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# In situ preactivation strategies for the expeditious synthesis of oligosaccharides: A review

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## Abstract

Carbohydrates have gained increasing appreciation over the last few decades for their fundamental roles in all essential areas of life. As a result, there has been a surge of activity in synthetic glycosylation strategies to construct useful oligosaccharides. This review evaluates the advances in synthetic carbohydrate chemistry, specifically preactivation methodologies, stereoselective β-mannosylations, and an automated, electrochemical preactivation method. Also discussed is the use of preactivation as a tool to study reactive intermediates, and applications of preactivation protocols in the one pot-synthesis of a hyaluronic acid decasaccharide and one-pot synthesis of a tristearoyl lipomannan containing a pseudotrisaccharide.

## Introduction

In recent years, carbohydrates have gained increasing appreciation for their fundamental roles in all essential areas of life. Carbohydrates are known to play integral roles in physiological processes which give rise to their many applications. [1–4] Many antibiotics, vaccines, and cytotoxic agents contain medically relevant carbohydrates and oligosaccharides. Though abundant in all living organisms, it is difficult to obtain oligosaccharides from nature with high purity and in useful quantities. Although technology exists for the automated synthesis of other classes of biopolymers, peptides, [5] and polynucleotides, [6] development of similar technologies for oligosaccharides remain in its infancy. The preactivation glycosylation methods discussed herein may indeed hold the key to promoting the field to the same level of scientific sophistication.

Over the last century, many synthetic strategies for glycosylations have been developed and perfected. These methods all form new glycosidic bonds with varying ratios of α and β products but differ by the nature of polymerization, anomeric leaving group, and activation method. [7,8] While several types of polymerization exist, for the purposes of this review, the loose categories of linear, convergent, and two-step activation are most relevant. In a linear glycosylation, a single monomer unit is added to the growing glycan chain. In a convergent glycosylation, building blocks of the desired oligosaccharide are synthesized independently, and then joined to yield the desired compound. The two-step activation method is a modern variation of linear glycosylation in which the glycosyl donor and glycosyl acceptor both possess the same leaving group initially.[7] Before glycosylation can occur, the leaving group of the glycosyl donor must be transformed into one that can be selectively activated over that of the donor.

Although many improvements have been made to traditional glycosylation methods, five main limitations still exist. (1) The installation of various protecting groups onto carbohydrate building blocks can be a complicated and time consuming process, as is the (2) purification of intermediates. (3) Maintaining control over anomeric stereochemistry has also remained a challenge, as obtaining mixtures of α/β products can significantly affect the yield. (4) Undesired self-coupling products due to aglycon transfer also contribute to lower yields. Finally (5) chemoselectivity of the donor and acceptor can limit which carbohydrate building blocks can be coupled. These limitations make traditional glycosylation strategies slow, low yielding, and overall inefficient.

To address these limitations, several groups have developed preactivation strategies. The preactivation method of glycosylation is a further modification of two-step activation. In preactivation, the glycosyl donor is preactivated in order to form the reactive intermediate without the glycosyl acceptor being present. Once activated, the glycosyl acceptor is added. This selective preactivation allows for activation of the leaving group of only the donor, so the acceptor can have the identical leaving group without acting as the donor. Leaving group differentiation through preactivation has the potential to address limitations due to reactivity, and may reduce the need for protecting groups on the acceptor. Combining a preactivation method into a one-pot synthesis can eliminate the need to purify intermediates.

In the following sections, several preactivation glycosylation methods will be discussed in further detail, including the development of preactivation for the study of reactive intermediates. Also explored are examples that apply preactivation as a modification of two-step activation to rapid, one-pot oligosaccharide syntheses, and as such, address one or more of the five limitations of traditional glycosylations.

## Preactivation to elucidate identities of reactive intermediates

While the preactivation glycosylation method has practical applications in oligosaccharide syntheses, historically many have used it as a means to study reactive intermediates that give rise to new glycosidic bonds. Nicolaou,[51] Danishefsky,[42,52,53] van der Marel, [54] Gin[55] have all contributed significantly to the study of preactivation glycosylations in general, notably, Crich,[56,57] Bols, [58] Whitfield, [49] Boons,[59] and Demchenko[60] have all exploited this minor modification of two-step activation to study such reactive intermediates.

Crich and co-workers[57] developed a preactivation method for glycosylation for their work with β-mannosylations. While employing the Kahne method[61] for β-mannosylation, the procedure was modified slightly so that the donor was premixed with the activator, triflic anhydride ($Tf_2O$), at −78 °C *before* the acceptor was added. This small and then-seemingly trivial modification resulted near complete activation of the donor and reaction completion with a high β/α ratio (Scheme 2).

In order to explore the mechanism of preactivation, the group conducted low temperature NMR experiments to identify intermediates of the reaction. A mannosylsulfoxide was subjected to activation with $Tf_2O$ and DTBMP in $CD_2Cl_2$ at −78 °C and was shown to be cleanly converted into the α-triflate within a few minutes. These findings were also shown by activating a glycosyl bromide with silver trifluoromethanesulfonate (AgOTf) at −78 °C,

which was then reacted with methanol to form the methyl-β-mannoside with good selectivity. This series of NMR experiments provided support for their proposed mechanism (Scheme 3).

While preactivation was the key to successfully synthesizing β-mannosides for Crich, the same was not the case for Bols and co-workers. Using their conformationally restricted 4,6-silylene-tethered thiomannosyl donor, mannosylation using non-preactivation conditions was surprisingly was β-selective (Scheme 4).[58]

From this surprising observation, the group proposed a mechanism for glycosylation (Scheme 5).

