).

The assembly of the oligogalactoside chain was accomplished as follows. Disaccharide acceptor **496** was glycosylated with pentenyl galactoside **494** bearing the 4-O-chloroacetyl group in the presence of NIS and triethylsilyl triflate followed by the removal of chloroacetate by the treatment with thiourea to form trisaccharide acceptor **504** in 88% yield over two steps. Tetrasaccharide acceptor **505** was prepared from trisaccharide **504** in a similar manner (in a total yield of 90%). The coupling of disaccharide donors **502** and **503** with acceptor **505** and subsequent deacetylation of the coupling products gave hexagalactosides **506** and **507** in 71% and 93% yields, respectively, over two steps (Scheme 67).

Scheme 66



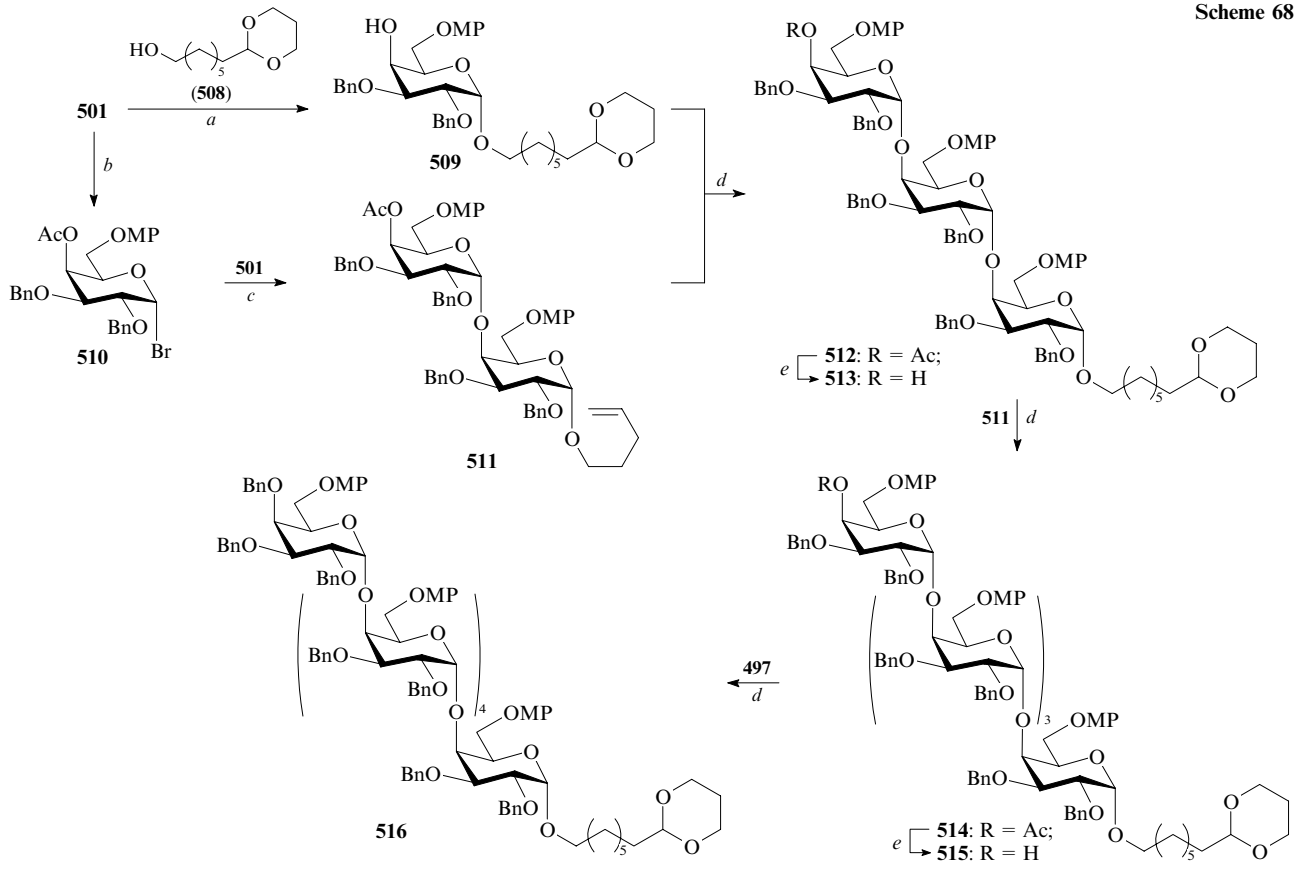
Scheme 67



In the final study, Clausen and Madsen [115] synthesized spacer-containing hexasaccharide from monosaccharide precursors **501** and **497**. The assembly of the oligosaccharide chain was accomplished *via* the [1 + 2 + 2 + 1] scheme. In the first step, the coupling of pentenyl galactoside **501** with alcohol **508** gave spacer-containing acceptor **509** (70% yield), which was used for further oligogalactoside chain elongation. The acetylation of the OH group in monosaccharide **501** and the treatment with bromine afforded bromide **510**, which was introduced into the orthogonal glycosylation reaction with compound **501** to form α-linked disaccharide **511** (71% yield). The reaction of this disaccharide with acceptor **509** gave trigalactoside **512** (71% yield). The removal of the only acetyl group from the latter produced trisaccharide acceptor **513**. The repeated glycosylation with donor **511** and deacetylation of coupling product **514** afforded pentagalactoside **515**. Pentenyl galactoside **497** served as the donor in the final glycosylation step, resulting in the formation of α-linked hexagalactoside **516** in 69% yield (Scheme 68).

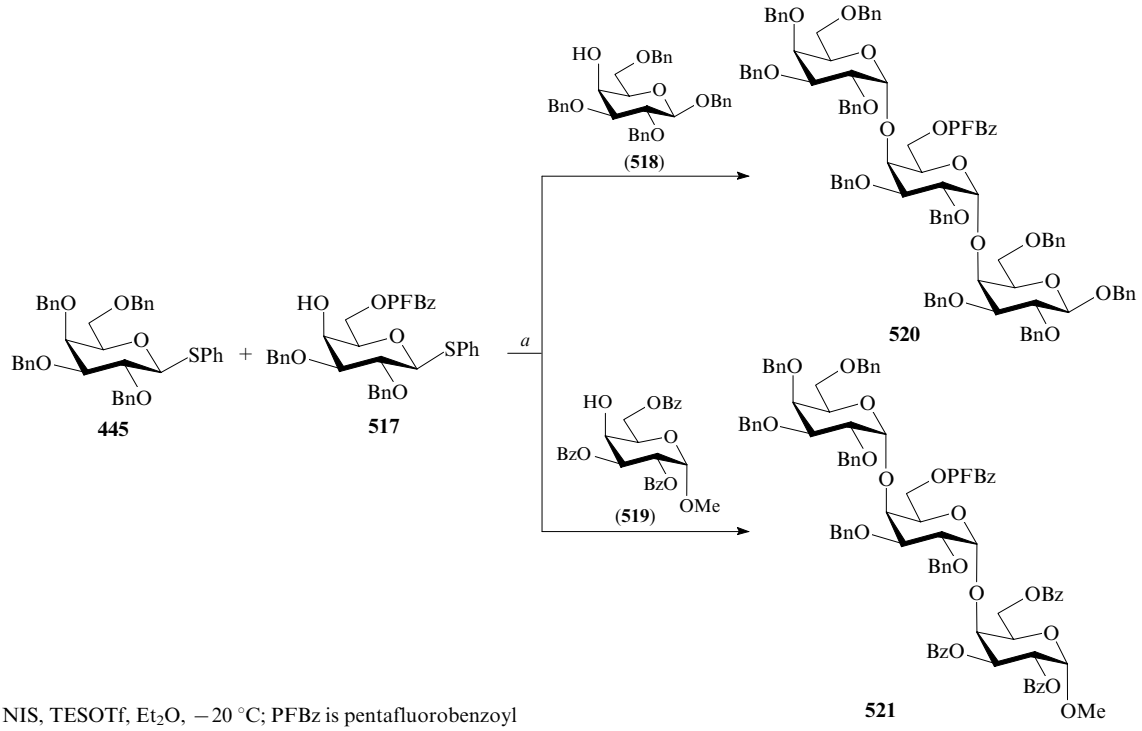
Two α-(1→4)-linked trigalactosides (**520** and **521**) were prepared [116] when investigating the so-called armed – disarmed effect of glycosyl donors for performing successive glycosylation reactions without isolation of intermediates. According to the armed – disarmed concept, the reactivity of glycosyl donors bearing identical anomeric groups can substantially vary depending on the character of protecting groups. Donors bearing alkyl protection are most reactive, while the replacement of the alkyl substituent by the acyl one even in a position remote from the anomeric centre leads to a decrease in the reactivity of the molecule. Thus, perbenzylated thioglycoside **445** was introduced into the reaction with thioglycoside **517**, which differs from the former by the presence of the free hydroxyl group and the electron-withdrawing 6-O-pentafluorobenzoyl group, in the presence of NIS and triethylsilyl triflate. Then an additional amount of NIS and a new glycosyl acceptor — compound

