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RECENT DEVELOPMENT OF STEREOSELECTIVE GLYCOSYLATION REACTIONS

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Abstract – Carbohydrates are the most abundant class among biological molecules. Advances in glycobiology have revealed the vital roles played by glycosides and glycoconjugates in biological events. In this context, access to homogenous oligosaccharides and glycoconjugates is critical for various biological investigations. Glycosylation is the cornerstone of glycoside synthesis, and during glycosylation, the control of stereoselectivity at the anomeric position is highly important. In this review, recent progresses in 1,2-*cis*-glycosylation reactions are summarized, with a focus on the influence of the protecting groups on the conformations of the glycosyl donors, role of reaction mixture additives, and synthetic utility of endocyclic cleavage of glycoside. Development of robust glycosylation reaction will contribute to biologically active oligosaccharide synthesis.

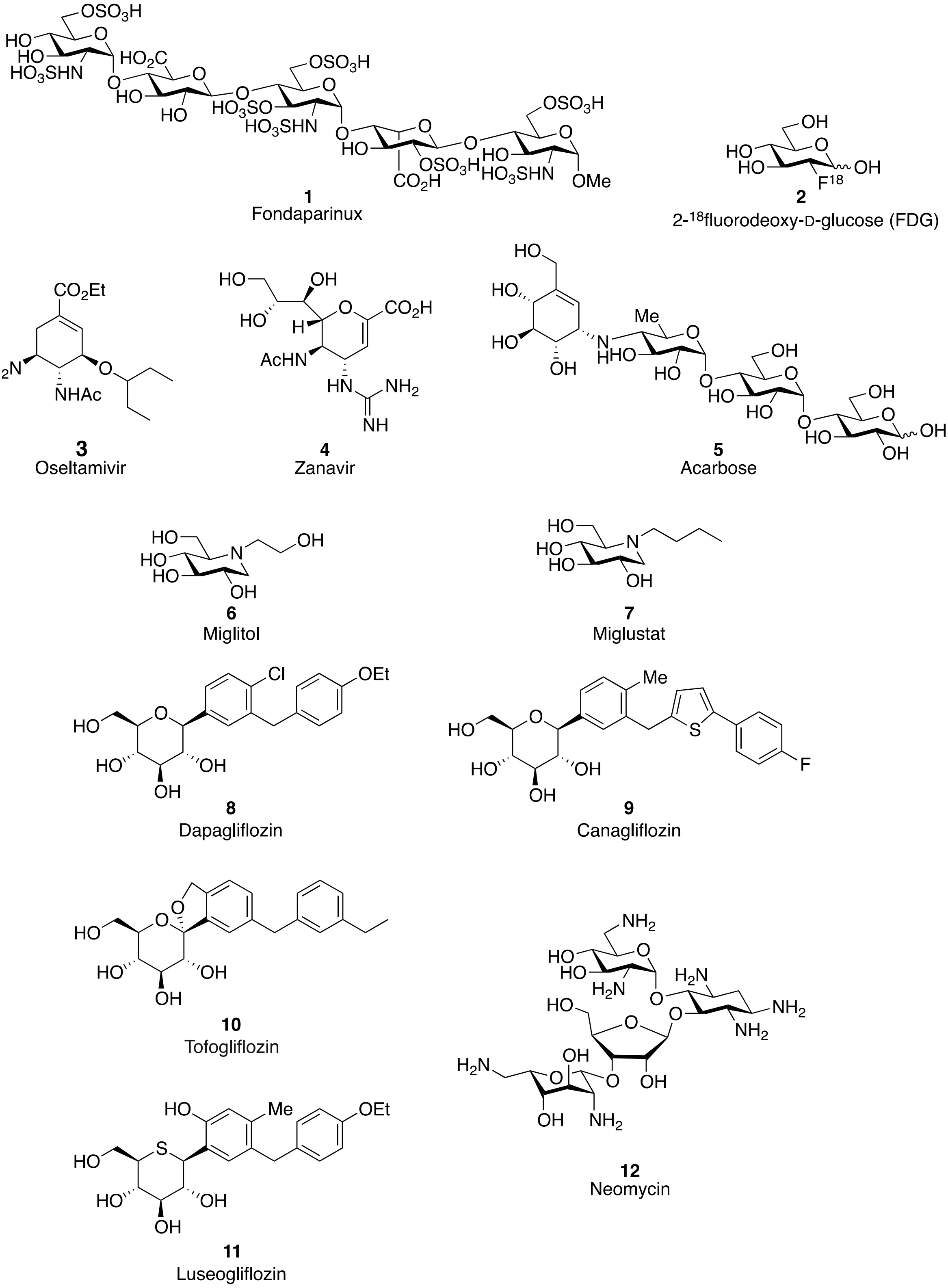
CONTENTS

7. Endocyclic cleavage reaction
8. α-Sialic acid (*N*-acetylneuraminic acid) synthesis
9. Site-specific modification and glycosylation methodologies with minimally protected sugar units

1. INTRODUCTION

Glycans associated with the cell surface, intracellular proteins, and lipids, contribute to critical biological events, such as protein quality control, cell adhesion, immunity, and pathogen invasion.[1] Glycosylation also affects the dynamics of glycoprotein endocytosis and cell surface half-life through binding to multivalent lectins and receptors. To aid the biological investigations of their roles, suitable quantities of homogeneous glycans are required. However, glycosides/glycoconjugates are not directly encoded by the genome, and hence amplification methods such as the polymerase chain reaction (PCR) are not available for accessing them in a straightforward manner. Naturally occurring glycans are typically present as heterogeneous mixtures owing to their complex biosynthetic pathways, and access to meaningful quantities of compounds from biological sources is highly challenging. In this context, the chemical synthesis of glycans and their conjugates would be a powerful tool for accessing them in homogeneous forms. In addition, chemical synthesis allows possibilities for the preparation of systematic libraries with well-defined structures, including the preparation of non-natural glycans for comparison to natural ones, fluorescent glycan probes, and biotin-tagged glycans.