Whitfield and co-workers[62] carried out a series of computational studies based on three-step activation, or preactivation, in order to determine the relationship between stereochemical outcomes and conformation preferences of the glycosyl donor in synthetic glycosylations. The three-step activation includes irreversible ionization of the donor (activation), nucleophilic attack by the acceptor, and proton transfer, which are the first three steps in an $S_N1$-like mechanism (Scheme 6). [63]

Through their preactivation-based computational study, Whitfield's group identified two key factors that affect stereoselective control in glycosylations: (1) The C-5 – O – C-1 – C-2 torsional angle decreases for α-attack and increases for β-attack due to the anomeric effect; and (2) intramolecular hydrogen bonding stabilizes ion-dipole complexes. Their proposed strategy based on these observations was to design glycosyl donors that are face discriminated, and consequently will exist in predominantly one conformation.

Boons and co-workers[59] developed a general strategy for stereoselective glycosylations using neighboring group participation of a (1S)-phenyl-2-(phenylsulfenyl)ethyl moiety at C-2 of the glycosyl donor (Scheme 7). Glycosylations using both non-preactivation and preactivation conditions yielded α-glycosides exclusively (Scheme 8).

To identify the intermediate that gave rise to exclusively α-anomers, glycosyl donor **34** was preactivated, and $^1$H, $^1$H-TOCSY, HMBC, and HSQC NMR spectra were obtained. Addition of methanol formed the α-methyl glycoside through inversion of configuration of an equatorially substituted sulfonium ion (**35**) at the anomeric center (Scheme 9).

## Preactivation-based one-pot combinatorial synthesis of a hyaluronic acid decasaccharide

Huang and Ye[49] expanded on the modification of two-step activation, coining the term preactivation and developing a general one-pot method for glycosylation. In their method, *p*-toluenesulfenyl triflate (*p*-TolSOTf) was utilized as the promoter[56,57,64–66] (formed *in situ* from *p*-toluenesulfenyl chloride (*p*-TolSCl) and AgOTf) in diethyl ether at −60 °C. In contrast to traditional non-preactivation glycosylation procedures, both the glycosyl acceptor and donor contained the same leaving group at the reducing end. Selectively preactivating the glycosyl donor in the absence of the acceptor is the key to using identical leaving groups in both building blocks.

To apply the preactivation method to multiple coupling steps, a one-pot protocol is used. The reaction mixture was warmed to room temperature between each subsequent glycosylation, which decomposes any excess activated donor that may interfere with the next step.

To show the full range and versatility of their method, Huang, Ye, and co-workers reported the first synthesis of a fully deprotected hyaluronic acid decasaccharide [67] (Scheme 10). The largest hyaluronic acid oligomer ever made prior to their publication were hepta-[68] and octasaccharides, [69] as well as a branched N-glycan dodecasaccharide. [70]

An unforeseen challenge faced by the group was the formation of a TCA-derived oxazoline side product due to neighboring group participation by the TCA group (Scheme 11). To shift the equilibrium from oxazoline **47** to the oxazolinium ion **44**, TMSOTf was added, and this resolved the oxazoline side product formation by shifting the equilibrium toward pathway a (Scheme 11A). One other challenge the group encountered was global deprotection of the large oligosaccharide. The compatibility of deprotection conditions with the base-sensitive glucuronic acids made choosing protecting groups critical for the success of the synthesis. The final deprotected decasaccharide was produced with an overall yield of 37%.

This noteworthy synthesis of a fully-deprotected hyaluronic acid decasaccharide by Huang, Ye, and co-workers provided insight into the challenges of extending the preactivation strategy towards the synthesis of longer oligosaccharides. As demonstrated by the unanticipated challenges in synthesis and deprotected faced by the group, as the length of the desired oligosaccharide increases, more individual optimization for the synthesis is likely required.

## Preactivation-based iterative one-pot synthesis of a tristearoyl lipomannan containing a pseudotrisaccharide

Gao and Guo[71] used Huang's method for preactivation in the synthesis of a lipomannan containing a pseudotrisaccharide (Scheme 12). Their application of the method showed its versatility in forming both glycosidic linkages as well as more complex pseudosaccharides in an iterative one-pot synthesis that averaged 73% yield per glycosylation step. All glycosylation steps resulted in α-linkages, and this stereoselectivity was attributed to neighboring group participation.

This convergent synthesis highlights the use of a preactivation-based glycosylation strategy to efficiently synthesize a tetramanoside stereoselectively, forming only α-linkages. Research is ongoing in the area of lipomannan-derived vaccines, and to aid in further conjugation to lipids, proteins, or other carrier molecules, PMB and TBS protecting groups were incorporated in the intermediates. Selective deprotection can allow attachment of the desired linker for future development and derivatization of lipomannan.

## Automated, anodic oxidative preactivation-based synthesis of oligoglucosamines

Nokami and co-workers[72] applied the general premise of preactivation glycosylation, that of preactivating the glycosyl donor before the addition of the glycosyl acceptor, to an electrochemical method. Instead of activation using electrophilic chemical promoters, activation was achieved using anodic oxidation, and the coupling reactions took place in a solution phase. The group developed a practical automated synthesizer to carry out the coupling reactions (Scheme 13).

The glycosyl donor was subjected to anodic oxidation in the presence of tetrabutylammonium triflate ($Bu_4NOTf$) in an electrolysis cell to form the glycosyl triflate, to which the glycosyl acceptor was added. After reacting the two glycosyl building blocks for 30 minutes at −60 °C, the automated synthesizer unit would raise the temperature to decompose any remaining activated donor, re-cool, and activate the new donor for the second coupling reaction in the series, all in one-pot. Up to five consecutive glycosylation steps (Scheme 7) were achieved in the one-pot automated set up with average yields per glycosylation ranging from 62 – 82% (Table 2).

