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New schemes for the synthesis of glycolipid oligosaccharide chains*

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Abstract: The driving force for the constant improvement and development of synthetic methodologies in carbohydrate chemistry is the importance of natural oligosaccharide chains in numerous biological phenomena such as cell growth, differentiation, adhesion, etc. Here, we report our syntheses of the spacer-armed oligosaccharides of sialylated *lacto*- and *neolacto*-, *globo*-, *ganglio*-, and sulfoglucuronylparagloboside-series, which include new rationally designed synthetic blocks, efficient solutions for the stereoselective construction of glycosidic bonds, and novel protection group strategies.

INTRODUCTION

Natural oligosaccharides and glycoconjugates play a crucial role, acting as lectin receptors, in the process of cell adhesion. This makes synthetic oligosaccharides and neoglycoconjugates thereof (i.e., molecular probes in which an oligosaccharide is attached, via a spacer, to a label or carrier) indispensable tools for the research into the carbohydrate lectin interactions to determine the structural features responsible for specific recognition of carbohydrate ligands, define the binding topology, and understand the biology functions and mechanisms of action of the corresponding natural glycoconjugates [1].

Recent studies of the mechanisms of cell recognition have revealed the key role of various natural glycoconjugates. Glycolipids of sialylated *lacto*- and *neolacto*-, *ganglio*-, *globo*-, and sulfoglucuronylparagloboside-series are of great interest in this area as they act as differentiation, growth, cell adhesion, and signal transduction regulators [2].

In this communication, we overview the schemes which we recently developed for the syntheses of the linear and branched sialylated *lacto*- and *neolacto*-oligosaccharides **1–9**, glycoprotein *O*-chains related tetrasaccharide **10**, the gangliosides GM1 **11** and Fuc-GM1 **12**, the globoside Gb_5 **13**, and the pentasaccharide sulfoglucuronyl paraglobosides **14** and **15** (glycolipid antigens HNK-1). The target compounds were obtained as the spacer-armed β-2-aminoethyl and β-3-aminopropyl glycosides suitable for further preparation of various labeled derivatives and neoglycoconjugates. The resulting molecular probes are being used to study the carbohydrate-binding proteins of selectin and galectin families, and the neurobiology processes mediated by HNK-1 carbohydrates.

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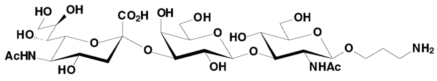

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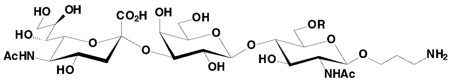

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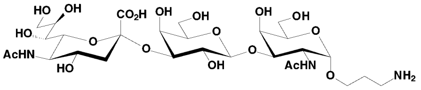
3 R = SO_3^-



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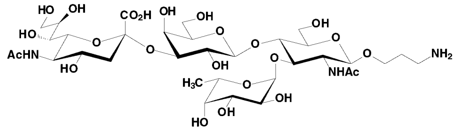

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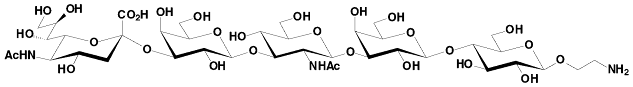

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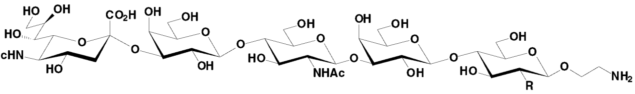
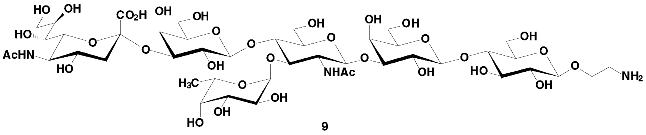


7 R = OH
8 R = NHAc



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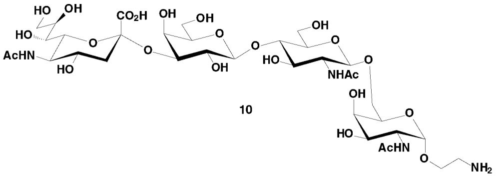