Because carbohydrates play vital roles in biological events, several medicines that are structurally related to carbohydrates have been approved. Among them, heparin is the most famous glycan-based therapeutic and is used for the treatment of thrombosis. Heparin has been isolated from porcine sources, but the pentasaccharide of heparin has also been chemically synthesized, and fondaparinux **1** is now in clinical use (Figure 1).[2] Fondaparinux **1** has a longer half-life, enhanced potency, and reduced risk of heparin-induced thrombocytopenia, which is observed with some isolated heparin samples. The importance of chemically synthesized heparin was emphasized when the oversulfated chondroitin-sulfate contamination led to an international health crisis.[3] Another example of the use of carbohydrates is the application of 2-^{18}fluorodeoxy-D-glucose (FDG) for positron emission tomography (PET)-based imaging.[4] FDG is absorbed by cancer cells more quickly though 6-phosphorylation and is not metabolized due to the lack of the 2-hydroxy group. Notably, the accumulation of FDG is useful for imaging cancer. The anti-influenza therapeutic oseltamivir (Tamiflu) **3**[5] and zanamivir (Relenza) **4**[6] bind to neuraminidases and halt the viral progression as well as entry of the virus into human cells. The glucosidase and amylase inhibitor acarbose (Precose, Glucobay) **5** is used for diabetes mellitus type 2.[7] The iminosugar, miglitol **6** is also used as a drug for diabetes mellitus type 2, and miglustat **7** is used for the treatment of the lysosomal storage disease, known as type 1 Gaucher disease. Furthermore, several medicines based on the sodium/glucose cotransporter 2 (SLGT2) inhibitors **8**-**11** have been approved for the treatment of diabetes mellitus type 2.[8] Furthermore, antibiotics often include carbohydrate moieties, and a representative antibiotic is neomycin **12**.



1 Fondaparinux

2 2-^{18}fluorodeoxy-D-glucose (FDG)

3 Oseltamivir

4 Zanavir

5 Acarbose

6 Miglitol

7 Miglustat

8 Dapagliflozin

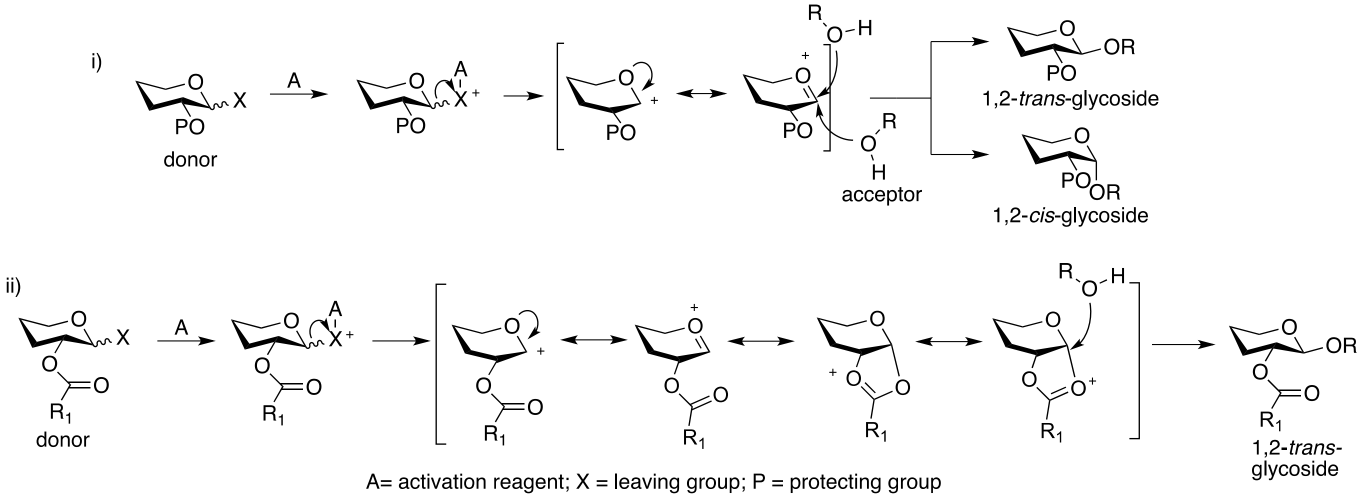
9 Canagliflozin

10 Tofogliflozin

11 Luseogliflozin

12 Neomycin

Figure 1. Approved carbohydrate-based medicines



A= activation reagent; X = leaving group; P = protecting group

Scheme 1. i) Simple overview of glycosylation reaction;
ii) 1,2-*trans*-glycoside synthesis by neighboring participation

While the structure of glucose was revealed by Emil Fischer as early as in 1880, carbohydrate chemistry has remained a difficult arena due to the structural complexity of sugars compared to other biomolecules. However, synthetic endeavors toward facile methods for producing large quantities of glycans have been undertaken for several decades.