Although this is not the first reported automated oligosaccharide synthesis, it differs from those such as the Seeberger[73] method in that it is a solution-phase synthesis. While solid-phase oligosaccharide syntheses have advantages such as ease of separation of products, it is costly, and reactivity of glycosyl building blocks can be reduced when bound. This alternative solution-phase synthesis method, while lacking the same ease of separation of products, does overcome the cost and reactivity challenges of an automated solid-phase synthesis.

## Addressing limitations of preactivation glycosylation methods

Although preactivation glycosylation conditions address some of the five main limitations of chemical glycosylations, it does have its limitations. The main limitation of preactivation using thioglycosides has been aglycon transfer. Aglycon transfer occurs when the sulfur atom of the glycosyl acceptor attacks the electrophilic reactive intermediate of the activated donor. [74] This destroys glycosylation products and reduces the efficiency of glycosidic bond formation. When carrying out a multi-step, one-pot synthesis, aglycon transfer will decrease the yield and efficiency of each successive glycosylation step.

While aglycon transfer is a challenge associated with glycosylation of thioglycosides regardless of activation conditions, Ye and co-workers[74] have recently developed a strategy to prevent aglycon transfer in a preactivation-based, one-pot oligosaccharide assembly. By employing sterically hindered *ortho*-methylphenylthioglycosides glycosyl building blocks, the steric hindrance of the leaving group in the acceptor prevented aglycon transfer with the activated donor (Scheme 15).

The *ortho*-methylphenylthioglycoside building blocks were employed in an iterative, one-pot preactivation synthesis of a trisaccharide with a final yield of 76% for both glycosylation steps.

## Conclusion

The aforementioned applications of preactivation glycosylation protocols all clearly address many of the five main limitations of traditional glycosylation methods by reducing the amount of required protecting group manipulation, reducing the necessity of purification of intermediates through use of one-pot procedures, and by using additives to direct anomeric stereochemistry, and even a strategy to avoid aglycon transfer. With such a simple modification as postponing the addition of the glycosyl acceptor until after complete activation of the glycosyl donor is achieved, the enhancement in speed, yield, and overall efficiency of such methods is quite noteworthy.

As demonstrated through the critical evaluation of these new methodologies, the preactivation approach to synthetic glycosylation is improving upon past limitations as well as providing countless potential applications in the ever-growing fields of carbohydrate chemistry, biology, pharmacology, immunology, and vaccine development.

Although quite promising in most respects, in the future, a few factors still remain to be addressed in order to harness the full synthetic potential of the preactivation strategy. For example, as seen in Huang's decasaccharide synthesis, as the length of the desired oligosaccharide increases, more individual optimization for the synthesis is likely required in terms of protection and deprotection strategies. With a little more investigation and optimization of yields and stereoselectivity, it is ensured that the preactivation glycosylation strategy will continue to be an integral tool for synthetic carbohydrate research and applications.

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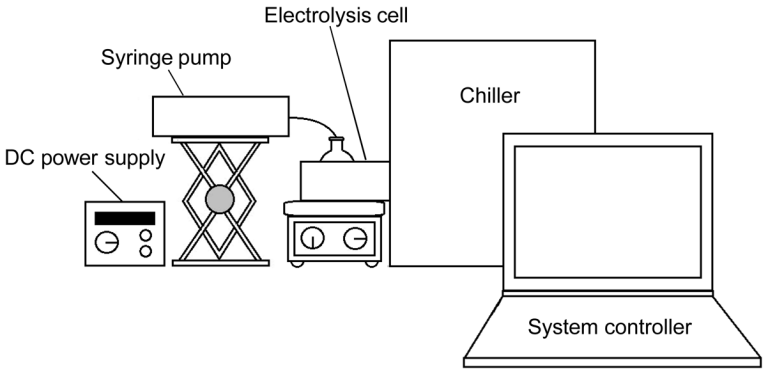
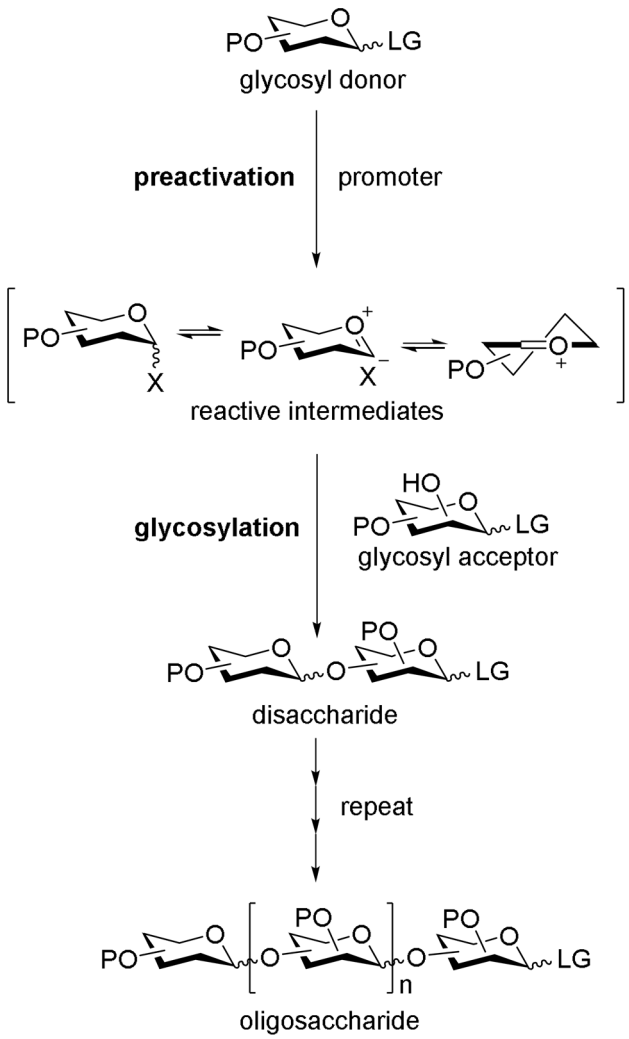
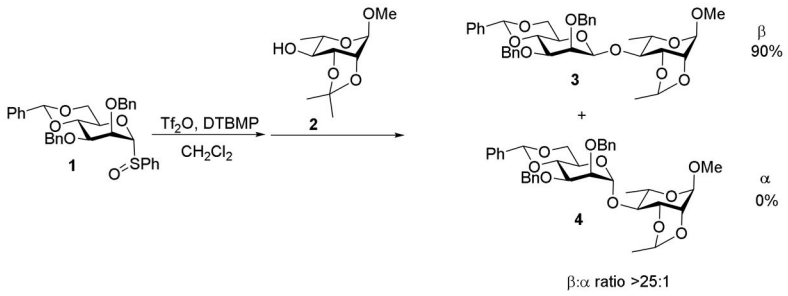