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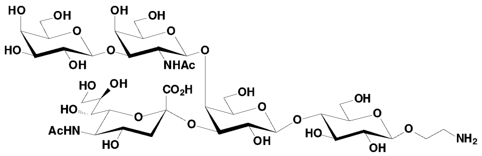

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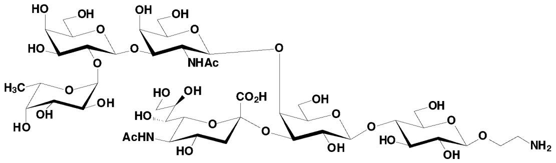

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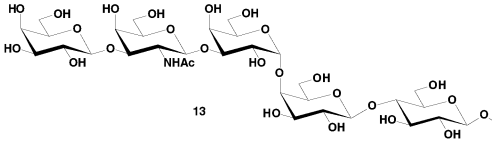

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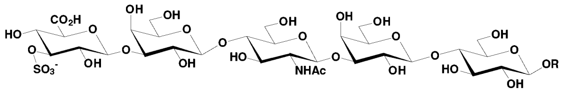


14 R = $CH_2CH_2CH_3$
15 R = $CH_2CH_2NH_2$

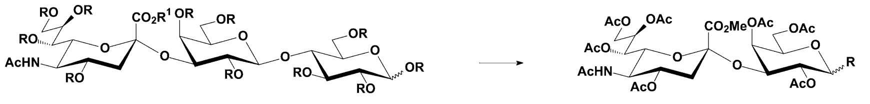
RESULTS AND DISCUSSION

The syntheses of the glycosyl ceramides related to the oligosaccharides **6** [3], **7** [4], **9** [5], **11** [6], **12** [7] **13** [8], and **14** [9,10] have been described earlier. Our syntheses of the spacer-armed oligosaccharides **1**–**15** involved new strategies in the design of the sialyl-galactosyl, glucuronyl-galactosyl, and galactosyl-galactosaminyl disaccharide blocks; efficient solutions for the stereoselective construction of the key (β-glucosaminyl, β-galactosaminyl, and β-glucuronyl) glycosidic bonds; novel protection group pathways, e.g., regioselective liberation of the 3-OH group in the glucuronic acid residue, and the choice of the masked form of spacer. As the latter, the 2-azidoethyl or 3-triflouroacetamidopropyl aglycons were selected in the present work. The availability of 2-azidoethyl glycosides from the corresponding allyl glycosides is an advantage, and we have documented the efficiency of such an approach to the syntheses of spacer-armed oligosaccharides [11].

Syntheses of sialylated lacto- and neolacto oligosaccharides 1–9 and glycoprotein *O*-chains related tetrasaccharide 10

The titled oligosaccharide chains, both linear and branched, have been of constant interest due to their unique biological activity, which is mainly associated with the presence of Neu5Ac residue. It has been well recognized that in the synthesis of sialylated oligosaccharides of these groups, the efficient and stereoselective construction of the Neu5Ac-α-(2→3)-Gal linkage is the main problem, and many approaches have been elaborated in order to improve the yield of the glycosylation with Neu5Ac donors [12–14].

In our work we declined the construction of the sialyl-galactose disaccharide from monosaccharides as a laborious and not very efficient, in terms of overall yield, sequence. Within the alternative approach we studied the expeditious preparation of the sialyl-α-(2→3)-galactosyl disaccharide glycosyl donors from not monosaccharides but the trisaccharide sialyl-α-(2→3′)-lactose **16**, which already contains the requisite sialyl-α-(2→3)-galactose fragment (Scheme 1). The trisaccharide **16** is an available compound which can be isolated from natural sources at laboratory [15] and industrial scale [16].