Glycosylation is the cornerstone of glycoside synthesis and is an essential reaction in synthetic carbohydrate chemistry. In a glycosylation reaction, the glycosyl donor is coupled with a glycosyl acceptor in the presence of a suitable activator (Scheme 1). The donor activation leads to the formation of the cyclic oxacarbenium ion after the departure of the leaving group, and the resulting cation benefits from enhanced stability compared to that of typical aliphatic carbocations. This stability is generally attributed to the delocalization of the positive charge at the anomeric carbon onto the neighboring ring oxygen. Then, the acceptor, a nucleophile, attacks either the α- or β-face of the oxacarbenium ion. Typically, glycosylation reactions proceed via the SN1 pathway. The stereoselectivity at newly generated anomeric carbon is one of the most important aspects of glycosylation reactions. The separation of the stereoisomeric mixtures obtained in the glycosylation reaction in solid/polymer-supported syntheses, as well as the synthesis of large-molecular weight oligosaccharides, is highly challenging. In this regard, reliable stereoselective glycosylations have been much sought after and have witnessed significant advances in the past two decades. Generally, stereoselective 1,2-*trans*-glycosylation is easily achieved by neighboring participation from the 2-acyl protecting group. In 1,2-*trans*-glycosylations, once the glycosyl donor is activated, the formed oxacarbenium ion is stabilized by neighboring participation and forms the cyclic five-membered cation. The acceptor then approaches from the opposite face of the five-membered ring to form the 1,2-*trans*-glycoside.

However, 1,2-*cis* stereoselective glycosylation has remained a challenging mode of glycosylation.[9] Typically, the trial-and-error approach is employed for the optimization of the selectivity and yield of 1,2-*cis* stereoselective glycosylation. In this manuscript, we summarize the recent developments of the concepts and advances in 1,2-*cis* stereoselective glycosylation.

2. SOLVENT EFFECT IN GLYCOSYLATION REACTION

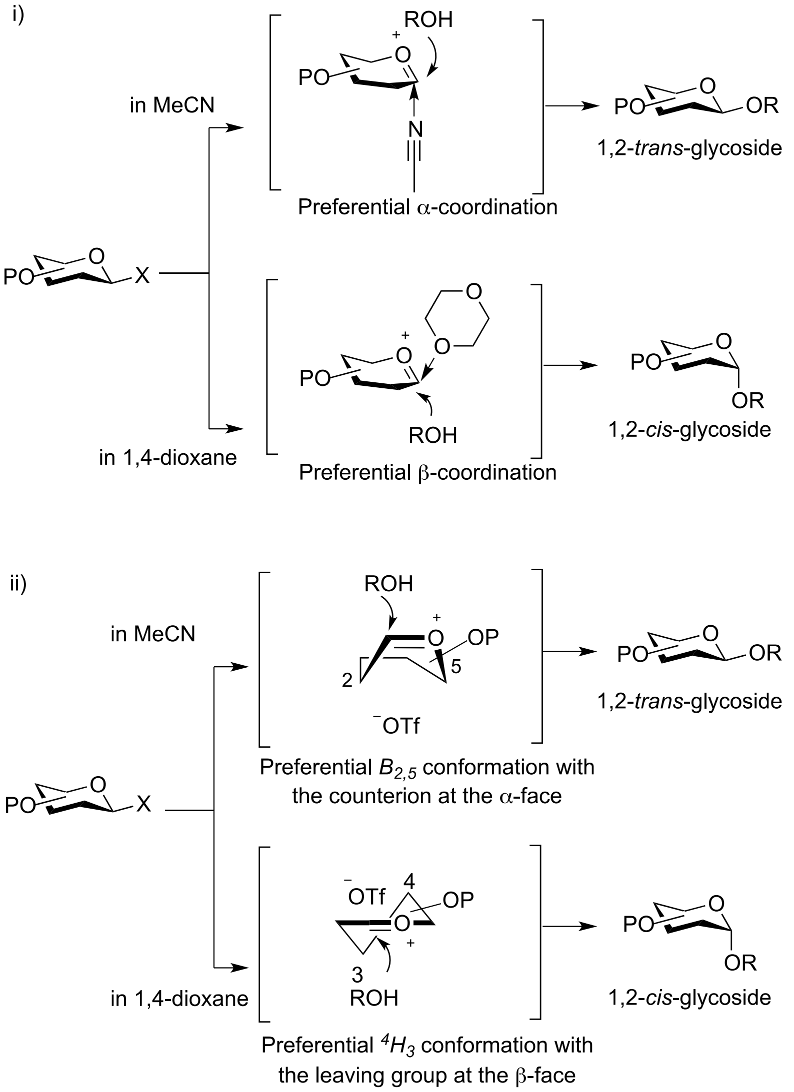
Solvents have been known to exert a strong influence on glycosylations.[10] Generally, 1,2-*cis*-glycosides are obtained in Et_2O and 1,4-dioxane in the absence of a neighboring participation group on the protecting group at the *O*2-position. On the other hand, 1,2-*trans*-glycosides are dominantly obtained in MeCN. These phenomena have been attributed to the preferential coordination of the Et_2O and 1,4-dioxane to the β-face of the ring at the anomeric position of the oxacarbenium cation, whereas MeCN coordinates from the α-face (Scheme 2). Then, the glycosyl acceptor approaches from the face opposite to that of the solvent coordination and forms the glycosyl bond (*solvent-coordination hypothesis*). Yu reported the solvent effect and the significant influence of dilution in an *N*-glycosylation reaction.[11] Kononov proposed the concept of supramers, in which, the aggregation stage of the glycosyl cation and reagents are different at the reaction concentration.[12]