Scheme 68



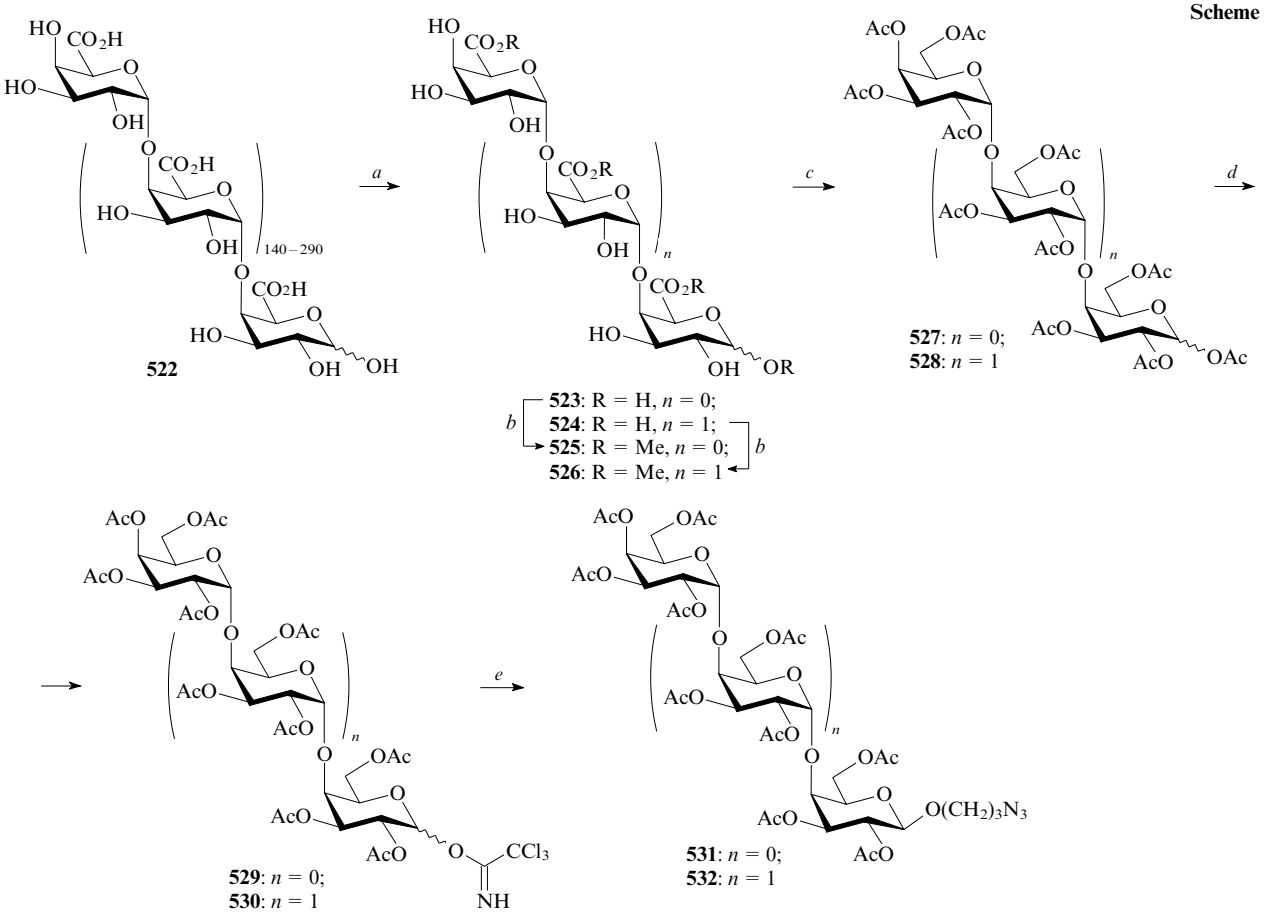
(*a*) 1) Br_2, CH_2Cl_2, 0 °C; 2) Et_4NBr, CH_2Cl_2, 0 → 20 °C; (*b*) 1) Ac_2O, DMAP, Et_3N, CH_2Cl_2; 2) Br_2, CH_2Cl_2, 0 °C; (*c*) AgOTf, MS 4 Å, CH_2Cl_2, −45 °C; (*d*) NIS, TESOTf, CH_2Cl_2, −20 °C; (*e*) MeONa, MeOH, THF

Scheme 69



(*a*) NIS, TESOTf, Et_2O, −20 °C; PFBz is pentafluorobenzoyl

Scheme 70

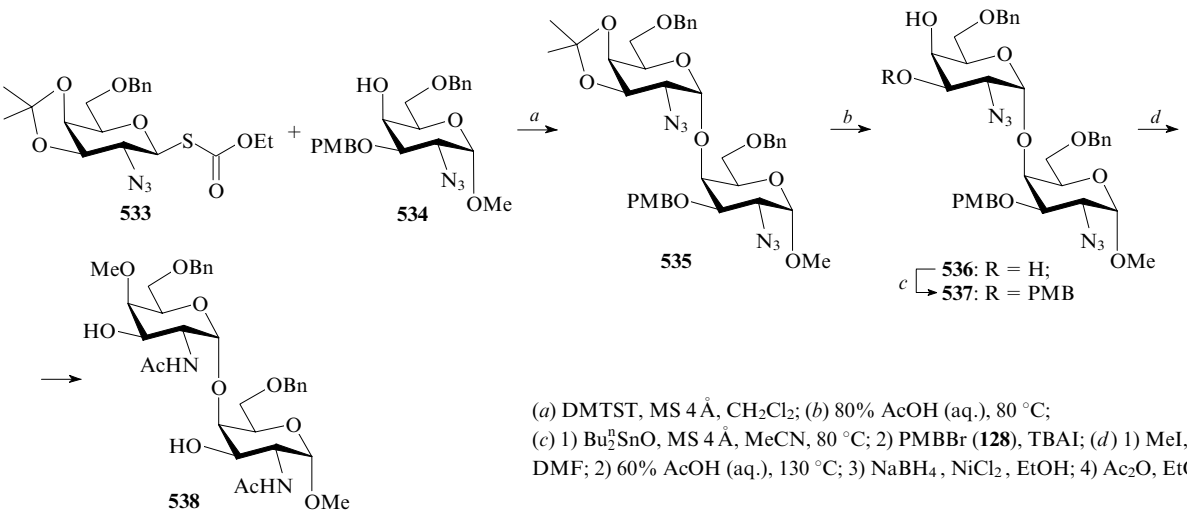


(*a*) Pectinase, pH 4.5, 40 °C; (*b*) Dowex-H$^+$, MeOH; (*c*) 1) $NaBH_4$, MeOH; 2) Ac_2O, Py; 3) H_2SO_4, Ac_2O; (*d*) 1) $NH_2NH_2 \cdot AcOH$, DMF; 2) Cl_3CCN, DBU, CH_2Cl_2; (*e*) 1) $HO(CH_2)_3Br$, TMSOTf, CH_2Cl_2; 2) NaN_3, DMF

518 or **519** — were added to the reaction mixture. Trisaccharides **520** and **521** were obtained in 52% and 61% yields, respectively (Scheme 69).

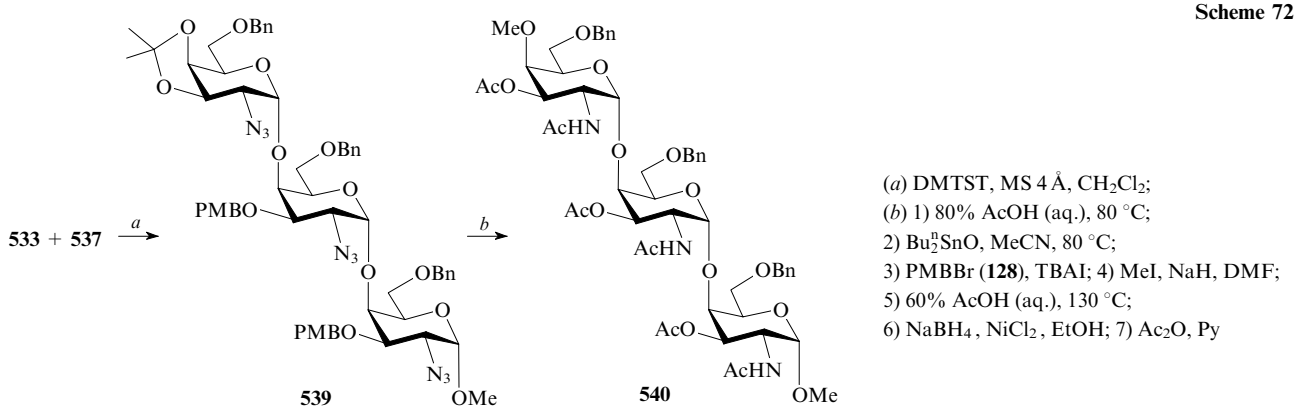
As opposed to most of the studies considered above, in which α-(1→4)-oligogalactosides served as precursors of oligomers of galacturonic acid, Branderhorst *et al.*[117] applied the opposite approach. Thus, polygalacturonic acid **522** served as the starting compound for the preparation of α-(1→4)-oligogalactosides (Scheme 70). This acid was split by pectinase into small fragments, with disaccharide **523** and trisaccharide **524** predominating. The latter fragments were converted into methyl glycoside methyl ethers **525** and **526** by acidic methanolysis (28% and 12% yields, respectively). The reduction of ester groups and acetolysis of methyl glycosides gave total acetates **527** and **528**. The selective removal of acetyl group from the anomeric position and the reaction with trichloroacetonitrile produced trichloroacetimidates **529** and **530**, which were

Scheme 71



(*a*) DMTST, MS 4 Å, CH_2Cl_2; (*b*) 80% AcOH (aq.), 80 °C;
(*c*) 1) Bu^n_2SnO, MS 4 Å, MeCN, 80 °C; 2) PMBBr (**128**), TBAI; (*d*) 1) MeI, NaH, DMF; 2) 60% AcOH (aq.), 130 °C; 3) $NaBH_4$, $NiCl_2$, EtOH; 4) Ac_2O, EtOH