16 R = H, R^1 = Na (3'-sialyllactose sodium salt)
17 R = Ac, R^1 = Me

18 R = α, β-OAc
19 R = α, β-OC(NH)CCl_3
20 R = β-SEt

Scheme 1 Transformation of 3′-sialyllactose trisaccharide into disaccharide glycosyl donors **19** and **20**.

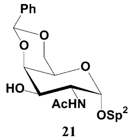
In order to cleave selectively the acetal-type galactoside linkage in the trisaccharide **16** but remain intact the ketal-type sialoside one, acetolysis of per-O-acetylated derivative **17** was studied, since the greater stability of sialoside linkage toward acetolysis as compared to hexapyranoside ones had been mentioned, in contrast to the well-known ease of its acidic hydrolysis [17–19].

The sialyl-α-(2→3′)-lactose sodium salt **16** (the product of Neose Technologies, Inc.) was subjected to total acid-catalyzed O-acetylation (5 % H_2SO_4 in Ac_2O at 40 °C) to give the expected acid in 96 % yield with no lactone formation, then the carboxy group was methylated with diazomethane into **17**. Thorough experimentation with the nature and concentration of various protic and Lewis acidic catalysts (H_2SO_4, BF_3•Et_2O, Bu_2BOTf, $ZnCl_2$, $AlCl_3$, $FeCl_3$, $SnCl_4$, $TiBr_4$, TMSOTf) as well as the reaction temperature and time showed that boron-derived electrophiles were the reagents of choice. Thus, acetolysis of the trisaccharide **17** in neat acetic anhydride in the presence of 10 % v/v of BF_3•Et_2O at 80 °C for 12 h gave the disaccharide **18** in 39 % yield, and acetolysis in the presence of Bu_2BOTf (10 equiv) at 70 °C for 3 h afforded **18** in 49 % yield.

The disaccharide **18** thus obtained was then easily transformed into the glycosyl-donors, trichloroacetimidate **19** and thioglycoside **20**, by anomeric deacetylation with hydrazine acetate followed by treatment with Cl_3CCN/DBU (→**19**, 76 %) or mercaptolysis with EtSH and BF_3•Et_2O (→**20**, 86 %), respectively. Compound **20** could also be obtained from the trichloroacetimidate **19** by the reaction with EtSH in the presence of TMSOTf and MS-4A (96 %).

Thus, the disaccharide sialyl-galactosyl donors **19** and **20** were prepared from the readily available trisaccharide **16** in 5 and 4 steps in 30–40 % overall yields, respectively, which are much higher than those in known syntheses by coupling of *N*-acetylneuraminic acid and D-galactose blocks.

The preparation of GlcNAc- and Fuc-GlcNAc-containing di-, tri-, and tetrasaccharide glycosyl acceptors **21**–**29** included the use of mono- and disaccharide donors with *N*-tricloroacetyl-D-glucosamine thioglycoside moiety. Systematic studies by others [20] and us [21] have revealed such a type of donors to be very efficient for stereospecific incorporating a β-D-GlcNAc residue into an oligosaccharide chain, even for glycosylations of low-reactive glycosyl acceptors with benzoyl-protected neighboring hydroxy groups. Furthermore, *N*-trichloroacetyl-protected sialyl-oligosaccharides can be deblocked directly in a single step by treatment with alkali, in contrast to *N*-phthaloyl-protected ones.



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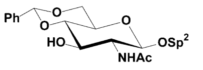

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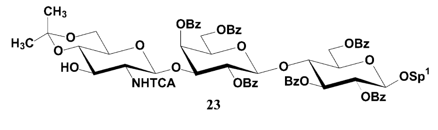

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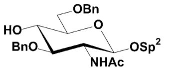

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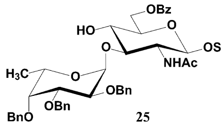

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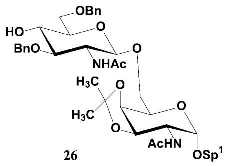