We recently proposed an alternative theory (*conformer and counterion distribution hypothesis*) for the solvent effect based on quantum-mechanical calculations and molecular dynamics.[13] The calculations revealed that the oxacarbenium ion mainly adopts the $^4H_3$ conformation in 1,4-dioxane, whereas the $B_{2,5}$ conformation is dominant in MeCN. The conformation of the oxacarbenium ion and preferential coordination of the counterion position are different in dioxane and MeCN. The acceptor approaches the oxacarbenium ion from the less hindered face to form the glycosyl bond.

While the solvent effect is generally applicable to a large variety of substrates, complete stereoselectivity is challenging to achieve.

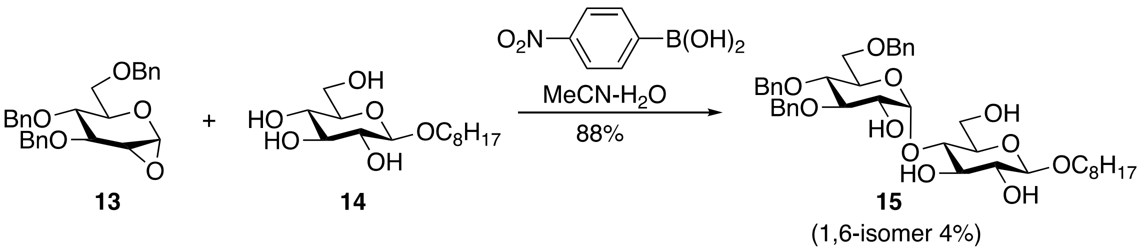
3. 1,2-*cis*-GLYCOSYLATION OF GLUCOSE AND GALACTOSE

Takahashi and Toshima reported a regioselective 1,2-*cis* stereoselective glycosylation mediated by a boronic ester. In this reaction, the 1,2-anhydro-glycosyl donor **13** reacts with a glycosyl diol acceptor via the formation of the acceptor-derived boronic ester.[14] After the initial success, this strategy was further extended to the reaction of the same donor with the minimally-protected acceptor **14** and delivered the α-1,4-glucoside **15** regioselectively in the presence of catalytic amounts of *p*-nitrophenylboronic acid (Scheme 3).[15] The 1,6-linked glucoside, a regioisomer of the product **15**, was suppressed to 4% yield in this reaction. Surprisingly, this reaction proceeds in the presence of water. ^{13}C kinetic isotope effect and density functional theory (DFT) calculations showed that this reaction proceeds via an SNi-type mechanism. The high stereoselectivity of the SNi reaction is reasonable considering the synchronicity of the leaving group activation and the nucleophilic attack of the acceptor.

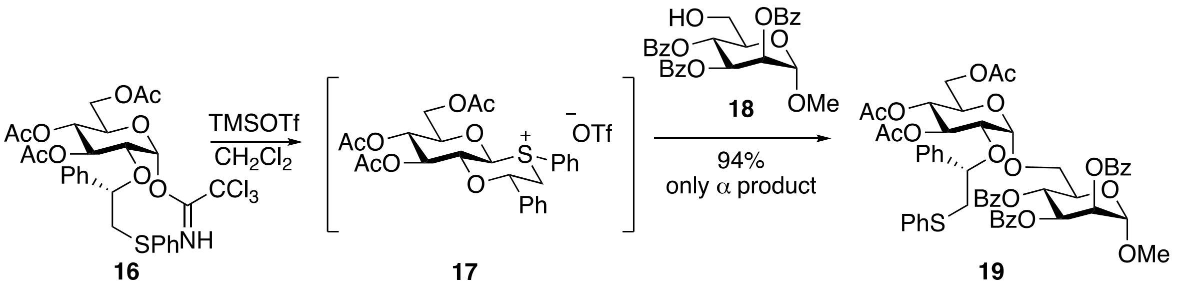


Scheme 2. Solvent effect in glycosylation reaction. i) conventional solvent-coordination hypothesis; ii) conformer and counterion distribution hypothesis based on quantum-mechanical calculations and molecular dynamics

Boons designed the glucosyl donor **16**, which comprises a sulfide moiety at the *O*2-group, that is used as an auxiliary (Scheme 4). Upon activation of the donor, the sulfide group reacts with the cation to form a *trans*-decalin type sulfonium ion due to the absence of an unfavorable gauche interaction and the equatorial phenyl group substitution.[16] Then, the reaction of the acceptor, via stereoinversion at the anomeric center delivers the product. A systematic investigation of the reaction revealed that the presence of an acetyl protecting group at the *O*3 enhances α-selectivity. The acetyl group recruits the acceptor via hydrogen bonding and facilitates the attack at the anomeric center from the α□side.[17] The arylsulfonium ion derived from the oxathiane also gave high α-selectivity.[18]



