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Automated Chemical Oligosaccharide Synthesis: Novel Approach to Traditional Challenges

Matteo Panza, **Salvatore G. Pistorio**, **Keith J. Stine**, and **Alexei V. Demchenko**[*]

Department of Chemistry and Biochemistry, University of Missouri–St. Louis, One University Boulevard, St. Louis, Missouri 63121, United States

Abstract

Advances in carbohydrate chemistry have certainly made common oligosaccharides much more accessible. However, many current methods still rely heavily upon specialized knowledge of carbohydrate chemistry. The application of automated technologies to chemical and life science applications such as genomics and proteomics represents a vibrant field. These automated technologies also present opportunities for their application to organic synthesis, including that of the synthesis of oligosaccharides. However, application of automated methods to the synthesis of carbohydrates is an underdeveloped area as compared to other classes of biomolecules. The overarching goal of this review article is to present the advances that have been made at the interface of carbohydrate chemistry and automated technology.

Graphical Abstract

[*]**Corresponding Author:** demchenkoa@umsl.edu.

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Notes

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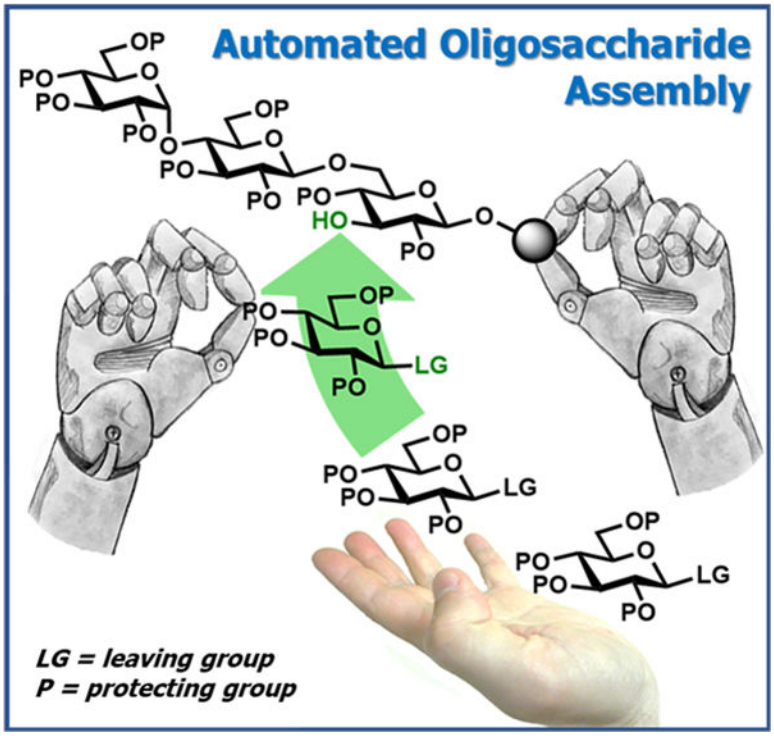

1. INTRODUCTION: CARBOHYDRATES, OLIGOSACCHARIDES, BIOLOGICAL ROLES AND MEDICAL IMPLICATIONS

Carbohydrates, the “essential molecules of life,”[1] play key roles in various biological processes. Carbohydrates are involved from the very beginning of life: fertilization occurs through the carbohydrate–protein interaction.[2] Carbohydrates contribute to human health by facilitating joint lubrication, cell growth, and the inflammatory and immune responses.[3] The exponential increase in interest in sugars and the notable growth of all areas of glycosciences also reveals the involvement of carbohydrates in processes detrimental for human health. Viral infections, bacterial- and parasite-related diseases, metastasis, and rejection of transplanted tissues are only a few of these processes that can be mentioned.[4] The pathogenesis of diabetes, septicemia, cancer, pneumonia, malaria, AIDS, and hepatitis are all carbohydrate-mediated processes. Understanding the roles of carbohydrates in these processes has stimulated many biomedical discoveries involving glycosciences.[5–7] Investigation of carbohydrate composition,[8] conformation,[9] interaction with other molecules and with themselves[10,11] are some other areas of inquiry in the field. Isolation of carbohydrates from natural sources represents a viable approach to providing samples for the biological testing of these molecules. However, it is chemical synthesis that allows access to both natural carbohydrates and their mimetics, which are often of interest due to their therapeutic[4,12] or diagnostic[13–15] potential. Challenges related to the synthesis and purification of carbohydrates and the lack of universal methods applicable to all systems is the key bottleneck of glycosciences. As a result, examples of large-scale development of

carbohydrate-based pharmaceuticals including heparin and its analogs,[16,17] antibiotics,[18,19] glycoconjugate-based vaccines,[20–24] and other applications[6,7,25] are still rare.

Oligosaccharide sequences are found in numerous natural compounds and constitute the core of many therapeutics. The presence of glycans in glycoproteins, glycolipids, glycosaminoglycans, and in other conjugates presents a treasure of potential information on cellular differentiation and condition. Over half of all proteins in the human body are N- or O-glycosylated,[3] and cell surfaces present a rich multitude of glycolipids and glycosaminoglycans, in addition to the presence of a variety of free oligosaccharides.[26] Glycans carrying information on biological significance are found in every body fluid, on cell surfaces, and within cells.

Glycan biomarker discovery is accelerating aided by advances in separation, mass spectrometric analysis,[27–29] and in glycanlectin array technologies.[30] Efforts to map the entire glycome of a cell have recently been reported.[31] Glycans have been identified as markers for many different forms of cancer including breast, colon, lung, etc.[32–34] Increases or decreases in the levels of certain glycans and changes in branching patterns can indicate the presence and progression of disease.[35] For example, one study showed that prostate cancer can be distinguished from benign prostatic hypertrophy via distinction of a specific glycoform by lectin binding.[36] In cerebrospinal fluid, the presence of a unique N-linked glycan on transferrin has been used to distinguish Alzheimer's disease from a condition arising from abnormal metabolism.[37] Profiling of N-glycans on IgG has been found useful for following the metabolic disorder of galactosaemia.[38]

Many families of glycoconjugates represent important therapeutic targets. High mannose, hybrid, and complex N-glycan families (Figure 1A) that are involved in many fundamental processes,[39–41] as well as in mediation of the pathogenesis of cancers,[42] AIDS,[43] Alzheimer's disease,[37] etc.[38] have stimulated many synthetic developments.[41,44–51] Another representative example is the globoside family of glycosphingolipids (Figure 1B; Neu, *N*-acetylneuraminic acid; Fuc, fucose), whose members present a broad range of significant biological roles as glycan biomarkers. For example, Gb3 is overexpressed in colorectal adenoma cells,[52] in Burkitt's lymphoma cells,[53] and in breast and ovarian cancer.[54] Gb3 is found on the glycolipid that accumulates in the lysosomes of individuals suffering from Fabry disease.[55] Iso-Gb3 is found on natural killer T cells.[56] Gb4 has been found to be enhanced and attached to longer fatty acid chains in vascular endothelial cells undergoing an inflammatory response.[57] Stage-specific embryonic antigens SSEA-3 and SSEA-4 are glycosphingolipids found on the surface of human embryonic stem cells but not on differentiated cells.[58] SSEA-4 was found expressed in a variant of nonsmall cell lung cancer cells[59] and on embryonal carcinoma cells in the ovaries.[60] Globo-H is a target antigen for the development of vaccines against prostate and breast cancer,[61] for which clinical trials are underway. Globo-H and SSEA-3 have been found expressed on breast cancer stem cells.[62] Many synthetic developments have been applied to the synthesis of globosides and Globo-H in particular.[63–68] More examples of the value of glycans and glycoconjugates as biomarkers are steadily emerging.

Oligosaccharides or glycans can be obtained by isolation from natural sources or prepared enzymatically and/or chemically. All three major approaches are viable, but none yet can significantly outperform the others. This review is dedicated to chemical synthesis, which, in spite of recent progress, remains challenging. As a result, synthesis of even moderately complex glycans and their conjugates still require significant resources. This limits accessibility of these essential targets to only a small circle of glycoscientists and inhibits their industrial production and application. Recent development of dependable techniques for oligosaccharide synthesis using traditional manual synthesis are introduced in section 2 of this review. An overview of very attractive and potentially transformative automated technologies that are expected to facilitate access to oligosaccharides is presented in section 3.

A majority of complex sugars are oligomers in which monomeric units (monosaccharides) are connected via glycosidic bonds. The latter are obtained by glycosylation, a reaction discussed in section 2.1. Certain mechanistic conventions discussed in section 2.1.1 have been established, and many factors that affect the outcome of glycosylations discussed in section 2 are known. Nevertheless, chemical glycosylation remains challenging. Oligosaccharide synthesis brings about further challenges (section 2.2). Both traditional (section 2.2.1) and expeditious strategies are known (section 2.2.2). Various one-pot strategies that offer a streamlined access to oligosaccharides have been developed (section 2.2.3). Supported and tagged synthesis has also been investigated (section 2.3). In particular, solid-phase synthesis, widely used in the preparation of oligopeptides and oligonucleotides, has also been applied to the preparation of oligosaccharides (section 2.3.1). This approach can streamline synthesis by eliminating the need to purify reaction intermediates and by simplifying the removal of excess reagents. Similar advantages are seen in the tagged synthesis wherein soluble polymer supports, ionic liquids, and fluorous-based protecting groups have successfully been used to expedite oligosaccharide assembly (section 2.3.1).

Dedicated attempts to automate oligosaccharide synthesis resulted in the development of a number of platforms and technologies for their automated chemical synthesis. These developments are reviewed in section 3. Early attempts by Takahashi and Wong to develop the automated chemical syntheses in solution set the benchmark in the field (section 3.1). Those early attempts have also shown difficulties associated with the automation. To expedite polymer-supported oligosaccharide synthesis, Seeberger introduced an automated approach. The automation was initially based on a modified peptide synthesizer (section 3.2). In 2012, Seeberger et al. reported the “first fully automated solid-phase oligosaccharide synthesizer” (section 3.4). Around the same time Pohl, Demchenko-Stine, and Nokami have developed alternative automation platforms discussed in sections 3.3, 3.5, and 3.6. Operation of all automated synthesizers is controlled by a computer. The greatest advantage of employing the computer interface along with liquid handling hardware and software is to allow recording successful automated sequences that can be then repeated over and over with an expected high degree of reproducibility.

2. TRADITIONAL MANUAL SYNTHESIS OF OLIGOSACCHARIDES

Glycosidic linkages are obtained by glycosylation, a reaction of the nucleophilic displacement of an anomeric leaving group (LG) on the glycosyl donor by a hydroxyl group of the glycosyl acceptor.[69] The remaining functional groups of both reaction counterparts (hydroxyls, amines, and carboxyls) are masked with respective temporary protective groups. A detailed mechanism of chemical glycosylation is unknown, but certain aspects, factors, and pathways have been established.[70–93] With a notable progress in the field of chemical glycosylation,[83,86–88,94] this reaction remains challenging. Beyond that, traditional stepwise oligosaccharide synthesis requires careful strategic planning to achieve protecting and/or leaving group introduction/removal between glycosylation steps. In addition, purification and reagent separation become difficult with large oligosaccharide sequences. Many selective, chemoselective, and regioselective strategies have been developed to streamline oligosaccharide synthesis by reducing the number of additional steps.[95] Other advanced techniques, such as solid-phase synthesis,[96,97] have been developed to streamline oligosaccharide synthesis. These approaches reduce the need to purify reaction intermediates and simplify the excess reagents removal.

2.1. Chemical Glycosylation

Glycosylation reaction is the central reaction in glycochemistry. The glycosylation involves a promoter or activator-assisted reaction between a glycosyl donor and glycosyl acceptor. Along with the formation of a glycosidic bond, a new chirality center is produced. Therefore, particular care should be taken of stereocontrol. Discussed below are basic principles of chemical glycosylation and factors that have an effect on the reaction outcome. In addition to the glycosylation reaction, there are many competing processes that may simultaneously occur. Side reactions that often complicate stereocontrol of glycosylation and may have a profound effect on yields include, but are not limited to, migration, elimination, cyclization substitution, and redox reactions.[69,98]

2.1.1. Reaction Mechanism.—The promoter-assisted departure of the leaving group leads to the formation of a glycosyl cation that is stabilized via an oxacarbenium ion intermediate (Scheme 1). The acceptor attack on the flattened oxacarbenium intermediate can take place either from the top or the bottom face of the sugar ring. As a result, uncontrolled glycosylations may lead to the formation of mixtures of 1,2-trans and 1,2-cis glycosides. Typical glycosylation conditions favor a unimolecular S_N1 mechanism, or may proceed at the S_N1-S_N2 interface,[99] and the reaction involves four major steps.[100]

Step 1. Formation of the activated donor as a result of the interaction of the LG and the promoter (A-B). This step can be either reversible or irreversible depending on the type of the leaving group used and the method of activation.[93] There are a few reports indicating that the glycosyl acceptor attack may be directed to the activated donor.[101–106] This S_N2-like displacement pathway is quite desirable because it would allow for the stereospecific inversion of the leaving group. Step 2. Dissociation of the LG, a typically irreversible expulsion of the activated leaving group (LGA), is the rate-determining step (RDS). It leads to the formation of a glycosyl carbocation and/or its stabilized resonance form, an

oxacarbenium ion. The latter is often responsible for scrambling the stereoselectivity of the reaction. Other intermediates, the existence of which is often ignored, or whose impact on the reaction is underestimated, may also form at this stage with or without counteranion B. Step 3. As a consequence of the sp^2-hybridization of the anomeric (C-1) carbon and the existence of the oxacarbenium ion in a flattened half-chair conformation, the subsequent attack of the glycosyl acceptor is possible from both the bottom face of the ring (pathway a) and the top face (pathway b). As a result, "uncontrolled" glycosylation often leads to the formation of a mixture of products. Step 4. Upon the proton transfer, the formation of the glycosidic bond becomes irreversible (the termination step).[80]

The earliest reactions performed by Michael,[107] Fischer,[108] and Koenigs and Knorr[109] at the turn of the 20th century showcased the complexity of the glycosylation reaction. At that stage, glycosylations of sugar acceptors were quite inefficient and even the synthesis of disaccharides represented a challenge. The first attempts to solve this problem gave rise to the development of new activators.[110–112] The early attempts to improve the glycosylation reaction have also revealed the necessity to find a delicate balance between the reactivity and stereoselectivity.[113,114]

2.1.2. Building Blocks: Glycosyl Donors and Acceptors.—One of the main directions has been the investigation of leaving groups beyond the original halides, hemiacetals, and peracetates introduced by Helferich in 1933.[115] Thus, in the 1970's to early 1980's, a few new classes of glycosyl donors were developed.[116,117] This first wave introduced thioglycosides,[118–121] 1,2-orthoesters,[122,123] *O*-imidates,[124,125] thioimidates,[126–128] and glycosyl fluorides[129] as alternative leaving groups. Many glycosyl donors introduced during that period have become common even to this day. The next wave of new methods arrived in the late 1980's. Among the new leaving groups introduced were glycosyl esters/carbonates,[130–132] thiocyanates,[133] diazirines,[134] xanthates,[135] glycals,[136,137] phosphites,[138,139] sulfoxides,[140] sulfones,[141] selenium glycosides,[142] alkenyl glycosides,[143–145] and heteroaryl glycosides.[146] These developments were followed by a variety of more recent methodologies and improvements. These include glycosyl iodides,[147] phosphates,[148] Te-glycosides,[149] sulfonylcarbamates,[150] disulfides,[151] 2-(hydroxycarbonyl)benzyl glycosides,[152] novel thio-,[153,154] and O-imidates[155,156] as well as alkynyl-based leaving groups.[157–166] In addition, a variety of very recent methodologies[167–169] have brought the use of classic glycosyl donors, such as glycals,[170,171] hemiacetals,[105,172,173] or halides[174,175] to an entirely different level of flexibility and versatility.

Beyond studying the anomeric leaving group, protecting group effects have been investigated. Seminal work of Lemieux[70] and Fletcher[176,177] has led to appreciation that the reactivity of glycosyl halides and the stereoselectivity of glycosylation is directly correlated to the nature of the protecting groups, especially at the neighboring C-2 position. The participation of the neighboring 2-O-acyl substituent typically leads to the formation of 1,2-trans linkages.[73,178] In this case, the oxacarbenium ion can be further stabilized via an acyloxonium (dioxalenium) intermediate. Since the bottom face of the sugar ring in the acyloxonium intermediate is blocked, the glycosyl acceptor will approach from the top face (Figure 2A). Following this method, a 1,2-trans linkage is typically produced with high

stereoselectivity; however, sometimes 1,2-orthoesters or 1,2-cis-linked glycosides are formed.

Demchenko and co-workers introduced glycosyl donors equipped with a 2-O-picolinyl ether participating group that provides entire 1,2-trans stereoselectivity in glycosylations (Figure 2B).[179,180] Mlynarski and co-workers investigated ortho-nitrobenzyl (NBn) as a participating group.[181] Liu and co-workers investigated another alkyl participating group, *o*-cyanobenzyl (CBn) at the C-2 position of a glycosyl donor.[104] An interesting feature of this glycosylation method is that a single glycosyl donor can yield either α- or β-linked products depending on the nature of the glycosyl acceptor.

The presence of a nonparticipating group at C-2 such as benzyl is typically necessary for the synthesis of 1,2-*cis* glycosides. However, the nonparticipating substituent alone cannot provide stereocontrol, which makes the synthesis of 1,2-cis glycosides much more challenging. Although the anomeric effect favors the formation of the α-product,[182] the stereoselectivity of uncontrolled glycosylations can be low. In these cases, other factors for controlling stereoselectivity such as structural features of the reactants and reaction conditions become increasingly important. For example, Boons et al. introduced chiral auxiliaries capable of producing trans-decalin-like intermediates depicted in Figure 2C.[183–187] This opposite face of the ring type of participation helps to obtain 1,2-cis linked glycosides with very high stereoselectivity.[188] Turnbull and coworkers designed a similar concept showing that an oxathiane donor is also capable of highly α-selective glycosylations.[189,190] Fairbanks showed the versatility of 2-(thiophen-2-yl)methyl derivatives for stereoselective 1,2-cis glycosylation.[191]

The effects of remote substituents, particularly those capable of steric hindrance, powerful electron-withdrawal, or long-range participation, have been known for some time.[192–196] Observed for a variety of sugar series including D-galacto,[197,198] L-fuco,[199,200] L-rhamno,[201] D-manno,[202] and D-gluco,[203] the remote effects can be weaker than those by the C-2 substituent. More recent studies, by Kim et al.,[204] Nifantiev et al.,[205] Crich et al.,[206,207] Hung et al.,[208] and others[209,210] showed how important the remote effects can be. A somewhat unexpected effect was noted for remote picolinyl ethers (Pic) and picoloyl esters (Pico). While 2-picolinyl participates at the anomeric center via the six-membered ring intermediate (see Figure 2B),[180] the action of the remote groups is different. It has been demonstrated that the nitrogen atom of the remote picolinyl/picoloyl groups is able to form a hydrogen bond with the hydroxyl group of the glycosyl acceptor. This leads to high syn-selectivity with respect to the picolinyl/picoloyl substituent.[211] This reaction named H-bond-mediated aglycone delivery or HAD gave high α-gluco[212] and β-manno[213] selectivity even at room temperature. As an extension to this study, the synthesis of β-mannan[213] and α-glucans[214] has been reported. Mong and coworkers applied 6-*O*-picoloyl-2-deoxy glycosyl donors to stereoselective synthesis of β-glycosides.[215] Very recently, De Meo[216] and Tsai[217] investigated the effect of picoloyl substituents on sialylations. Yang et al. employed a similar 2-quinolinecarbonyl group to stereoselective synthesis of β-D- and β-L-arabinofuranosides.[218]

Torsional effects induced by the cyclic protecting groups may also affect both the reactivity of glycosyl donors and/or the stereoselectivity of glycosylations. The work by Crich et al. on the synthesis of β-mannosides[76,87,219–221] is the best known example of the deactivating (and stereodirecting) effect of the 4,6-O-benzylidene substituent. The benzylidene effect is due to torsional strain[222] that restricts the conformational flexibility of the pyranose ring and also enhanced electron-withdrawal.[223] A variety of other cyclic groups have been investigated. In particular, studies of 2-amino glycosyl donor protected with 2,3-*trans*-oxazolidinone by Kerns et al.,[224–227] Oscarson et al.,[228] Ye et al.,[229–232] and Ito et al.,[233,234] yielded useful techniques for the synthesis 1,2-cis glycosides and glycosyl donors with switchable selectivity. Crich et al. demonstrated the utility of the 2,3-*O*-carbonate protection for α-selective for mannosylation and rhamnosylation,[206,235] as well as β-glucosylation.[236] The effect of 3,4-*O*-carbonate protection is weaker, and it shows a slight bias toward β-selectivity.[237] The 4,5-*O*,*N*-oxazolidinone protection of sialyl donors often provides high yields and α-stereoselectivities in sialylations and helps to suppress competing elimination.[238–240]

The effect of the glycosyl acceptor on the stereoselectivity of glycosylation has also been investigated. The mechanistic outline of the glycosylation reaction (vide supra) implies that the RDS is unimolecular and should not be affected by the nature of the glycosyl acceptor (Scheme 1). However, the donor–acceptor mismatch concept of Paulsen[241] and Fraser-Reid and Lopez[242–246] as well as the double stereodifferentiation phenomenon[247] present a strong counterargument. In fact, different selectivities are often obtained for different glycosyl acceptors. Typically, the alcohol reactivity is inversely correlated with the stereoselectivity, whereas the most reactive hydroxyls give the lowest α/β-ratios. For instance, glycosylation of axial 4-OH of galactose often gives excellent 1,2-cis stereoselectivity. Occasionally, primary hydroxyl groups can lead to higher selectivity than their secondary counterparts, particularly for reactions partially proceeding via the bimolecular mechanism. Toshima et al. introduced a new technique that is based on the chiral recognition of aglycones.[248]

2.1.3. Reaction Conditions.—Several other factors including temperature, solvent, amount, and type of promoter used can influence the outcome of chemical glycosylation by affecting its stereoselectivity and yield. Kinetically controlled reactions at low temperatures favor the formation of β-linked products,[249,250] although opposite results have also been obtained.[251,252] The solvent effect on the stereoselectivity of glycosylation reactions has been widely studied.[256,258–263] In general, polar reaction solvents increase the rate of the β-glycoside formation via charge separation between O-5 and β-O-1. If the synthesis of α-glycosides is desired, CH_2Cl_2, $ClCH_2CH_2Cl$, or toluene would be suitable candidates as the reaction solvents. However, there are more powerful forces than simple solvation. Thus, ethereal solvents are beneficial for α-selective glycosylation because diethyl ether,[253] tetrahydrofuran,[253] and dioxane[254] have a tendency to form the equatorial O-linked intermediate. Conversely, nitrile solvents help the formation of β-glycosides because these reactions were thought to proceed via the axial glycosyl nitrilium cation intermediate.[195,255] More recently, the Mong group suggested that in addition to the anomeric effect the formation of 1,2-cis nitrilium species is further reinforced by the participation of the oxygen atom at C-2.[256] This would result in the formation of the glycosyl oxazolinium intermediate

that is leading to the β-product as a result of the top-face nucleophilic attack (see refs 255, 257–262, 254, 256, 261, 254, 256–261, 254, 256–261, 253, 255–260, 253, 255–260, 252, 254–259).

Many decades ago, glycosylations of unreactive acceptors were very inefficient.[109,110] Initial attempts to improve the glycosylation reaction by Zemplen[111] and Helferich[112] have also showed that faster reactions may result in lower stereoselectivity.[113,114] Some reactive glycosyl donors can be activated under Lewis acid catalysis. The best-known examples of these leaving groups include trichloroacetimidoyl (TCAI),[263,264] *N*-phenyl trifluoroacetimidoyl (PTFAI),[265] and phosphites/phosphates.[266] The use of transition metal catalysts based on palladium[267,268] and nickel[270,271] developed by Nguyen et al. for TCAI donors offers new opportunities for stereocontrol.[167] Many other current methodologies for glycosylation, such as glycosylation with S-aryl/alkyl thioglycosides, use stoichiometric promoters. Bi(V)[269,270] and Au(III)[191] catalyzed activations of thioglycosides represent other new promising directions in glycosylation chemistry.[169,269] Recently there has been an explosion in the study of gold-catalyzed activation of alkynes to exploit the low oxophilic character of gold and the excellent functional group compatibilities these catalysts exhibit.[159,162,271–274]

Another emerging approach is the use of (thio)ureas as organocatalysts for glycosylations with glycosyl chlorides.[170,174,175,275,276] The underpinning idea for developing alternative methodologies for the promotion of glycosyl chlorides is to avoid the heavy metal catalyst utilized in traditional Koenigs-Knorr reactions.[109,110] Ye and co-workers developed a catalytic system that makes advantage of the hydrogen-bond donor ability of urea.[174] These activation conditions allowed for smooth glycosidation of per-benzylated galactosyl, mannosyl, and rhamnosyl chlorides. The glycosides were achieved in high yields and excellent α-stereoselectivities, but these reactions required the use of benzene as a solvent, high temperature, and long reaction times. For example, as depicted in Scheme 2A, activation of donor **1** with the urea-derived catalyst **3** for the reaction with glycosyl acceptor **2** in the presence of K_2CO_3 afforded disaccharide **4** in excellent stereoselectivity and yield. A phosphine additive, TTMPP, was found advantageous in achieving good selectivity with glucosyl donors.

Very recently, Jacobsen and co-workers studied a series of chiral thiourea catalysts for the activation of glycosyl chlorides.[175] In contrast to the previous example, the reaction affords disaccharides with high β-stereoselectivity, even in the absence of the neighboring participating group. The direct access to the formation of β-mannosides is another advantageous application of this reaction. For example, as depicted in Scheme 2B, activation of donor **5** with the chiral thioureaderived catalyst **7** for reaction with glycosyl acceptor **6** in the presence of isobutylene oxide (IBO) afforded disaccharide **8** in high β-stereoselectivity and yield. IBO is used as an electrophilic trap to scavenge HCl produced in these reactions. The reaction mechanism has been studied and some features, such as stereospecific inversion, in combination with the independence from the stereochemical relationship between electrophile and nucleophile suggest the S_N2-like nature of the displacement.