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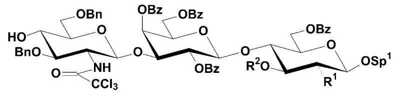
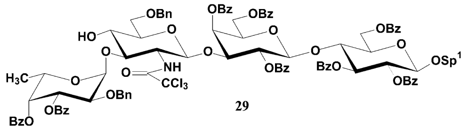


27 R^1 = OBz, R^2 = Bz
28 R^1 = NHAc, R^2 - Bn

$Sp^1 = CH_2CH_2N_3$, $Sp^2 = CH_2CH_2CH_2NHC(O)CF_3$



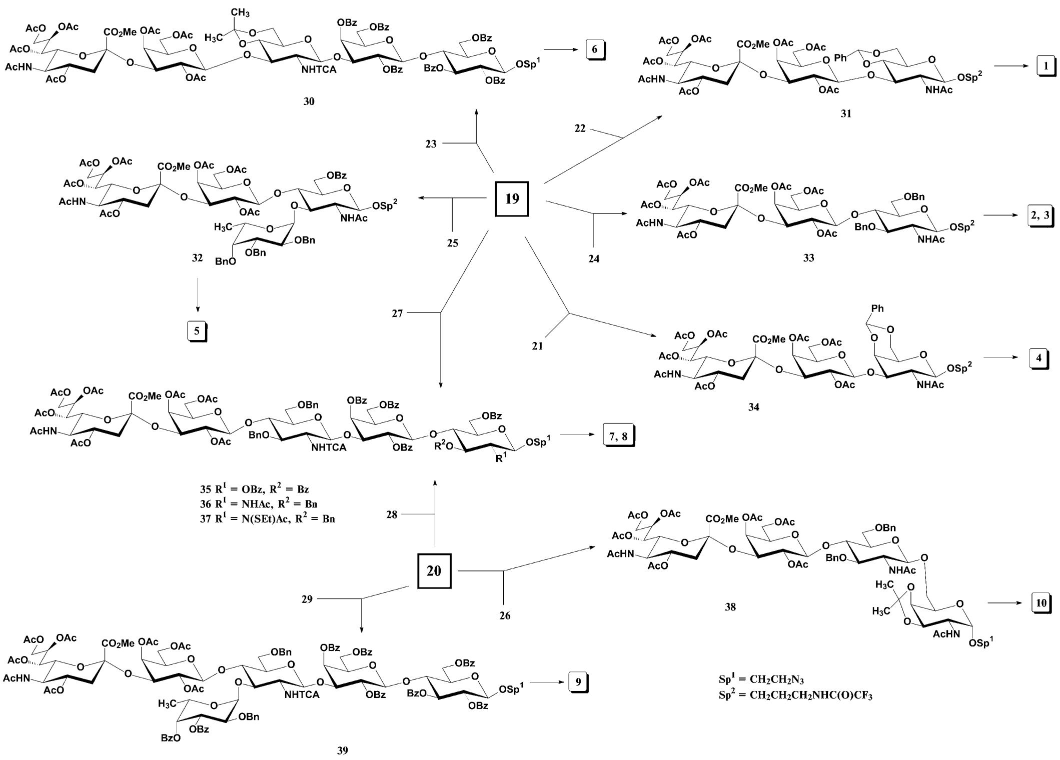
29

In order to achieve efficient introduction of protecting groups in the course of the preparation of compounds **21**–**29**, efficient methods were developed for the benzylation of monosaccharide derivatives bearing base-labile *N*-trichloroacetyl group [21] and the opening of 4,6-*O*-benzylidene acetals of hexapyranosides into the corresponding 4-hydroxy,6-*O*-benzyl derivatives. Particularly, it was found [22] that the acidic reagent formed in situ from anhydrous $AlCl_3$ and H_2O in 3:1 ratio is much more efficient promoter for the reductive opening with $Me_3N{\cdot}BH_3$ in tetrahydrofurane than the $AlCl_3$ alone as in the original procedure (see the refs. cited in [22]).