Scheme 3. Stereoselective and regioselective glycosylation via SNi reaction

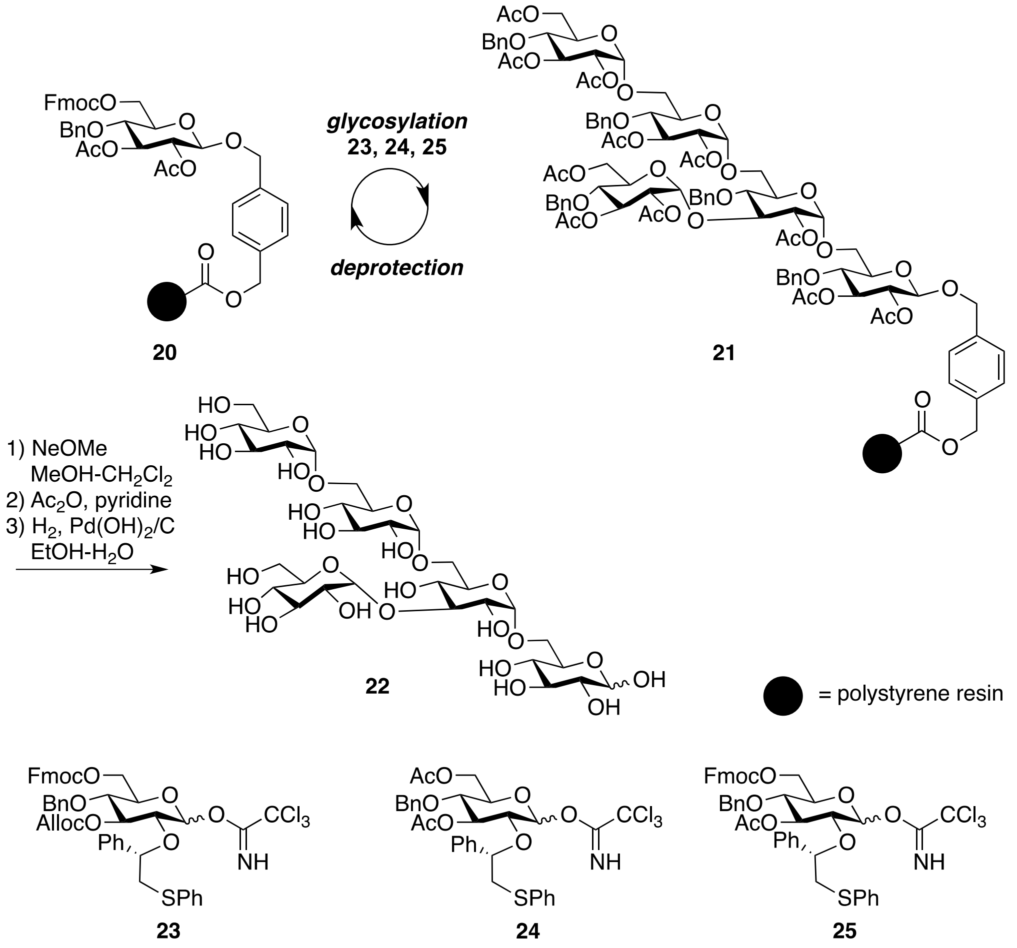


Scheme 4. α-Selective glucosylation through intramolecular sulfonium ion intermediate **17** formation

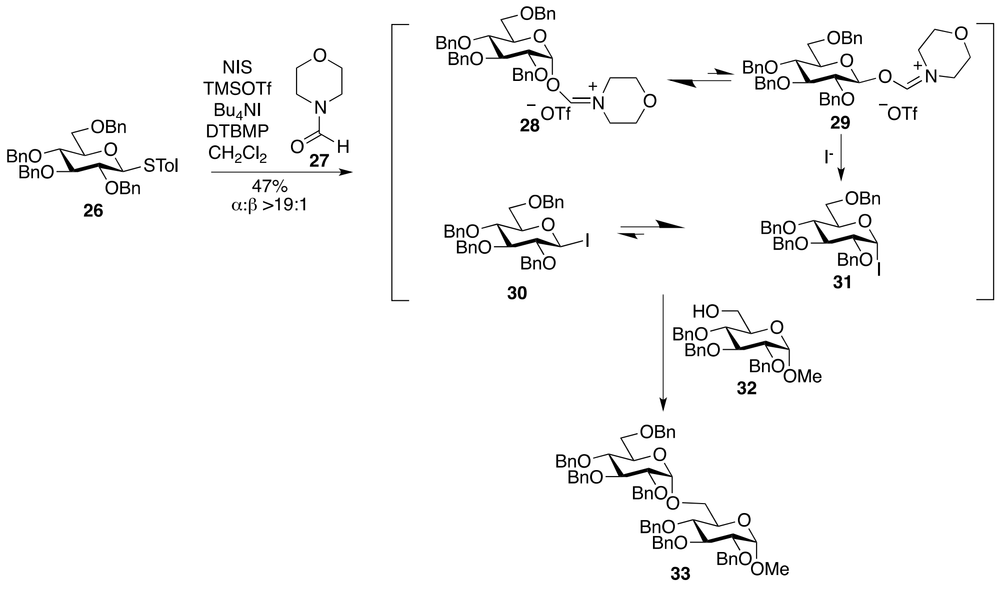
Solid-phase oligosaccharide synthesis has received significant attention for the development of automated oligosaccharide synthesis. Solid-phase oligosaccharide synthesis requires multiple glycosylation reactions and the deprotection of temporary protecting groups. Since the purification of the product after each reaction is not possible on solid-phase synthesis, high stereoselectivity and yield are necessary for solid-phase oligosaccharide synthesis. Due to these reasons, the synthesis of oligosaccharides on solid-phase is normally limited to 1,2-*trans*-glycoside synthesis due to the lack of completely stereoselective 1,2-*cis*-glycoside syntheses (Scheme 5). The sulfonium ion-assisted 1,2-*cis* selective oligosaccharide reaction with the donors **23**-**25** was applied to the synthesis of the branched pentasaccharide **22** isolated from *Streptococcus pneumoniae*.[19] Four α-glucoside containing oligosaccharide **21** was generated on the solid-phase, and the synthesized pentasaccharide **22** was fully characterized by NMR.