**Figure 1.**

Setup of the automated synthesizer consisting of a system controller, temperature control device, magnetic stirrer, electrolysis cell, syringe pump, and a DC power supply. (Adapted from reference 72.)

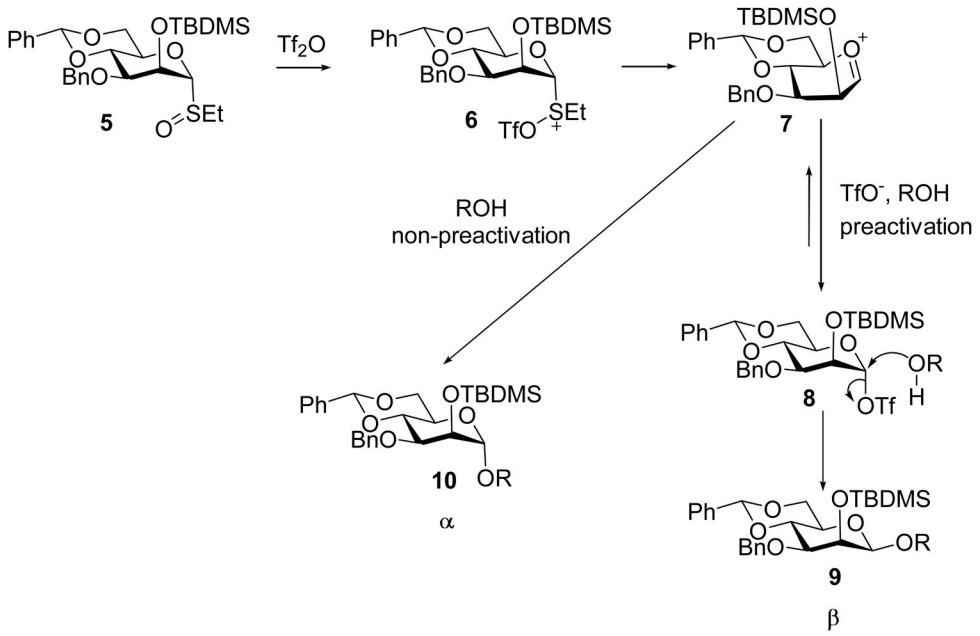



**Scheme 1.**
General scheme for preactivation[49,50]



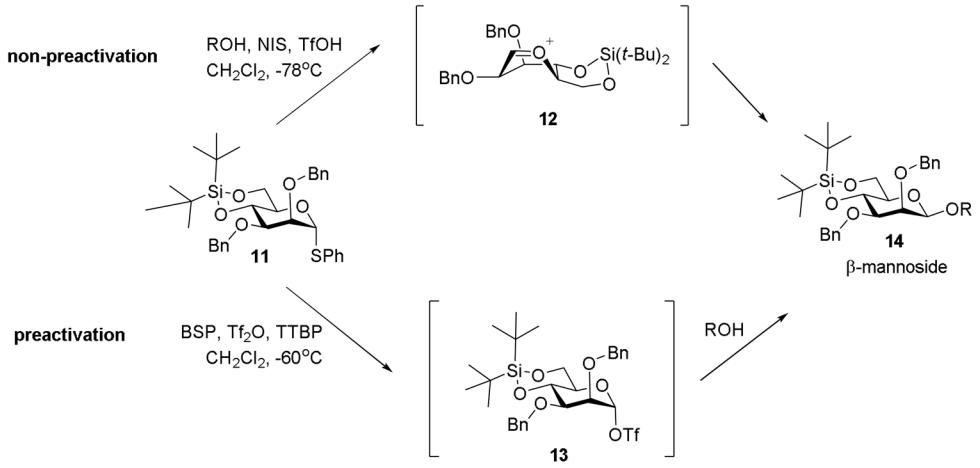

**Scheme 2.**

Preactivation method for stereoselective β-mannosylation. DTBMP is 2,6-di-*tert*-butyl-4-methylpyridine. [57]