In addition, over the recent years there has been a noticeable shift in focus of the mechanistic glycosylation chemistry field toward studying stereoelectronics and conformation of the starting material and key reaction intermediates.[74,75,77,79,80,82,84,91,100,172,223,277–290] While the stereoelectronic and conformational effects on reactivity have been studied extensively, the impact of these effects on stereoselectivity remains elusive. Although some model studies helped to establish general trends,[75,82,277–280,290,291] practical application of the conformational factors to stereocontrol of glycosylation is still limited. Reagent- or additive-controlled glycosylations and reactions with reagent-dependent switchable selectivity are becoming active areas of research.[105,292–299]

2.1.4. Special Cases and Indirect Methods.—While some sugar series follow general trends, there are classes of compounds and linkages that require special methods. These special cases of glycosylation include the following major classes of compounds. 2-Deoxysugars,[300,301] that are discussed in a separate review in this special issue.[302] 2-Amino-2-deoxy sugars[303] require additional steps and a careful selection of suitable protecting groups at C-2, most commonly 2,2,2-trichloroethoxycarbonyl (Troc) or phthaloyl (Phth), for the synthesis of 1,2-trans and azide for the synthesis of 1,2-cis linked glycosides. The difficulty of the direct β-mannosylation[304] was addressed by developing a variety of indirect approaches such as C-2 oxidation–reduction, C-2 inversion, anomeric alkylation, and intramolecular aglycone delivery (*vide infra*).[305,306] Crich and co-workers discovered that 4,6-*O*-benzylidene protected donors provide excellent β-manno stereoselectivity.[76,87,219–221] The HAD method developed by Demchenko provides nearly complete β-selectivity in mannosylation at room temperature.[213] Other useful approaches to the synthesis of β-mannosides include Kim's o-carboxybenzyl leaving group approach[152] and van der Marel's C-5 carboxylate approach.[307–310]

An area of intramolecular glycosylation has also been developed to enhance the production of difficult glycosidic linkages. A better stereocontrol is achieved by tethering the reaction counterparts and restricting the glycosyl acceptor attack.[311–318] The best known example, intramolecular aglycone delivery (IAD), was introduced by Barresi and Hindsgaul.[319] Over the years, IAD has evolved into a powerful means to perform glycosylations of complex targets with high efficiency and yields.[320–323] The major improvement of this approach has emerged with the implementation of a 2-naphthylmethyl group (Nap) as a tether group.[323] A representative example is depicted in Scheme 3. The treatment of a mixture of donor **9** and acceptor **10** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) produces a mixed acetal that can be directly glycosidated in the presence of MeOTf and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) followed by acetylation to give disaccharide **11** in an excellent yield of 90% and complete β-selectivity.[323] Initially investigated for the synthesis of β-mannosides, α-glucosides, and β-arabinofuranosides,[323] this approach was extended to the synthesis of β-rhamnosides[324] and other challenging targets.[315,325–331]

The synthesis of 1,2-trans furanosides can be achieved with 2-O-acylated glycosyl donors.[332,333] The synthesis of 1,2-cis furanosides is more difficult due to high conformational flexibility of the five-membered ring and lack of the anomeric effect. Recent advancements make use of glycosyl donors with the furanose ring locked into a single conformation. This

was achieved with 2,3-anhydro,[334,335] 3,5-O-(di-*tert*-butylsilylene),[336,337] or 3,5-*O*-tetraisopropyldisiloxanylidene[338] protection. Young and co-workers successfully applied the HAD approach to 1,2-cis glycofuranosylation.[218]

In spite of extensive efforts and notable progress, the chemical synthesis of α-sialosides also remains challenging.[339–344] Destabilizing electron-withdrawing carboxylate and the lack of a substituent at C-3 often drive sialylation reactions toward competitive elimination. This side-reaction leads to the formation of a 2,3-dehydro derivative. In addition, the lack of a participating group means that stereoselectivity of sialylations can be low. To overcome these problems, a variety of leaving groups, participating auxiliaries, and activation conditions for sialylations have been developed. In recent years, it became evident that the remote N-substituent at C-5 may have a strong effect both on stereoselectivity of sialylations and the reactivity of sialyl donors.[342] A particular advance has been made with 4,5-*O,N*-oxazolidinone derivatives,[238–240] and more recently with 5-isothiocyanate,[345] that provide high yields and stereoselectivities in sialylations and help to suppress the competing elimination. An investigation of the effect of remote picoloyl groups at C-4 in the presence of excess of triflic acid offered new mechanistic insights into the sialic acid chemistry.[216] This methodology has been extended to the synthesis of 7,8-dipicoloylated donors bearing benzoyl protection at the other positions.[217]

A number of methods that do not include a formal glycosylation step have been developed.[346,347] Since these indirect procedures include multistep syntheses, practical application of these techniques is envisaged for the synthesis of glycosidic linkages that cannot be easily accessed by conventional technologies. O'Doherty developed a wellrounded methodology for Pd(0)-catalyzed glycosylations, wherein carbohydrate chirality centers are installed postglycosylationally. The *de novo* asymmetric synthesis methodology was instrumental for obtaining many mono-, di-, and oligosaccharide derivatives by means of palladium-catalyzed reactions.[348–351]

2.2. Oligosaccharide Synthesis

Glycosylation is only part of the challenge synthetic chemists confront during the synthesis of oligomeric sequences. A traditional stepwise approach requires additional manipulations after each glycosylation step. This multistep reaction cycle is then repeated again until oligosaccharide of the desired chain length is obtained. This becomes increasingly inefficient at the advanced stages of the assembly,[95,352] often leads to a dramatic drop in yield, and as a consequence, lesser availability of glycans. Many advanced strategies that streamline oligosaccharide assembly by minimizing or even eliminating leaving or protecting group manipulations between coupling steps are based either on chemoselective or on selective activation of leaving groups.[95] One-pot strategies help to expedite the oligosaccharide synthesis further. The one-pot sequences typically consist of the glycosylation steps only, but a minimal number of deprotection steps may also be included. Since all the sequential reactions are performed in a single flask (pot), the purification is only performed at the stage of the final product and purification of the intermediates is not required.

2.2.1. Conventional Linear and Convergent Block Synthesis.—A traditional stepwise approach requires additional synthetic steps for the conversion of the disaccharide intermediate into the second-generation glycosyl donor or acceptor. Modified disaccharides are then coupled with a glycosyl donor (or acceptor) to obtain a trisaccharide. This reaction sequence is then repeated again until oligosaccharide of the desired chain length is obtained. Despite the need for additional protecting group manipulations between the glycosylation steps, the linear approach is still in common use and a relevant example, the synthesis of the blood-group determinant H-type II pentasaccharide **23** is depicted in Scheme 4.[353] Galactosyl phosphate **12** is glycosylated with acceptor **13** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), followed by removal of the temporary levulinoyl (Lev) protecting group. The sequence is repeated with TCAI and phosphate donors, as well as Lev and 2-azidomethylbenzoyl (AMB) removable protecting groups, to afford the target pentasaccharide in 60% overall yield. Numerous improvements of this basic concept include the use of solid-supported synthesis[354] or fluorous protecting groups[355] that significantly facilitate separation of products from the reactants (*vide infra*).

The convergent building block approach is a faster way to obtain larger oligosaccharides.[356–358] In accordance with this strategy, oligosaccharide fragments are presynthesized and then converged by means of a glycosylation reaction. Additional protection/deprotection steps may still be required but the overall assembly is faster due to the use of oligomeric building blocks. The block synthesis is particularly useful for the purpose of the introduction of a “difficult” linkage at an earlier stage of the saccharide assembly.[359] Convergent block synthesis also streamlines the formation of oligosaccharide sequences containing two or more repeat units.

A relevant recent example, the synthesis of ganglioside GP3, developed by Kiso and co-workers is illustrated in Scheme 5.[360] The synthesis of this complex structure was designed to avoid the introduction of “difficult” units including ceramide, α-galacto, and unusual internal α-sialo linkages. Tetrasaccharides **24** and **25**, both of which were obtained using a convergent [2 + 2] glycosylation strategy, were coupled in the presence of *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH) at 0 °C. As a result, an octasaccharide was obtained in 91% yield. The latter was reprotected and converted into TCAI donor **26** that was coupled with glycosyl ceramide acceptor **27** in the presence of TMSOTf affording the target ganglioside **28** in 77% yield. The recent synthetic effort in the area of convergent assembly field[49,361–368] has culminated in the synthesis of a large mycobacterial arabinogalactan oligosaccharide containing 92 monosaccharide residues (92-mer) by Ye and co-workers.[369]

2.2.2. Expeditious Strategies for Oligosaccharide Synthesis.—Expeditious strategies streamline oligosaccharide assembly by minimizing or even completely eliminating manipulations between coupling steps.[95] All of these approaches can be classified into the following major categories. First, chemoselective approaches wherein the reactivity of building blocks is modulated by the protecting groups. Second, selective approaches that are based on selective activation of certain leaving groups. Third, preactivation-based approaches that can be used with any protecting and leaving groups.

Fourth, regioselectivity-based approaches rely on the differential reactivity of different acceptor groups.

Fraser-Reid's seminal work on armed-disarmed approach showed that the building block reactivity can be modulated through the choice of protecting groups.[370,371] Thus, benzylated (electronically activated, armed) building blocks are significantly more reactive than their acylated (Bz, disarmed) counterparts (Scheme 6A). Usually, protecting groups in both reaction components and careful selection of mild reaction conditions have to be taken into consideration to allow direct chemoselective activation of the armed glycosyl donor over the disarmed glycosyl acceptor. The convenience of this approach is that the same leaving group can be used for all building blocks in the sequence. However, "protecting groups do more than protect,"[372] and this can affect the stereochemical outcome and limit the scope of the method. For instance, the classical armed-disarmed approach can only lead to the formation of cis–transpatterned oligosaccharide sequences.

In recent years, the scope of the original armed-disarmed concept has been expanded,[373] and a number of efforts to quantify or even predict the reactivity of building blocks have been reported by Fraser-Reid,[222,374] Ley,[375] Wong,[376] and others.[377] Wong's study also revealed a number of building blocks that extend beyond the traditional armed-disarmed boundary. Boons showed that 2,3-O-carbonate protected glycosyl donors are less reactive than disarmed acylated derivatives.[378] Subsequently, Demchenko reported that 2-Bn-3,4,6-tri-Bz protected donors are even less reactive than their disarmed per-Bz counterparts (superdisarmed). This unexpected protecting group effect was explained by the existence of the O2/O5 cooperative effect that takes into consideration the stabilization of reaction intermediates rather than only the electronics of the starting material.[379] In this case, the destabilization of the glycosyl cation is due to the electronpoor environment of O-5 and the lack of anchimeric assistance.

Two concepts for superarming glycosyl donors have also emerged, further expanding the original scope of the armed-disarmed approach. First, Bols showed that superarming can be achieved by changing the equatorial-rich $^4C_1$ conformation to an axial-rich skew-boat conformation by creating steric congestion with TBDMS protecting groups at the C-2, −3, and −4 positions.[84,285–288] These donors showed a hefty 20-fold increase in reactivity over the armed per-benzylated counterparts because the conformational change simplifies transition of the starting material into the oxacarbenium ion that is most stable in the all-axial half-chair arrangement.[75,277,278,280,291] Second, Demchenko reported building blocks wherein the superarming was achieved via the O2/O5 cooperative effect. Glycosyl donors equipped with the superarming 2-Bz-3,4,6-tri-Bn pattern were 10-fold more reactive than their armed counterparts.[380–382] In this case, the stabilization of the glycosyl cation is possible both from the electron-rich O-5 and from 2-Bz via the anchimeric assistance. With the two different approaches to superarm glycosyl donors, conformational and anchimeric, Bols and Demchenko jointly developed a 2-Bz-3,4-di-TBS-protected glycosyl donor. Glycosylations with the hybrid donors were swift, high yielding, and β-selective.[383,384] This study showed that the conformational arming is a powerful tool to increase the reactivity and to achieve excellent yields. The anchimeric arming effects are weaker, but the participation ensures complete 1,2-trans selectivity.

Another general concept to expedite oligosaccharide synthesis is to achieve selective activation of different leaving groups, and it is practically independent of the nature of the protecting groups (Scheme 6B). One example presented below has a unique alignment of six different leaving groups, which were selectively activated affording hexasaccharide **39** in only five steps (Scheme 7).[385] First, thiocyanate glycoside donor **29** was activated with $Cu(OTf)_2$ over *S*-thiazolinyl (STaz) acceptor **30** in 89% yield. Subsequently, disaccharide **31** was coupled with *S*-benzoxazolyl (SBox) glycosyl donor **32** in the presence of benzyl bromide to achieve the trisaccharide **33** in 67% yield. The latter was coupled with fluoride acceptor **34** in the presence of MeOTf to produce tetrasaccharide **35** in 87% yield. Tetrasaccharide **35** was then reacted with SEt acceptor **36** in the presence of $AgClO_4$/Cp_2ZrCl_2 to afford the pentasaccharide **37** in 84% yield. Lastly, the coupling of *O*-pentenyl acceptor **38** with the pentasaccharide **37** using MeOTf as an activator produced hexasaccharide **39** in 72% yield.

Among all known selective activation strategies,[95] Ogawa's orthogonal concept is arguably the most advantageous.[386,387] This technique used two chemically distinct glycosylation reactions, and the selective activation of two orthogonal leaving groups is then reiterated (Scheme 6B). The classic variation of the orthogonal activation involves building blocks bearing *S*-phenyl and fluoro leaving groups.[388] As shown in Scheme 8, phenyl thioglycoside **40** is selectively activated over fluoride acceptor **41** in the presence of NIS/AgOTf. The fluoro leaving group of disaccharide **42** is then activated over thioglycoside acceptor **43** in the presence of $Cp_2Hf_2Cl_2$/AgOTf. This selective activation sequence is then reiterated to provide tetrasaccharide **44**. Ideally, the orthogonal approach allows for an unlimited number of reiterations of the two orthogonal leaving groups, which is conceptually very attractive. In practice, however, the yields, which are typically inversely correlated to the size of the glycosyl donor involved, decreased dramatically at the later stage of the assembly. A number of complementary combinations of orthogonal leaving groups and conceptual modifications have been implemented.[385,387,389–399]

A number of concepts for selective activation have been introduced.[145,398,400] For example, in the two-step activation approach both glycosyl donor and glycosyl acceptor initially bear the same type of leaving group. In order to couple these two reactants, a different leaving group is introduced into the glycosyl donor. Upon the selective activation of the donor, this two-step activation sequence can be reiterated. Discovered for thioglycoside conversion into bromides,[356] this approach was extended to other systems.[371,401–403] For example, Danishefsky's reiterative assembly approach involving glycal precursors that are converted into 1,2-anhydrosugars with dimethyldioxirane (DMDO)[404] clearly illustrated the versatility of this strategy.[137,405–407] Thus, 1,2-anhydrosugar **47** generated from glycal **46** could be activated over glycal acceptor **48** in the presence of $ZnCl_2$ to afford 1,2-trans-linked disaccharide **49** in 81% (Scheme 9). The epoxidation-glycosylation sequence can be then reiterated to yield larger oligosaccharides.

More recently, the versatility of the two-step activation was demonstrated by a one-pot preactivation procedure,[408–410] according to which *S*-tolyl glycosides are converted in situ into a reactive intermediate. These preactivation types of couplings cannot be formally classified as oligosaccharide synthesis via selective activations, and it occupies its own

niche.[66,229,230,232,237,260,411–416] This strategy is particularly advantageous in conjunction with the one-pot oligosaccharide synthesis that will be discussed below.

A number of useful expeditious approaches are based on regioselectivity of different acceptor groups. Thus, a two-directional strategy for glycan synthesis makes use of a building block capable of reacting first as a glycosyl donor and then as an acceptor. For example, building block **50** is first glycosidated with the reactive glycosyl acceptor **51** and then glycosylated directly at the deactivated position (synthesis of **54**, Scheme 10).[417] Hydroxyl deactivation can be achieved by introducing electron-withdrawing groups at surrounding positions. The use of temporary masking moieties (trityl, silyl) that can act as protecting groups in the first step and then be removed directly during glycosylation has become a logical extension of this technique.[418,419] The use of the glycosyl donor/acceptor unit on the solid support is another efficient way to "deactivate" the hydroxyl moiety in comparison to the solution-based acceptor (*vide infra*).[420]

2.2.3. Oligosaccharide Synthesis in One Pot.—One-pot strategies allow to streamline glycan synthesis because all glycosylations are performed in a single flask (pot) and do not require purification of intermediates.[421–423] All one-pot strategies are based on the following five major concepts. The first approach discovered by Kahne and co-workers, [424] remains the only pure one-pot concept because the synthesis is performed with all reaction components present in the reaction flask from the beginning. In all other approaches, the reactants are added sequentially, typically upon the consumption of the first batch of compounds. The fact that all reactants are present from the beginning implies that fine-tuning of all reaction components is required. In accordance with this concept, the most reactive leaving group reacts with the most reactive hydroxyl first. Subsequent reaction between the second-ranked reactive leaving group and second-ranked hydroxyl takes place after the first step has been completed, etc. The concept of the conformational superarming developed by Bols et al.[287,288] was also applied to a one-pot synthesis with all three reaction components present from the beginning.[287,384]

The second approach is based on chemoselective activation wherein the reactivity of the glycosyl donor and acceptor is differentiated by varying the electronic properties of protecting groups.[375–377] A relevant example is shown in Scheme 11 (synthesis of **59**) wherein the sequential activation of **55**, **56**, and **57** was based on their relative reactivity, which was found to be 17000/162.8/13.1, respectively.[376] In contrast to the first concept, building block **57** is added only after the reaction between **55** and **56** is completed, etc.

The third approach is based on selective activation of one leaving group over another. Since the number of leaving groups that can be aligned for multistep sequential activation is still limited only a few examples are known. Highlighted herein is the synthesis of a linear tetrasaccharide derivative **62** that was accomplished in 73% yield over three sequential glycosylation steps.[425] This was achieved by the stepwise activation of SBox donor **60** over S-ethyl glycoside **61**. The S-ethyl moiety of the disaccharide intermediate was then activated over STaz acceptor **30**. Finally, the STaz leaving group of the trisaccharide intermediate was activated for the reaction with glycosyl acceptor **2** (Scheme 12).

The fourth approach is based on preactivation, and hence it is practically independent of the building block reactivity. A representative example illustrated in Scheme 13 deals with a straightforward synthesis of the tumor-associated carbohydrate antigen Globo-H hexasaccharide.[66] Thus, preactivation of fucosyl donor **63** at −78 °C with *p*-TolSCl and AgOTf was followed by the addition of acceptor **64** along with a hindered base 2,4,6-tri(t-butyl)-pyrimidine (TTBP). The temperature was then increased to −20 °C, and the trisaccharide intermediate was formed. The reaction mixture was cooled again to −78 °C followed by the addition of AgOTf and p-TolSCl. After that, galactose acceptor **65** and TTBP were added, and the reaction mixture was warmed to −20 °C. When acceptor **65** has disappeared, the temperature was lowered to −78 °C and the sequence was reiterated for glycosylation of lactose acceptor **66**. The resulting Globo H hexasaccharide α−**67** was formed in 47% yield based on the four-component reaction that required only 7 h to complete the assembly.

The fifth concept for one-pot oligosaccharide synthesis relies on the differentiation between various hydroxyl groups, such as primary versus secondary or equatorial versus axial, have been explored.[426]

2.3. Supported and Tagged Oligosaccharide Synthesis

Further breakthroughs in the area of synthetic chemistry came with the development of supported or tagged organic synthesis techniques. As a consequence, the last two decades have also witnessed dramatic improvements in the area of supported oligosaccharide synthesis. Supported synthesis is very attractive as it allows for the rapid synthesis of oligosaccharide sequences without the necessity of purifying (and characterizing) the intermediates. Another important advantage of supported oligosaccharide synthesis is that it simplifies reagent excess removal. It can be achieved either by filtration if insoluble polymer or other solid phase supports are used or, alternatively, by fractionation, extraction, or precipitation if soluble polymer supports or other supports/tags are employed.

2.3.1. Synthesis on Solid Phases.—

Solid-phase synthesis using insoluble polymer supports (beads)[96,97] has been widely used in the preparation of many classes of molecules of interest.[96,97,427,428] Preparations of oligopeptides[429] and oligonucleotides[430] have been reported using insoluble supports. Merrifield[431] was the first to report the synthesis of peptide chains using polystyrene beads. The introduction of solid phases into the carbohydrate synthesis is credited to Fréchet and Schuerch who reported the first oligosaccharide synthesis on solid support.[432] Since those pioneering studies, the solid-phase synthesis has been widely utilized in a routine preparation of oligosaccharides and glycopeptides, and it is attracting renewed attention in connection with combinatorial chemistry[433] and automation.[354,434]

The two main strategies used for solid-phase synthesis of oligosaccharide are called donor-bound and acceptor-bound. In the first approach depicted in Scheme 14A, the acceptor is bound to the resin either through the anomeric position or one of the positions away from the anomeric center. This approach has an important conceptual advantage by using highly reactive solution-based monosaccharide donor. As a result, the yields remain high, even at

the advanced stages of the assembly. With the increasing size of the oligosaccharide, the solid phase bound reaction sites extend further into solution phase, which also contributes to high yields that are achieved by means of this strategy.

The second concept, the donor-based approach depicted in Scheme 14B, relies on the donor bound to the polymer support. After the glycosylation has occurred, the temporary protecting group on the acceptor is turned into a suitable leaving group and the chain elongation steps can be reiterated. In principle, the chain elongation can be continued directly, if a suitable set of orthogonal leaving groups is chosen. However, the main disadvantage of the donor-bound approach relates to the origins of the glycosylation mechanism. Glycosyl donors are much more prone to side reactions than are glycosyl acceptors. Donor that underwent a side reaction, or simply was hydrolyzed, cannot conduct further chain elongation and this will ultimately terminate the oligosaccharide sequencing. Also, the templated approach outlined in Scheme 13C, wherein both components are connected to the same polymer support has been investigated. Two-directional techniques, combining conventions of approaches A and B, are also known.[63,420]

Polymer beads or resins are the most commonly used supports for solid-phase synthesis. Polystyrene beads crosslinked with 1% divinylbenzene found broad acceptance in all fields since their introduction by Merrifield (Figure 3A).[431] Initially invented for peptide synthesis applications, the resin was successfully introduced into the solid phase synthesis of oligosaccharides.[432] The high loading capacity and the compatibility with many reaction conditions have been crucial for the popularity of polystyrene-based resins. Since then, different solid supports with different swelling characteristics have been explored: polystyrene grafted with different lengths of polyethylene glycol (PEG) groups led to the development of Tentagel (Figure 3B), Hypogel, and Argogel.

These resins are able to swell efficiently in both polar and nonpolar solvents and are capable of higher loading capacity. Another approach made use of modifying the cross-linker by employing a tetrahydrofuran-derived bridge (Figure 3C).[435] This resin has been commercialized with the trade name of JandaJel. Although polystyrene resins are fairly inert, it is noteworthy that some of these resins tend to partially decompose in the presence of large amounts of TMSOTf.[435] To address possible instability of polymeric resins, nonswelling porous materials have also been evaluated for solid-supported oligosaccharide synthesis, and controlled-pore glass[436] and nanoporous gold[437,438] are two such materials to mention (*vide infra*).

The linker plays a central role in the synthesis of oligosaccharides using solid-phases. Due to its labile nature, the linker itself has to be taken into account for orthogonality in respect to all protecting (or leaving) groups that will be manipulated during the various steps. For the same reason, various linkers stable under many different conditions have been developed for carbohydrate synthesis.[354,439] In addition to known and widely used protecting group-derived linkers, such as succinoyl, alkoxybenzyl, and silyl-based linkers, a new wave of photoreactive, metathesis, or hydrogenation-removable linkers had emerged.[44,440–455] In the subsequent effort to develop new linkers with a versatile installation and/or removal profile, recent developments included Reichardt's spacer/linker,[452] as well as Seeberger's "Lenz

linker,"[456] safety catch linker,[457] and photocleavable linker.[458] Some examples of recently developed linkers are summarized in Figure 4. More recently, Seeberger at al. developed a traceless photocleavable linker that is capable of producing oligosaccharides with the free reducing end.[459] The linker offered stability and yields comparable to the parent structure, making it a suitable choice for future applications. The cleavage is achieved using a flow photoreactor, shown to be far more efficient than the classical batch reactors.[460]

As mentioned, most of the solid-phase syntheses involve glycosyl acceptor-bound approach. One of the classical examples of this approach involves Schmidt's synthesis of a branched saccharide **73** depicted in Scheme 15.[461] Lactose derivative **68** was attached glycosidically to the carboxypolystyrene resin support in the presence of TMSOTf. The chain was then extended by sequential removal of the orthogonal protecting groups fluorenylmethoxycarbonyl (Fmoc) with triethyl amine Et_3N and Lev with hydrazine acetate. Upon cleavage from the resin, achieved by the treatment with NaOMe/MeOH, and subsequent global acetylation with Ac_2O/pyridine, hexasaccharide **73** was obtained in 43% overall yield.

More recently, Boons et al. reported the synthesis of all-α-linked oligosaccharide **79** using chiral auxiliary mediated 1,2-cis glycosides on polymer support.[186] As depicted in Scheme 16, glucosyl donor **74** was attached glycosidically to the hydroxypolystyrene resin support in the presence of TMSOTf. The chain was then extended by sequential removal of the orthogonal protecting groups Fmoc (with piperidine) and allyloxycarbonyl (Alloc) with $Pd(PPh_3)_4$. Upon cleavage from the resin and subsequent reprotection, pentasaccharide **79** was obtained in 25% overall yield.

Most of the known syntheses involve a glycosyl acceptorbound approach, but examples involving glycosyl donor bound have also emerged. As reported by Danishefsky et al.,[462] glycal **80** was attached to a Merrifield resin via a silyl linkage in the presence of diisopropylethylamine (DIPEA, Scheme 17). The polymer-bound glycal was then epoxidized with DMDO, and the resulting 1,2-anhydro sugar was glycosidated with acceptor **80** in the presence of $ZnCl_2$ to provide the immobilized disaccharide. This synthesis was reiterated until the desired oligosaccharide was obtained. The latter was then cleaved off by the treatment with Bu_4NF/AcOH to afford pentasaccharide **82** in 58% yield. Another similar example of the donor-bound approach include the synthesis of the Le^b blood group antigen[354,463] and selective activation of the SBox donor over solution phase thioglycoside acceptor.[464]

The application of orthogonal strategy, which is another example of a donor-bound approach in polymer supported synthesis, was introduced by Ogawa.[465] A more recent example of this approach is illustrated in Scheme 18. As reported by Kanie et al.,[391,392] polymer-bound donor **83** was activated selectively over fluoride acceptor **84** in the presence of dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST). The immobilized glycosyl fluoride was then activated over *S*-phenyl acceptor **85** in the presence of $Cp_2Hf(OTf)_2$. Finally, the immobilized *S*-phenyl trisaccharide was glycosidated with octanol in the presence of DMTST. The resulting oligosaccharide was cleaved off and all eight diastereomers of **86** were separated by HPLC to provide a useful combinatorial library.[391]

Short peptide chains immobilized on the solid support have been investigated as templates for streamlining the oligosaccharide synthesis by Fairbanks et al.[466–468] and Warriner.[469] As shown by Warriner, conjugate **87** containing the hydroxyproline-linked glycosyl donor and acceptor pair with the glycine unit in between produced (1 → 4)-linked disaccharide **89** in high yields (Scheme 19). A differential and highly substrate orientation-dependent stereoselectivity was observed by employing differently sequenced templates, such as **88**.

The application of emerging nanomaterials to organic synthesis has created the basis of the STICS (surface-tethered iterative carbohydrate synthesis) technology, which is a functionalized “stick” made of chemically stable high surface area nanoporous gold that allows performance of cost-efficient and simple synthesis of oligosaccharide chains.[438] Nanoporous gold can be prepared by dealloying Ag from Au–Ag alloy or from Au–Ag alloy electrodeposited onto a gold surface in the presence of nitric acid.[470–473] As depicted in Scheme 20, a stack on NPG plates, carrying acceptor **91** anchored to the gold surface with a thiolate linker, is assembled in a Teflon-shelved reactor. The oligosaccharide assembly is accomplished by alternating the glycosylation, deprotection, washing, and drying steps. Thus, 6-*O*-TBDPS protected *S*-benzoxazolyl (SBox) glycosyl donor **90** was coupled to the immobilized acceptor **91** in the presence of MeOTf. Then, after a rinse, the tethered disaccharide intermediate was treated with Bu_4NF to remove the silyl group to afford the second generation glycosyl acceptor. After being dried in vacuum, the latter was reacted with SBox donor **60**. At the end of the synthesis, the oligosaccharide can be cleaved off from the gold surface offering a useful potential alternative both for directed and combinatorial synthesis.

2.3.2. Tagged Synthesis (Soluble Polymer Supports, Ionic, Fluorous).—

Soluble polymer supports, many of which are based on a polyethylene glycol core, have also found their application in oligosaccharide synthesis. This method has emerged to address problems of the resin-supported synthesis associated with slow reactions and reactivity mismatch between unreactive solid-phase based and highly reactive solution-based reactants.[474,475] These supports, and everything attached to it, are freely soluble in the reaction media but could be precipitated by the addition of diethyl ether or other suitable solvent and recovered by filtration.[476–478] Alternatively, nanofiltration or a size-exclusion separation offer other possible alternatives for separation of polymer-bound molecules and the rest of the reaction components.[479] An elegant synthesis that combines advantages of the soluble polymer-supported technology and convergent building block strategy was applied to the synthesis of hexasaccharide **100** (Scheme 21).[480] In this application, fluorenylmethoxycarbonyl (Fmoc) and diethylisopropylsilyl (DEIPS) are used as temporary substituents that could be removed with Et_3N and TBAF, respectively, without affecting the linker. The polymer-bound intermediates obtained, such as **98**, could be purified by recrystallization from absolute ethanol.