The key step of the preparation of the tetrasaccharide acceptor **29** was 3-*O*-fucosylation of ethyl 4,6-*O*-benzylidene-1-thio-2-trichloroacetamido-β-D-glycopyranoside [21] by 2-*O*-benzyl-3,4-di-*O*-benzoyl-α-L-fucopyranosyl trichloroacetimidate [23]. This coupling proceeded in good 69 % yield to give the desired α-linked 3-*O*-fucosyl-glycosaminide disaccharide stereoselectively without any formation of the side product of SEt transfer, in contrast to some other related cases [21].

Study of glycosylation of acceptors **21**–**29** (Scheme 2) revealed that the optimal reaction conditions depended on the location of free OH-group to be glycosylated. Thus, the 3-*O*-glycosylation of the acceptors **21**–**23** by trichloroacetimidate **19** could be best performed when the 20 % excess of acceptor was used and the reaction was promoted by TMSOTf in CH_2Cl_2 in the presence of MS-4 Å at room temperature. In these conditions, the β-linked oligosaccharides **30**, **31**, and **34** were obtained in the yields of 71 % [21], 80 % [24], and 80 % [24], respectively.

On the contrary to above case, the 4-*O*-glycosylation with trichloroacetimidate **19** of the acceptors **24**, **25**, and **27** needed the use of excess of the donor **19** (2.1 equiv), performing the reaction in CH_2Cl_2 at low temperature of –20 °C, and promotion with $BF_3{\cdot}Et_2O$ (0.1 equiv with respect to the imidate **19**) in the presence of acid-washed molecular sieves MS AW-300. Under these conditions, the target β-linked oligosaccharides **33**, **32**, and **35** were obtained in the yields of 40 % [24], 56 % [24], and 81 % [21], respectively.



Scheme 2 Synthesis of spacer-armed sialylated oligosaccharides **1–10**.

Study of another donor, thioglycoside **20**, showed that it was more reliable than the imidate **19**. Thus, the coupling of the tetrasaccharide acceptor **29** with the imidate **19** (3 equiv) gave in the best case the sialyl Lewis X hexasaccharide **39** in 50 % yield while the glycosylation of **29** by thioglycoside **20** (2.7 eqiuv) under promotion with NIS, TfOH, and MS-4 Å afforded to **39** in 65 % yield.

Glycosylation of the acceptor **28** with thioglycoside **20** deserves special comments. The reaction was promoted with NIS, TfOH, and MS-4 Å in CH_2Cl_2, and gave ca. 20 % yield of the expected pentasaccharide **36** together with another pentasaccharide product (ca. 30 %). The ^1H and ^{13}C NMR analysis of the latter with the use also of our previous observation [25] allowed determining its structure as the *N*-thioethylated derivative **37**. Since this side *N*-thioethylation reaction could not be avoided, we sought for the conditions for the efficient **37** → **36** conversion and found that treatment with the excess of thiourea in 3:1 MeOH–AcOH for 30 min at room temperature was quite reliable protocol [26]. Thus, condensation of **20** with **28** followed by dethioethylation of the crude reaction products gave the pentasaccharide **36** in total yield of 48 %.