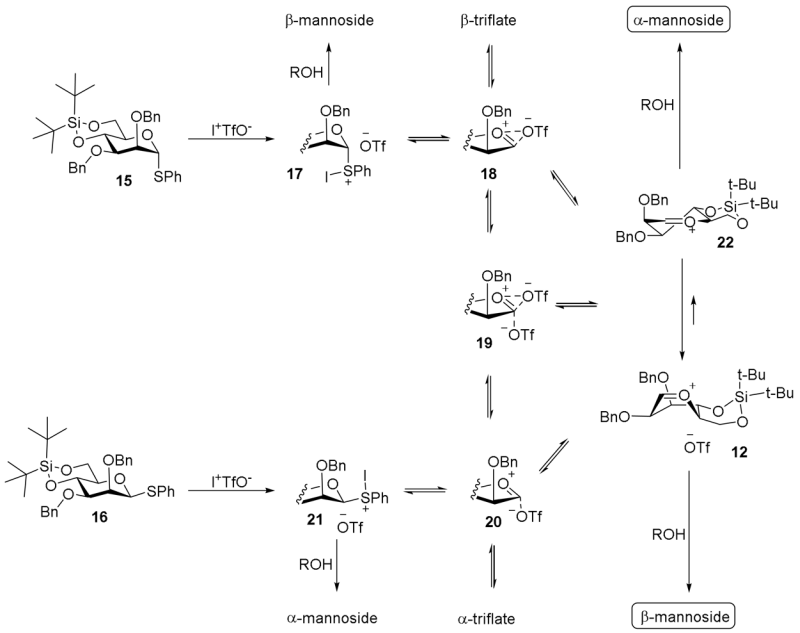

**Scheme 3.**

Proposed mechanism for α- and β stereoselective mannosylation through preactivation and non-preactivation protocols. TBDMS is *tert*-butyldimethylsilyl.[57]



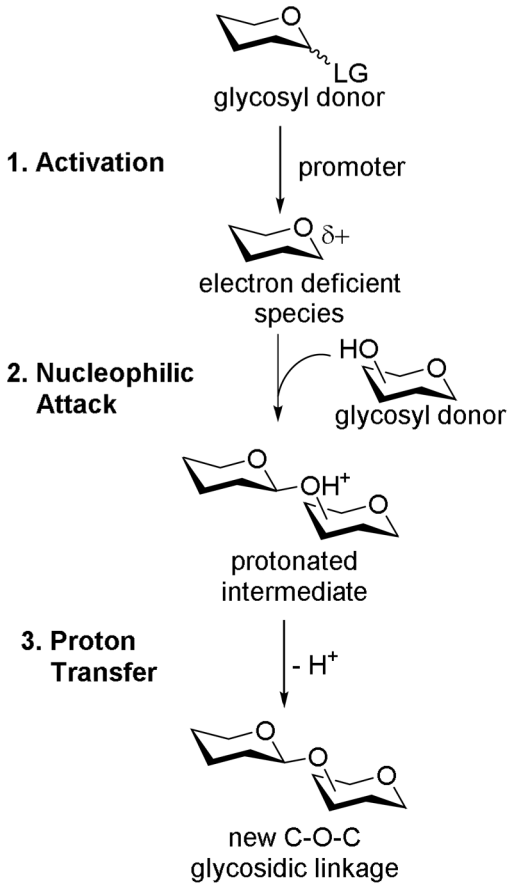

**Scheme 4.**

Mannosylations of the conformationally restricted donor are β-selective using both preactivation and non-preactivation conditions. [57,58] BSP is 1-benzenesulfinyl piperidine, and TTBP is 2,4,6-tri-*tert*-butylpyrimidine.



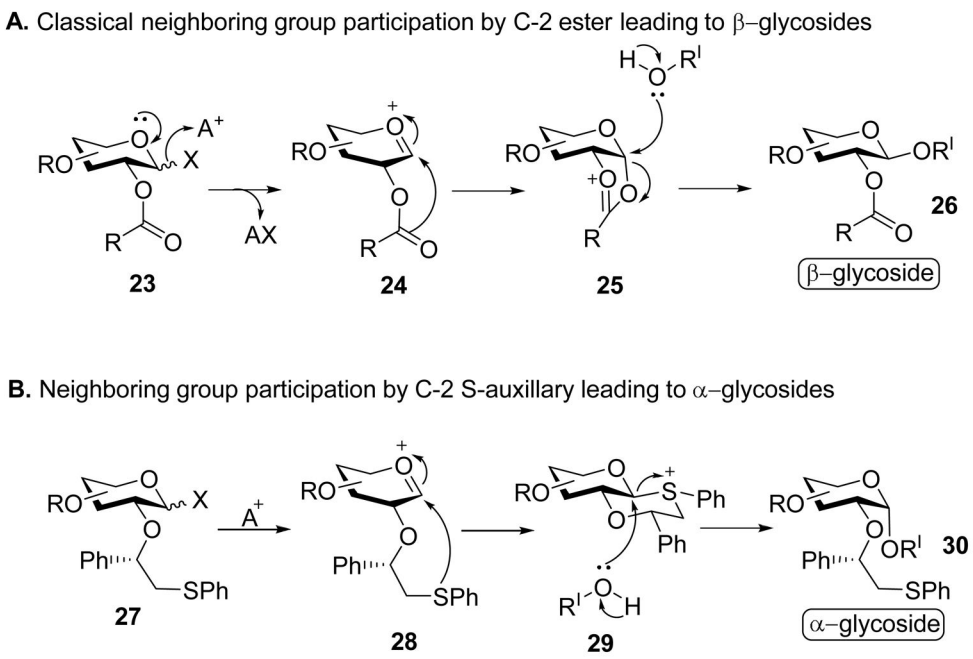

**Scheme 5.**

Proposed mechanism for glycosylation of 4,6-silylene-tethered thiomannosyl donor using NIS/TfOH. [58]