Among other improvements of the supported oligosaccharide synthesis, fluorous tags incorporating a long per-fluorinated alkyl chain allow the separation of all fluorinated from nonfluorinated species by partitioning between perfluorohexanes and methanol (or toluene). The synthesis of oligosaccharide **105** is shown in Scheme 22.[355] Triol **101** was protected at the O-2, O-3, and O-4 positions with fluorous protecting groups, using DCC/DMAP-

mediated coupling with the fluorous acid **102**. The resulting "tagged" compound was detritylated with CSA (camphorsulfonic acid) and LiCl to provide acceptor **104**. The latter was glycosylated with glycosyl donor **103** in the presence of TMSOTf in $EtOC_4F_9$–diethyl ether to provide the respective tagged disaccharide. Desilylation with HF in pyridine followed by glycosylation were reiterated until the desired pentasaccharide **105** was obtained. More recently, less heavily fluorinated tags and compounds have found a broad application in automated synthesis (*vide infra*).

Another promising technique for tagged oligosaccharide synthesis that makes use of an ionic-liquid support has recently emerged.[481,482] Ionic liquid-supported assembly also expedites oligosaccharide synthesis by eliminating the need for chromatographic purification of the intermediates. After the desired reaction of the tagged compound has been completed, the reaction mixture is concentrated. The excess of organic reagents is removed by extraction with low polarity solvents in which the tagged compounds are insoluble. Using the same principle, the inorganic reagents are eliminated with aqueous washings to afford the pure target compound tagged with the ionic liquid. This approach is illustrated by a synthesis that incorporates elements of an orthogonal strategy making use of alternating activations of STol and F leaving groups and the convergent approach depicted in Scheme 23.[483,484] (1-Methylimdazoliumhexafluorophospho) acetyl ionic liquid tag was introduced via the corresponding 6-chloroacetylated starting material by reaction with *N*-methylimidazole and potassium hexafluorophosphate. The tagged mannosyl fluoride donor **106** was glycosylated with thioglycoside acceptor **107** to afford the IL-tagged disaccharide **110**. Meanwhile, the analogous disaccharide **111** was produced using thioglycoside **108** as the donor and fluoride **109** as acceptor. Each disaccharide was split into portions, and the tag was removed from one portion. This gave a library of two disaccharide donors (**110** and **111**) and two disaccharide acceptors (**112** and **113**) that were converged to produce two tetrasaccharides. One of the tetrasaccharides was untagged to produce glycosyl acceptor **114**. Finally, the synthesis is concluded with a [4 + 4] glycosylation between the tagged tetrasaccharide fluoride donor and thioglycoside acceptor **114** to afford the final mannan octasaccharide **115**. Gouhier and co-workers[485] reported efficient 1,2-cis glycosylations using ionic liquid-supported thioglycoside in a two-directional[419,420] manner.

3. AUTOMATED SYNTHESIS OF OLIGOSACCHARIDES

All traditional oligosaccharides contain multiple glycosidic linkages. This linkage is obtained by a glycosylation reaction, which, in spite of significant progress overviewed in section 2.1 remains challenging due to the requirement to achieve stereocontrol and suppress side reactions. Beyond that, as overviewed in section 2.2, oligosaccharide synthesis offers further challenges that may require further manipulations between each glycosylation step. Due to significant advances, the chemical synthesis of many glycans can now be streamlined by using various methods and strategies in solution. Solid-phase and tag-assisted syntheses, which were overviewed in section 2.3, eliminate the need for purifying intermediates and simplify the removal of excess reagents. Following significant advancements in the preparation of peptides[429,486] and oligonucleotides,[430] since 1971 solid-phase synthesis has become a viable means for the preparation of oligosaccharides.

However, there are significant differences between glycosylations in solution and solid-phase synthesis that particularly affect glycosylation. Among a plethora of leaving groups developed, a vast majority of glycosylations in solution make use of thioglycosides[487–490] and TCAI.[125,263,264,491,492] Solid phase synthesis commonly demands highly reactive TCAI, PTFAI,[265,493,494] or phosphates.[148,495–499] A series of novel S-and O-imidates have been tested in reactions on solid phases, but their comparison with more common donors showed no drastic difference.[438,464,500–502] The use of thioglycosides as donors in solid phase has also been reported (*vide supra*), but their relatively low reactivity profile and the requirement for stoichiometric promoters limit their application. Only recently, the use of thioglycosides in solid phases has been brought to practical realization.[503]

The discoveries made over the course of traditional synthesis, wherein all manipulations are performed manually, have laid the basis for considering their automation as an aid in synthesis manipulations. Automation introduces an idea of operational simplicity, attractive for transferable methods, and the development of accessible methods for glycan production is essential for further innovations and practical applications in all areas of glycosciences. The development of automated oligosaccharides synthesizers offers a potential of revolutionizing the way oligosaccharides are produced. Hence, the development of a broadly useful technology for scalable and transformative automation has emerged as a timely and significant area of research.

Many automation platforms make use of a computer interface and liquid handling equipment. This helps to minimize the human error factor and improve the reproducibility of results and transferability to other platforms.[504,505] The underpinning idea of automation is that a successful automated sequence is recorded as a computer program that can then be reproduced with a “press of a button”. In addition, many automation platforms implement some tool for real-time reaction monitoring, which, in turn, helps reduce the reaction time and the amount of reagents and solvents needed. This section is dedicated to the overview of major research efforts dedicated to the refinement and implementation of various automated platforms that have emerged in the past decade following early efforts to automate solution-phase manual synthesis by Wong[376,506,507] and Takahashi[508] and Seeberger’s peptide synthesizer-based platform for automated synthesis on solid phase.[509,510] Discussed below is the development of “the first fully automated solid-phase oligosaccharide synthesizer” by Seeberger et al., initially in its experimental form,[456] that in 2014 was marketed as Glyconeer 2.1. Also discussed are other automation efforts, primarily by Takahashi,[511,512] Pohl,[513] Demchenko and Stine,[514] and Nokami and co-workers[515] that have been also emerging during about the same time-period.

3.1. Early Developments

As aforementioned, Wong et al. assigned relative reactivity values (RRVs) to a wide library of building blocks that were then used for oligosaccharide assembly in one-pot.[376] The determination of RRVs was made with tolylthio glycoside donors activated in the presence of an NIS/TfOH promoter system under standardized reaction conditions. The reactivity data was then compiled into a computer program named Optimer[376] that was used to synthesize various oligosaccharides.[516–518] Refer to Scheme 10 for a relevant example of a reactivity-

based oligosaccharide synthesis in one pot. Not being strictly automated, this approach brought up an idea of standardizing the reactions and using computers in quantifying and even predicting the reactivity of different building blocks. Fraser-Reid,[374] Ley,[375,519,520] and others[521] also created relative reactivity scales for oligosaccharide synthesis.

Takahashi et al. investigated a number of platforms for the automation of solution-based oligosaccharide synthesis in onepot. While the Wong approach was strictly chemoselective, in applications executed by Takahashi, selective activation of different leaving groups was employed. In 2000, they adapted a semiautomated parallel synthesis instrument Quest-210 by Argonaut Technologies to the one-pot synthesis of linear and branched oligosaccharides.[508]

Thus, for the synthesis of trisaccharide **119** shown in Scheme 24, bromide donor **116** was selectively activated over thioglycoside acceptor **117** in the presence of AgOTf. The anomeric thiophenyl leaving group of the resulting disaccharide intermediate was then activated by the addition of NIS, TfOH, and glycosyl acceptor **118** to afford trisaccharide **119** in 79% yield over two steps. Takahashi and co-workers further extended this effort to a number of automation platforms, such as L-COS by Moritex, that allowed one to automate temperature control, stirring, and rate of reagent addition for deprotection and glycosylation steps.[511,522,512,523] The synthesizer could be supplemented with Combi Flash automated chromatograph to purify the final products.

3.2. Peptide Synthesizer-Based Automation

The automated approach Seeberger and co-workers relied on is the acceptor-bound one, where donor and promoter are in liquid phase.[509] Since the early developments are already discussed in detail in other review articles,[25,498,510,523–525] we will only briefly overview the key milestones and achievements. The main focus in this discussion will be placed on the dedicated effort and progress toward the synthesis of difficult glycosidic linkages. The instrument introduced by Seeberger and co-workers was derived from an Applied Biosystems Inc. Model 433A peptide synthesizer. It was modified to allow for performing reactions at low temperatures that were deemed necessary for the oligosaccharide assembly.[509] The solid support chosen was Merrifield resin, well-known in the peptide world, for its good chemical inertness and ideal swelling properties in solvents utilized in glycan assembly. As it has been discussed previously, the choice of the linker is critical since it should resist conditions required during the synthesis. An olefin-type linker was chosen for its versatility and good behavior in both acidic and basic media, as well as the mild cleavage conditions. In the first synthesis depicted in Scheme 25, octenediol-functionalized resin **121** was glycosylated with TCAI donor **120** (10-fold excess) in the presence of TMSOTf. The ester group was then cleaved using Zemplen conditions to generate the disaccharide acceptor. The glycosylation and deprotection steps were repeated until the oligomers of the desired length, up to decasaccharide, had been achieved. Each step was performed in two iterations, to avoid the formation of deletion sequences, and hence maximize the yield and simplify the final purification. The linker was then removed using Grubbs' catalyst to afford penta-, hepta-, and decasaccharides **122a–122c** equipped with the anomeric pentenyl moiety. The high promise of the automated approach was evident immediately. Thus,

heptasaccharide **122b** was synthesized in 24 h in 42% overall yield. In comparison, whereas their previous manual synthesis was less efficient (9% overall yield in 14 days).[443]

After this first milestone and with the intention of extending the scope of the new technology, the subsequent efforts performed by Seeberger et al. focused on the synthesis of oligosaccharides containing various challenging linkages.[458,526–528] This included sialic acids,[529] furanosides,[530] 1,2-cis glycosides,[67] glycopeptides,[460] and branched oligosaccharides.[509] The expertise acquired in the development of this methodology for the synthesis of various glycosidic linkages and sequences led to an impressive synthesis of Globo-H hexasaccharide.[67] As shown in Scheme 26, phosphate donor **123**, was used to glycosylate hydroxylated resin **121** using TMSOTf as a promoter. The temporary Fmoc substituent at C-4 was removed using piperidine leading to the formation of the polymer-bound disaccharide acceptor. Fmoc is commonly used in oligosaccharide synthesis because it is highly stable in acidic conditions common for glycosylation, and it is easily removable in mildly basic conditions. In this particular application, the cleavage product of Fmoc, dibenzofluorene, is a convenient marker to monitor the progress of the reaction via colorimetric assay.[531] The synthetic sequence consists of glycosylation steps with two or three iterations, using either glycosyl phosphate (**123–126**) or glycosyl PTFAI donors (**127** and **128**) followed by the deprotection of the Fmoc group with piperidine.

The final product **129** was cleaved off the solid support using ethylene in the presence of Grubbs' catalyst[532] in 30% yield. The stereoselectivity of the 1,2-cis glycosylation step was enhanced by using diethyl ether, which is known to favor the formation of axial products (*vide supra*). As aforementioned, Globo H is an important synthetic target of high biomedical significance for the development of anticancer vaccines.[22,25,533–537] The biological importance of the Globo-H antigen is so widespread throughout the scientific community that many synthetic approaches have been developed.[63–66,68]

Seeberger and co-workers also developed reaction conditions to achieve β-mannosylation on a solid phase using an automated approach.[538] They started from the methodology developed by Crich[539] involving 4,6-O-benzylidene-protected mannosyl donors bearing a sulfoxide leaving group. In the original procedure, the donor is preactivated with Tf_2O and then reacted with the nucleophile. To adjust the procedure to the automated synthesis, the solvent adopted was dichloromethane, and the preactivation was abolished. Unfortunately, although the selectivity of the test reaction was high, the yields were only moderate at best. On this basis, the next method of interest was the *o*-carboxybenzyl donor developed by Kim.[152] After the initial study in the solution phase that revealed high yields and selectivities, the selected donor was tested on solid phase to synthesize a series of di- and trisaccharides. The stereoselectivity fluctuated from 3.5:1 to 9:1 in favor of the desired diastereomer, showing a partial erosion of the selectivity compared to that achieved in reactions in solution. Further, to facilitate the elongation of a sequence containing a β-mannosidic linkage, the donor was equipped with a triisopropylsilyloxymethyl ether (Tom) at C-3.[540] This protecting group is removed under the same mild conditions as those that make the silyl protecting group ideal for synthetic application. The Tom substituent, however, is much less bulky than conventional silyl protecting groups, which is strategically significant for β-mannosylation.[541] The donor was successfully used in the synthesis of a trisaccharide containing multiple

β-linkages in excellent yield and good selectivity (Scheme 27). Mannose trisaccharide **133** was isolated in 50% yield as a mixture of anomers (8:1:1.3), and the pure β,β-linked product was isolated by HPLC. Van der Marel, Codee, and their co-workers have successfully applied a similar approach to the synthesis of ManA oligosaccharides.[542]

3.3. Fluorous-Tag-Assisted Automated Synthesis

Fluorous-tag-assisted technology has emerged as a new and attractive approach to oligosaccharide synthesis with good prospects for automation. As discussed previously, extensively fluorinated species and highly fluorinated protecting groups allow for the separation of the fluorine-containing components, typically glycosyl acceptors, from the nonfluorinated glycosyl donors, with the principle of different phase partitioning between per-fluoroalkenes and methanol.[355] On the other hand, Seeberger showed that the chemistry of solution-based microreactors, developed in the late 1990's, could be applied to carbohydrate chemistry.[543] The benefits of using a microreactor include: safety, a much greater control of the reaction temperature, and compatibility with various analytical techniques. Microreactors are amenable to automation, and the syntheses can be scaled up by increasing the number of reactors.

By merging these two technologies, fluorous-tagged synthesis and chemistry in microreactors, the synthesis of a homotetramer **136** was accomplished as depicted in Scheme 28.[497] Three different syringe pumps delivered the solutions through the inlets into the mixing zone. The concentration can be controlled by the concentration of the original solution and the flow-rate at which each reagent is delivered into the system. The reaction occurs inside the reaction loop. Glycosyl phosphate donor **134** was first glycosidated with fluorous tag **135** in the presence of TMSOTf.

This was followed by the removal of the Fmoc group with piperidine and TBAF to afford the fluorous monosaccharide acceptor. Tetrabutylammonium fluoride proved necessary for removal of the 6-O-TMS byproducts. The latter was glycosylated with donor **134**, and the deprotection-glycosylation sequence was repeated until the desired compound has been obtained. The product was then cleaved off from the fluorous support by the treatment with Grubbs' catalyst to provide tetrasaccharide **136**. The reaction can be followed by pairing the reactor with different detection systems including UV–vis detectors, IR, or mass spectrometers. The reaction times for the glycosylations were 20 s for the formation of the disaccharide and 60 s each for the tri- and tetrasaccharides. The yields for the reactions after purification were 97, 90, and 95% for the di-, tri-, and tetrasaccharides, respectively.

The Pohl group applied the fluorous-tag-assisted glycosylation approach to developing an alternative automation technology. This was accomplished by using a commercially available automated liquid handler and the fluorous solid phase extraction (FSPE) technique (Scheme 29).[513] The handler was modified to accommodate cartridges for the FSPE. In this approach, the fluorous-tagged glycosyl acceptor **138** was glycosylated using an excess of TCAI donor **137** in the presence of TMSOTf as the promoter. The obtained tagged disaccharide was then separated using an automated three-step FSPE. This consists of loading into a separation column, and elution of all fluorine-free components using 20%

solution of water in methanol. At last, the retained fluorinated molecules are released from the solid-phase using methanol or THF, which are fluorophilic solvents.

This procedure can be automated by using commercially available devices capable of applying a positive pressure at the top of the column or, alternatively, vacuum at the exit of the eluate. After purification, the disaccharide was treated sequentially with TBAF and hydrazine to remove TMS and Lev protecting groups, respectively. The resulting triol acceptor **139** was triglycosylated using TCAI donor **120**, to afford the desired pentasaccharide **140** in an excellent yield of 92%.

In an effort to pair an automated purification to the automated solution-phase synthesizer, Pohl's group worked on HPLC as the preferred instrument to accomplish this purpose. An alternate-pump system that differs from a direct-pump design because it is based on recycling the analyte through two identical columns using a 10-port switch valve was utilized.[544] The advantage of this alternate-pump design is that peak broadening is avoided. The broadening is caused by the internal volume of the mobile-phase solvent pump the analyte goes through, when pumped back into systems with direct-pump design. The valve switches between two different positions, A and B, as shown in Figure 5. Starting from position A, the compound elutes through the first column and the UV detector. When the analyte reaches the half of the second column, the system switches to position B, so that the second column is directly connected with the first one. When the compound travels back to column 1, halfway through column length, the system switches back to position A, and the system is now back to the original set up, with the UV detector between columns 1 and 2. Thus, the analyte passes through the detector every odd-numbered column, so after every run through column 1, for its purity to be assessed.

After choosing the purification setup, the most suitable stationary phase was selected. Three different phases were considered: the commonly used C5, a phenyl hexyl, and a pentafluorophenyl (PFP) modified silica. The latter two were found superior in the separation of both monosaccharides and oligosaccharides with methanol as an organic modifier. In particular, after numerous tests, the PFP-modified silica was found to be more suitable for the separation of acylated monosaccharides and aromatic group-protected compounds, whereas the phenyl hexyl-modified silica worked better toward acyl protected oligosaccharides, respectively.[545] This new methodology was used to purify the product of a reaction conducted in the automated synthesizer. The authors detected that sugars equipped with achiral linkers proved to be the most challenging compounds to purify through manual separation. In this case, the product was successfully purified using a PFP-modified stationary phase and seven effective columns.

Over the recent years, the Pohl group has applied the fluorous-tag-assisted automated synthesis to the synthesis of a number of glycan sequences.[546–549] Among this is the synthesis of manno oligosaccharides connected via challenging β-linkages. This approach was based on the C-5 carboxylated mannosyl donor methodology developed by van der Marel for manual reactions.[307] At first, the synthesis of 1,4-linked β-oligomanno-sides was automated using alternative glycosylation, TBS-deprotection steps to achieve the mannuronic hexasaccharide **144** sequence (Scheme 30).[547] After each glycosylation and

deprotection step, a FSPE is performed before reiterating the procedure to elongate the chain.

As shown in Scheme 30, mannuronic acid donor **141** was used to glycosylate fluorous-tagged glycosyl acceptor **142** in the presence of TMSOTf as the promoter. The resulting disaccharide was treated with TBAF and acetic acid to remove the TBS protecting group and was subsequently purified using the automated FSPE. The sequence was repeated three times with the automated purification. The fourth iteration, followed by the benchtop purification, afforded the tagged compound **142**. The latter was reinjected into the synthesizer, the TBS group was removed using tetrabutylammonium fluoride, and the resulting compound **143** was purified using FSPE. At the end of the assembly, the carboxyl groups are reduced with DIBAL-H using the automated platform to afford the desired β-linked hexamannose **144**. More recently, Tang and Pohl applied a similar approach to the synthesis of other positional isomers of mannans.[549] For the synthesis of 1,2- and 1,3 linked oligomers, glycosyl donors bearing an easily removable temporary PMB substituent at the respective positions were employed. At the end of the sequencing, the mannuronates were reduced with lithium triethylborohydride before the final benzyl removal leading to excellent yields. In the case of the synthesis of 1,6-linked mannans, the reduction of the carboxylic group is performed before the subsequent glycosylation instead of the protecting group removal.[549] Excellent stereoselectivity for the glycosylation of all positions has been achieved; however, the elongation of the 1,2-, 1,3-, and 1,6-linked oligomannans beyond trisaccharides proved to be difficult. The reasons for this are not clear, but it could relate to the increased steric demand as the size of the acceptor increases.

This approach was also applied to the synthesis of branched, all-mannosylated N-linked glycan structures.[546] The core N-glycan structure is characterized by the presence of a β-mannoside carrying two α-mannosides at O-3 and O-6 (refer to Figure 1). As shown in Scheme 31, the formation of the difficult linkage is addressed using the strategy of the C-5 carboxylate methodology (*vide supra*). The branching point has a PMB to mask O-3 and the carboxylic group working both as directing and protecting group. The automated sequence consists of the glycosidation of donor **145** with the fluorous tag **146**. *p*-Methoxybenzyl group is removed in the presence of CAN, followed by the automatic purification of the tagged monosaccharide using the FSPE. Further benchtop purification to eliminate the undesired α-isomer afforded mannuronate **147** in 78% yield. The latter was reduced to obtain free hydroxyl at the C-6 position, and the product was purified. The subsequent glycosylation performed with six equivalents of donor allowed for bis-mannosylation. Benchtop Zemplen reaction afforded trisaccharide **148** in 50% yield. The synthesis was completed by removing the benzyl group and the fluorous tag.

3.4. Glyconeer 2.1 as a Dedicated Oligosaccharide Synthesizer

After proving that a peptide synthesizer-based apparatus may be a viable platform for oligosaccharide synthesis, Seeberger and co-workers took one step further. In 2012, they reported the “first fully automated solid-phase oligosaccharide synthesizer”.[456] This dedicated apparatus is a sophisticated system, consisting of a syringe pump-driven part and a solenoid valve-driven part. The reaction vessel is double-jacketed to allow for the circulation

of the cryogenic fluid. It is connected to the inlet tubes to avoid splashing of the solution injected and to allow for washing the vessel walls. The bottom of the vessel is equipped with a porous glass filter and pipelines that can be directed to waste or to a fraction collector. An exhaust opens only if a positive pressure of argon is used. This also helps to ensure the compete isolation from external atmosphere. The system is built with two syringe pumps, but only one is used.

It is filled exclusively with 1,2-dichloroethane to avoid solvent contamination. Four rotary valves are designated to regulate the delivery of building blocks and reagents for activation and deprotection. The solenoid valves are used to deliver solvents, mix reactions solutions, and manage the waste delivered from the reaction vessel. In addition to the parts already described, a cryostat operating between −50 °C and −90 °C and a fraction collector are important features of the synthesizer. The instrument is paired with a computer that helps to design, record, and control glycosylation and deprotection protocols. This setup provides complete automation for reactions, temperature control, cleavage, and collection of the final product. The complexity and the number of channels available, combined with the positive pressure of Argon throughout the whole system, make the Glyconeer 2.1 the most complete and versatile synthesizer currently available, allowing for achieving a significant variety of reaction conditions. The versatility of the new system was tested by performing the synthesis of a range of oligomers, including a high mannose-type branched glycan **153** as illustrated in Scheme 32. The new linker **150** was also developed for this purpose. This linker helps to ensure better stability during the glycosylation conditions.

The chitobiose portion of the core pentasaccharide sequence was assembled first, using glycosyl donor **149** for both units. After the two glycosylation-deprotection cycles, a challenging β-mannosyl residue was introduced by utilizing glycosyl donor **131** equipped with the 2-(hydroxycarbonyl)benzyl leaving group originally developed by Kim and co-workers. Subsequent treatment with TBAF to remove the silyl protecting group at C-3 and a selective opening of the benzylidene group afforded the desired 3,6-diol, which was subjected to bis-mannosylation using glycosyl donor **151** to afford a branched pentasaccharide. Cleavage from the solid support was performed using MeONa, affording the precursor **152** as a mixture of two anomers (α/β = 1/3) in 3.5% overall yield. Preparative HPLC separation was used to isolate the desired product, which underwent global deprotection using hydrogenation to afford the final product in 78% yield.

Subsequently, relying on a similar technology, Seeberger et al. obtained an α-(1 → 6)-linked oligomannan sequence containing 30 monosaccharide residues (triantamer).[550] To achieve this challenging target, a modified Merrifield resin **155** carrying a photocleavable linker was used. The solid support was repeatedly glycosylated using phosphate donor **154** in the presence of TMSOTf as a promoter (Scheme 33). To avoid the formation of many deletion sequences and to make the final separation easier, the unreacted hydroxyls were capped with Ac_2O in pyridine. Piperidine in dimethylformamide was used for the cleavage of the Fmoc protecting group from C-6 to afford the next generation glycosyl acceptor. The presence of benzoyl esters on the other positions allowed for complete stereoselectivity of the glycosylation reactions and high yields. The 29-mer resulting from 28 iterations of the glycosylation-capping-deprotection sequence was then glycosylated with donor **156**,

equipped with a spacer to perform a very effective cap-and-tag purification. Therefore, upon removal of the oligosaccharide **158** from the solid support, a conjugation step to magnetic beads through the *ε*-aminocaproic ester spacer was performed. The purification step consisted of a magnetic separation of the tagged 30-mer **159**, followed by release using Zemplen conditions also to remove benzoyl protecting groups. Finally, hydrogenation was performed to free the terminal amine of the linker from the Cbz group, resulting in the fully unprotected 30-mer **160**, obtained in 1% yield, which corresponds to 96% yield per synthetic step.

In the further development of the Glyconeer synthesizer, Seeberger et al. successfully synthesized mannosyl 50-mer **162** (penindamer), the longest sequence ever obtained with a solid phase automated approach.[551] The approach is similar to the one used for the synthesis of the 30-mer, although an important methodological advancement has emerged with the implementation of the ethylthio glycoside as the glycosyl donor (Scheme 34). In this application, the glycosyl donor **161** was activated with NIS in the presence of TfOH at −40 °C. The temperature was immediately ramped up to −20 °C, and the reaction was completed in 20 min. The study of the most suitable building block highlighted a donor carrying a permanent benzoyl group at position 2, to ensure neighboring group participation and therefore high selectivity. C3 and C4 are protected with arming benzyls[370] and position C6 is carrying a temporary Fmoc group, removed with Et_3N in DMF every iteration. To facilitate the purification process, which revealed to be challenging for deletion sequences longer than *n*-5, a capping step was introduced after every glycosylation step. Furthermore, in the latest cycles, from 46 to 50, a second glycosylation was added to the sequence to ensure even better conversion during the elongation. Since these additional steps are expensive in terms of time, a 25-mer was synthesized as a proof of concept, to show that the capping steps become necessary only in the latest stages of the sequence. The approach proved to be successful allowing an easy separation of the desired product from the shorter oligomers and a higher average yield for each step. The purification was achieved by HPLC before the deprotection steps and later on using dialysis and size-exclusion chromatography.

For expanding the scope of the automated oligosaccharide synthesis, the Seeberger group also worked on refining reaction conditions for the formation of other challenging glycosidic linkages. For example, a number of efforts were dedicated to the formation of sialylated oligosaccharides. Previously, sialic acid containing disaccharides were presynthesized and then used as building blocks in the convergent solid phase synthesis.[529] More recently,[499] the use of more sophisticated sialyl building blocks based on the 4,5-oxazolidinone chemistry[238–240] allowed for direct sialylation in the synthesizer. These new sialyl donors were also equipped with chloroacetyl protecting groups at positions C-7 and C-8, and position C-9 was protected with Fmoc. A similar protecting group pattern, along with the phosphate leaving group, showed good levels of reactivity in sialylation reactions in solution developed by Wong and Wu.[552] After optimizing the glycosylation conditions and reaction temperature, this approach was successfully applied to the automated synthesis of *α*-(2,6)-linked sialosides. A representative example is shown in Scheme 35, wherein the target disaccharide was synthesized from building blocks **161** and **162**. The immobilized

disaccharide **165** was obtained from the reaction of the photocleavable linker **155** with donor **163** in the presence of TMSOTf.