Scheme 72

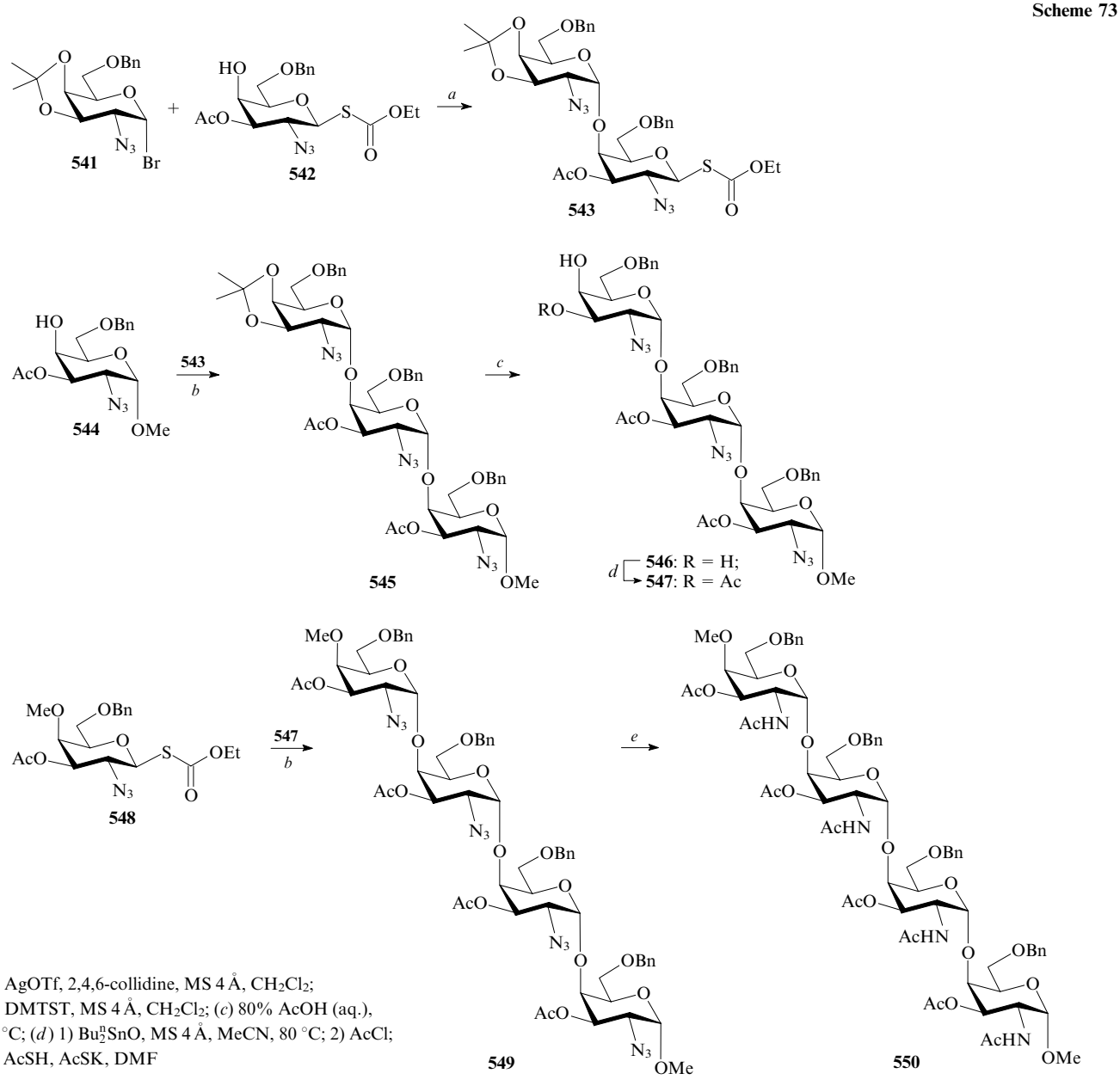


used to glycosylate 3-bromopropanol. The replacement of the bromine atom in the resulting compounds with the azido group gave oligogalactosides **531** and **532**.

VII.2. Synthesis of α-(1→4)-oligogalactosamines

This Section surveys studies devoted mainly to the synthesis of oligomers of galactosaminuronic acid, as in the case of α-(1→4)-oligogalactosides. However, in these studies, oligogalactosamines with different protection patterns served

Scheme 73



as intermediates for the synthesis of target structures. Therefore, these approaches are also applicable to the synthesis of free α-(1→4)-oligogalactosamines.

Shi-Shun *et al.*[118] described the synthesis of oligosaccharide fragments of capsular polysaccharide from *Salmonella typhi*. The α-glycosidic linkage between galactosamine residues was created *via* glycosylation with 2-azido-2-deoxygalactosyl xanthate containing the 3,4-O-isopropylidene group as temporary protection. It should be noted that the α-stereoselectivity of glycosylation reactions was moderate. Although the β-anomer that formed as a by-product is not shown in the Schemes, it was produced in each glycosylation step. In the first step, the reaction of methyl galactoside **534** with donor **533** in the presence of DMTST gave α-digalactoside **535** (53% yield) along with β-anomer (16%). The isopropylidene deprotection and subsequent selective *p*-methoxybenzylation of the 3-OH group of diol **536** afforded acceptor **537**, which was used to prepare, on the one hand, trisaccharide, and, on the other hand, disaccharide **538**, which is a precursor of the target α-(1→4)-linked *N*-acetylgalactosaminuronic acid dimer (Scheme 71).

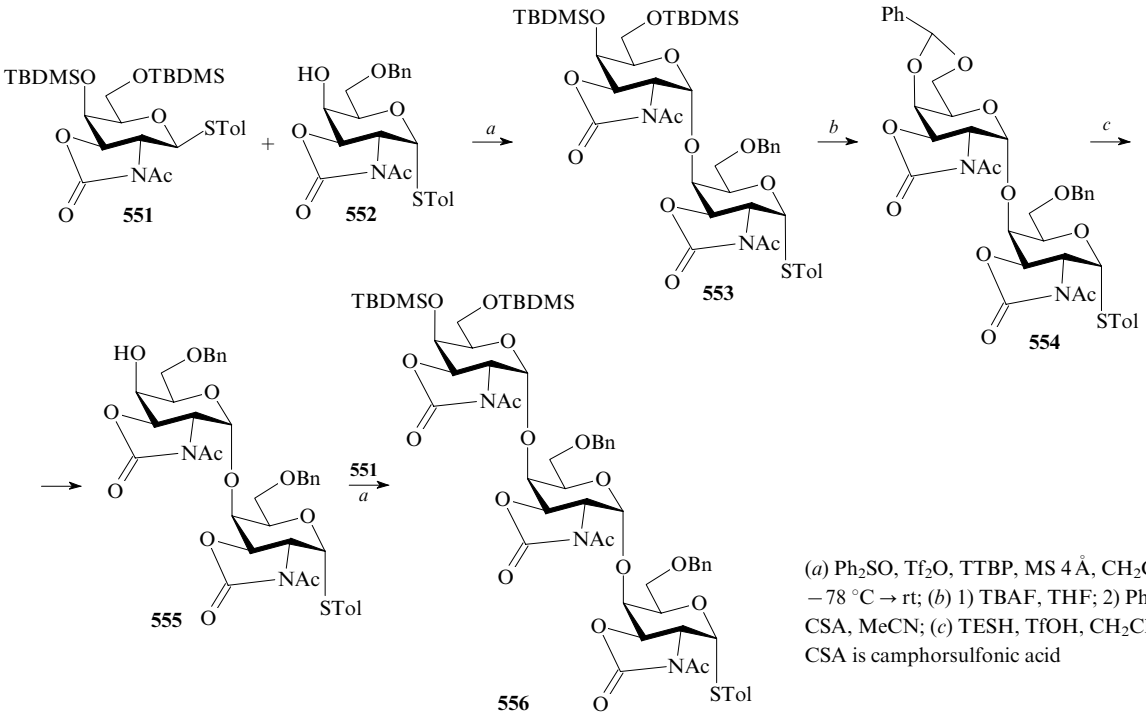
The chain elongation was performed *via* glycosylation of disaccharide acceptor **537** with donor **533**. The yield of target α-trisaccharide **539** was 51%; that of β-anomer was 17%. The further reaction sequence, similar to that shown in Scheme 71 for disaccharide **535**, was employed to convert compound **539** into derivative **540** — a precursor of the *N*-acetylalgalactosaminuronic acid trimer (Scheme 72).

The next oligomer, tetrasaccharide, was synthesized *via* the [1 + 2 + 1] scheme. This method differs from the syntheses of di- and trisaccharides described above in that it utilizes the acetyl group instead of the *p*-methoxybenzyl moiety to protect the 3-OH group (Scheme 73). After the orthogonal glycosylation of xanthate **542** with bromide **541** in the presence of AgOTf, disaccharide donor **543** was isolated in 54% yield along with the corresponding β-anomer (17%). The coupling of this donor with acceptor **544** gave trigalactoside **545** in 52% yield (and the β-anomer in 6% yield). The removal of isopropylidene protection from the latter followed by selective 3-O-acetylation of diol **546** produced acceptor **547**. Its glycosylation with donor **548** produced target tetrasaccharide **549** in 60% yield and the latter was transformed into α-(1→4)-tetra-*N*-acetylgalactosaminide **550** — a precursor of the *N*-acetylgalactosaminuronic acid tetramer.