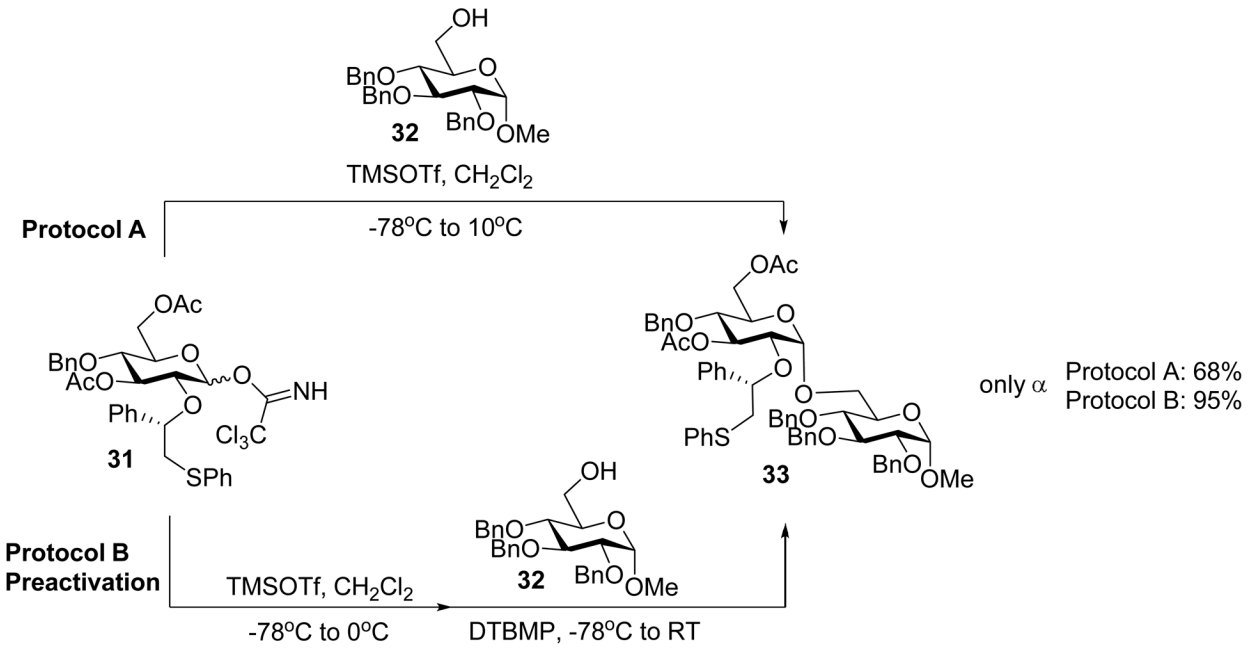

**Scheme 6.**

Three-step activation (preactivation) model of the glycosylation reaction. (Adapted from reference 62.)



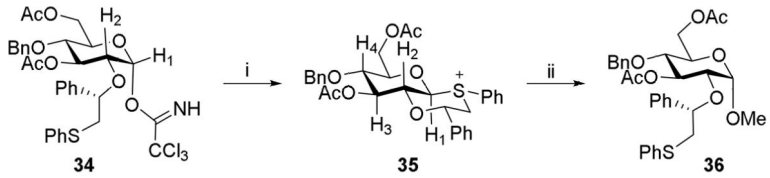

**Scheme 7.**

Approaches to stereoselective glycosylation. (Adapted from reference 59.)



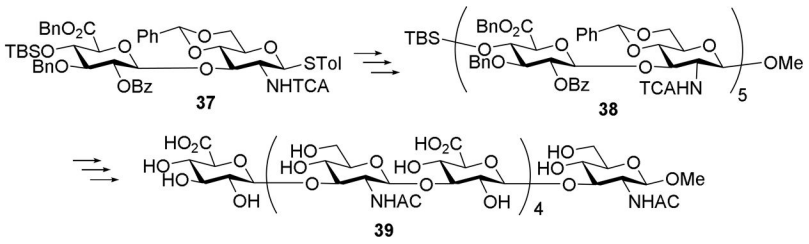

**Scheme 8.**

Stereoselective glycosylations with two activation methods. [59]