Capping of the unreacted linker with acetic anhydride in pyridine, followed by removal of the Fmoc protecting group with triethylamine (TEA) in dichloromethane, afforded the immobilized acceptor. Phosphate sialyl donor **164** was then activated in the presence of TMSOTf. Finally, the photocleavage provided the target compound **165** in 10% overall yield. The yields for the formation of α-(2,3)-linkages were lower. Another approach to sialooligosaccharides involved a chemoenzymatic synthesis.[553] In accordance with their strategy, a desired oligosaccharide sequence was assembled using the synthesizer first. After the cleavage from the solid support, the target compound underwent the entire protecting group removal followed by enzymatic sialylation. This step was accomplished in the presence of α-(2,3)-sialyltransferase from *Pasturella Multocida* that was originally introduced by the Chen group.[554] As a result, the desired α-(2,3)-linked products were isolated in 78–89% yields.[553]

Seeberger and co-workers also studied the automated synthesis of 1,2-cis-linked residues that are abundant both in microbial glycans and in the mammalian glycome. In particular, reactions assisted by the remote group participation were of particular interest to this application. An overview of compounds **170–176**, synthesized using the Glyconeer 2.1, is depicted in Figure 6.

A systematic study of differently protected galactosyl and glucosyl donors was performed.[555] The highest stereoselectivity was obtained with the galactosyl donor carrying acetates at the C-3 and C-4 positions. Glucosyl donor required esters at the C-3 or C-6, and depending on the desired propagation site, either a removable Fmoc carbonate or more permanent acetate were used. A representative example is the all α-linked oligomer **169** depicted in Scheme 36, achieved from glucosyl donors **166**, **167**, and **168**. Thus, donor **166** was glycosylated in the presence of NIS and triflic acid to the photocleavable linker. The Fmoc protecting group was removed with triethylamine in DMF to obtain the immobilized monosaccharide acceptor.

The sequence was repeated to obtain the disaccharide. Then donor **167** was glycosylated in the previous conditions, and Fmoc protecting group was removed, affording the immobilized trisaccharide. Finally, donor **168** was reacted with the trisaccharide acceptor and photocleavage was performed to afford the final tetrasaccharide **169** in 20% overall yield and with excellent α selectivity.

Among other useful methodologies for the synthesis of 1,2-cis-linked oligosaccharides is the solid-phase synthesis of β-mannosides developed by Codee and co-workers.[542] Glyconeer 2.1 was used as a platform for automation of glycosidation of mannuronic acid donor **177** equipped with a *N*-phenyl-trifluoroacetimidoyl leaving group. Glycosylations promoted with TfOH at −40 °C produced oligosaccharides in high yields and complete β-selectivity. Thus, as depicted in Scheme 37, a 1,2-cis-linked dodecasaccharide **179** was synthesized in 11% overall yield. Donor **177** was first coupled to linker **178**, and each glycosylation step was repeated twice with about 90% coupling efficiency. The Lev protecting group removal was

achieved with hydrazine acetate in a mixture of pyridine and acetic acid. Upon completion of the assembly, cleavage from the solid support was performed using a metathesis reaction with ethylene in the presence of Grubbs I catalyst. Complete selectivity of the target compound was proven by NMR.

Within a plethora of applications for the Glyconeer 2.1 automated synthesizer, there has been the synthesis of a number of oligosaccharides containing furanosyl residues. The first result accomplished was the synthesis of a series of linear and branched oligoarabinofuranides,[530] as depicted in Scheme 38. Thus, ethylthio glycosyl donor **180** is glycosidated with linker acceptor **150**, followed by removal of Fmoc group at C-5 in the presence of piperidine in DMF. The donor **181**, used for branching, is coupled to the immobilized monosaccharide in the presence on NIS and triflic acid, followed by treatment with piperidine in dimethylformamide to remove both Fmoc protecting groups. The resulting disaccharide was treated with donor **180** in the presence of NIS and TfOH, followed by a deprotection step, in two iterations, to obtain the immobilized pentasaccharide. Finally, treatment with sodium methoxide in methanol and catalytic hydrogenation afforded the target compound **182** in 63% yield. The synthesis was completed in only 42 h. The first application of the use of furanose building blocks in solid phase was the synthesis of oligoxylanopyranosides.[556] These structures are based on a linear series of β-(1,4) linked xylosides with the furanoses as branches in selected position. The oligosaccharides obtained in good yield are used to study the binding preference of antixylan monoclonal antibody[557] on microarray systems.[558]

The other two series of compounds synthesized by Seeberger and co-workers are types I and II arabinogalactan (AG).[559,560] These are present in plant cells, and they can be useful to study arabinogalactan-directed antibodies binding specificity. Type I is present in pectic polysaccharide as a decoration of the main backbone and characterized by β-(1,4) linkages connecting Gal units for the linear chain, and the branching is achieved by α-(1,3) bonds between arabinofuranosides and galactosides.[561] Type II, on the other hand, is present as a highly branched polysaccharide attached to a hydroxyproline-rich peptide structure. The linear backbone of the glycan is based on β-(1,3) linkages, while the branching occurs through β-(1,6) bonds.[562] The arabinofuranoses present on the branching are connected by α-(1,3) linkages as in the case of the type I AG. The target compounds were obtained in good-to-excellent yields. The effort in the assembly of various arabinofuranosides containing oligosaccharides culminated in the formation of 2 complex structures containing the former and mannopyrano-sides.[563] These oligosaccharides are present on the cell surface of the *Mycobacterium tuberculosis*[564] and constitute a synthetic challenge for their complexity. Three different building blocks are required for the assembly of the product. They are all ethylthio glycosides and protected with Fmoc on the position of elongation and branching.

Another important application of this dedicated system is to the synthesis of different families of GAGs (glycosaminogly-cans). These compounds are connected to a transmembrane core protein, with the function of transducing signals to the interior of the cells from extracellular environment.[17] The first target was chondroitin sulfate, containing β-D-glucuronic acid and *N*-acetyl-β-D-galactosamine, presenting various sites of acetylation

and sulfation. The advantage of the solid phase in the preparation of this polysaccharide is the establishing of a general method that with a few building blocks allows reaching a wide number of targets, hence the possibility of better understanding their biological relevance.

The selected chondroitin sulfate-A and chondroitin sulfate-C hexasaccharides are similar in structure and differ only in the site of sulfation along the chain. As in cases previously described here, donors contain the phosphate leaving group, the selected protecting group for the chain elongation is Fmoc, allowing mild cleavage conditions, while Lev esters mask the hydroxyl used for the introduction of sulfates. The amino group in the galactosyl building block **183** carries a trichloroacetate as a protecting group and the linker **155**, already utilized by Seeberger and coworkers, is UV labile. The synthetic sequence is based on the coupling step with alternating GalNAc **183** and GlcA **184** building blocks followed by deprotection of the Fmoc group. The acetylation at the end of the chain, the Lev group removal, and the sulfation are also performed using solid phase protocols, affording the desired compound **185** in good yield (Scheme 39).

The second target was dermatan sulfate, which is a polysaccharide composed by a disaccharide repeating unit, consisting of *N*-acetyl-*β*-D-galactosamine and L-iduronic acid.[565] Seeberger et al. developed a synthesis of a di- and a tetrasaccharide using the Fmoc protection at the oligosaccharide propagation position and the Lev ester at the future sulfation sites. Galactosamine is readily available in a small number of steps, while iduronic acid requires a more complex synthesis.[566] Both donors are equipped with a phosphate leaving group, and the linker utilized is the photocleavable one found in many other automated assemblies developed by the group. The yield of the two compounds obtained, a disaccharide and a tetrasaccharide, are high and consistent even when the larger acceptor is involved, averaging both 93% for each step.[567]

Other families of GAGs studied by Seeberger and co-workers include oligo-*N*-acetyllactosamine and keratan sulfate.[563] The automated glycan assembly was employed to achieve a fast and facile access to a large library of compounds. For this purpose, the photocleavable linker and three orthogonal protecting groups (Fmoc, Lev, and Nap) have been utilized. The orthogonal protecting groups gave a streamlined access to keratan sulfate oligosaccharides with differential sulfation sites. The obtained products were printed on microarrays and used to study the interaction with viral receptors. One of the keratan sulfate tetrasaccharides was identified as a specific interaction partner of receptor AAVrh10.

Codee and co-workers reported the synthesis of different chains of hyaluronic acid (HA), another common class of GAGs.[542] HA is a major component of connective tissue and extracellular matrix. Besides structural functions, HA has a role in inflammatory response, cell–cell adhesion, and recognition. Being able to access fragments of HA would be beneficial for studying its interaction with protein CD44, related to tumors proliferation. Common challenge for all GAG syntheses is the low reactivity of building blocks that has been addressed by applying them in large excess. As depicted in Scheme 40, the assembly started with PTFAI glucosamine donor **186** that was coupled with linker **178** in the presence of TfOH. The chain is then elongated with the removal of the temporary Lev protecting group and subsequent glycosylation with disaccharide donor **187**. After repeating the

glycosylation-deprotection cycle, the products are released through olefin metathesis and purified using HPLC to afford the desired hepta-, undeca-, and pentadecasaccharide in 26, 32, and 18% yield, respectively.

To show the versatility and the wide range of application the automated glycan assembly system is suitable for, Seeberger and co-workers developed a sequence where peptide and oligosaccharide solid phase syntheses are coupled.[460] Homogeneous glycopeptides are extremely valuable because regularly these compounds are isolated in heterogeneous mixtures that make difficult the determination of the structure–activity relationship. Normally the strategies for construction of a glycopeptide require the preformation of glycosylated amino acids in the solution phase.[368,568] The presented approach is advantageous because it utilizes a simple building block, readily available and with minimum synthetic requirements. Elongation of the peptide chain proceeds through Fmoc approach, using HBTU as coupling reagent and piperidine to remove the protecting group. Serine and threonine side chains are protected as tert-butyl or trityl ether to be removed before the glycosylation step, achieved using TMSOTf.

To illustrate the versatility of the approach, three glycopeptides were synthesized, including compounds with 1,2-cis linkages, requiring elongation on the glycan side and with more than one glycosylation site. All the syntheses were performed in good yields and selectivity and established the Glyconeer as a promising system to address the challenges in glycopeptides assembly (Scheme 41). The possibility of accessing large and complex oligosaccharides is particularly powerful in terms of understanding the specificity of various enzymes. The knowledge acquired through the synthesis of furanose-containing oligosaccharides was useful to study the xylan-degrading enzyme since the arabinoxylans are suitable for a large number of applications, including biofuels and nutritional and pharmaceutical functions. The synthetic approach is based on the Fmoc strategy for the elongation of the linear chain and using fully orthogonal Nap and 2-(azidomethyl)benzoyl (Azmb) for the branching. After incubation with the enzyme, the fragments were studied using LC–MS.[569]

A similar strategy has been used to study the hydrolysis of mixed-linked glucan chains by lichenase enzyme. This family of glycans is composed by linear 1,3- and 1,4-linked glucans, which form a gel-like material, important for the structural functions of the cells. Although the synthetic approach is similar to the general one used by Seeberger and co-workers, the formation of the 1,3-linkages was particularly challenging, requiring two glycosylation steps to avoid the formation of the deletion sequence. Again, the oligosaccharides were incubated with the enzyme and the digestion product analyzed via LC-MS, revealing new important features of the behavior of the enzyme.[570]

The synthesis of oligosaccharide libraries has become one of the most useful applications of Glyconeer 2.1. In addition to the aforementioned examples, Seeberger and co-workers have recently synthesized libraries of homo- and heterooligomers of mannose, glucose, and glucosamine. The purpose of the library was to understand the correlation between the oligomer conformation and their macroscopic properties.[571] A combination of the automated glycan assembly and computational studies revealed a significant structural

diversity within a series of synthetic oligomers, even within the ones comprising the same structural constituents albeit with a different position of the glycosidic linkages. The study clearly showcases the power of the automated synthesis as a tool for a better understanding of the biological significance of oligosaccharides.

Pfrengle and co-workers also contributed to the field by synthesizing numerous libraries of plant-related oligosaccharides.[556,569,572] Two significant examples include the assembly of arabinoxylans and galactoxyloglucans, both being epitopes for monoclonal antibodies that could be used as probes to study the cell wall properties. The approach for the synthesis of both libraries is similar. The backbone is assembled using dibutyl phosphate donors, and the branching is achieved using ethyl thioarabinofuranosides or galactosyl phosphates. The xylogluco disaccharides were presynthesized prior to the automation step to bypass the challenge of introducing 1,2-cis linkage at the later stage of the synthesis.

As depicted in Scheme 42, the assembly of the galactosylated xyloglucan **200** involved the reiteration of the glycosylation and deprotection steps with glucose building block **197**. The leaving group was activated with TMSOTf, and the temporary Fmoc group was removed with triethylamine in dimethylformamide. The immobilized trisaccharide was then glycosylated with the preassembled disaccharide **198** to obtain the xylose-decorated sequence. At last, the oligosaccharide was further elongated using galactosyl donor **199**, and the target was cleaved and deprotected to afford the desired hexasaccharide **200** in 7% overall yield.

3.5. HPLC-Assisted Oligosaccharide Synthesis

Demchenko, Stine, and their co-workers developed a new experimental setup based on an unmodified HPLC instrument. The system consisted of an Omnifit column containing preswelled beads of the TentaGel-NH_2 polymer. The column was then connected to the HPLC system consisting of a ternary reciprocating pump, a UV detector with variable range, and a computer to operate the instrument through regular HPLC management software.[514] The glycosyl acceptor was already loaded on the resin prior to the insertion into the column, and two different solutions containing glycosyl donor and promoter were mixed in the pump head and then the activated donor was delivered to the column. The reaction time needed for such a protocol was short, typically 30–60 min, and afterward the system was purged with fresh solvent leaving the clean resin carrying the disaccharide, which could be further elongated through deprotection-glycosylation cycles. The efficacy and the versatility of the HPLC approach has to be proven, but the first application revealed its potential.

As shown in Scheme 43, the synthesis of pentasaccharide **201** was successfully accomplished starting from the TentaGel-NH_2 resin preloaded with acceptor **202**. However, the loading could also be performed directly using the HPLC sequence. Donor **201**, equipped with benzoyl ester in a neighboring position to ensure stereoselectivity and Fmoc protecting group at C-6 for chain elongation, was pumped into the system together with a solution of TMSOTf as promoter. After 1 h of recirculation of the solution, the system was washed with dichloromethane, followed by the deprotection of Fmoc performed with piperidine in DMF for 5 min, and again a sequential purging step using dichloromethane. The glycosylation-washing-deprotection-washing sequence was repeated until

oligosaccharide of the desired length was obtained. After that, the product was cleaved from the solid support by using a recirculating solution of NaOMe in methanol-dichloromethane to afford pentasaccharide **203** in 62% yield in 7 h total time (vs 14 days for manual synthesis).

The most recent contribution by Demchenko and Stine is the use of autosampler in a new HPLC system as solution for delivering the promoter in the glycosylation step.[502] Autosamplers in modern HPLC have the advantage of being easily programmable to enhance automation of the polymer-supported synthesis. The study covered many aspects, starting from the efficiency of different solid phases, revealing JandaJel to be the most attractive for HPLC-mediated synthesis. The effectiveness of different leaving groups ranging from reactive O-imidates and phosphate to less reactive thioimidates and thioglycosides was investigated. The chosen TCAI allowed one to obtain pentasaccharide **206** in 67% yield over three glycosylation steps and two deprotection steps (Scheme 44).

To address some drawbacks of the solid phase synthesis using polymer supports, Demchenko and Stine introduced the surface-tethered iterative carbohydrate synthesis (STICS, *vide supra*).[438] For the purpose of the automation experiment, small pieces of nanoporous gold were integrated in the Omnifit column,[437] and the synthesis was conducted as in polymer-supported HPLC-based synthesis. The immobilization of the glycosyl acceptor **208** on the support is achieved using sulfur-containing linkers, such as lipoic acid, and the glycan assembly is performed. The HPLC pump was used to circulate donor **207** through the Omnifit column containing nanoporous gold chips (Scheme 45). To investigate the effect of the spacer, C4, C8, and C8OC8 were considered, and the series of parallel experiments showed that longer chain spacers between the glycosyl acceptor and the lipoic acid anchor increase the yield of disaccharide 209 from 60% to 90%.[437]

3.6. Electrochemical Activation Platform for Automation

Chalcogenoglycosides that can be activated by electrochemical methods[573–578] served as a novel automation platform introduced by Nokami and co-workers.[515] The glycosylation step is based on electrochemical activation of thioglycoside donors with the formation of the corresponding glycosyl triflate as the reactive intermediate. A dedicated synthesizer was developed specifically for this application, using commercially available components. Thus, the instrument was equipped with a chiller and a cooling bath, a power supply for constant current electrolysis, and a syringe pump. The assembly and all the hardware are controlled using the LabVIEW software. The reaction occurs in a H-type divided cell, with a carbon-felt anode and a platinum plate cathode. The glycosyl donor is activated in the anodic chamber, and the acceptor is added using the syringe pump.

In the original application, the synthesis of a series of β-(1 →6)-linked N-acetylglucosamino glycans were assembled. As depicted in Scheme 46, the optimized aryl thioglycoside donor **210** was preactivated via anodic oxidation at −80 °C and 1.0 F/mol at 1.73 V for 40 min, resulting in the formation of the anomeric triflate **211** which reacted with the glycosyl acceptor **212** at −50–60 °C for 30 min. The obtained disaccharide **213** was then ready for activation, since the reaction proceeds with the growth of the glycan on the donor side, and the illustrated preactivation-glycosylation steps were repeated to synthesize the

pentasaccharide **214** in 31% overall yield, with an average of 75% yield per cycle. The whole assembly required 10 h.[515]

Given the potential of such a method, which has the advantages of both the solution-phase and the automated synthesis, Nokami and co-workers recently developed a few additional applications for the electrochemical activation of chalcogenides.[579–582] One target reported by Nokami was TGM-chitotriomycin,[579,580,582] a molecule of interest for the development of safer pesticides due to its selectivity in the inhibition of fungal and entomic glucosaminidases. This 1,2-trans linked glucosamino glycan was assembled using a similar approach, affording a tetrasaccharide product in 41% overall yield. Another molecule of interest was a GPI anchor core trisaccharide, an oligomannoside of interest to show the advantages of novel strategies for oligosaccharide synthesis.[581] The study started with the evaluation of the oxidation potential of different building blocks, all characterized by a participating group at the C-2 or the C-6, such as acetyl or pivaloyl. The studied compounds were compared to the 4-fluorophenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranoside, and to better understand the changes in the potential, DFT calculations were performed. To verify the selectivity of the selected donors, a test was performed with the assembly of different disaccharides using the electrochemical preactivation strategy (*vide supra*). Anodic oxidation was performed at −80 °C in the presence of Bu_4NOTf with 1.00 F/mol of electricity. The proposed mechanism involves the formation of the anomeric triflate, which is then displaced by the neighboring group to form an acyloxonium ion, which undergoes substitution to afford the desired product. This was applied to the assembly of the core trisaccharide of GPI anchor oligosaccharide as shown in Scheme 47. The sequence was completed to provide trisaccharide **220** in 40% overall yield.

4. CONCLUSIONS AND OUTLOOK

To keep pace with the expanding areas of glycosciences, it is critical to make glycans more accessible to the general chemical, biomedical, and industrial audiences. The advancement of automation strategies and their broader adoption will be crucial to meeting this need. Fundamental new developments will be required both in the generalization of the automation strategies and in the optimization of methods for glycoside synthesis and oligosaccharide assembly needed for reliable implementation into automation. Manual strategies for oligosaccharide synthesis in solution require specialist knowledge of all aspects of carbohydrate chemistry and fine-tuning of reactivity levels and reaction conditions. Manual polymer- or tag-supported synthesis helps to streamline the synthesis and purification but still requires specialized knowledge of carbohydrate synthesis. The automated platform developed by Seeberger introduces an idea of operational simplicity; however, it requires a sophisticated and expensive synthesizer and dedicated and appropriately trained personnel.

More recent developments of automation platforms make use of common laboratory equipment, including parallel synthesizers syringe pumps, microreactors, and HPLC components. These approaches offer a promise to deliver simple automation using commonly available and relatively inexpensive equipment. The modular character of these synthesizers allows for endless opportunities to implement existing accessories, including

reagent delivery modules and detecting systems that can be operated by standard computer software. Some automation platforms already are capable of reaction monitoring in real-time helping to reduce the amount of reagents needed and the reaction time. Although viability of these new approaches and platforms has been demonstrated, many, if not all, automation platforms are still in need of major refinement. Further development of existing and new platforms for the automated synthesis is becoming a significant area of research.

One of the greatest unsolved challenges is the need for dedicated automation-amenable reaction conditions. Many aspects of the automated synthesis including polymer supports and tags, large scale synthesis amenability, availability of affordable “off-the-shelf” reagent kits, catalytic, stereoselective and operationally simple glycosylations, streamlined synthesis, or broader commercial availability of building blocks still need to be improved to expedite the synthesis of glycans. Broad availability of synthetic glycan sequences and libraries and/or affordable and accessible tools and technologies for automation will greatly enhance study of the roles of carbohydrates in biological and disease pathways. The produced libraries of synthetic compounds can be readily integrated with the currently available glycan microarray technologies.

The full potential of automated techniques is yet to be explored, and the versatility has to be improved to reach the diversity of manual, solution phase techniques. While most automated platforms are still in development, manual synthesis in solution will remain as an important tool to obtain complex oligosaccharides or particularly challenging sequences.

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Biography

Matteo Panza graduated from the Università degli Studi di Milano (Italy) with a B.S. in chemistry in 2012 and a M.S. in chemical sciences in 2014. He moved to St. Louis to start the Ph.D. program at the University of Missouri–St Louis in 2015, where he joined the laboratory of Professor Alexei Demchenko. He is currently a Ph.D. candidate, and his research focuses on automated techniques for solid phase oligosaccharide synthesis.

Salvatore Pistorio graduated from the Università degli Studi di Catania (Italy) with a Master’s degree in Pharmaceutical Chemistry in 2011. He moved to St. Louis (USA) in 2012, where he joined the laboratory of Professor Alexei Demchenko at the University of Missouri–St. Louis. During his graduate studies, he conducted research focused on the development of a new strategy for the automation of oligosaccharide synthesis on solid supports. In 2016, he was awarded his Ph.D. in Organic Chemistry, after which he joined Monsanto (St. Louis) as a Process Chemist. In 2018, he moved back to Catania where he is a Downstream Process Tech Transfer Specialist at the animal health company, Zoetis.

Keith Stine received his B.S. degree in chemistry with honors from Fairleigh Dickinson University in Madison, New Jersey, in 1984. He also received a B.A. degree in Mathematics

and Computer Science. He earned his Ph.D. from MIT in 1988, working with Professor Carl W. Garland. After a postdoctoral position at University of California–Los Angeles in the laboratory of Professor Charles M. Knobler, he joined the Department of Chemistry at University of Missouri–Saint Louis in 1990. He was promoted to Associate Professor in 1996 and to full Professor in 2008. His research interests include the surface modification of gold nanostructures with a focus on their prospective applications in bioanalytical chemistry such as in immunoassays, sensors, or in separations. He is also interested in the field of supported synthesis of carbohydrates using nanoporous gold and related materials.

Alexei Demchenko graduated from the Mendeleev University of Chemical Technology of Russia with a Diploma in Chemical Engineering (1988) before joining the laboratory of the late Professor Nikolay Kochetkov at the Zelinsky Institute of Organic Chemistry in Moscow. In 1993, he was awarded a Ph.D. in organic chemistry, and after two postdoctoral years under Professor Kochetkov, he joined Professor Geert-Jan Boons' group at the University of Birmingham (U.K.) as a BBSRC postdoctoral research fellow. In 1998, he moved with Professor Boons to the Complex Carbohydrate Research Center, University of Georgia (USA), as a research associate. In 2001, he joined the faculty at the University of Missouri–St. Louis as an Assistant Professor, where he was promoted to the rank of Associate Professor with tenure (2007) and Professor (2011). In 2014, Alexei Demchenko was appointed Curators' Distinguished Professor of Chemistry and Biochemistry. His research interests are in the area of synthetic carbohydrate chemistry that include novel glycosylation methods, stereocontrol of the glycosidic bond formation, strategies for expeditious assembly of complex oligosaccharides, and solid phase automated synthesis.

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(582). Sasaki N; Nokami T; Itoh T Synthesis of a TMG-chitotriomycin precursor based on electrolyte-free electrochemical glycosylation using an ionic liquid tag. Chem. Lett. 2017, 46, 683–685.

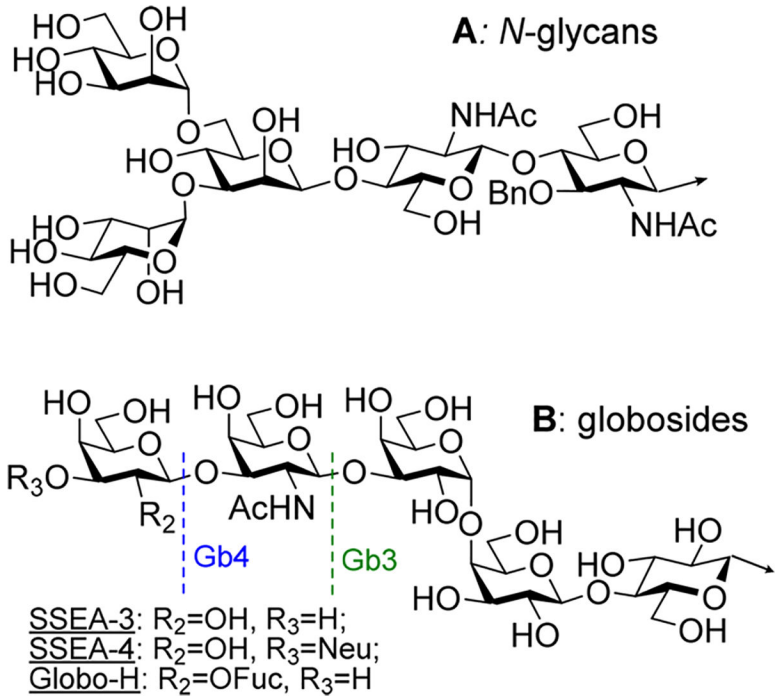


Figure 1.
Representative structures of common linear and branched oligosaccharide motifs.

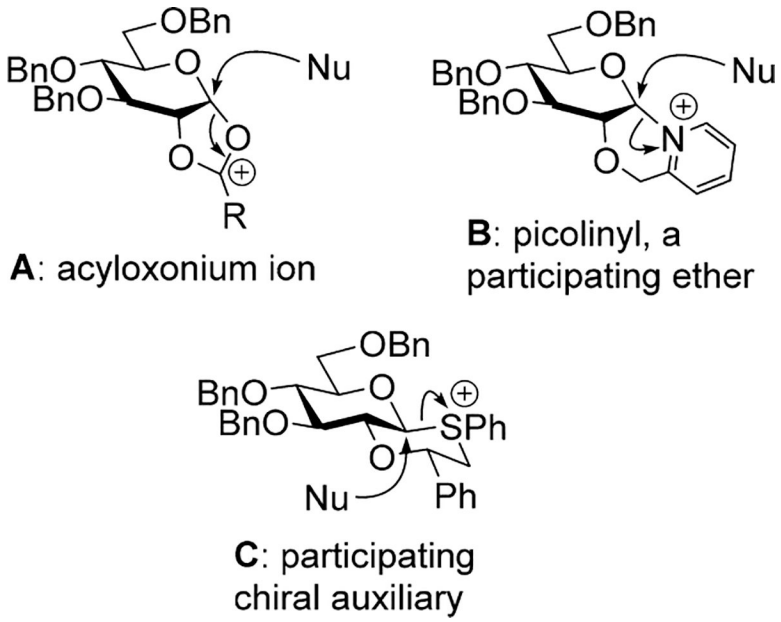


Figure 2.
Directing neighboring participating groups at C-2.