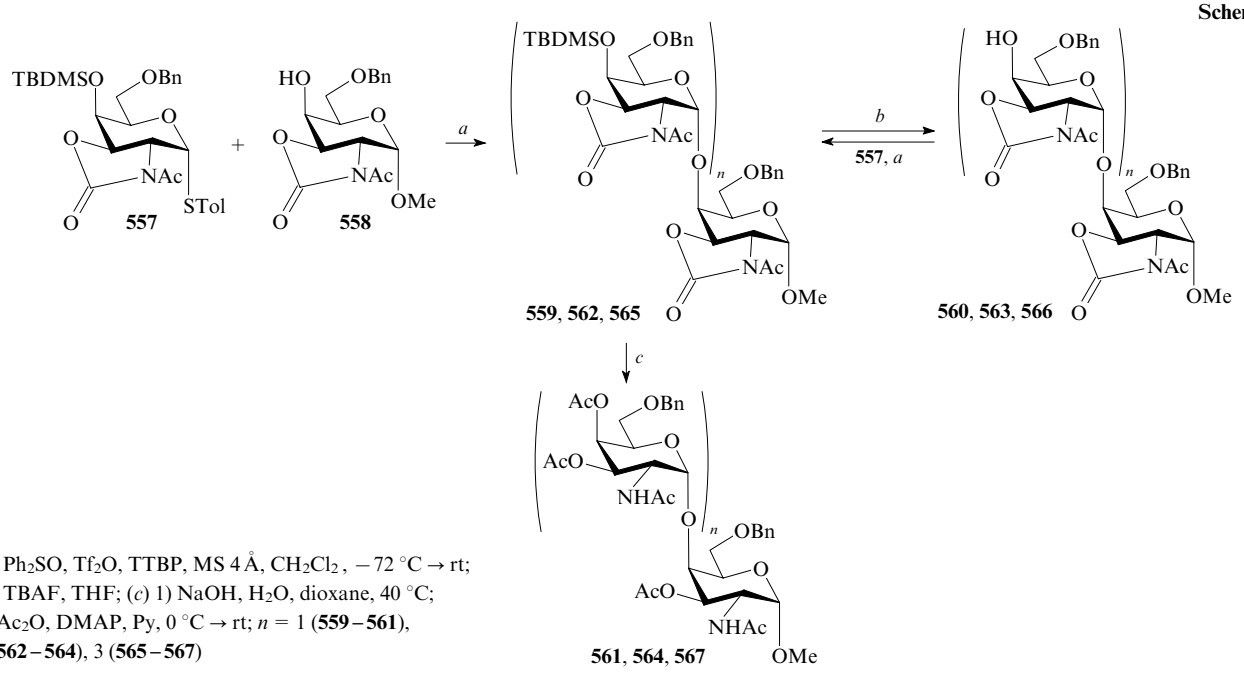
As opposed to the above-considered studies, in which galactosyl donors bearing the non-participating azido group at the C(2) atom were used to construct the α-linkage between galactosamine units, Yang and Ye[119] employed donors containing the 2-N,3-O-cyclocarbonate protecting group combined with the N-acetyl group. In rigid bicyclic donors of this type, the latter group cannot be involved in substitution reactions at the anomeric centre due to steric factors, thus providing high α-stereoselectivity of glycosylation with their participation. Thus, the glycosylation of acceptor **552** with structurally similar thioglycoside donor **551** under the preactivation protocol (see Scheme 22) gave disaccharide **553** in 74% yield, while the β-anomer was not detected (Scheme 74). The replacement of silyl groups in compound **553** by 4,6-O-benzylidene protection followed by its selective reductive cleavage in disaccharide **554** afforded digalactoside acceptor **555** in 80% yield. The glycosylation of the latter with the same donor **551**, also under preactivation conditions, produced exclusively α-trisaccharide **556** (68% yield).

In continuation of this work, Yang *et al.*[120] synthesized a series of oligosaccharides up to tetrasaccharide (compounds **560**, **563**, **566**) *via* chain elongation by successive attachment of one monosaccharide unit using donor **557**. This donor, unlike thioglycoside **551**, contains a combination of protecting groups, which allows the one-step conversion of the glycosylation product into a new glycosyl acceptor. Thus, the coupling of donor **557** with methyl glycoside **558** gave exclusively α-linked disaccharide **559** in 72% yield. The removal of the silyl group afforded acceptor **560**, which was also glycosylated with donor **557** to form trisaccharide **562** (61% yield). Tetrasaccharide **565** (53%

Scheme 74



Scheme 75



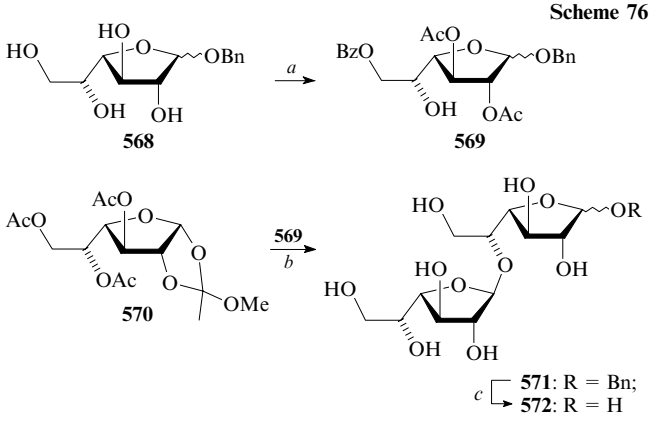
(*a*) Ph_2SO, Tf_2O, TTBP, MS 4 Å, CH_2Cl_2, −72 °C → rt; (*b*) TBAF, THF; (*c*) 1) NaOH, H_2O, dioxane, 40 °C; 2) Ac_2O, DMAP, Py, 0 °C → rt; *n* = 1 (**559 – 561**), 2 (**562 – 564**), 3 (**565 – 567**)

yield) was synthesized from trisaccharide **562** by repeating silyl deprotection and glycosylation steps. The cyclocarbonyl groups were removed from the oligosaccharides by alkaline hydrolysis, and the subsequent acetylation gave protected oligomers of acetylgalactosamine **561, 564** and **567** in 89%, 80% and 70% yields, respectively (Scheme 75).

VIII. Synthesis of oligosaccharides corresponding to fragments of galactomannan from *Aspergillus*

The first study [121] on the synthesis of oligosaccharide containing a β-(1→5)-glycosidic linkage between two galactofuranose residues dates back to 1977. In this publication, the authors described the preparation of β-(1→5)-digalactofuranoside **572**, although the aim was not to synthesize an oligosaccharide corresponding to a fragment of cell wall galactomannan from *Aspergillus*. Galactofuranoside **569** was constructed in three steps from unprotected precursor **568** without the isolation of intermediates, and its condensation with orthoester **570** was performed in the presence of mercuric bromide (Scheme 76). The reaction mixture was deacetylated, without the separation, and disaccharide **571** was isolated in low yield (12%). Subsequent debenzylation gave target product **572**.

Scheme 76

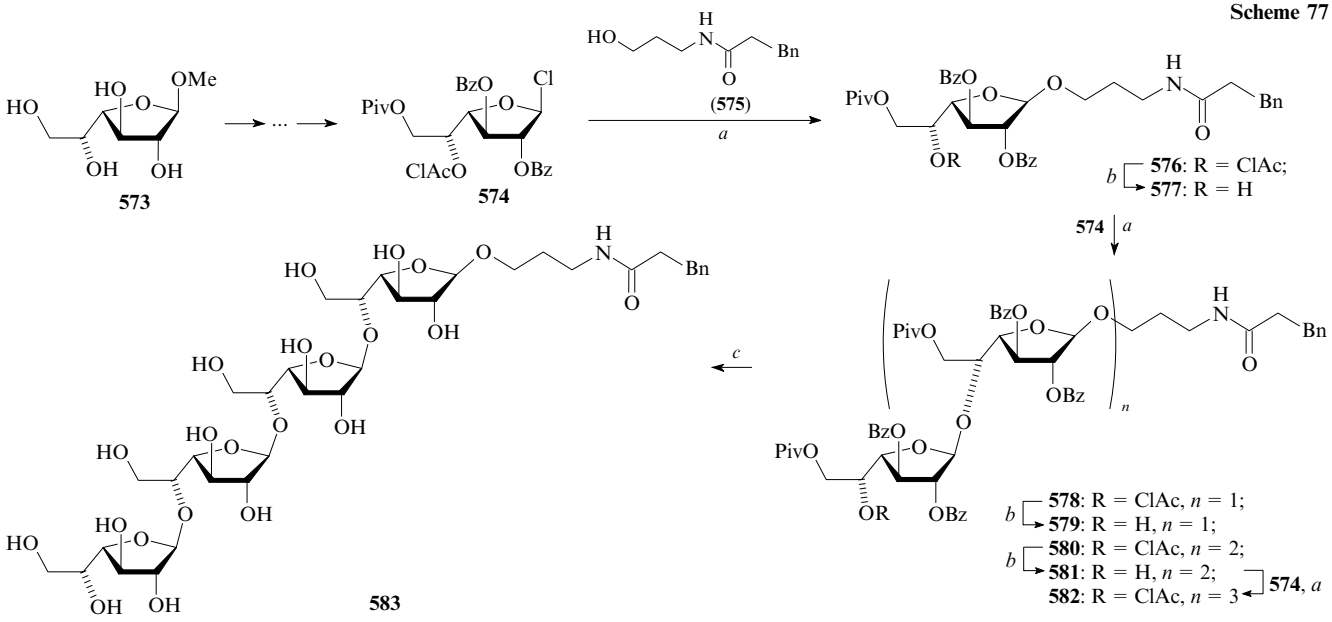


(*a*) 1) $PhC(OMe)_2NMe_2$, CH_3Cl; 2) Ac_2O, Py; 3) AcOH (aq.); (*b*) 1) $HgBr_2$, $MeNO_2$; 2) MeONa, MeOH; (*c*) H_2, Pd/C, EtOH, H_2O

The synthesis of longer β-(1→5)-oligogalactofuranosides by efficient glycosylation methods was described ten years later by Veeneman *et al.*[122, 123] A tetramer was synthesized [122] by successive chain elongation using galactofuranosyl chloride **574**, which contained the chloroacetyl group as temporary protection at the O(C5) atom and which was prepared from methyl galactofuranoside **573** in 7 steps. Then this donor was used in Helferich-type glycosylation with N-protected 3-aminopropanol **575** giving monogalactoside **576** in 95% yield. The removal of the chloroacetyl protecting group with hydrazine dithiocarbonate afforded acceptor **577** also in high yield. The repeated glycosylation and removal of the chloroacetyl group resulted in the successive construction (through the formation of primary chain elongation products **578** and **580**) of dimeric (**579**) and trimeric (**581**) glycosyl acceptors in 91% and 92% yields, respectively. The final glycosylation of trisaccharide acceptor **581** with donor **574** produced tetragalactoside **582** (92% yield), and the final unprotected oligosaccharide **583** was isolated in 97% yield after the alkaline treatment of tetramer **582** (Scheme 77).