Similar to the sulfonium ion-mediated glycosylation, formamide-modulated glycosylation also afforded α-glycosides.[20] Various formamides, such as DMF, *N*,*N*-diisopropylformamide, *N*-formylpiperidine, and *N*-formylmorpholine **27,** were efficient in modulating the reactivity and selectivity. Notably, the imidinium intermediates **28** and **29** were observed by low-temperature NMR. Further, *N*-formylmorpholine enhanced the reaction rate, and the addition of Bu_4NI increased the selectivity

(Scheme 6).[21] The 1,2-*cis* imidinium intermediate **28** and iodide **31** were the dominant intermediates in the ^{1}H-NMR spectra; however, the nucleophile attacks through the highly reactive β-intermediates **29** and **30**.

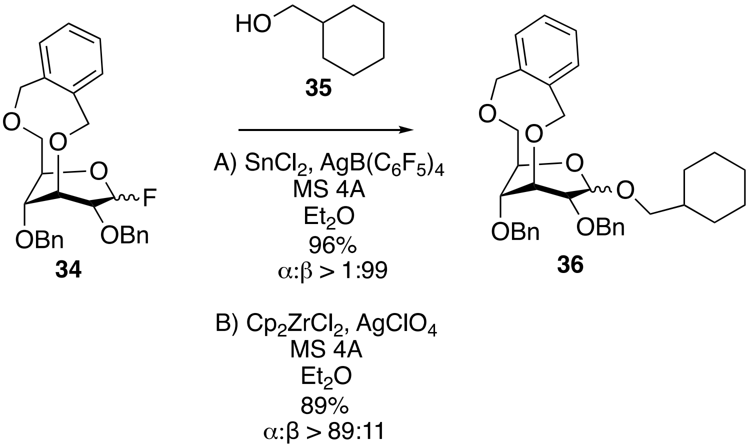


Scheme 5. Solid-phase oligosaccharide synthesis of 1,2-*cis*-glucosides via sulfonium ion-assistance



Scheme 6. Stereoselective α-glucosylation though imidinium and iodide intermediates **28**-**31**

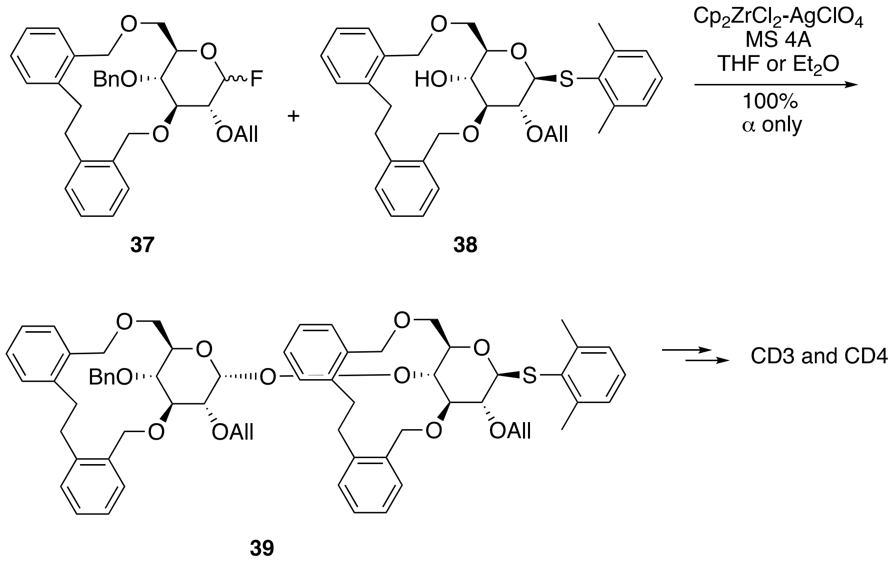
The 3,6-*O*-(*o*-xylylene)-bridged glucose donor exists in an axial-rich conformation. The donor **34** showed β-selectivity when $SnCl_2$-$AgB(C_6F_5)_4$ was employed as an activator through anomerization (Scheme 7).[22] On the other hand, the same donor **34** gave high α-selectivity when the combination of Cp_2ZrCl_2-$AgClO_4$ was used as an activator in the presence of MS 4A in Et_2O.[23] The shift to the β□selectivity in the absence of molecular sieves indicates that molecular sieves may act as acid scavengers. ^{1}H-NMR coupling constants and nuclear Overhauser effect spectroscopy (NOESY) measurement analysis indicated that the 3,6-*O*-(*o*-xylylene) bridge protecting group alters the conformation of the pyranosides. Further, DFT calculations of the corresponding cation showed that the aromatic group of 3,6-*O*-*o*-xylylene shields the cation from the β-face.