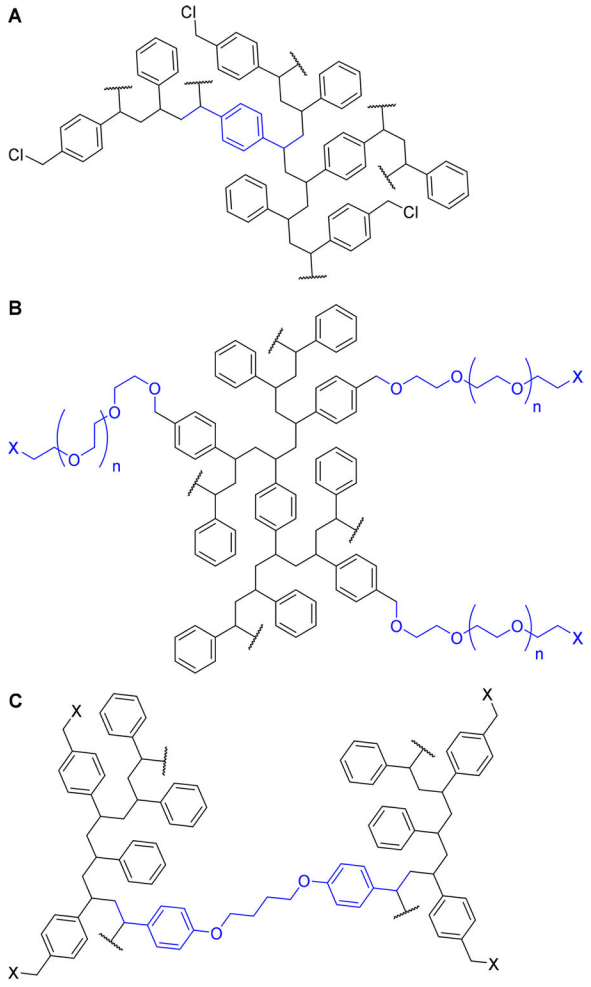


Figure 3.
Solid supports for oligosaccharide synthesis: (A) Merrifield's resin, (B) Tentagel, and (C) JandaJel.

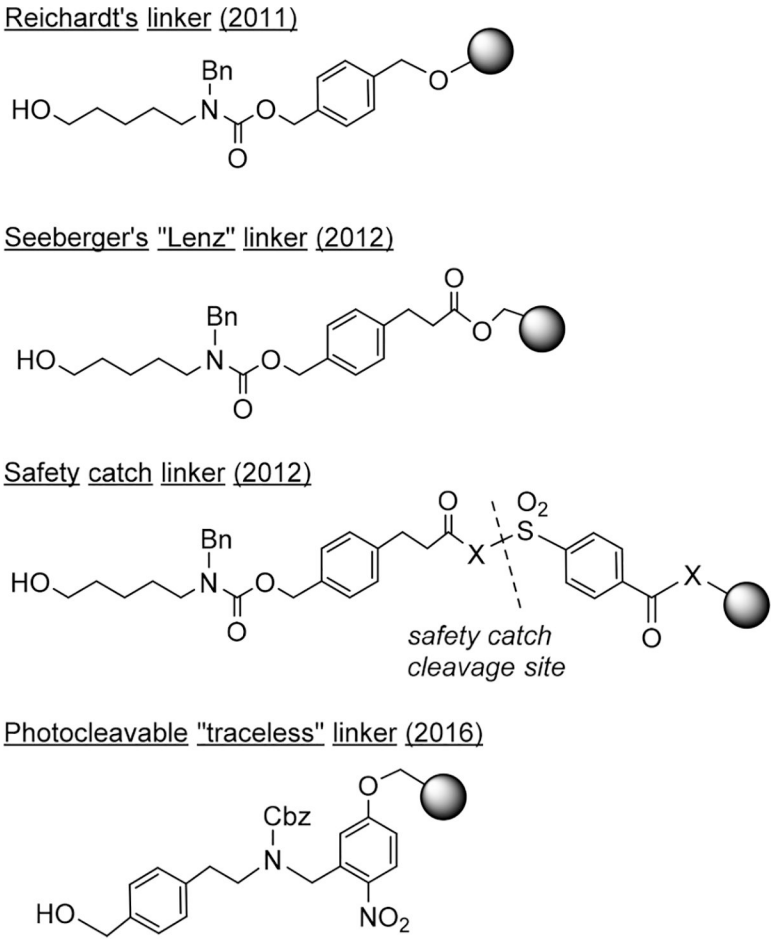


Figure 4.
Recently introduced linkers for polymer-supported oligosaccharide synthesis.

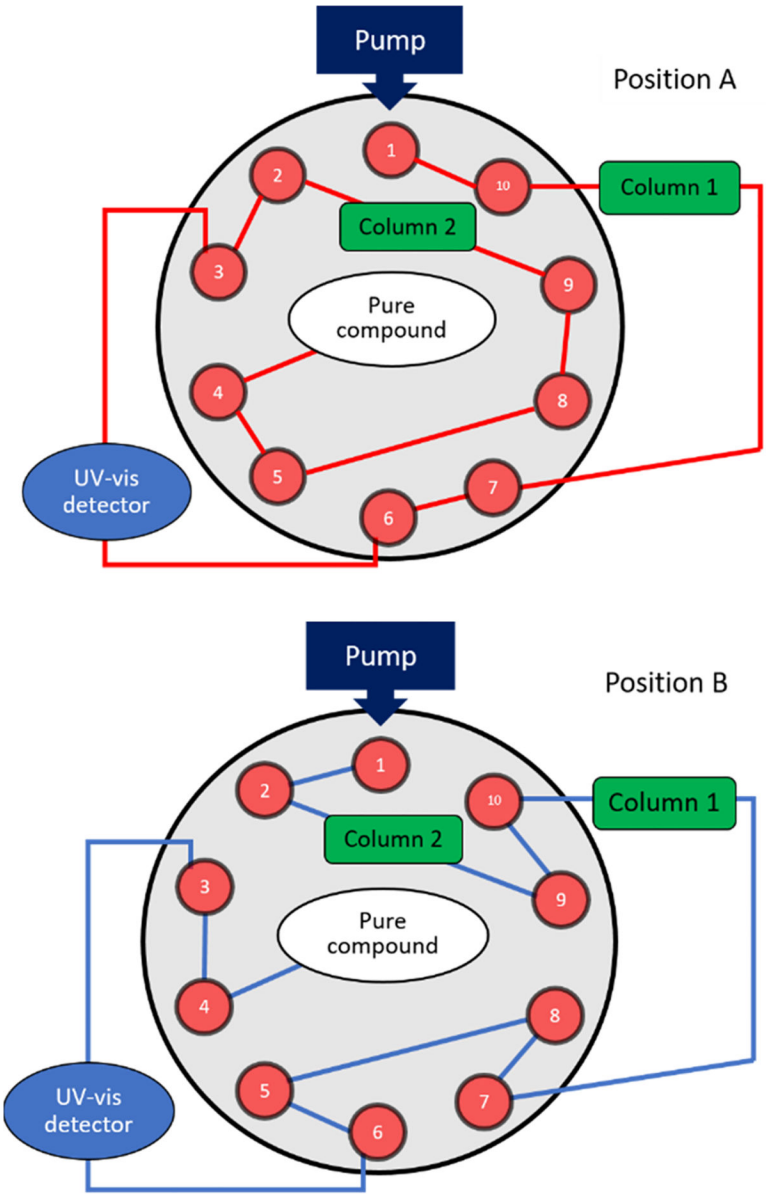


Figure 5.
Split-valve setup for the alternate-pump system.

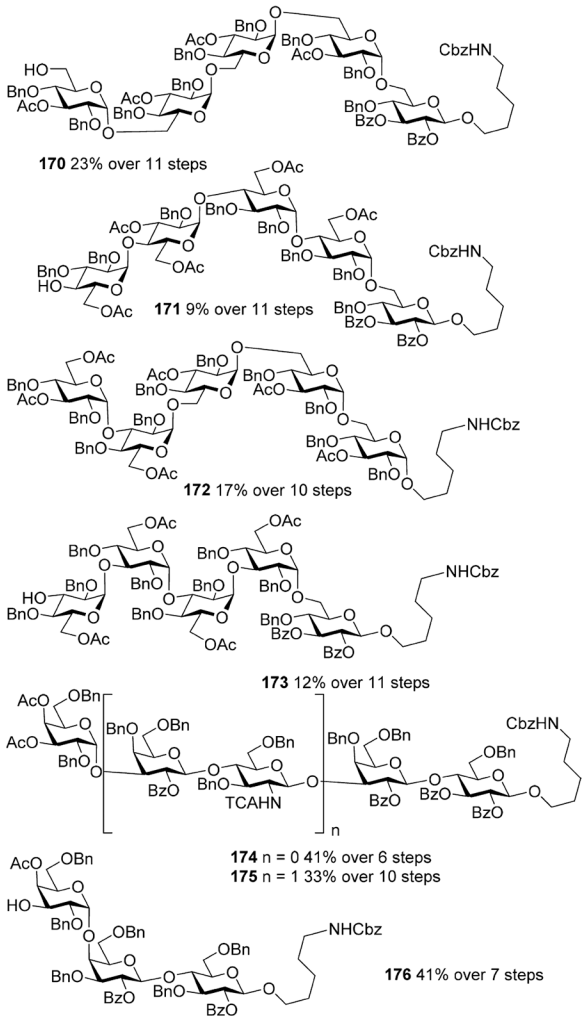
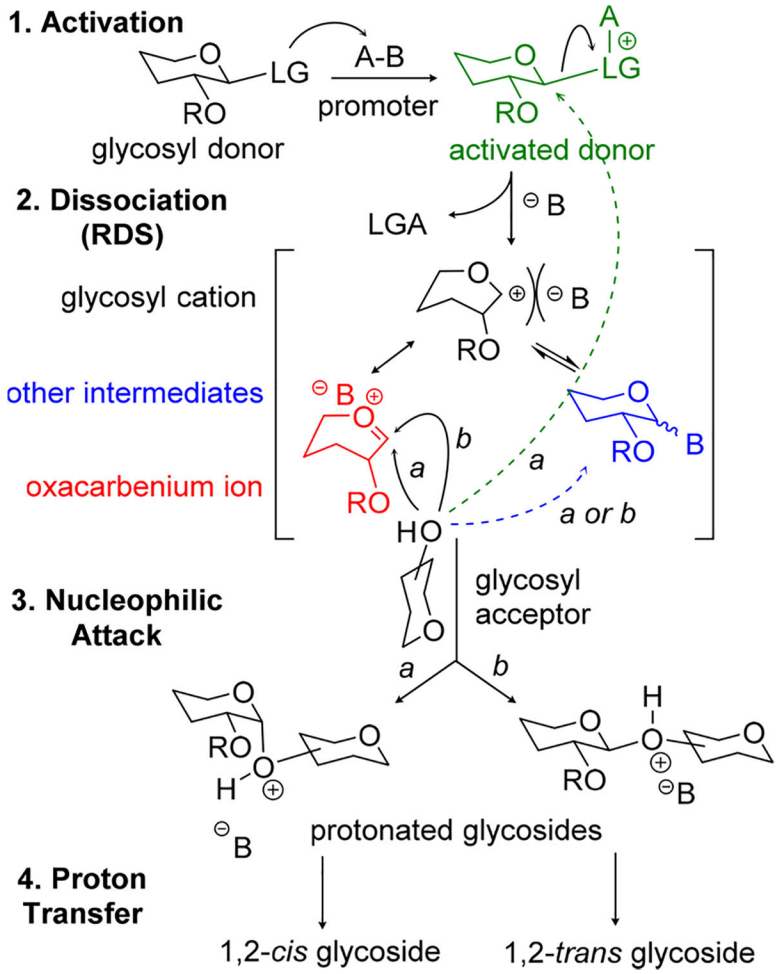
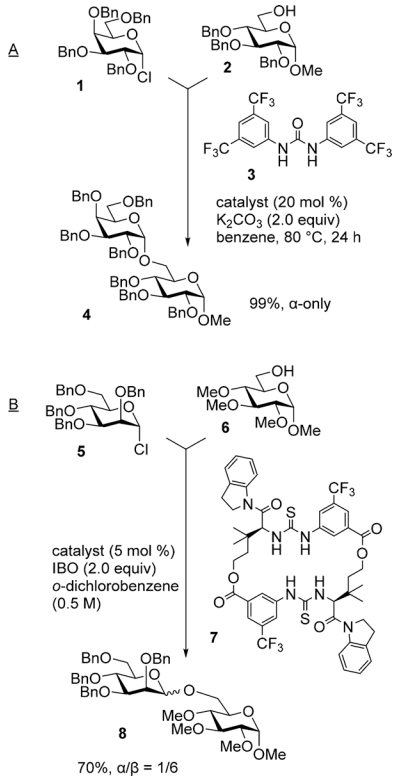


Figure 6.

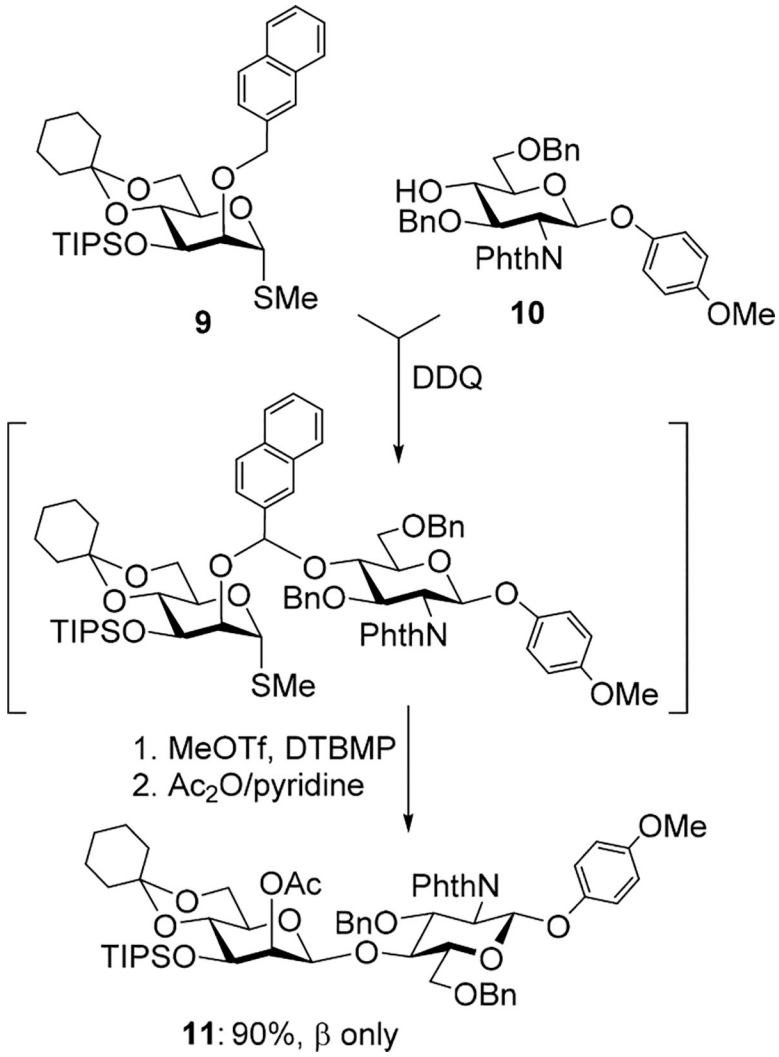
Representative 1,2-cis-linked oligosaccharides synthesized using Glyconeer 2.1



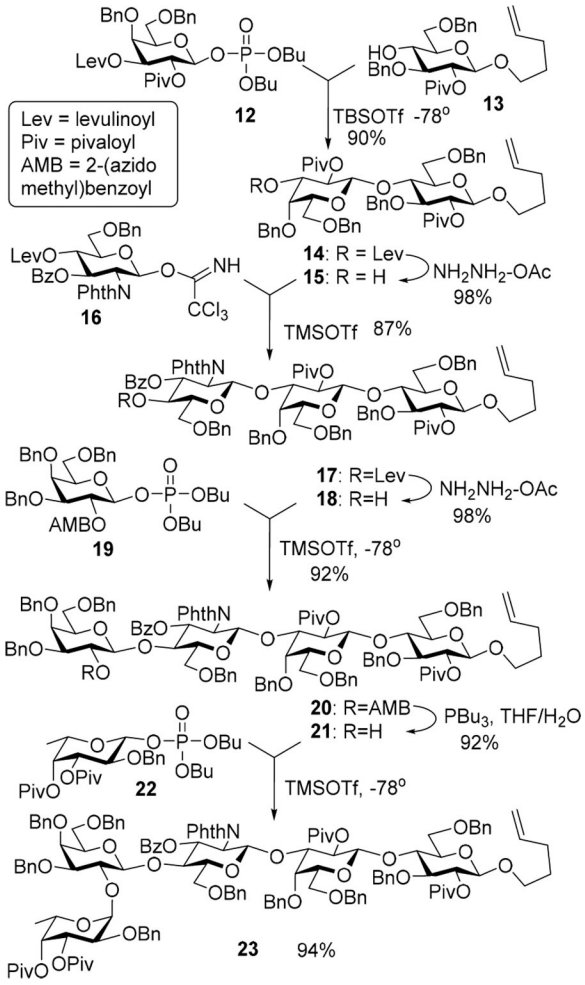
Scheme 1.
General Outline of the Chemical Glycosylation Reaction



Scheme 2.
Examples of Urea and Thiourea-Based Organocatalytic Reactions

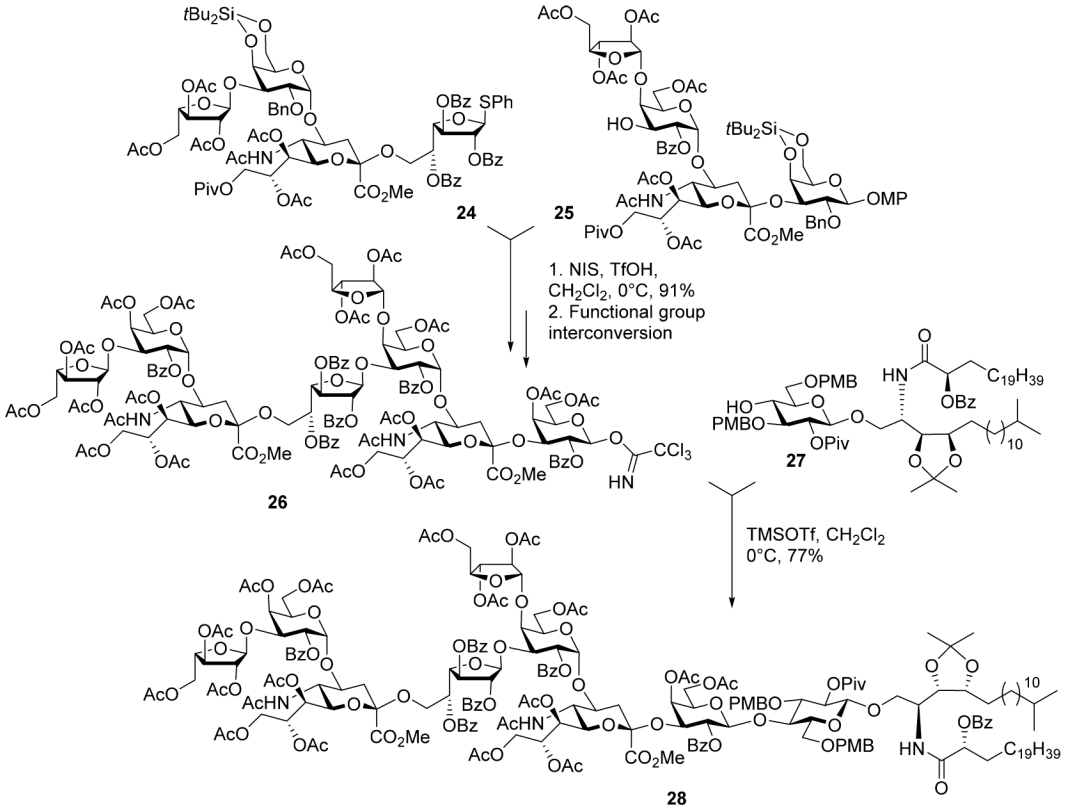


Scheme 3.
Synthesis of β-Mannosides via Intramolecular Aglycone Delivery

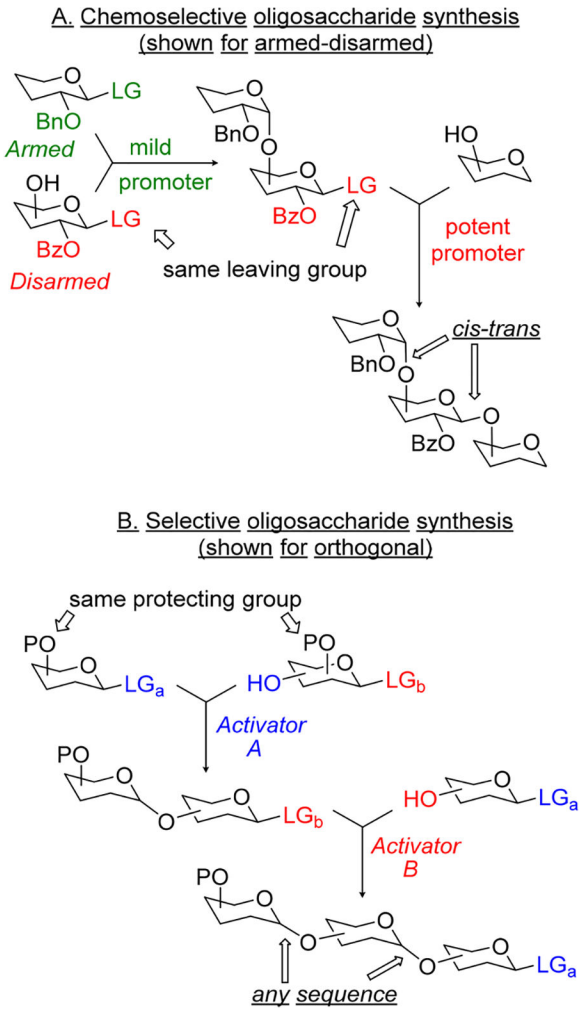


Scheme 4.

Conventional Linear Oligosaccharide Synthesis with Alternating Glycosylation and Deprotection Steps

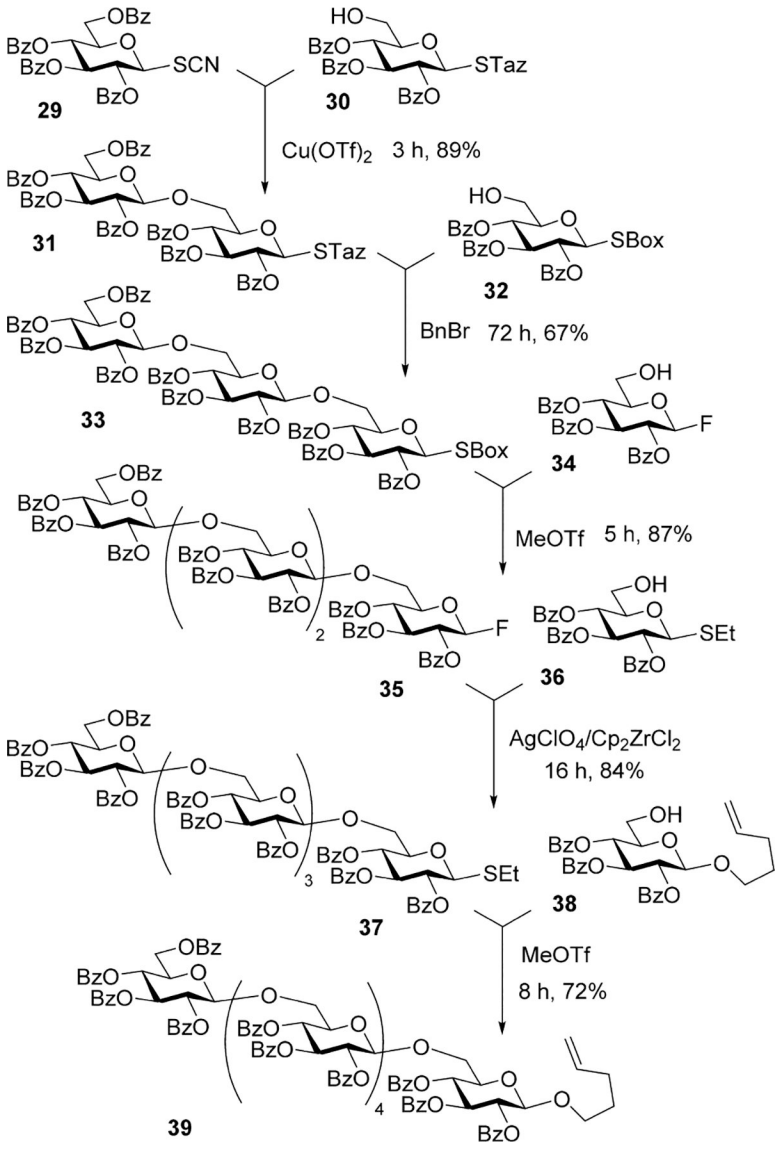


Scheme 5.
Convergent Block Synthesis of Ganglioside GP3

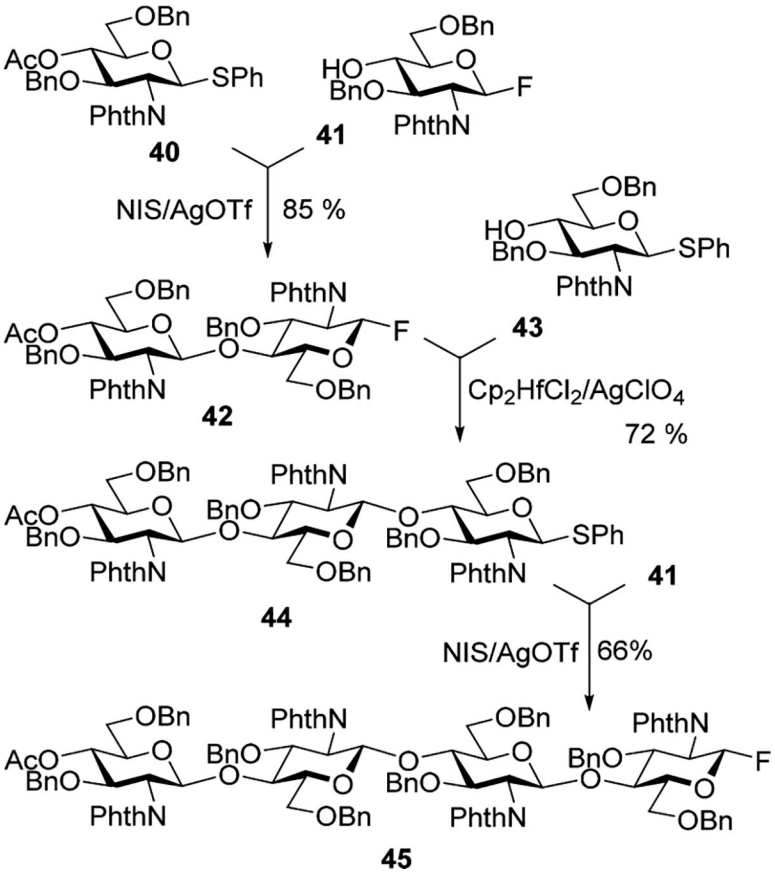


Scheme 6.