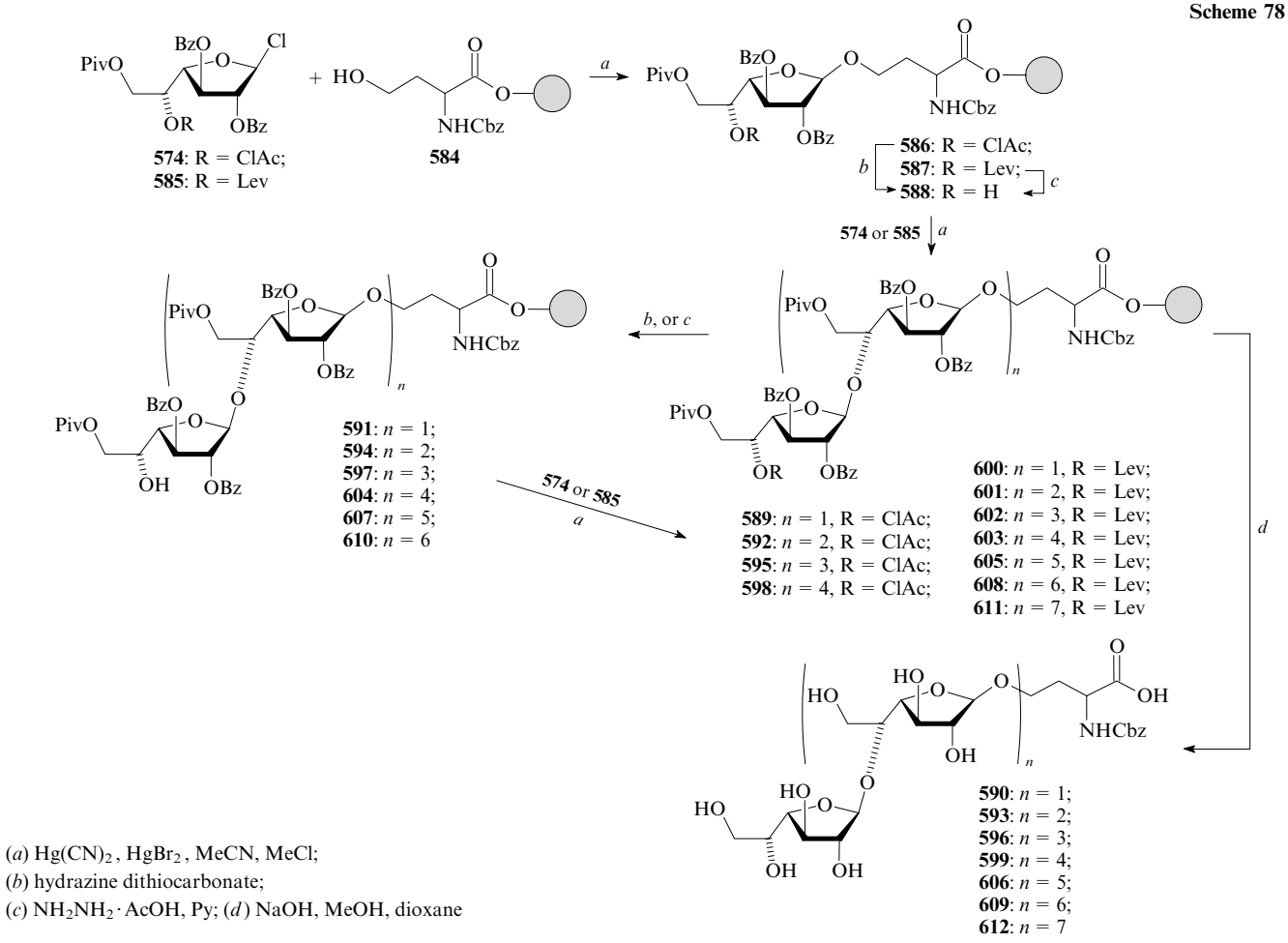
In the subsequent study, this research team [123] synthesized longer oligogalactofuranosides *via* a solid-phase approach. In the first step, chloride **574** reacted with amino acid derivative **584** attached to a polymer support (Scheme 78). The chloroacetyl group was removed from glycoside **586** and then acceptor **588** was introduced into the reaction sequence similar to that shown in Scheme 77. This resulted in the synthesis of disaccharide **589** and then disaccharide acceptor **591**. Then the reaction cycle was repeated: disaccharide acceptor **591** → trisaccharide **592** → trisaccharide acceptor **594** → tetrasaccharide **595** → tetrasaccharide acceptor **597** → pentasaccharide **598**. Oligosaccharides **589**, **592**, **595** and **598** served also as the starting compounds for the preparation of free oligogalactofuranosides **590**, **593**, **596** and **599**. However, the authors found that pentasaccharide **598** contained a significant amount of shorter oligogalactofuranosides. In order to

Scheme 77



(*a*) $Hg(CN)_2$, $HgBr_2$, MeCN; (*b*) hydrazine dithiocarbonate; (*c*) NaOH, MeOH, dioxane

Scheme 78



(*a*) $Hg(CN)_2$, $HgBr_2$, MeCN, MeCl;
(*b*) hydrazine dithiocarbonate;
(*c*) $NH_2NH_2 \cdot AcOH$, Py; (*d*) NaOH, MeOH, dioxane

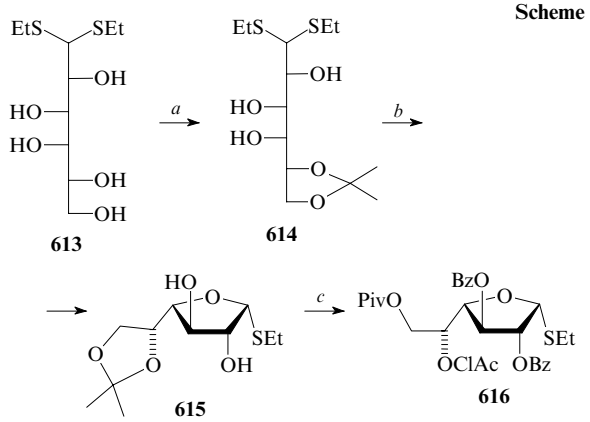
decrease the amount of short oligomers, the free hydroxyl group of the unreacted acceptor was blocked with the acetyl protecting group after each glycosylation event (not shown in the Scheme). However, under the acetylation conditions used (Ac_2O, Py, DMAP), the chloroacetyl group gave quaternization products with pyridine. Therefore, the levulinoyl protecting group was employed instead of the chloroacetyl moiety in subsequent reactions, and all steps,

Table 1. Overall yields of free β-(1→5)-oligogalactofuranosides (see Scheme 78).

Product (from precursors with R = Lev)	*n*	Yield (%)
590	1	90
593	2	77
596	3	65
599	4	50
606	5	36
609	6	28
612	7	23

including intermediate acetylation, were repeated for chloride **585**. The reaction sequence was as follows: monosaccharide **587** → monosaccharide acceptor **588** → disaccharide **600** → disaccharide acceptor **591** → trisaccharide **601** → trisaccharide acceptor **594** → tetrasaccharide **602** → tetrasaccharide acceptor **597** → pentasaccharide **603** → pentasaccharide acceptor **604** → hexasaccharide **605** → hexasaccharide acceptor **607** → heptasaccharide **608** → heptasaccharide acceptor **610** → octasaccharide **611**. After deprotection, oligosaccharides composed of two to eight monosaccharide units were obtained. Their overall yields are given in Table 1.

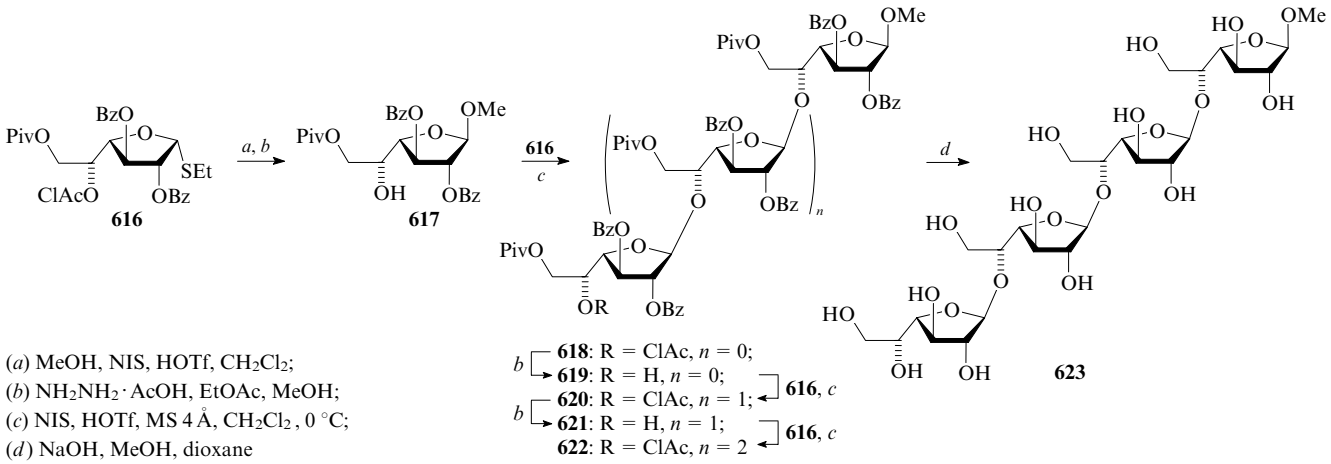
Scheme 79



(*a*) $Me_2C(OMe)_2$, CSA, DMF; (*b*) HgO, $HgCl_2$, MeCN;
(*c*) 1) BzCl, Py, dioxane, 0 °C; 2) AcOH, H_2O, 60 °C;
3) PivCl, Py, dioxane, 0 °C; 4) $(ClAc)_2O$, $NaHCO_3$, DMF, 20 °C