Scheme 7. Reagent-controlled stereoselectivity-switching glycosylation

Cyclodextrins (CDs) are a family of cyclic oligosaccharides comprising a macrocyclic ring of glucose subunits joined by α-1,4 glycosidic bonds. Typically, the number of glucose units in CDs range from 6 to 8. While the existence of smaller CDs with less than four glucose subunits, or CD4, has been under discussion, it was also argued that the steric overlap in smaller ring CDs renders the synthesis of CD3 and CD4 highly challenging.[24] The donor **37** was employed for the synthesis of the smallest cyclodextrins, CD3, and CD4 (Scheme 8).[25] The bulky 2,6-dimethylphenylthio group was used for the acceptor **38**, instead of the phenylthio group, to block the attack of the glycosyl cation at the sulfur atom.[26] The conformation of the 3,6-*O*-*o*-xylylene-bridged glucose is highly distorted and exits in the $^5S_1$ conformation in CD3, and in the $^4C_1$-$^2H_1$ conformation in CD4.[27] This distorted conformation of the donor might be suitable for enabling ring closure for the formation of small-ring CDs.

Galactose and *N*-acetylgalactosamine have an axial hydroxy group at C4. The presence of a hindered cyclic protecting group at the 4,6-diol blocks the β-face of the pyranoside ring. For instance, the 4,6-*O*-di-*tert*-butylsilylene (DTBS) protecting group in galactose and *N*-galactosamine showed high 1,2-*cis* stereoselectivity even in the presence of a neighboring functionality on the C-2 position.[28]



Scheme 8. Synthesis of cyclodextrins CD3 and CD4 with conformationally distorted 3,6-*O*-(*o*-xylylene)-bridged glucosyl donor **37**

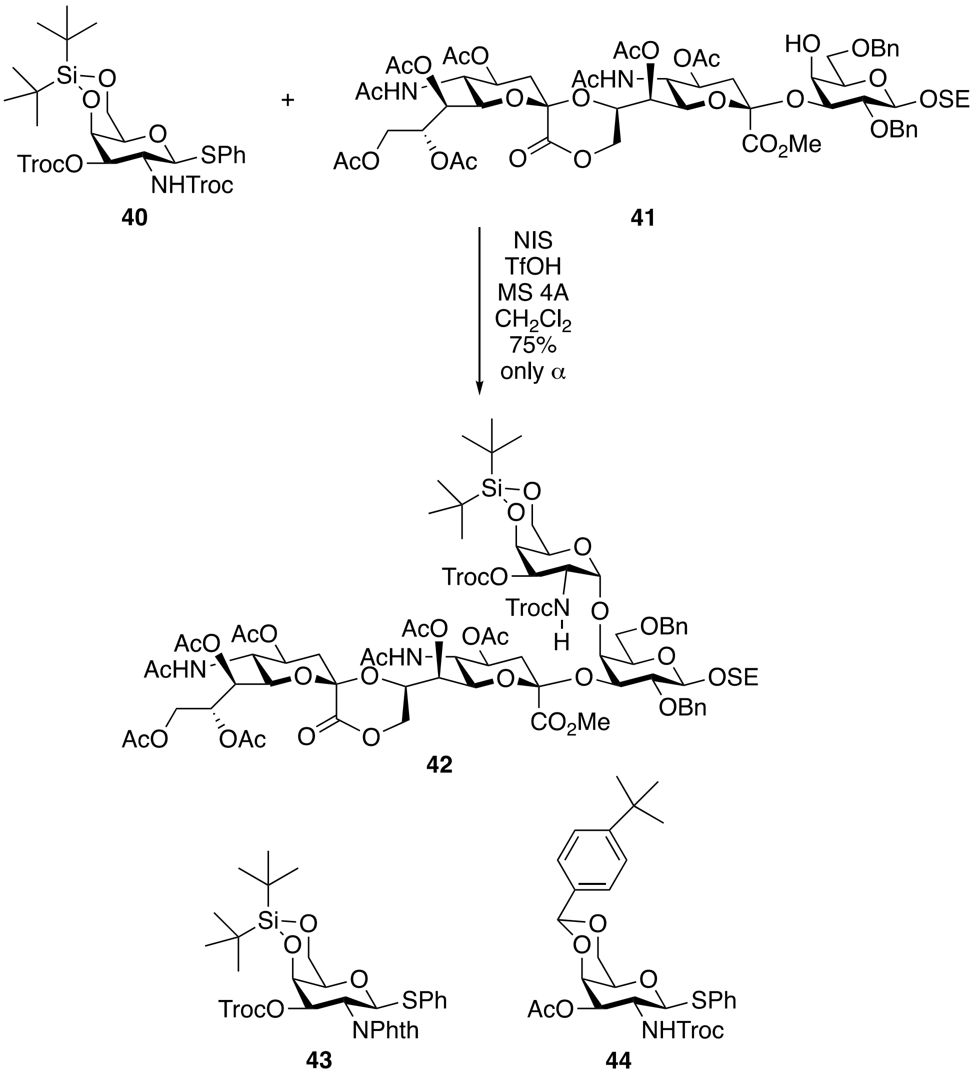
This effect was also observed in the donor **40** comprising the DTBS group, which upon NIS-TfOH activation gave the tetrasaccharide **42** in 75% yield with complete α-selectivity (Scheme 9) despite the presence of the Troc group at C-2. X-ray analysis of compound **43** revealed that the pyranose ring was distorted to a near half-chair, and one of the bulky *tert*-butyl groups of the DTBS moiety blocked the anomeric carbon from the β-face. On the other hand, the donor with the *p*-*tert*-butylbenzylidene group **44** showed β-selectivity.[29]