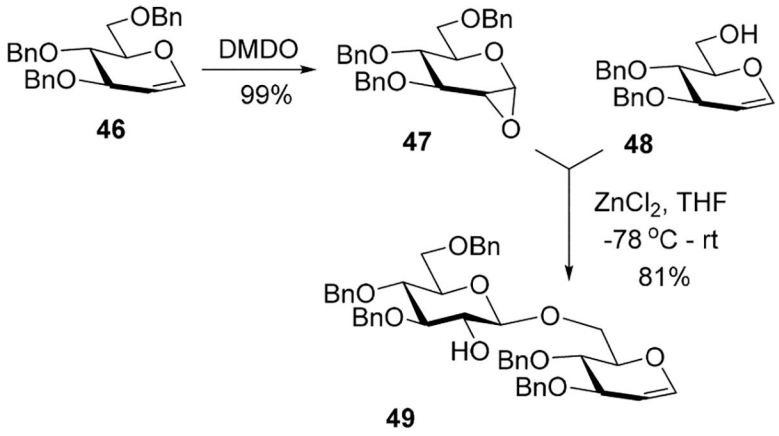
(A) Chemoselective and (B) Selective Activation Approaches to Expeditious Oligosaccharide Synthesis



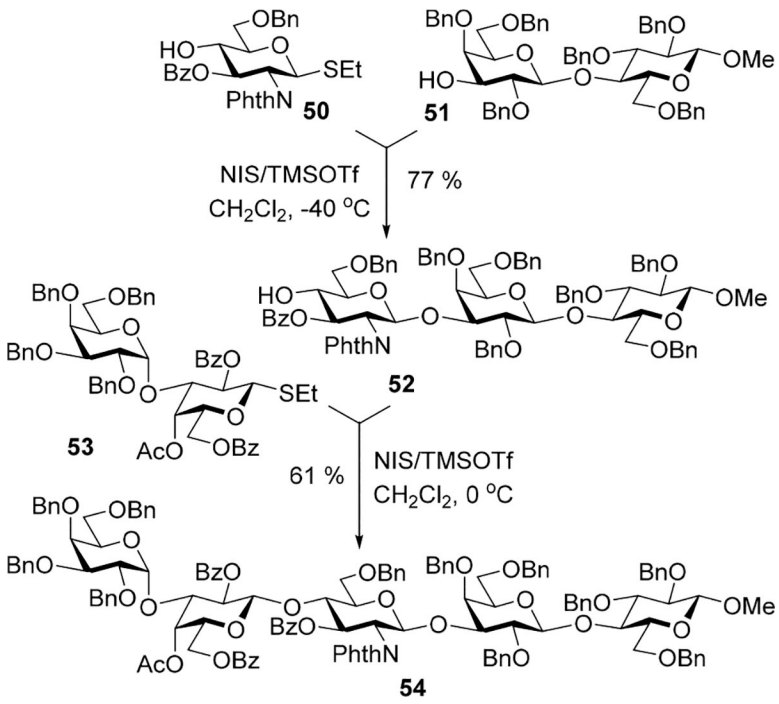
Scheme 7.
Hexasaccharide Synthesis in Five Selective Activation Steps



Scheme 8.
Orthogonal Activation of Phenylthio Glycosides and Fluorides

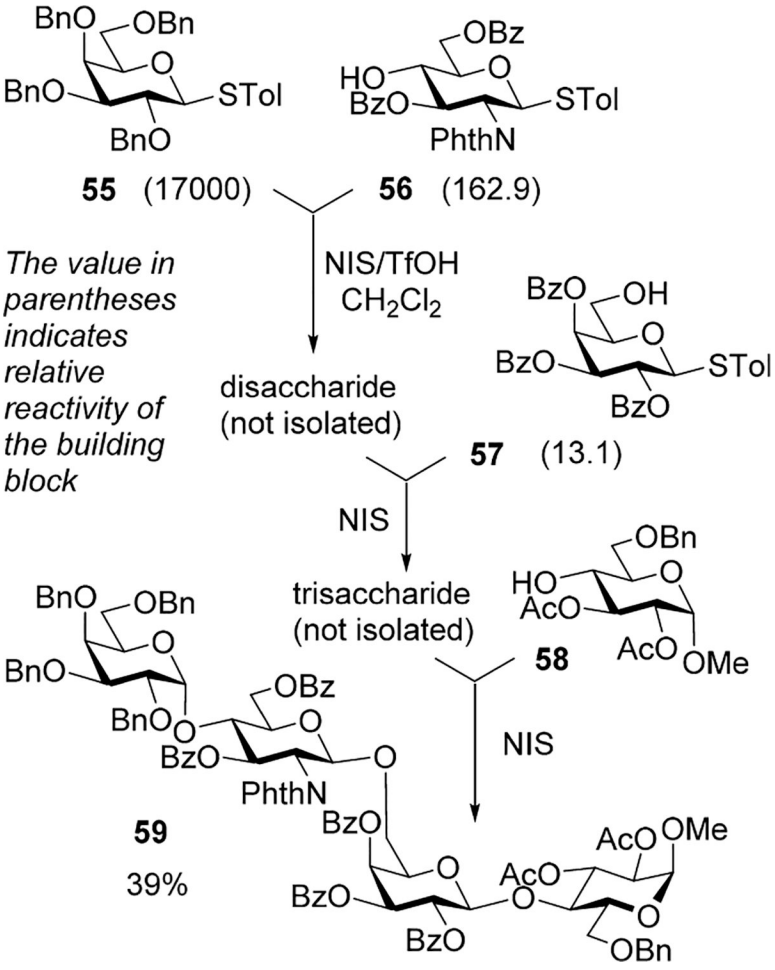


Scheme 9.
Glycal-Epoxide Method for Iterative Oligosaccharide Synthesis

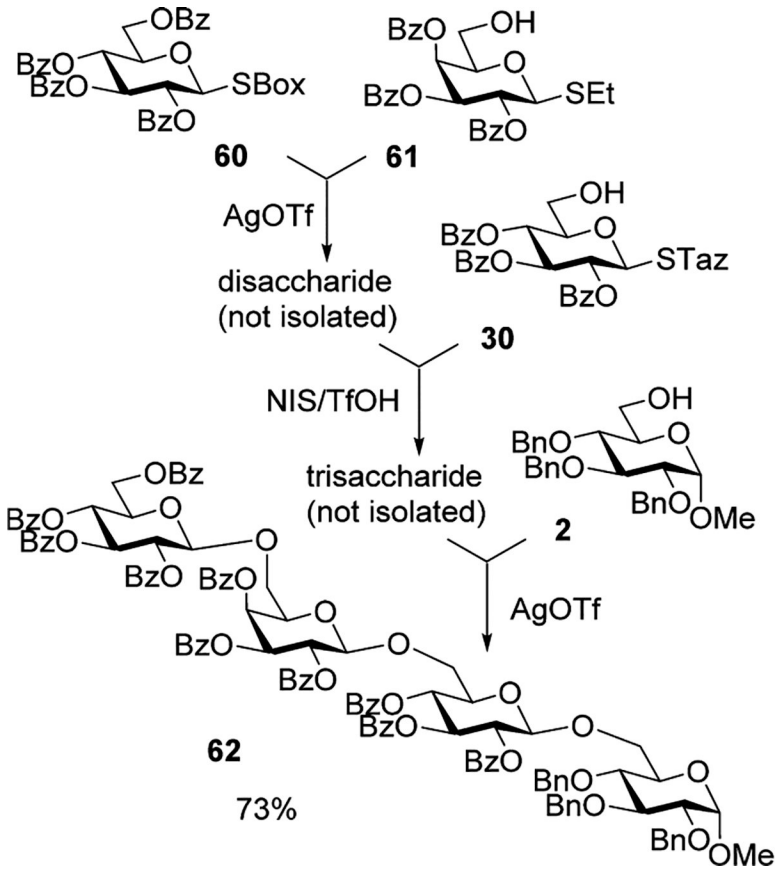


Scheme 10.

Two-Directional Approach for the Synthesis of Pentasaccharide 54

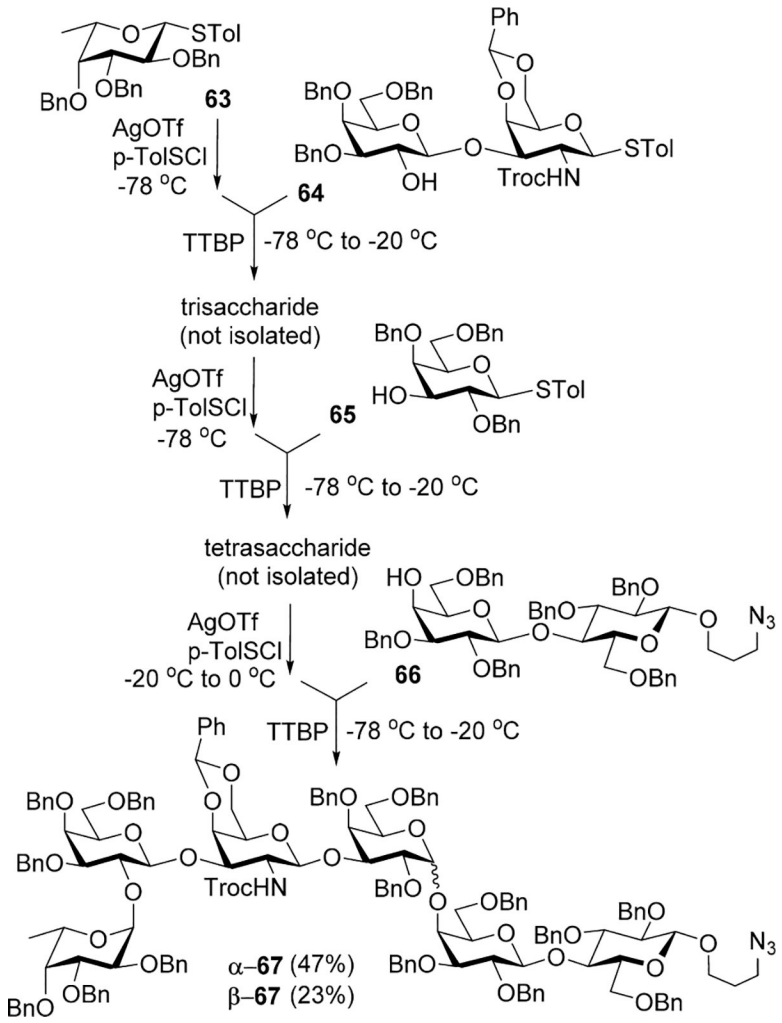


Scheme 11.
One-Pot Synthesis of Tetrasaccharide 59 via Chemoselective Activation



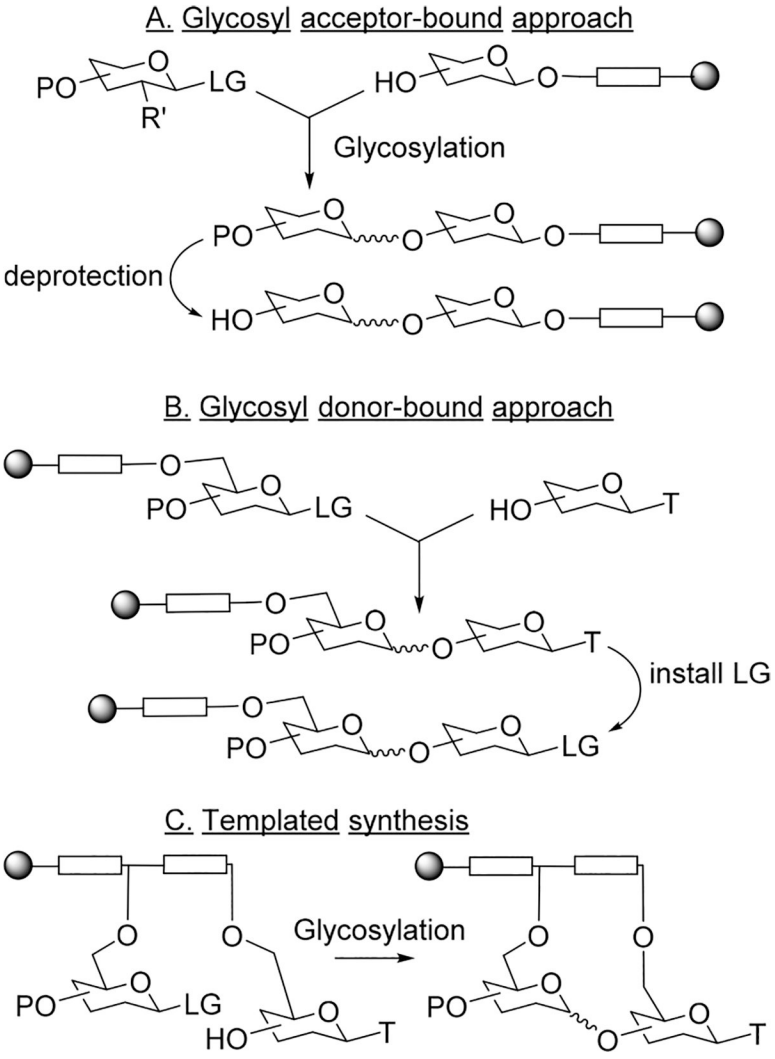
Scheme 12.

One-Pot Synthesis of Tetrasaccharide 62 via Sequential Selective Activation of Building Blocks Equipped with Different Leaving Groups

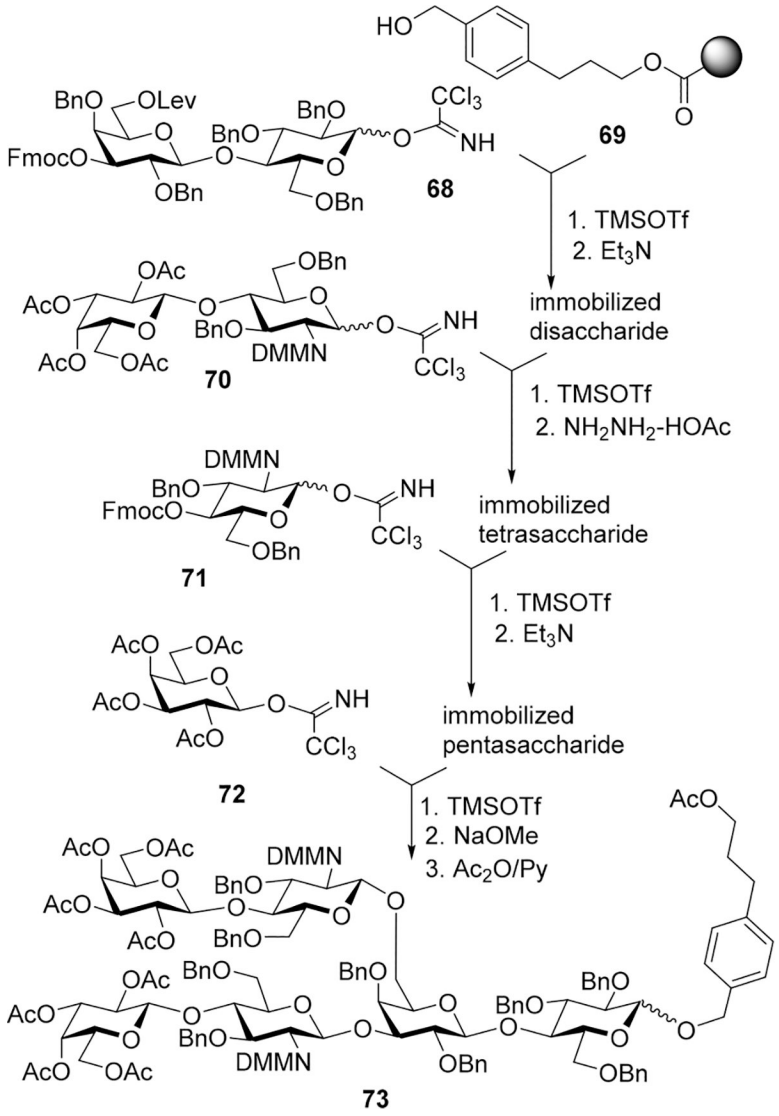


Scheme 13.

Preactivation-Based One-Pot Synthesis of Globo-H Hexasaccharide 67

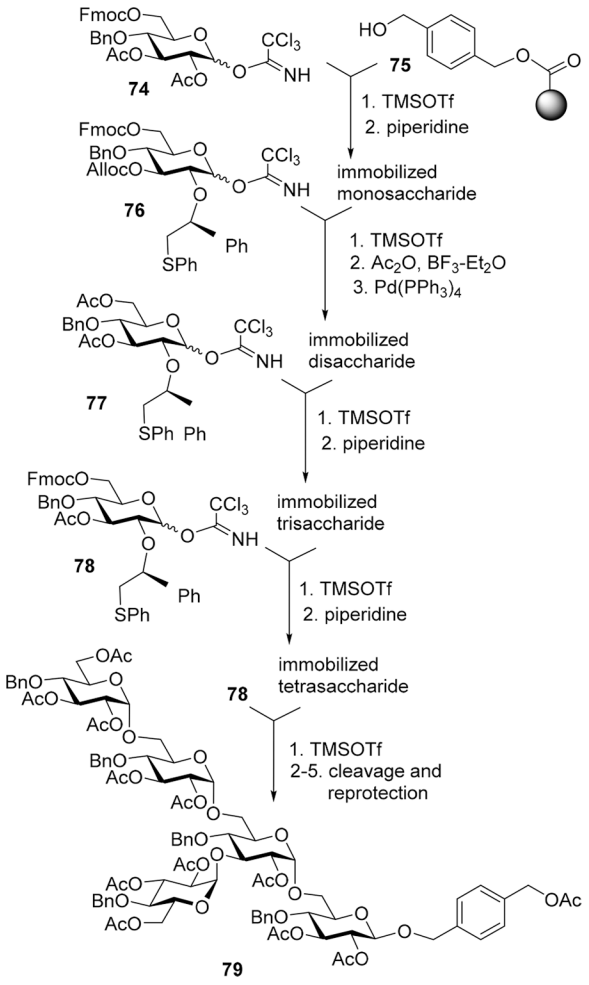


Scheme 14.
Glycosylation on Polymer Support



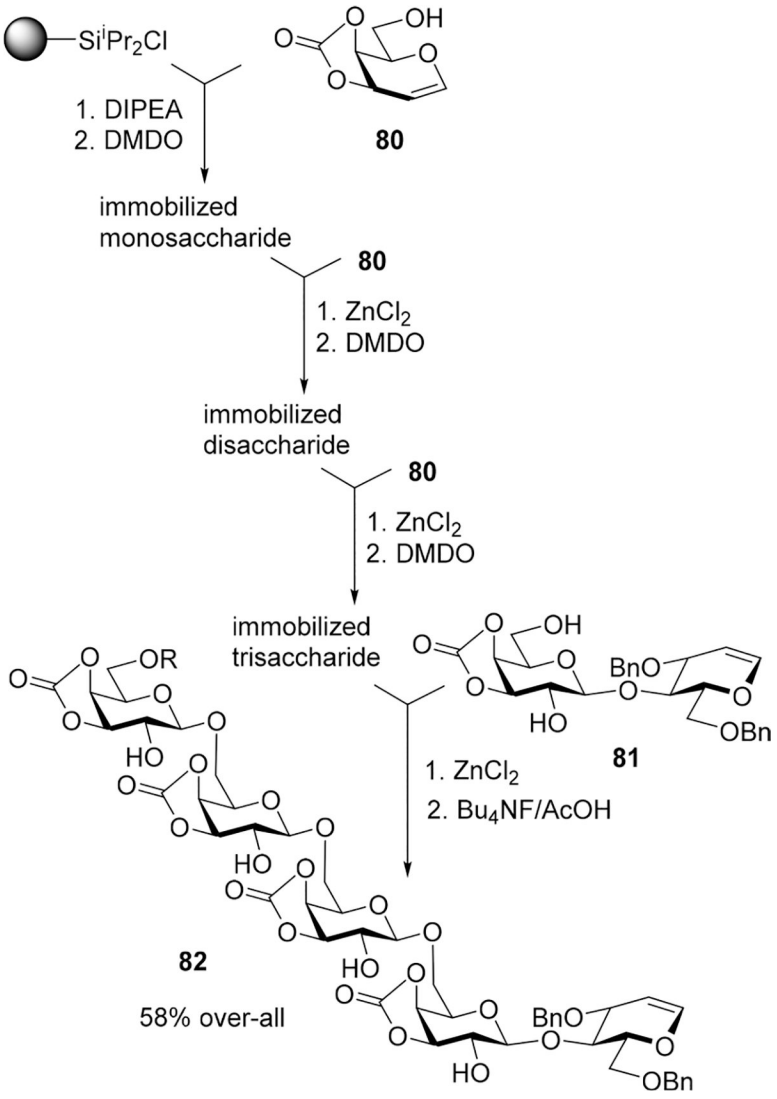
Scheme 15.

Acceptor-Bound Approach to the Synthesis of Oligosaccharide 73

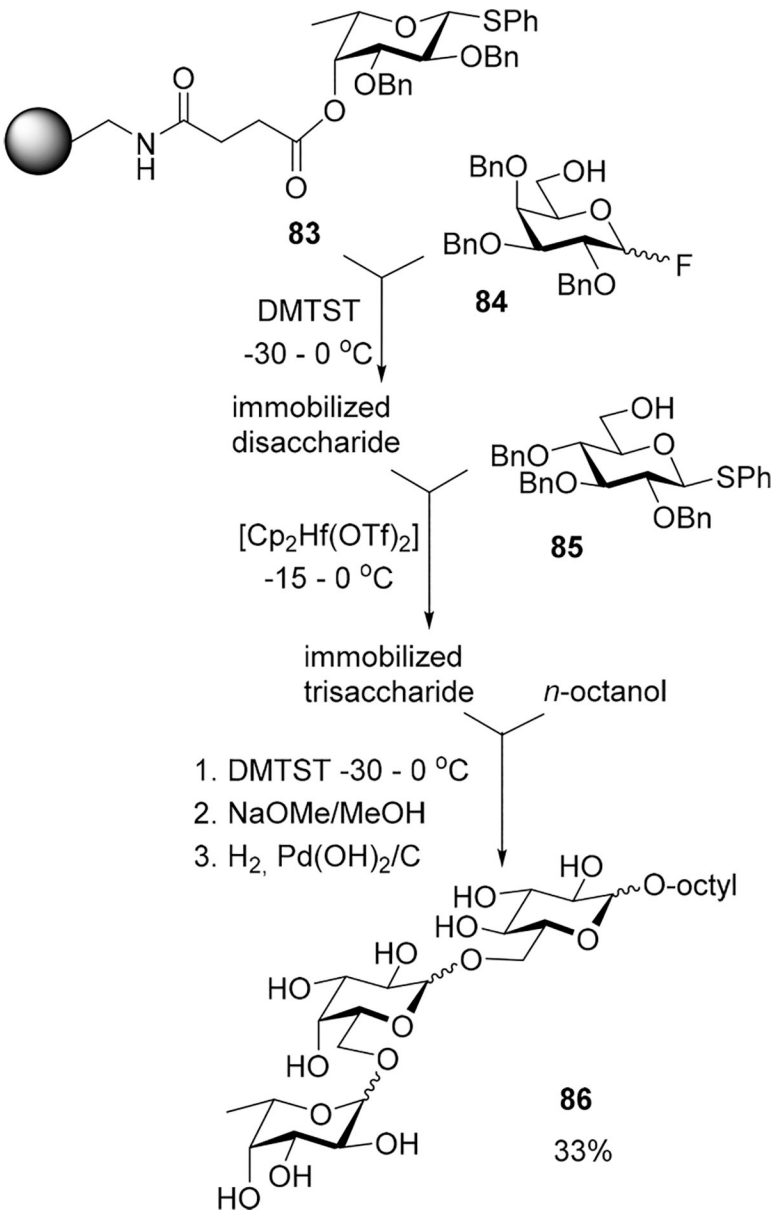


Scheme 16.

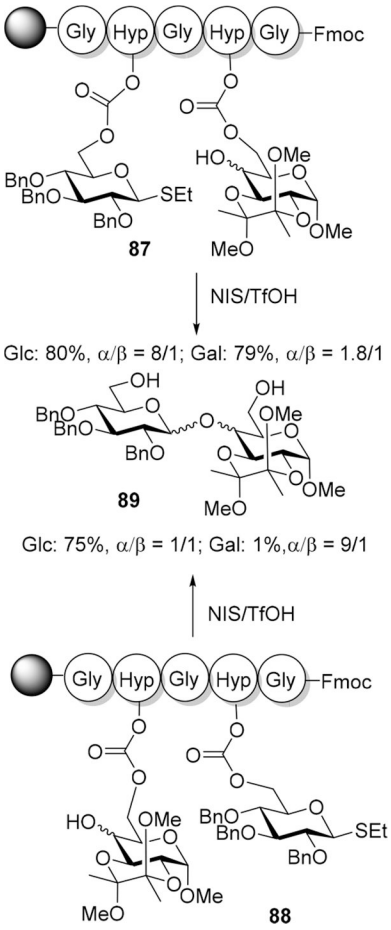
Chiral Auxiliary-Assisted Synthesis of 1,2-cis-Linked Oligosaccharide 79



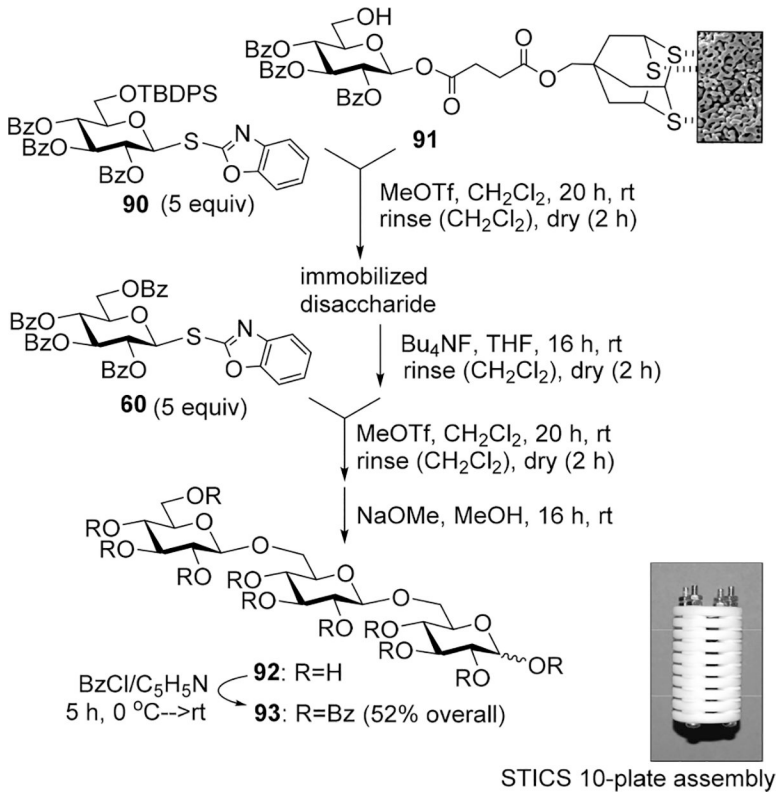
Scheme 17.
Donor-Bound Synthesis of Pentasaccharide82



Scheme 18.
Orthogonal Synthesis of a Combinatorial Library on Solid Phase

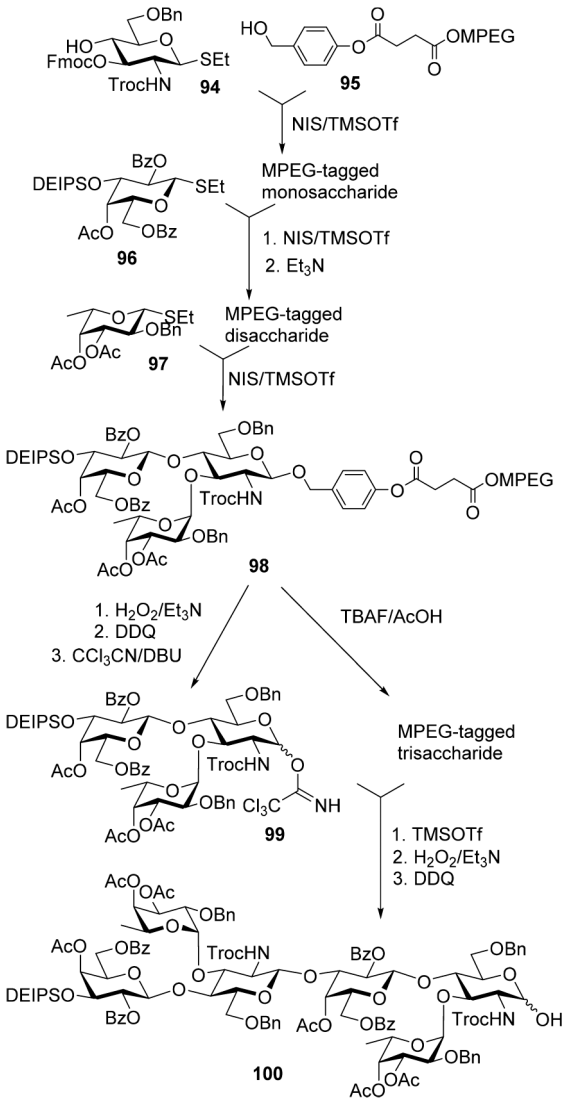


Scheme 19.
Peptide-Templated Oligosaccharide Synthesis on Polymer Support



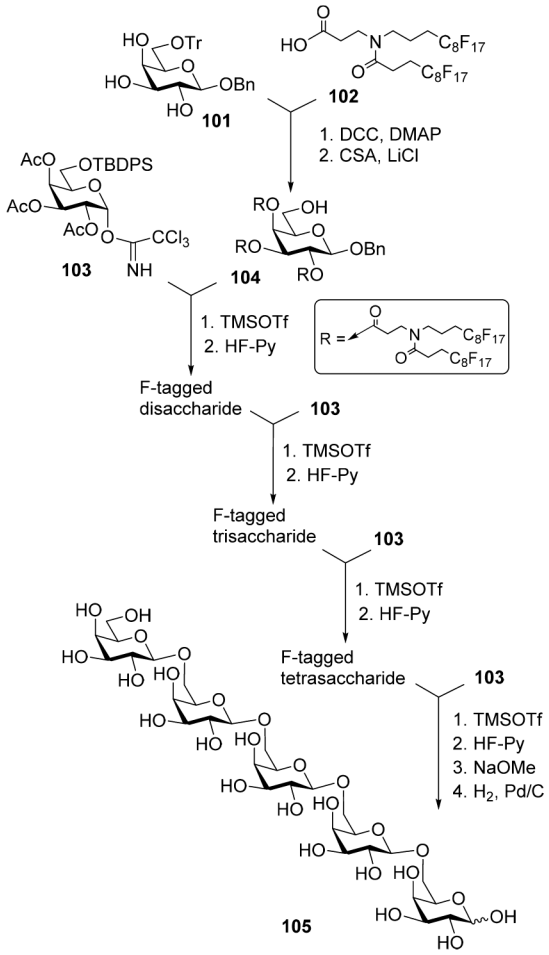
Scheme 20.