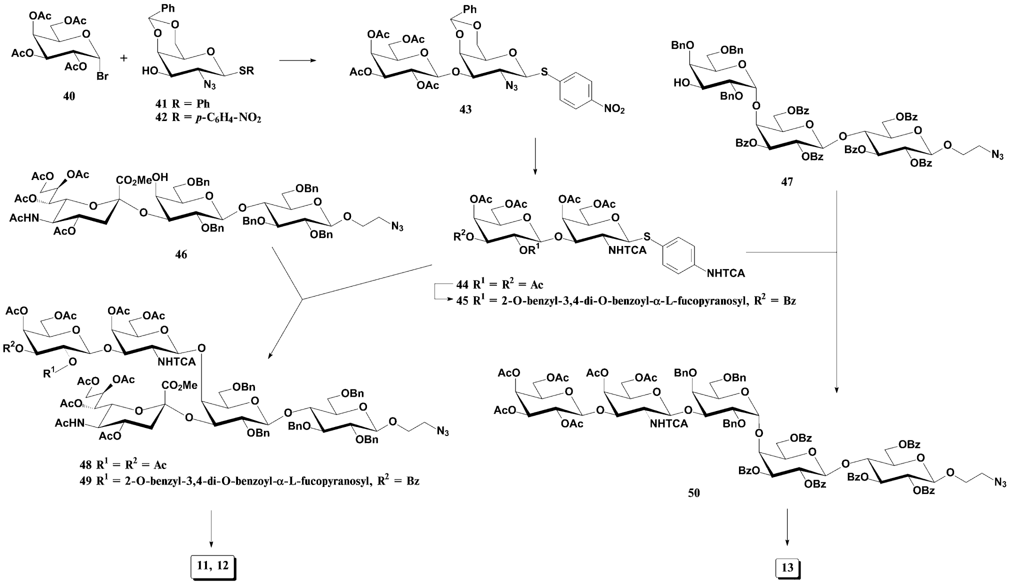
In the similar fashion, the glycosylation of the GlcNAc-(1→6)-GalNAc acceptor **26** with **20** promoted by NIS-TfOH-MSAW-300 in CH_2Cl_2, afforded, after treatment of the crude reaction products with thiourea, the tetrasaccharide **38** in 55 % yield.

In order to deblock the compounds **30**, **35**, **36**, **38**, and **39**, they were first subjected to the simultaneous alkaline hydrolysis of methyl ester, *O*-acyl protections, and N-TCA group. Subsequent *N*-acetylation of the liberated amino group in the internal GlcN residue followed by the catalytic hydrogenolysis for de-*O*-benzylation and azido group reduction gave the target oligosaccharides **6**, **7**, **8**, **10**, and **9**, respectively [21]. Compounds **31–34** were first de-*O*-benzylated by catalytic hydrogenolysis and then saponified with aqueous NaOH into the oligosaccharides **1**, **5**, **2**, and **4**, respectively. Compound **33** was also transformed into the 6-*O*-sulfated trisaccharide **3** by de-*O*-benzylation, selective 6-*O*-monosulfation of the corresponding 3,6-diol formed, and saponification.

In conclusion, the described above new synthetic methods enabled the efficient and stereoselective preparation of the spacer-armed sialylated lacto- and neolacto-oligosaccharides.

Syntheses of the spacer-armed oligosaccharide chains of gangliosides GM1 (11) and Fuc-GM1 (12) and globoside Gb_5 (13)

The oligosaccharide chains of the gangliosides GM1 and Fuc-GM1 and the globoside Gb_5 (**11–13**) contain the common disaccharide fragment Gal-β-(1→3)-GalNAcβ. We have elaborated a new efficient glycosyl donor **44** for one-step introduction of this sequence into various oligosaccharide chains (Scheme 3).



Scheme 3 Synthesis of spacer-armed oligosaccharide chains of globoside Gb_5 and gangliosides GM1 and Fuc-GM1 (**11–13**).

In order to prepare the disaccharide glycosyl-donor, the galactosylation under different condition of pheny 2-azido-2-deoxy-1-thio-β-D-galactoside derivatives with free OH-groups at C3,4 was studied first [27]. However, these reactions resulted in preferential formation of (1→4)-linked disaccharides, but not the desired (1→3)-ones. In the alternative way, we also attempted to prepare the necessary disaccharide by glycosylation of phenyl thioglycoside **41** with acetobromogalactose **40** under various conditions. But no desirable product could be obtained due to the competitive reaction of phenylthio group transfer. Replacement of the phenylthio group by less nucleophilic *p*-nitrophenylthio one suppressed completely the aglycon transfer and allowed us to obtain the target disaccharide **43** in good 58 % yield. In order to convert the nonparticipating azido group into the participating trichloroacetamido one and enhance the reactivity of the thioglycoside, both nitrogen functions in **43** were subjected to simultaneous reduction with Zn in AcOH and subsequent bis-*N*-trichloroacetylation to give the donor **44** in 61 % yield [27].