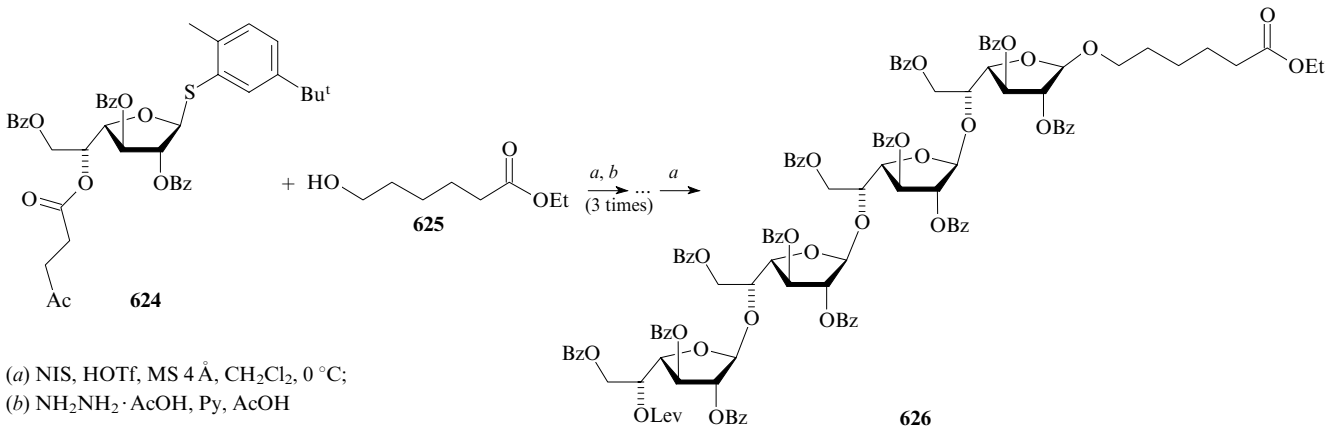
Zuurmond *et al.*[124] continued research on the synthesis of oligogalactofuranosides. They used thioglycoside instead of the chloride as the donor for oligosaccharide chain elongation. According to the authors, this replacement should improve the yields of the products in the glycosyla-

Scheme 80



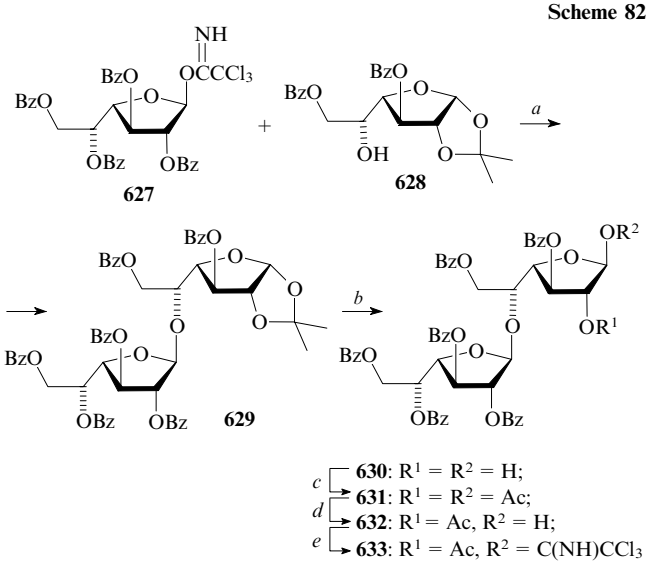
(*a*) MeOH, NIS, HOTf, CH_2Cl_2;
(*b*) $NH_2NH_2 \cdot AcOH$, EtOAc, MeOH;
(*c*) NIS, HOTf, MS 4 Å, CH_2Cl_2, 0 °C;
(*d*) NaOH, MeOH, dioxane

Scheme 81



tion step, since this research team had a positive experience with glycosylation of sugars using thioglycosides in the presence of NIS and HOTf.[125] For this purpose, 5,6-isopropylidene-protected derivative **614** was synthesized from galactose dithioacetal **613** and then cyclized with mercuric chloride and mercuric oxide to form thiogalactofuranoside **615** (68% yield). The subsequent selective protection pattern gave rise to the required synthetic building block **616**, which differed from the chloride employed previously only by the presence of the thioethyl group at the anomeric position (Scheme 79).

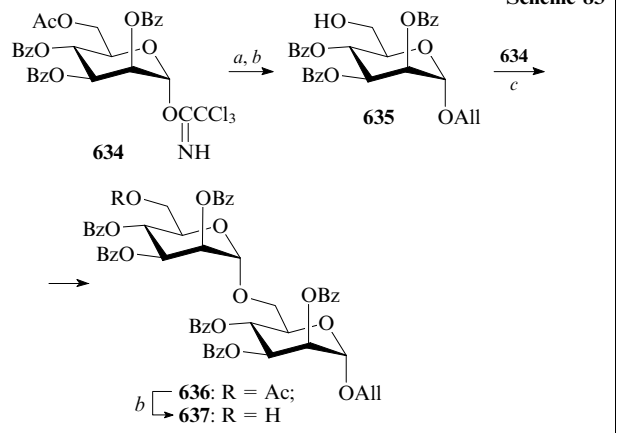
Scheme 82



(*a*) TMSOTf, MS 4 Å, CH_2Cl_2, −20 °C → rt;
(*b*) $CHCl_3$ – TFA (10 : 1); (*c*) Ac_2O, Py; (*d*) $BnNH_2$, THF;
(*e*) CCl_3CN, K_2CO_3, CH_2Cl_2

The oligosaccharide chain was assembled *via* successive elongation by one unit. The glycosylation of methanol in the presence of NIS and HOTf followed by the selective removal of chloroacetyl protection with hydrazine acetate produced terminal building block **617** in 73% yield over two steps. The repeated glycosylation and dechloroacetylation gave oligosaccharides **618** and **620**, which were converted into dimeric (**619**, 76% yield) and trimeric (**621**, 79%) acceptors. The final chain elongation step afforded tetragalactoside **622** in 94% yield. Free methyl glycoside **623** was prepared by alkaline hydrolysis of acyl protecting groups in tetramer **622** (Scheme 80).

Scheme 83



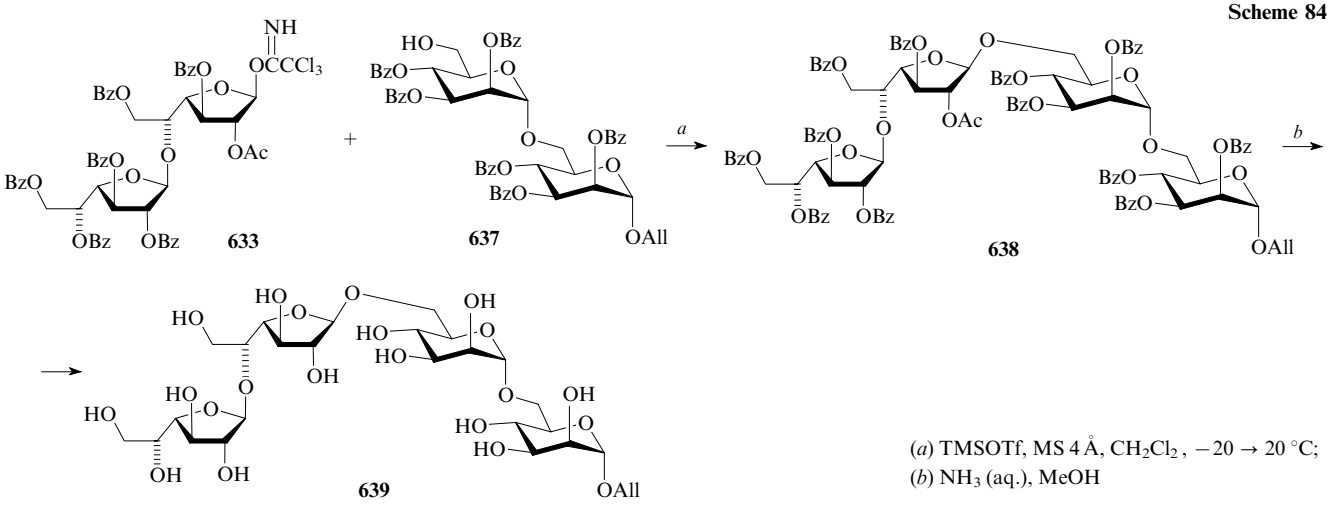
(*a*) AllOH, TMSOTf, CH_2Cl_2; (*b*) 1% AcCl, CH_2Cl_2, MeOH;
(*c*) TMSOTf, MS 4 Å, CH_2Cl_2, −20 °C → rt

Cattiaux *et al.*[126] used a similar scheme of chain assembly with the participation of donor **624** (Scheme 81). The latter contained the levulinoyl residue at the 5 position as temporary protection and benzoyl groups as permanent protection. The oligosaccharide chain elongation was accomplished starting from hydroxy ester **625** to prepare tetrasaccharide **626**. However, the yields in glycosylation steps were lower than those achieved in the above-considered study:[124] 68%, 60%, 68% and 75% for mono-, di-, tri- and tetragalactosides, respectively.