STICS: Surface-Tethered Iterative Carbohydrate Synthesis

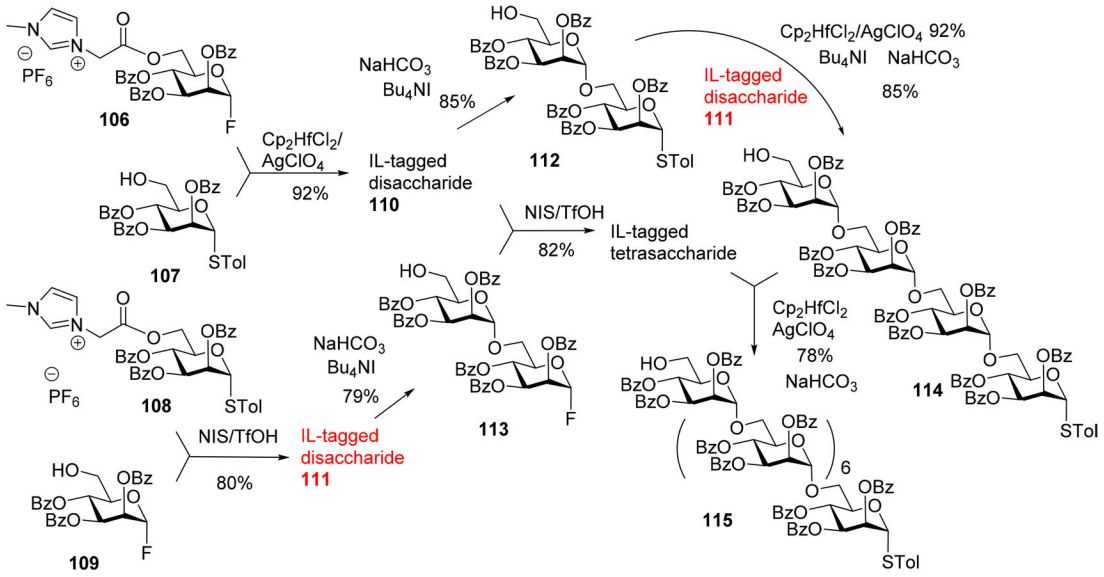


Scheme 21.

Synthesis of Dimeric Le^x Hexasaccharide Using Soluble Polymer Support

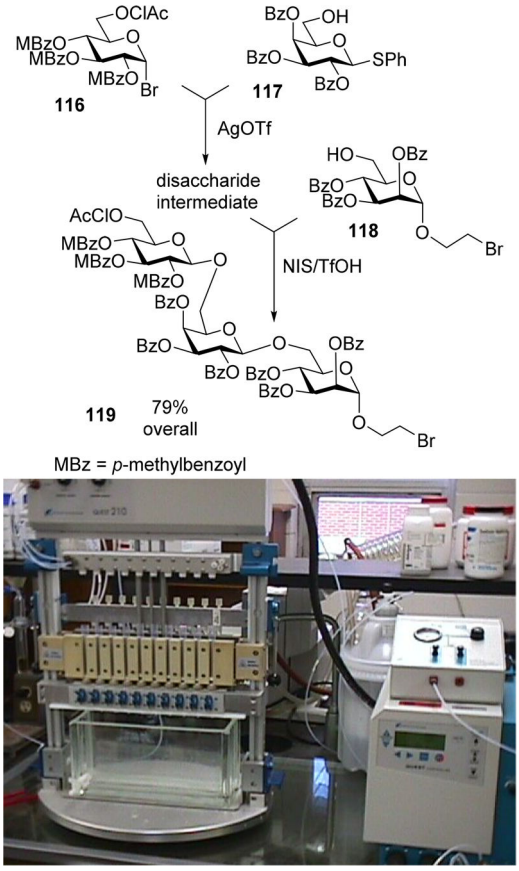


Scheme 22.
Fluorous Tag-Assisted Synthesis of Pentasaccharide 105



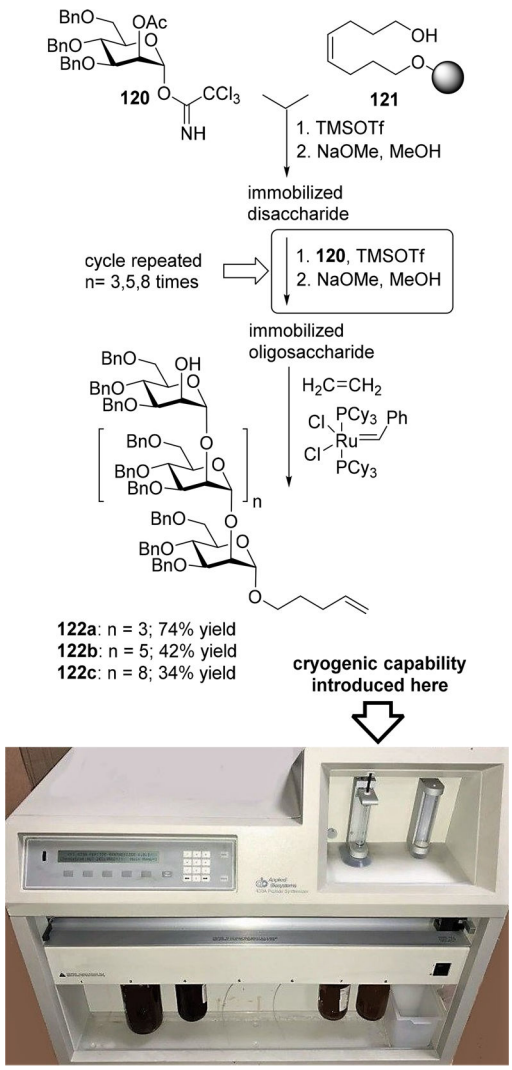
Scheme 23.

Convergent/Orthogonal Ionic Liquid-Tagged Synthesis of Mannans



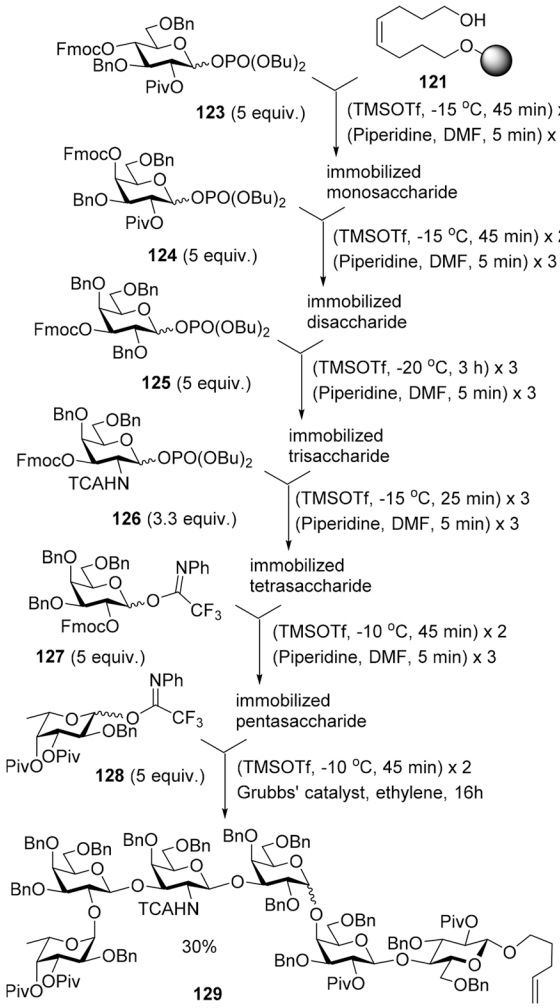
Scheme 24.

Solution Phase Automation of the Oligosaccharide Synthesis in One Pot Using Parallel Synthesizer Quest 210[a]



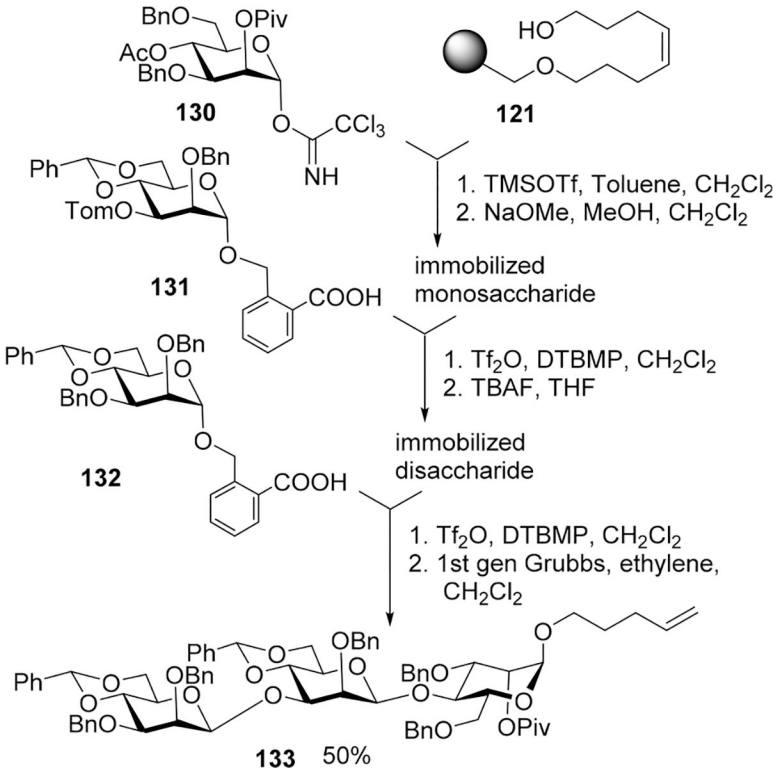
Scheme 25.

Synthesis of Oligosaccharides 122a–122c Using a Modified Peptide Synthesizer

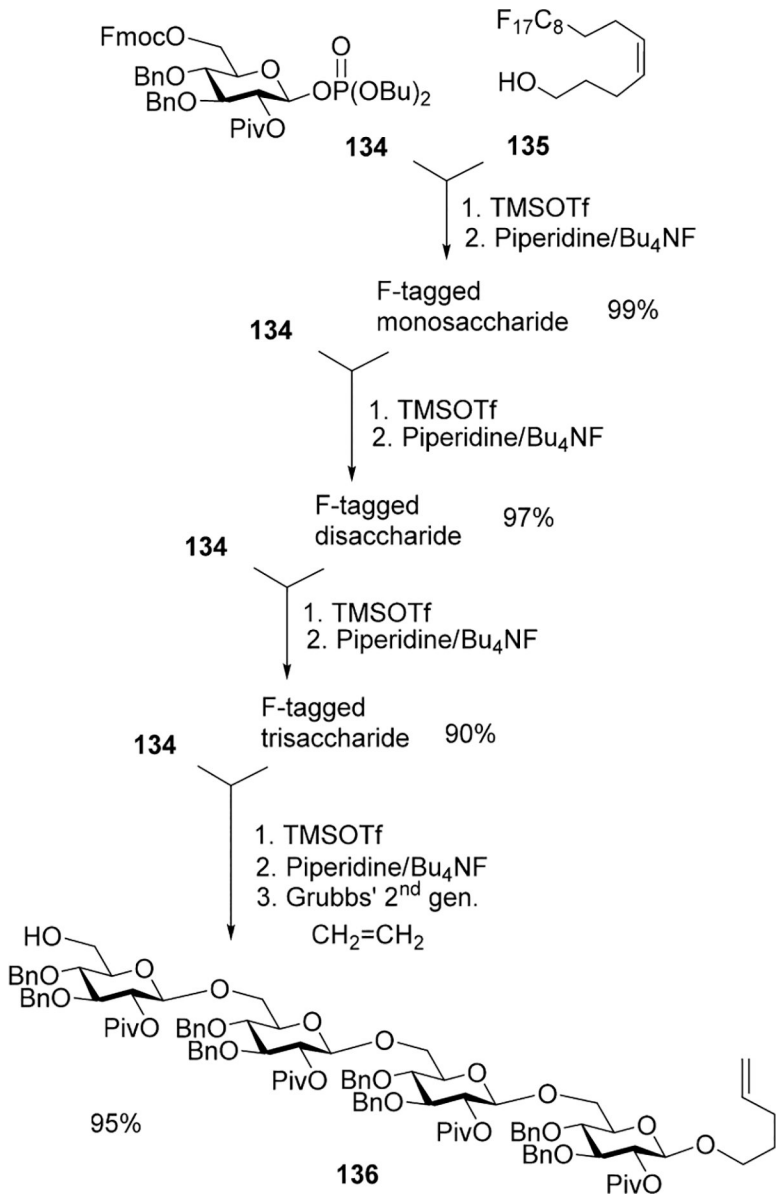


Scheme 26.

Automated Synthesis of Globo H Hexasaccharide

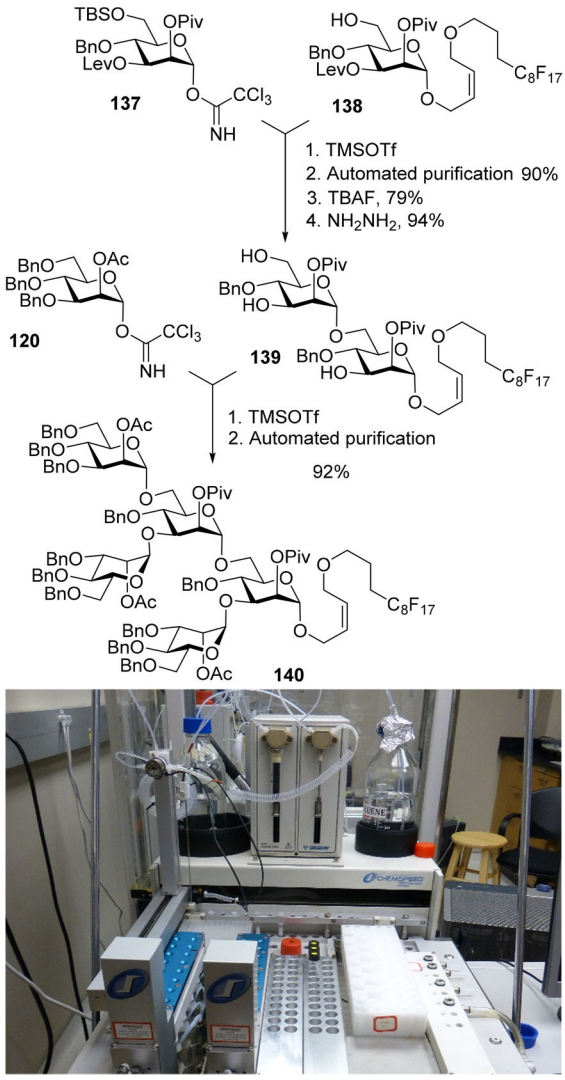


Scheme 27.
Automated Synthesis of β-Mannosides



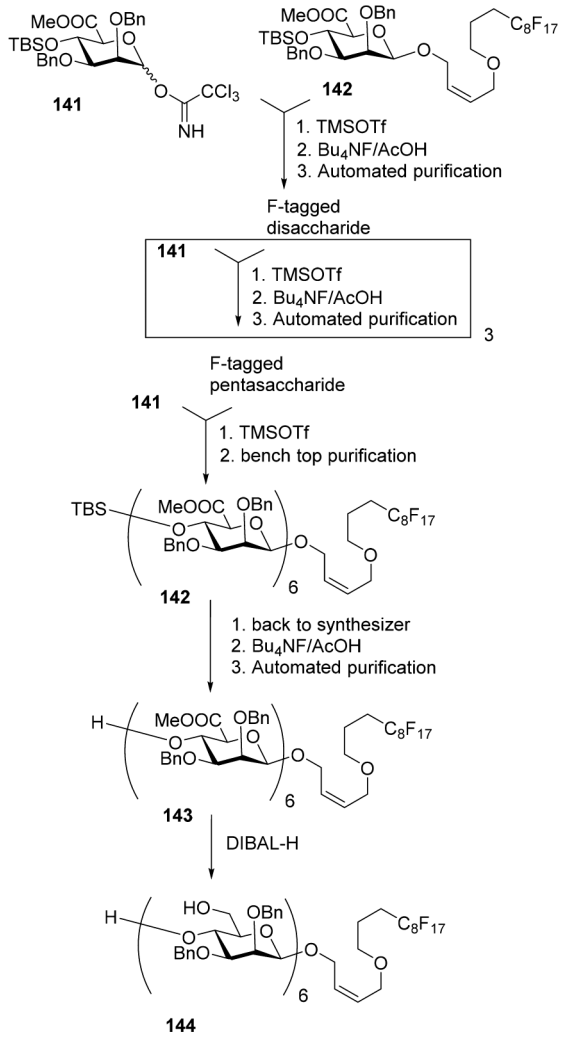
Scheme 28.

Fluorous Tag Supported Synthesis of a Tetrasaccharide 322 in a Microreactor



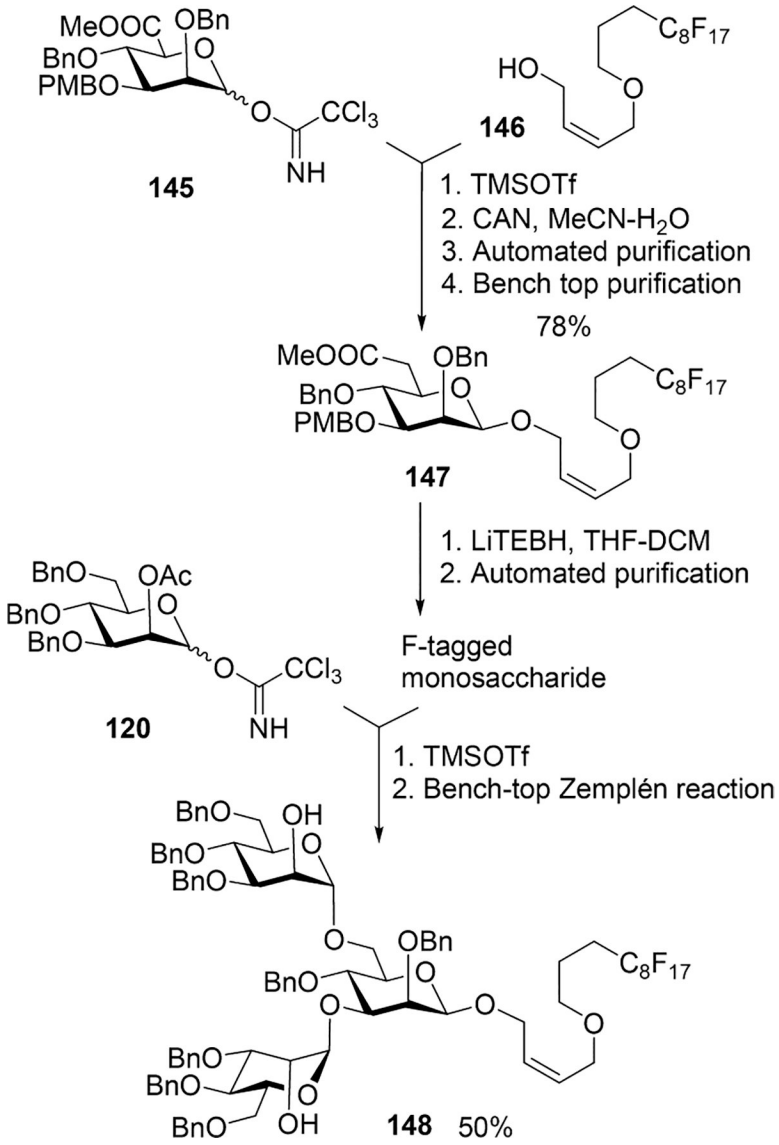
Scheme 29.

Automated Synthesis of Pentamannose 140 Using Fluorous Support[a]



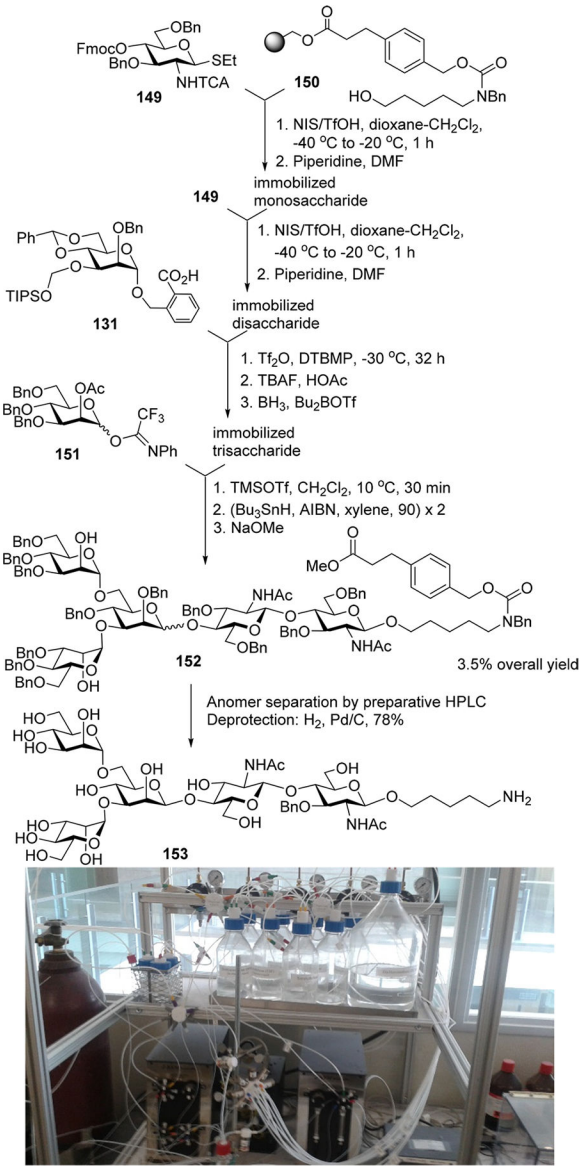
Scheme 30.

Automated Synthesis of β-Mannuronan and β-Mannan



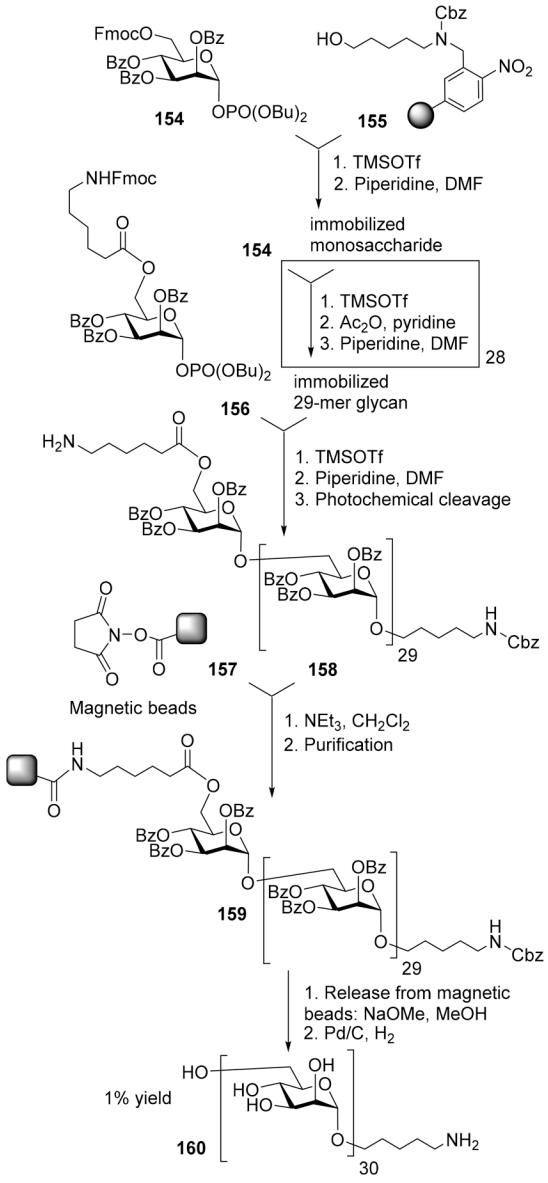
Scheme 31.

Automated Sequence to the Branched Oligomannan Fragment from N-Glycans

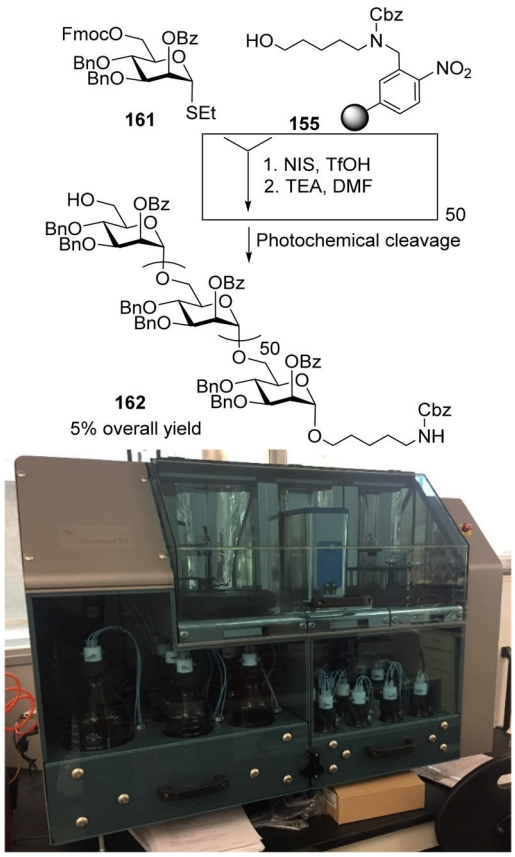


Scheme 32.