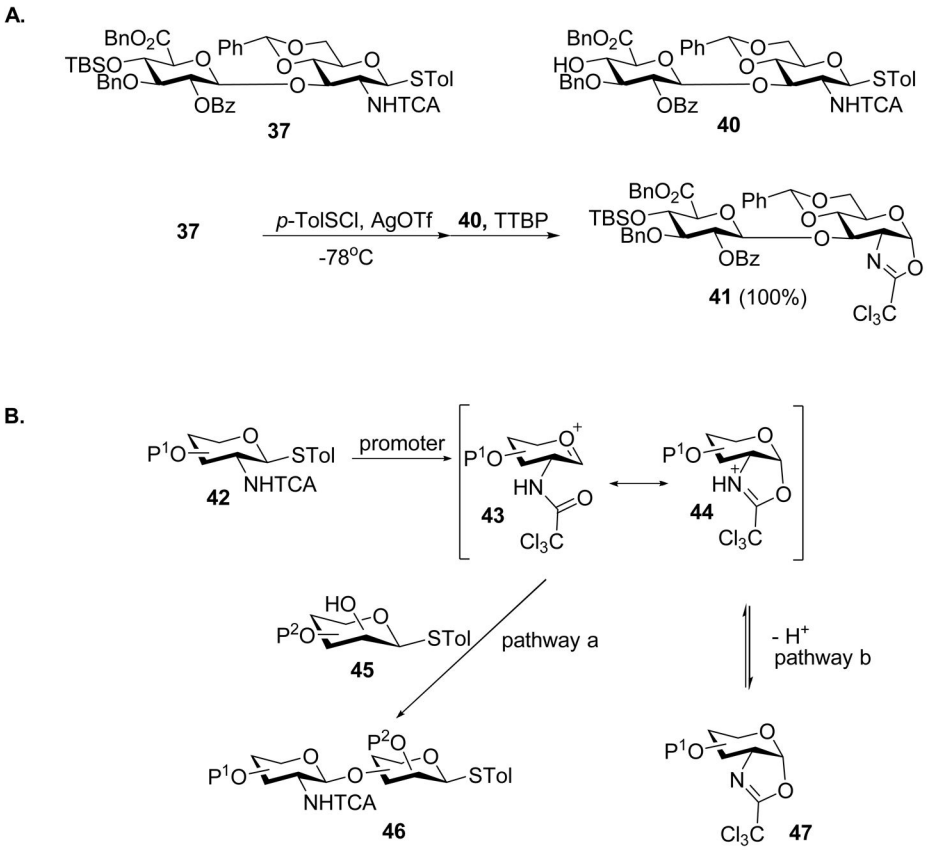

**Scheme 9.**

The presence of the quasi-stable sulfonium ion intermediate was confirmed by NMR. (i) TMSOTf, $CH_2Cl_2$, −50 to 0°C; (ii) MeOH, −20 to 0 °C. (Adapted from reference 59.)



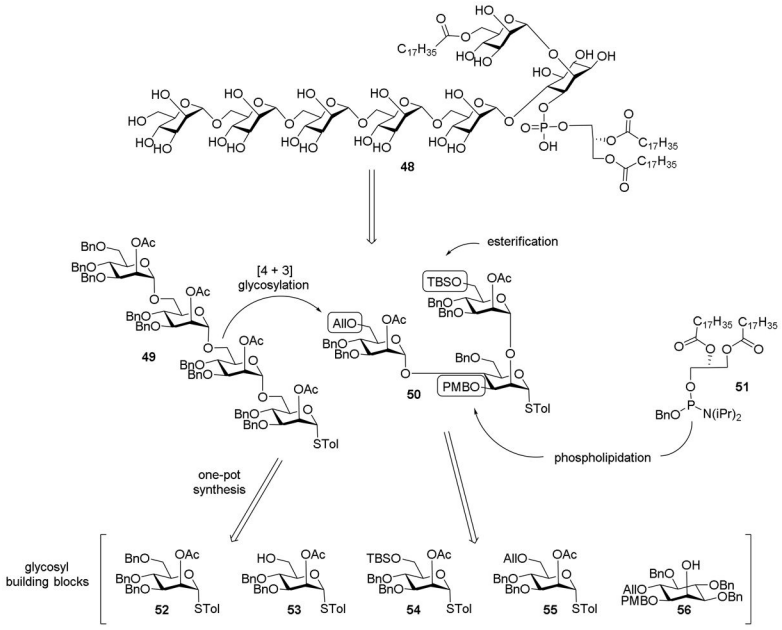

**Scheme 10.**

Chemical synthesis of a hyaluronic acid decasaccharide using preactivation-based stereoselective glycosylation protocol. [67]



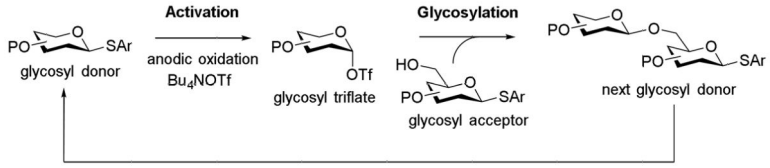

**Scheme 11.**

Proposed mechanism for the formation of the TCA-derived oxazoline side product. (Adapted from reference 67.)



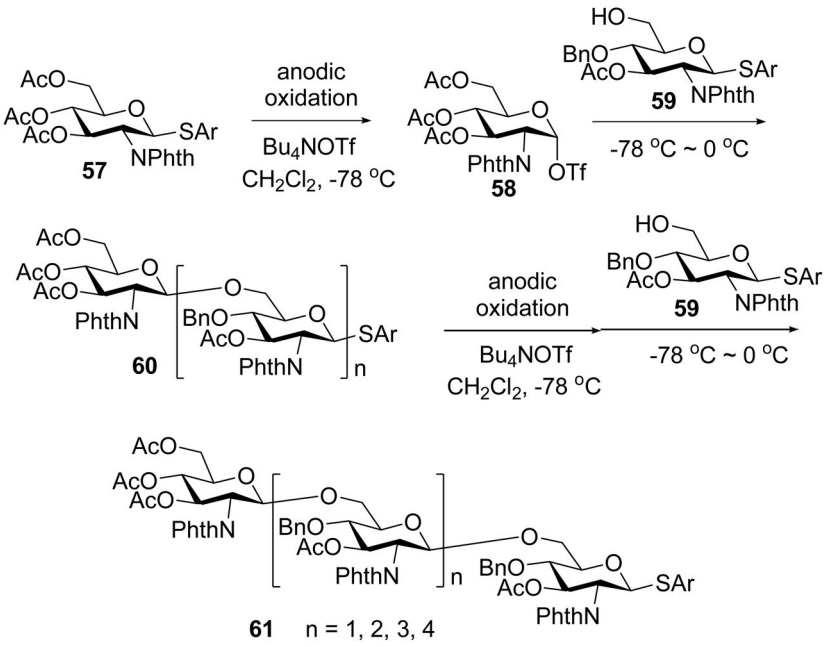

**Scheme 12.**

Retrosynthetic method for construction of target tristearoyl lipomannan from glycosyl building blocks, *myo*-inositol derivative, and lipid derivatives. (Adapted from reference 71.)