The first synthesis of an oligosaccharide composed of both the oligogalactofuranoside and oligomannoside fragments was publsihed [127] in 2005. Digalactofuranoside donor building block **633** was constructed as follows. The coupling of trichloroacetimidate donor **627** with acceptor **628** produced digalactoside **629** in 93% yield. The latter was converted into trichloroacetimidate **633** through the intermediate formation of diol **630**, diacetate **631** and hemiacetal **632** (Scheme 82).

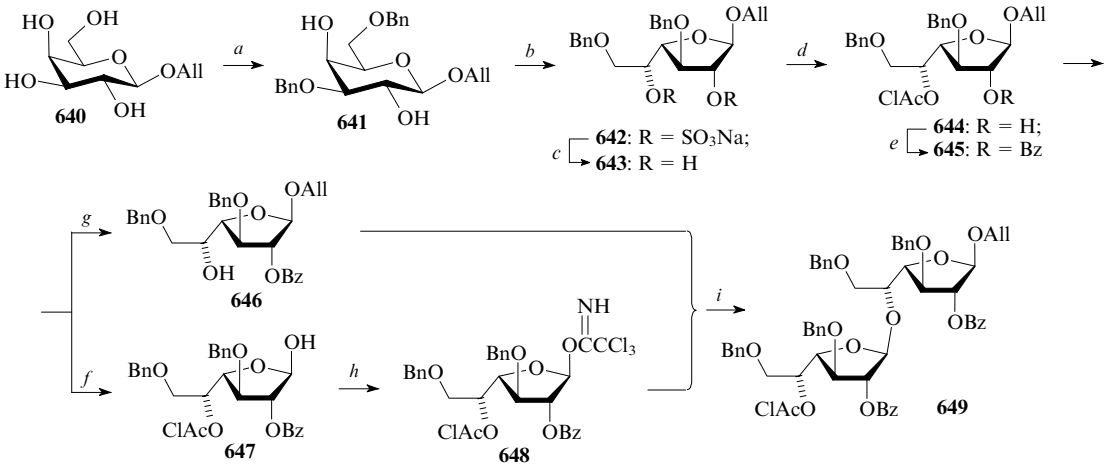
A dimannoside fragment was constructed using trichloroacetimidate **634** as the glycosyl donor. The glycosylation of allyl alcohol with this donor followed by acidic

Scheme 84



(*a*) TMSOTf, MS 4 Å, CH_2Cl_2, −20 → 20 °C;
(*b*) NH_3 (aq.), MeOH

Scheme 85



(*a*) 1) $(Bu^n_3Sn)_2O$, PhMe, Δ; 2) BnBr, TBAI, 100 °C; (*b*) 1) $Py\cdot SO_3$, HSO_3Cl, DMF, 40 °C; 2) $NaHCO_3$ (aq.); (*c*) IR-120 resin (H^+ form), dioxane, Δ; (*d*) ClAcCl, Py, −78 → 0 °C; (*e*) BzCl, Py, CH_2Cl_2; (*f*) $PdCl_2$, MeOH; (*g*) $(NH_2)_2C(S)$, 2,4,6-collidine, MeOH; (*h*) CCl_3CN, DBU, CH_2Cl_2; (*i*) TMSOTf, MS 4 Å, CH_2Cl_2, −78 → −20 °C

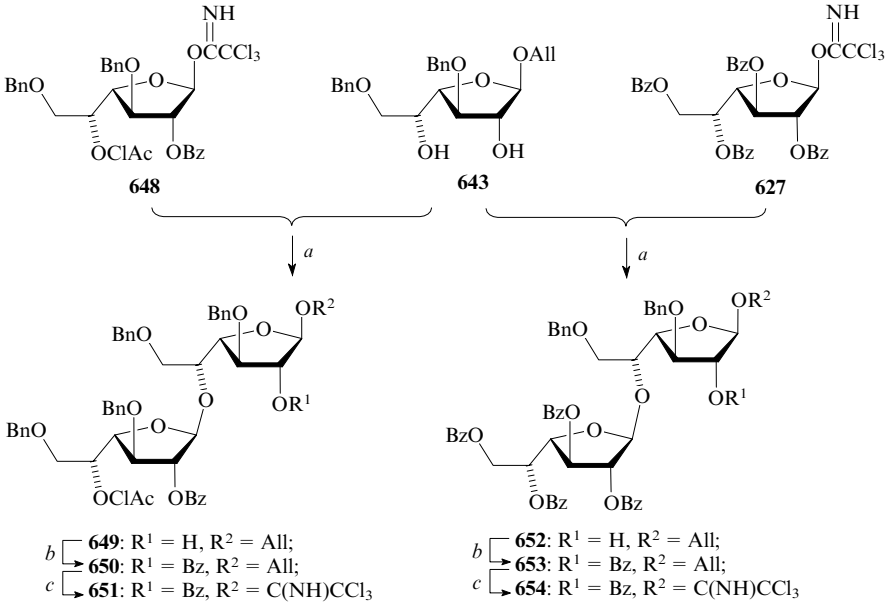
removal of the acetyl group at the O(C6) atom afforded mannoside **635** in a total yield of 81%. The coupling of the same donor with acceptor **635** gave dimannoside **636**, and the removal of the acetyl group from the latter produced target acceptor building block **637** in 90% yield over two steps (Scheme 83).

In the final step, the [2 + 2]-glycosylation of acceptor **637** with donor **633** gave rise to target protected tetrasaccharide **638** in 85% yield. All protecting groups, except for the allyl one, were removed by alkaline hydrolysis with aqueous ammonia in methanol (87% yield) (Scheme 84).

Two isomeric pentasaccharides containing an oligogalactofuranoside chain attached at different positions of the mannose residue were synthesized at the Laboratory of Glycoconjugate Chemistry of the ZIOC RAS.[128] The recently discovered [129, 130] pyranoside-into-furanoside rearrangement that occurs during sulfation made it possible to convert free allyl galactopyranoside **640** into partially protected allyl galactofuranoside **643** through a rather small number of steps. Starting pyranoside **640** was selectively benzylated to form compound **641**. The latter was rearranged into product **642** by the treatment with the complex $Py\cdot SO_3$ under acidic conditions followed by desulfation (Scheme 85). Furanoside **643**, which was obtained in 59% yield over two steps, was selectively chloroacetylated at the 5 position, and the unreacted hydroxyl group at the C(2) atom was benzoylated, resulting in the formation of allyl galactoside **645**. The removal of the allyl group from monosaccharide **645** followed by the reaction of hemiacetal **647** with trichloroacetonitrile gave imidate **648** (reaction products were obtained in 67% and 88% yields), while the removal of the chloroacetyl group afforded acceptor **646**. The coupling of donor **648** with acceptor **646** produced disaccharide **649** in 68% yield.

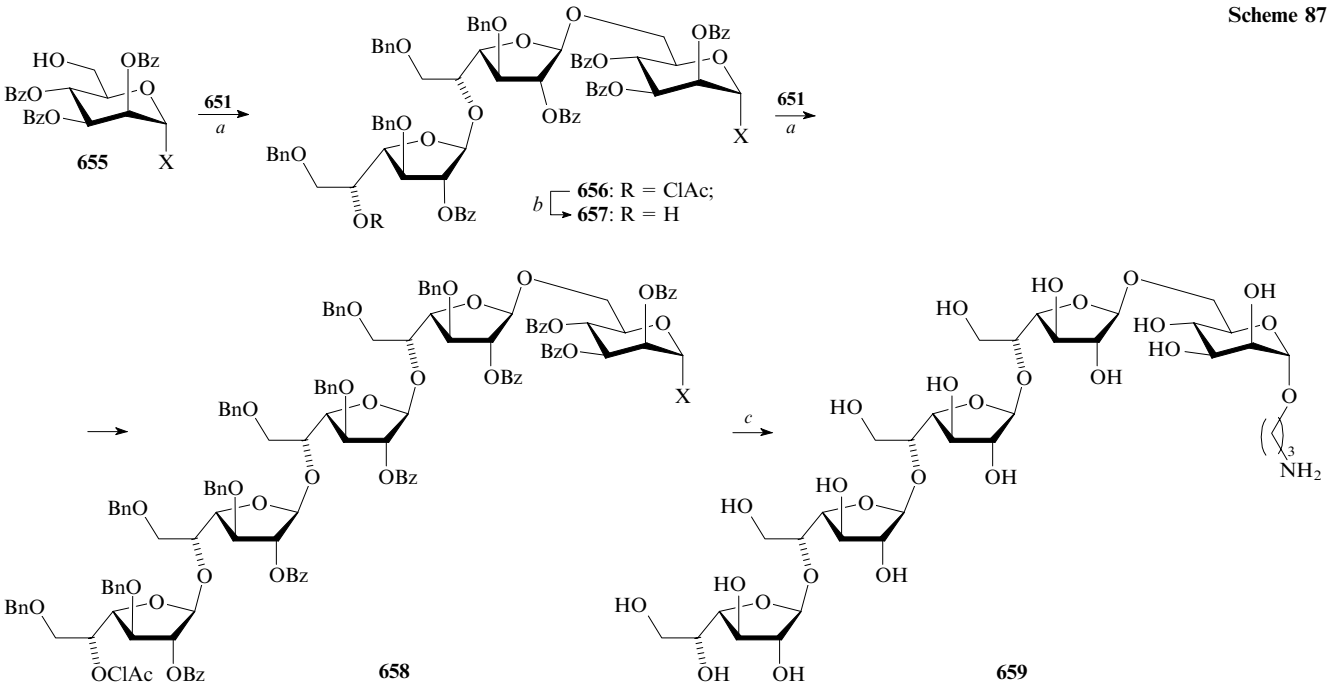
The possibility of selective 5-O-chloroacetylation of compound **643** brought the authors to perform selective glycosylation of this compound. The following two donor were chosen for this purpose: imidate **648** that has been used previously and totally benzoylated analogue **627**. Actually, the glycosylation occurred selectively at the 5-OH group, while the (1→2)-linked product formed in trace amounts and was easily separated by chromatography (Scheme 86).