The efficacy of the disaccharide donor **44** is illustrated by successful syntheses of the pentasaccharide Gb_5 [28] and GM1 [29]. The glycosylation of the trisaccharide acceptors **46** and **47** with **44** promoted by NIS-TfOH in CH_2Cl_2 in the presence of MS-4 Å at –30 to –40 °C afforded the pentasaccharides **48** and **50** in 73 and 85 % yield, respectively.

Further introduction of monosaccharide residues into the disaccharide **44** enabled the preparation of more complex oligosaccharide donors applicable to the synthesis of higher oligosaccharides. Thus, **44** was transformed into α-fucosylated analog **45** (61 % overall yield for 6 steps) by *O*-deacetylation (MeONa, MeOH), bis-4,6,4′,6′-*O*-benzylidenation [$PhCH(OMe)_2$, CSA, DMF], selective mono-3′-*O*-benzoylation (BzCN, CH_3CN, Et_3N, 90 %), stereospecific α-fucosylation with 2-*O*-benzyl-3,4-di-*O*-benzoyl-α-L-fucopyranosyl trichloroacetimidate (TMSOTf, CH_2Cl_2, MS-4 Å at –30 °C, 93 % yield), deacetalation (80 % aq. AcOH, 80 °C), and *O*-acetylation (Ac_2O, Py, DMAP). Subsequent coupling of the acceptor **46** with **45** (under the same conditions as described above) gave the hexasaccharide **49** (76 %) with the structure of Fuc-GM1 hexasaccharide.

Deprotection of the oligosaccharide **50** was performed by alkaline hydrolysis followed by *N*-acetylation, and subsequent catalytic hydrogenolysis as described above for the preparation of sialylated oligosaccharides.

Deprotection of the oligosaccharides **48** and **49** was also started from alkaline hydrolysis followed by N-acetylation. However, subsequent catalytic hydrogenolysis for *O*-debenzylation and simultaneous reduction of the azido group could be performed efficiently only in the presence of Boc_2O [11]. The last step was the removal of Boc protection from the spacer amino group with aqueous CF_3CO_2H.

In conclusion, the disaccharide block **44** was shown to be a reliable tool for the efficient construction of various oligosaccharides of globo- and ganglio series. Another versatility of the approach described is the possibility to employ the azido disaccharide **43**, the precursor of **44**, in the syntheses of the oligosaccharides with α-linked Gal-β-(1→3)-GalNAc disaccharide unit.

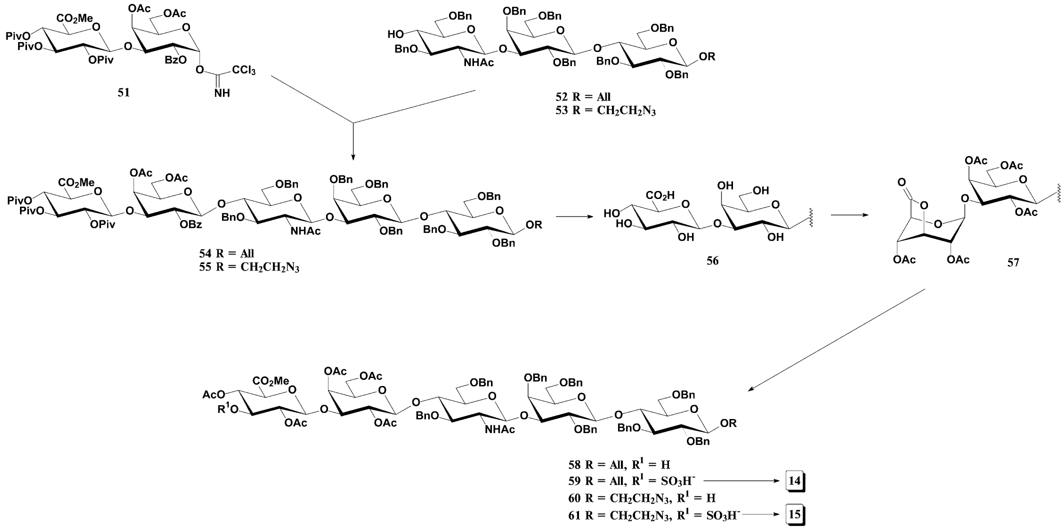
Syntheses of 3-*O*-sulfoglucuronylparaglobosides 14 and 15