Automated Synthesis of N-Glycan Core Using the Dedicated Synthesizer

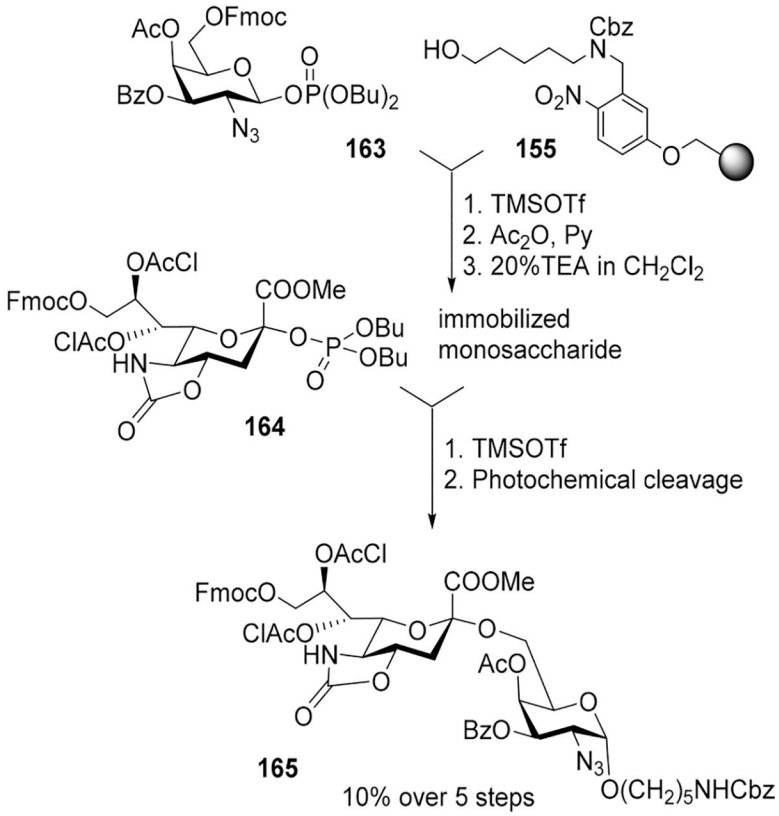


Scheme 33.
Automated Synthesis of Manno Triantamer 160

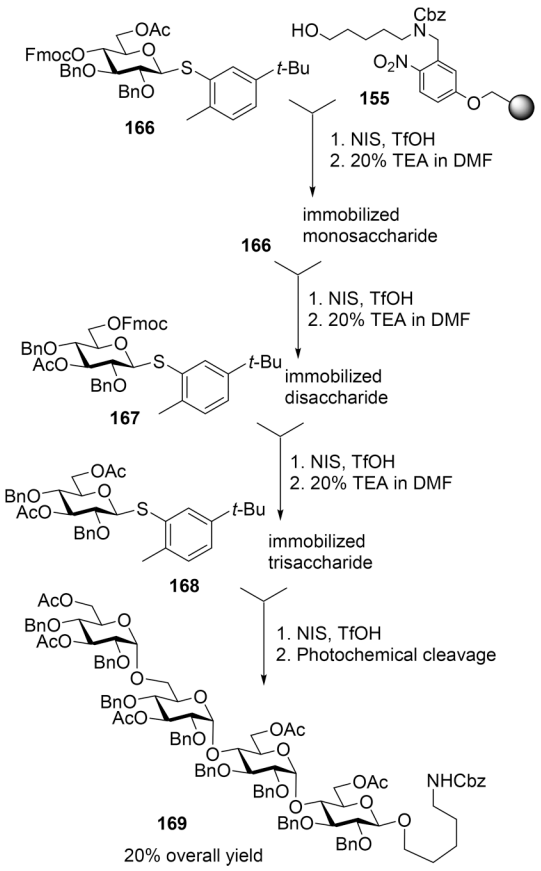


Scheme 34.

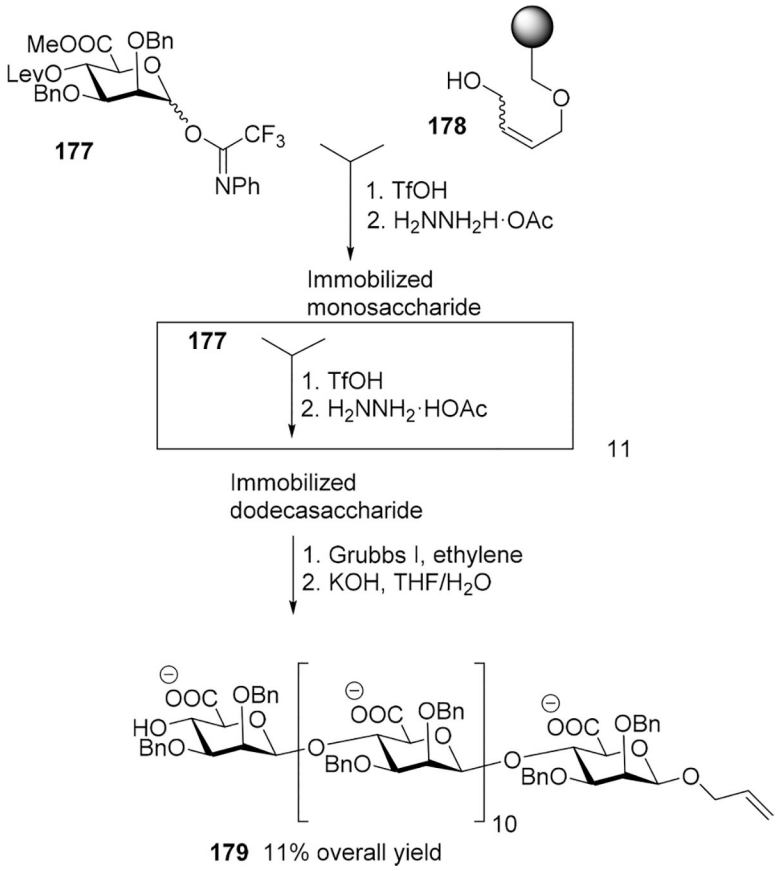
Automated Synthesis a 50-mer 162 Using Glyconeer 2.1[a]



Scheme 35.
Automation of the Sialylation Reaction

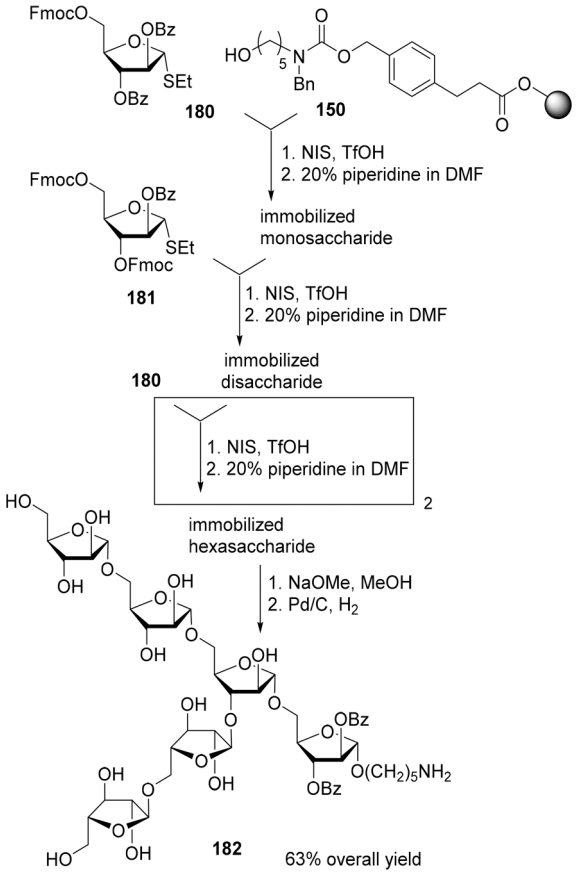


Scheme 36.
Automation of 1,2-cis Glycosylation



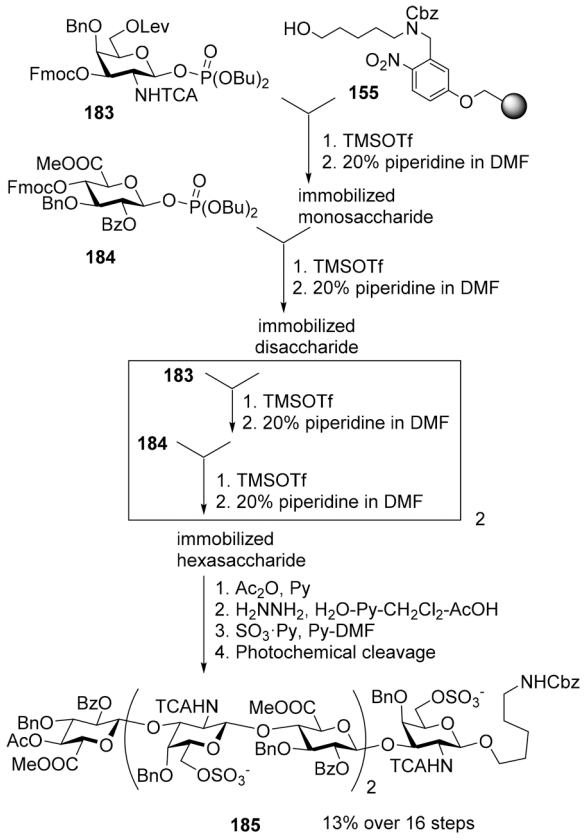
Scheme 37.

Automated Synthesis of β-Manno-Linked Dodecasaccharide 179



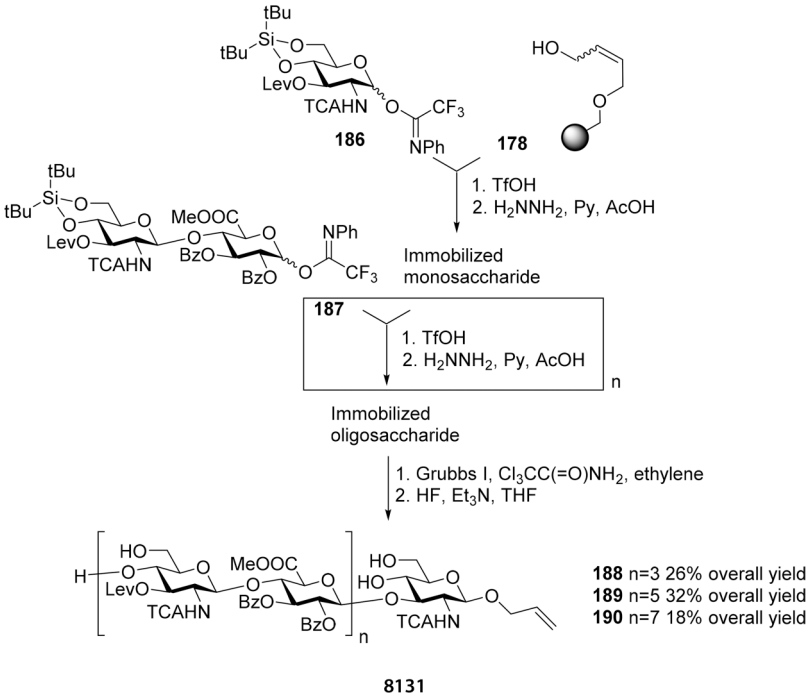
Scheme 38.

Synthesis of the Branched Hexasaccharide Composed of Multiple Arabinofuranosyl Residues

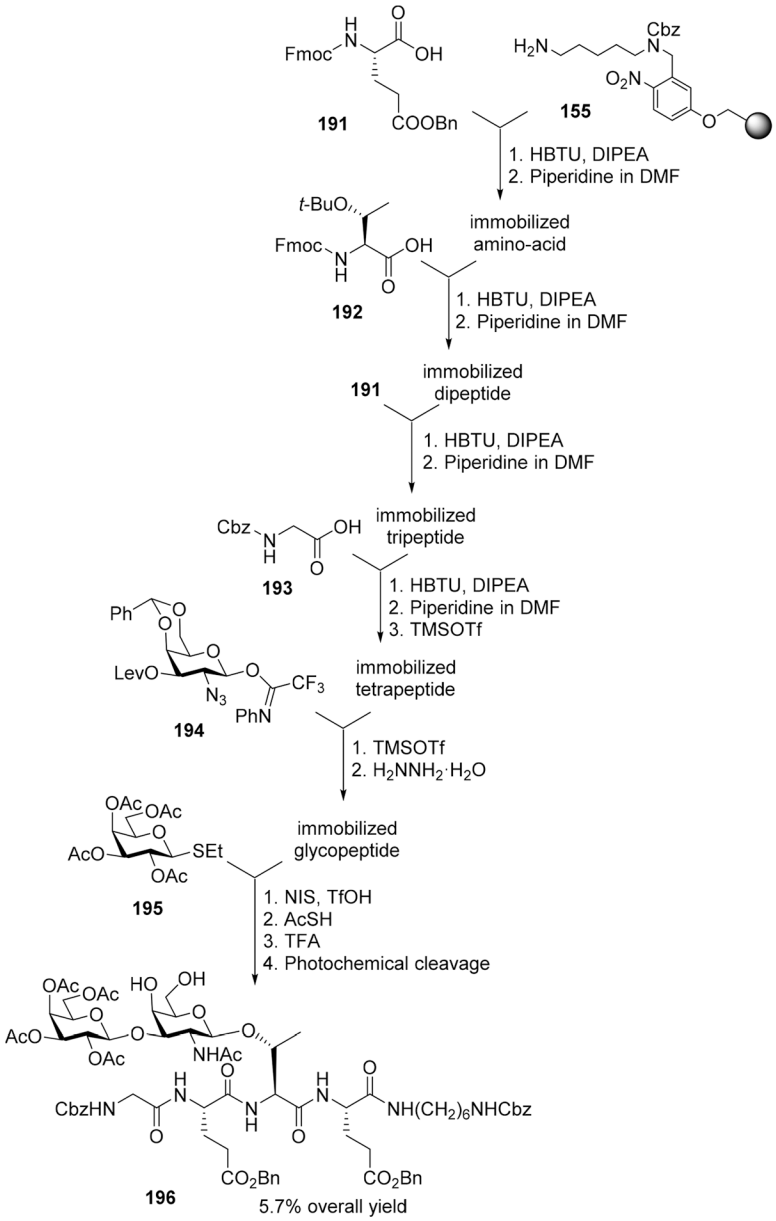


Scheme 39.

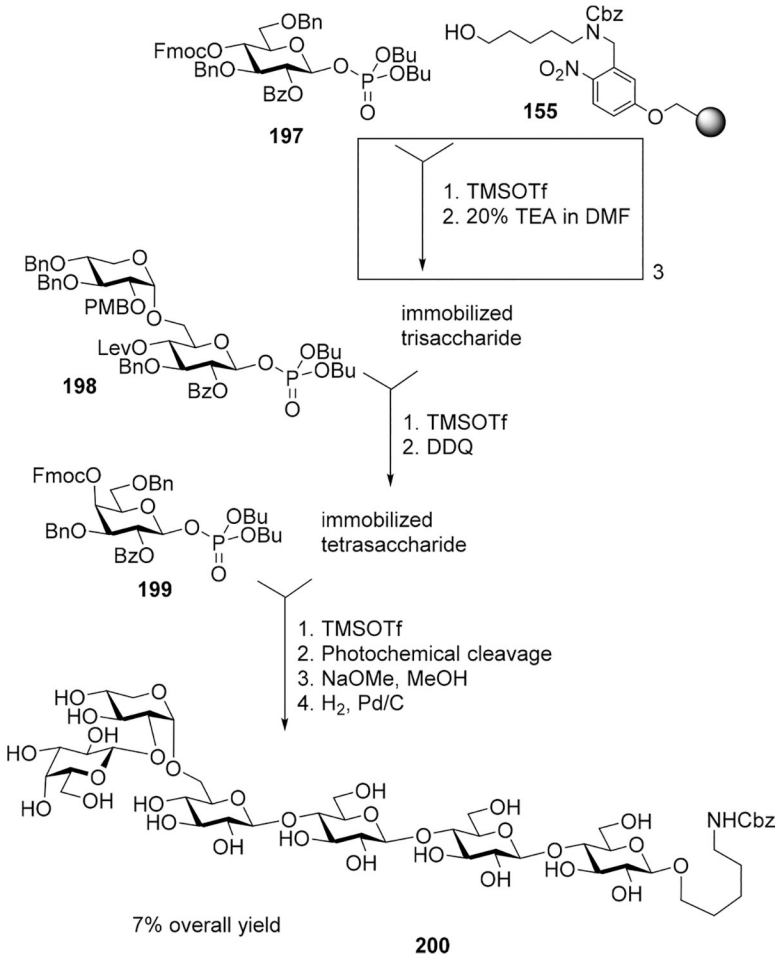
Synthesis of a Chondroitin Sulfate



Scheme 40.
Synthesis of Hyaluronic Acid Fragments

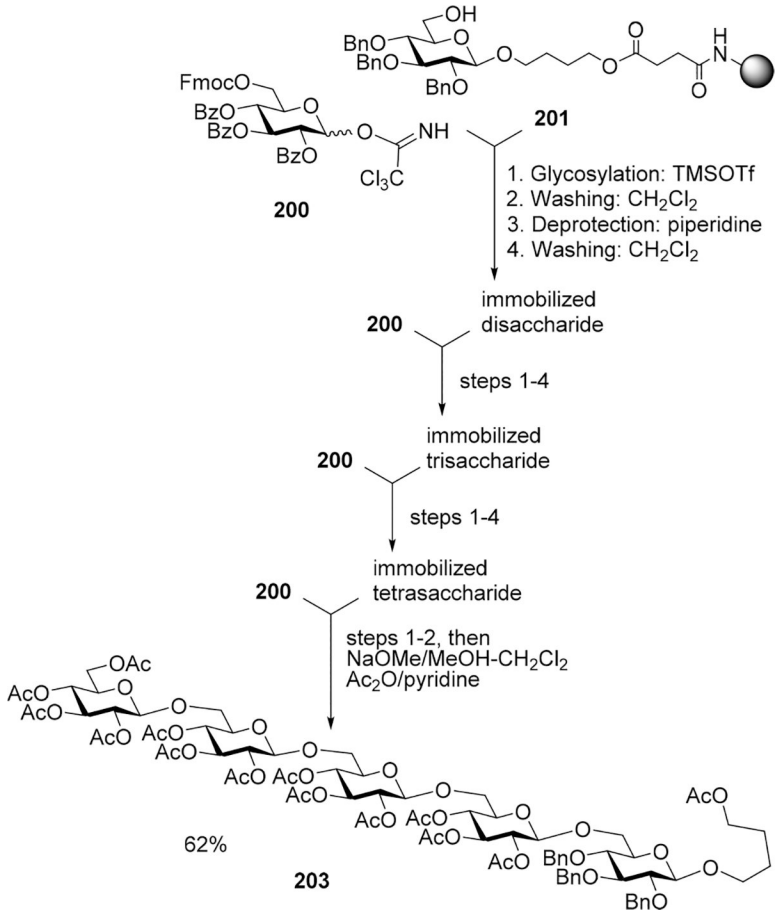


Scheme 41.
Glycopeptide Synthetic Sequence

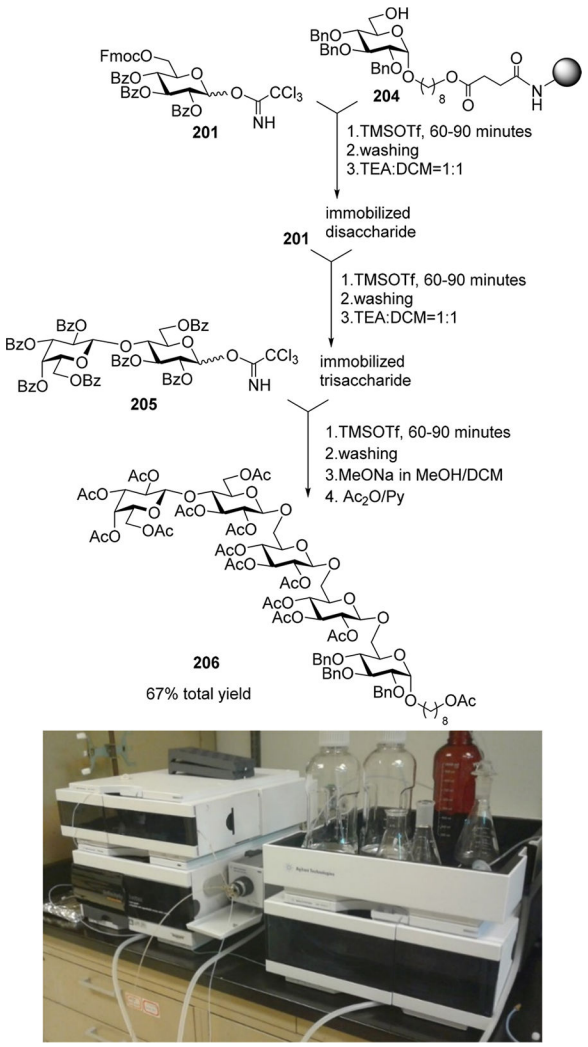


Scheme 42.

Synthesis of a Representative Galactosylated Xyloglucan for Generating of Oligosaccharide Libraries

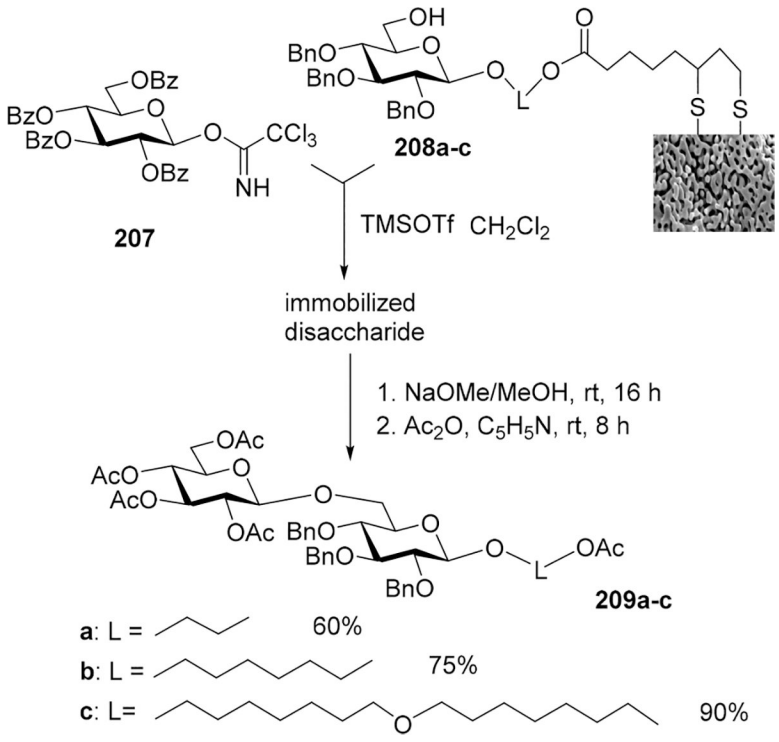


Scheme 43.
HPLC-Assisted Automated Oligosaccharide Synthesis

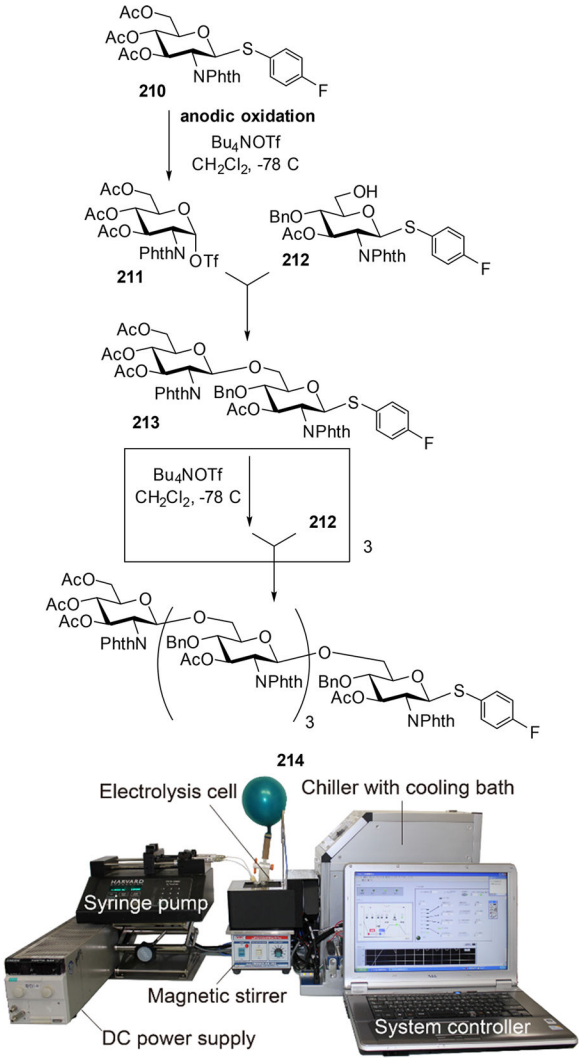


Scheme 44.

Use of an Autosampler As the Mode for Reagent Delivery for the HPLC-Based Automation

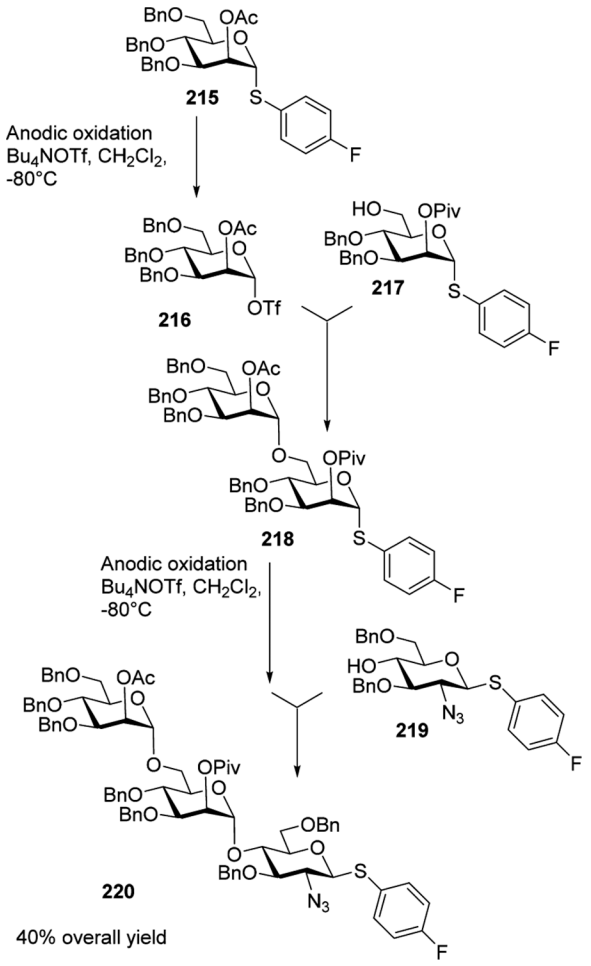


Scheme 45.
HPLC-Assisted Surface-Tethered Synthesis of Disaccharides 209



Scheme 46.

Automated Solution Phase Synthesis Using Electrochemical Activation[a]



Scheme 47.

Electrochemical Approach to GPI Anchor'S CoreTrisaccharide