Scheme 86



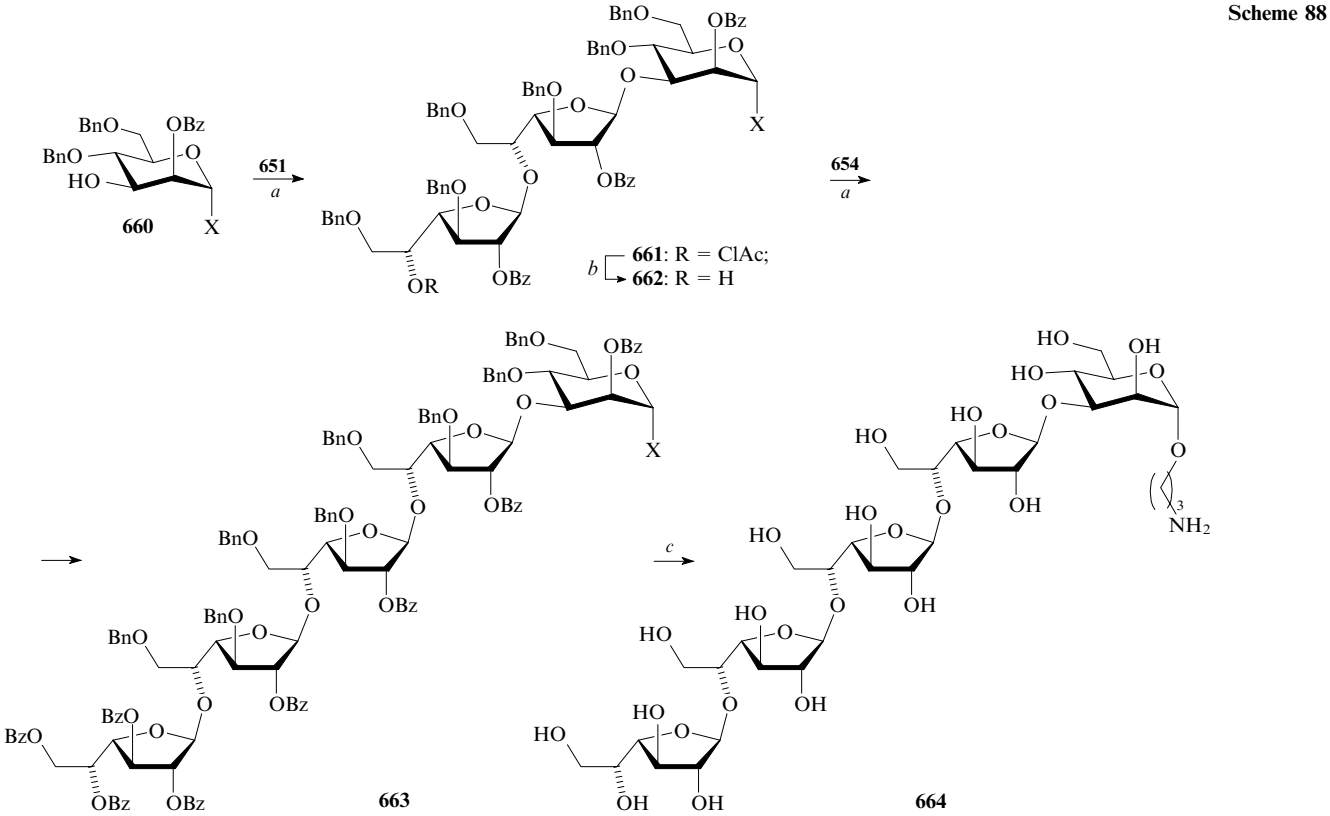
(*a*) TMSOTf, MS AW-300, CH_2Cl_2, −78 → −20 °C; (*b*) BzCl, Py, CH_2Cl_2; (*c*) 1) $PdCl_2$, MeOH; 2) CCl_3CN, DBU, CH_2Cl_2

Scheme 87



(*a*) TMSOTf, MS 4 Å, CH_2Cl_2, −78 → −20 °C; (*b*) $(NH_2)_2C(S)$, 2,4,6-collidine, MeOH; (*c*) 1) H_2, Pd/C, MeOH, EtOAc; 2) MeONa, MeOH, then NaOH (aq.); X = $O(CH_2)_3NHC(O)CF_3$

Scheme 88



(*a*) TMSOTf, MS AW-300, CH_2Cl_2, −78 → −20 °C; (*b*) $(NH_2)_2C(S)$, 2,4,6-collidine, MeOH; (*c*) 1) H_2, Pd/C, MeOH, EtOAc; 2) MeONa, MeOH, then H_2O; X = $O(CH_2)_3NHC(O)CF_3$

The yields of the products were also comparable with those obtained in the glycosylation of acceptor **646**: 65% for digalactoside **649** and 62% for compound **652**. Then both allyl glycosides were benzoylated to form products **650** and **653**, which were converted into glycosyl donors **651** and **654** by two-step replacement of the allyl group with the trichloroacetimidate one.

The synthetic building blocks constructed according to this scheme were used for the assembly of the oligosaccharide chain of target pentasaccharides **659** and **664**. The former pentasaccharide was constructed as follows. Mannoside acceptor **655** bearing the free 6-OH group was glycosylated with imidate **651**. Then the chloroacetyl group was removed from trisaccharide **656**, which was isolated in 85% yield, to form acceptor **657**. This acceptor was glycosylated with the same donor giving pentasaccharide **658** (71% yield). The complete deprotection *via* hydrogenolysis and alkaline hydrolysis afforded free pentasaccharide **659** (Scheme 87).

Pentasaccharide **664** containing a (1→3)-linkage between the mannose and galactose residues was synthesized in almost the same manner. In the first step, the 3-O-glycosylation of acceptor **660** gave trisaccharide **661** in 60% yield followed by the removal of the chloroacetyl protecting group. In the final glycosylation reaction of acceptor **662**, imidate **654** containing benzoyl protecting groups served as the glycosyl donor. Pentasaccharide **663** was isolated in 80% yield and the removal of all protecting groups from the latter gave free pentasaccharide **664** (Scheme 88).

IX. Conclusion

The data presented in this review demonstrate that all essential cell wall polysaccharide components from the fungi Candida and Aspergillus have attracted attention, to one degree or another, of synthetic chemists. Thus, numerous studies were focused on the synthesis of oligosaccharides corresponding to various structural motifs of mannans from Candida and other yeast species. Virtually all types of oligosaccharide structures found in these glycoproteins — linear and branched, composed of α-linked mannose residues — were successfully synthesized. During the past decade, significant progress was made in the synthesis of oligosaccharides containing β-(1→2)-oligomannoside chains, which were considered as one of the challenges in chemical synthesis at the end of the 20th century. Since that time, homo-β-(1→2)-oligomannosides, phosphorylated β-(1→2)-oligomannosides and mixed oligomannosides containing both α- and β-(1→2)-linked fragments have been accessible to investigation.

Known methods for the construction of linear β-(1→3)-oligoglucosides (the development of these methods, including those using ionic liquids,[131] is still in progress) provide an efficient route to oligosaccharides, which are comparable in length with the low-molecular-weight natural β-(1→3)-glucan laminaran isolated from brown algae. Synthetic oligosaccharides of this type are widely used as model compounds in research on the mechanisms of biological activity of β-(1→3)-glucans, as well as in the design of antifungal vaccines.[57] Another important field of application of synthetic oligoglucosides structurally related to fungal β-glucans is the development of enzyme immunoassay diagnostic kits[132] in order to replace commonly used kits for LAL-based assays.[133 – 136]

Methods for the synthesis of chitooligosaccharides are quite well developed. These methods are applicable to the preparation of both homooligomers composed only of N-acetylated or free glucosamine residues and oligosaccharides with specified distribution patterns of N-acetyl groups in the chain.

Despite a limited number of studies concerned with oligosaccharides related to galactomannan fragments and, particularly, α-(1→3)-glucan from the fungi Aspergillus, key issues of the synthesis of such structures are, in our opinion, have been successfully solved and the synthesis of certain oligosaccharides of this type should not present significant difficulties. Available modern synthetic approaches to such oligosaccharides would be expected to serve as the basis for the development of improved methods for the detection of the causative agent of aspergillosis that will be superior to the currently employed methods possessing certain drawbacks.[137, 138]

Only the recently discovered galactosaminogalactan from Aspergillus fumigatus has escaped so far attention of synthetic chemists. Quite numerous publications covered in Section VII of the present review were devoted to methods for the synthesis of α-(1→4)-linked protected oligomers of galactose or galactosamine, which usually serve as intermediates for the construction of target products belonging to other types of natural polysaccharides, most frequently, of oligomers of the corresponding uronic acids. Meanwhile, studies aimed at the synthesis of oligosaccharides corresponding to structural motifs of galactosaminogalactan are absent in the literature. However, investigations along this line would be expected to be published in the near future taking into account important biological functions of this glycopolymer,[27, 139, 140] detailed investigation of which requires appropriate model synthetic oligosaccharides, and its unusual structure challenging for synthetic chemists.

This work was supported by Russian Science Foundation (Grant No. 14-50-00126)

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