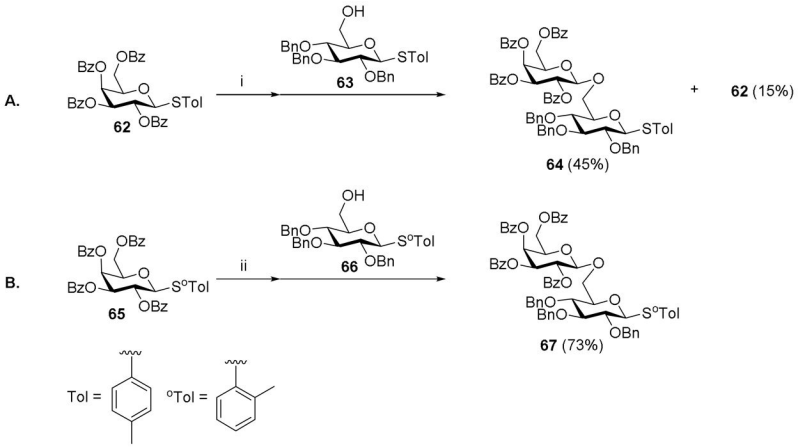

**Scheme 13.**

General procedure for electrochemical preactivation-based glycosylation strategy.



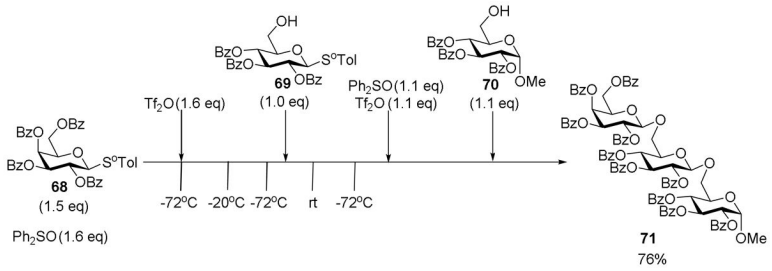

**Scheme 14.**

Stepwise synthesis of oligoglucosamine di- through hexasaccharides.




**Scheme 15.**

(A) Aglycon transfer occurred with preactivation conditions; (B) preactivation protocol using *ortho*- methylphenylthioglycosides; Reagents and conditions: (i) $Ph_2SO$, $Tf_2O$, 4Å molecular sieves, $CH_2Cl_2$; (ii) $Ph_2SO$, $Tf_2O$, 4Å molecular sieves, $CH_2Cl_2$. −72°C to −20°C, then cooled to −72°C.[74]

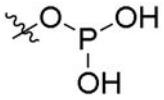
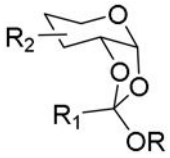
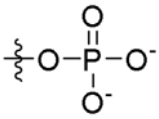
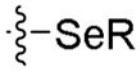
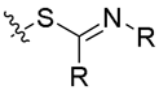
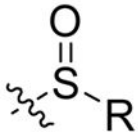
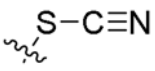
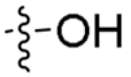
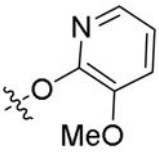
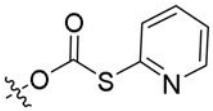
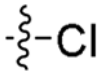
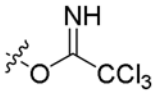
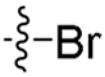
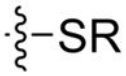
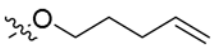
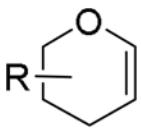



**Scheme 16.**

Preactivation-based one-pot assembly of trisaccharide **71** from *ortho*-methylthioglycoside building blocks. (Adapted from reference 74.)

**Table 1**

Commonly employed leaving groups in synthetic glycosylation reactions, and their corresponding activating reagents.

| Leaving Group | Promoter | Leaving Group | Promoter |
|---|---|---|---|
|  | TMSOTf or TfOH[9] |  | $TrClO_4$ or AgOTf or NIS/TfOH[10–13] |
|  | TMSOTf[14] |  | NBS, $Bi(OTf)_3$, dioxane [15–19] |
|  | NIS/TfOH or AgOTf or MeOTf [20–23] |  | $AgOTf/K_2CO_3$[16,17] |
|  | $TrClO_4$ [24] |  | $Ph_2SO/Tf_2O$ [25,26] |
|  | $Cu(OTf)_2$ [27–29] |  | Ag(OTf) [27–29] |
|  | Heavy metal salts [30,31] |  | TMSOTf [32–34] |
|  | | | |
|  | $SnCl_2/AgClO_4$ [35,36] |  | AgOTf [37,38] |
|  | IDCP or $Yb(OTf)_3$ or $NIS/BF_3Et_2O$[11,39–41] |  | or DMDO[42] |

TMSOTf = trimethylsilyl trifluoromethanesulfonate; TfOH = trifluoromethanesulfonic acid; AgOTf = silver trifluoromethanesulfonate; $TrClO_4$ = triphenylmethylium perchlorate; NIS = *N*-iodosuccinimide; DMDO = 2,2-dimethylioxirane; NBS = *N*-bromosuccinimide; IDCP = iodonium

dicollidine perchlorate; $Ph_2SO$ = diphenylsulfoxide; $Tf_2O$ = trifluoromethanesulfonic anhydride; $Cu(OTf)_2$ = Copper (II) trifluoromethanesulfonate; For additional leaving groups, see references 43–48.

**Table 2**

Isolated yields of oligoglucosamines

| | | % yield (average % yield per cycle) | |
|---|---|---|---|
| **cycles** | **oligoglucosamine** | **condition A**[a] | **condition B**[b] |
| 2 | n = 1 | 50 (71) | 69 (82) |
| 3 | n = 2 | 34 (70) | 52 (81) |
| 4 | n = 3 | 17 (64) | 31 (75) |
| 5 | n = 4 | 9 (62) | 15 (68) |

[a] Condition A (glycosylation temperature: −60 °C).

[b] Condition B (glycosylation temperature: −50 °C). (Adapted from reference 72.)