Natural carbohydrates that bear HNK-1 epitope participate in neurite outgrowth and neural cells adhesion, play an important role in a number of other developmentary processes of mammalian nervous system and are recognized by L- and P-selectins [30–32]. This epitope is present in glycolipid penta- or heptasaccharide chains 3-*O*-sulfo-GlcA{β1-[3Gal(β1-4)GlcNAc(β1-]$_n$3}Gal(β1-4)Glcβ (*n* = 1,2) [33] and in several glycoproteins and proteoglycans of neural tissues [32].

The bottleneck of the previous syntheses of the glycosyl ceramides related to the pentasaccharides **14** and **15** was multistep and laborious introduction of protecting groups into glucuronic acid in order to differentiate by temporary levulinoyl protection the OH-group at C3, which is sulfated in the target molecules [9,10].

Our synthesis of the pentasaccharides **14** and **15** [34–36] included selective liberation of the OH-group at C3 of glucuronic acid residue via 6,3-lactonization-methanolysis procedure (Scheme 4). This key feature allowed us to use the readily available disaccharide trichloroacetimidate **51** which does not contain *any* temporary protecting group at O3 of the GlcA residue, instead of much less available selectively protected derivatives which were used in known syntheses of HNK-1 related oligosaccharides [9,10]. Preparation of the disaccharide donor included glycosylation of allyl 2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside with per-*O*-pivaloylated methyl glucuronyl bromide under Helferich conditions. This combination of protecting groups as well as the nature of glycosyl donor and promotor was found to be the most efficient [34,35].

Condensation of the disaccharide trichloroacetimidate **51** with the trisaccharide acceptors **52** and **53** gave the pentasaccharides **54** (82 %) and **55** (62 %) which were then saponified into the corresponding carboxyhexaols **56**. Their lactonization by heating in Ac_2O gave the per-*O*-acetylated derivatives of the type **57**, which were then subjected to mild AcONa-catalyzed methanolysis to afford the 3-hydroxy derivatives **58** and **60** in 74 and 35 % overall yields, respectively. At last, *O*-sulfation into **59** and **61**, followed by deprotection gave the spacer-armed pentasaccharide **15** and its propyl glycoside **14**, respectively [35,36].



Scheme 4 Synthesis of 3-*O*-sulfoglucuronylparaglobosides **14** and **15**.

Further elaboration of the lactonization-methanolysis procedure gave ready access to other selectively benzoylated or pivaloilated derivatives of glucuronic acid including methyl (ethyl 2,4-di-*O*-benzoyl-1-thio-β-D-glucuronopyranoside)onate, methyl (allyl 2,4-di-*O*-benzoyl-β-D-glucuronopyranoside)onate, methyl (allyl 2,4-di-*O*-pivaloyl-β-D-glucuronopyranoside)onate, methyl (allyl 4-di-*O*-benzoyl-β-D-glucuronopyranoside)onate, and methyl (allyl 4-*O*-pivaloyl-1-thio-β-D-glucuronopyranoside)onate [37].

In conclusion, the lactonization-methanolysis procedure allowed straightforward and efficient synthesis of the 3-*O*-sulfoglucuronylparagloboside pentasaccharides **14** and **15**, their fragments and nonsulfated analogs which are currently being used to study of the biosynthesis of HNK-1 positive carbohydrate chains and their role in neurobiology processes [38,39].

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