4. β-MANNOSYLATION AND RHAMNOSYLATION

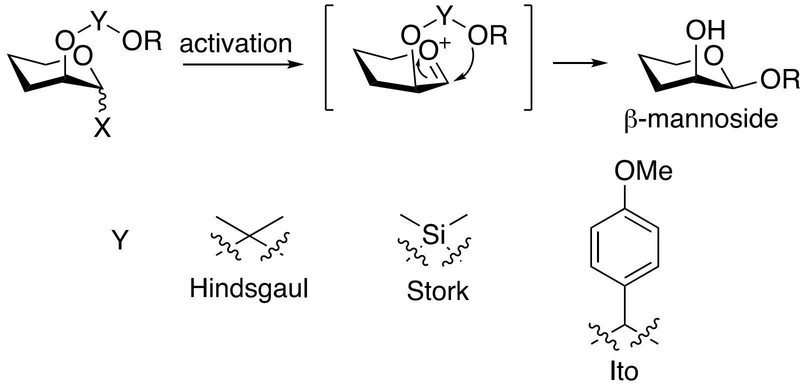
β-Mannosylation has been one of the most challenging topics of carbohydrate chemistry over the past two decades. Because β-mannosides have a 1,2-*cis*-structure and as the equatorial orientation of the *O*-glycoside is against to anomeric effect, stereoselective β-mannosylation is highly challenging.

Hindsgaul,[30] Stork,[31] and Ito,[32] independently reported intramolecular aglycon delivery (IAD) strategies for the synthesis of β-mannosides (Scheme 10). The axial hydroxy group at C-2 was used for tethering the acceptor as a mixed-acetal before activation of the donor. Upon activation, the acceptor, tethered to the mixed-acetal, attacks the anomeric carbon from the β-side, thus preferentially forming the β-mannoside.

The 4,6-*O*-benzylidene acetal protecting group has been reported to play an important role in controlling the stereoselectivity of the β-mannosylation reaction.[33,34]

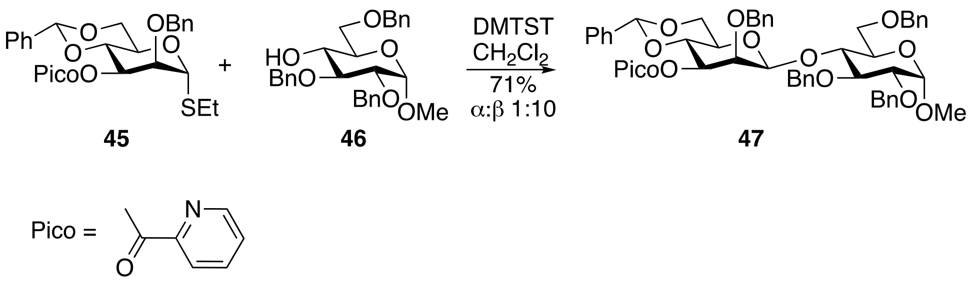


Scheme 9. α-Selective glycosylation with 4,6-DTBS donor **40**



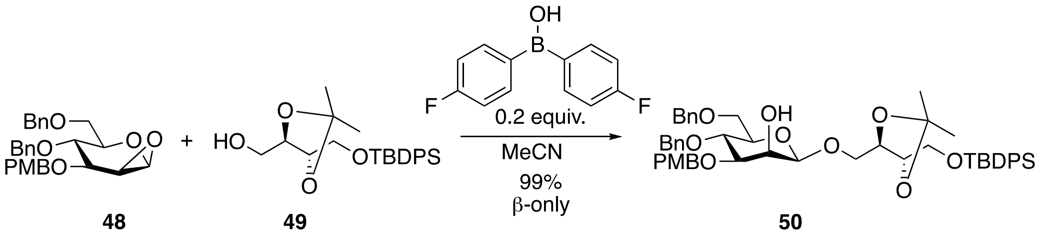
Scheme 10. Intramolecular aglycon delivery strategy for β-mannosylation

Demchenko proposed hydrogen bonding as an alternative for tethered aglycone delivery (Scheme 11). The thioglycoside with the *O*3 picolyl group gave high β-selectivity.[35] Hydrogen bonding between nitrogen atom of picolyl group and hydroxy group of acceptor determined orientation of acceptor approach.



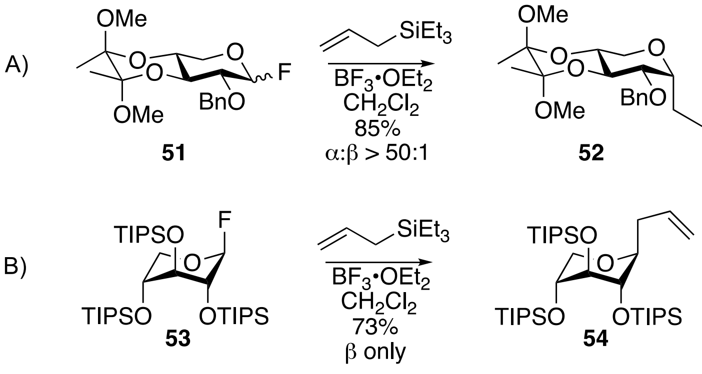
Scheme 11. Hydrogen bond-assisted β-mannosylation

As described in the 1,2-*cis*-glucoside synthesis, the 1,2-anhydromannose **45** upon activation with catalytic amounts of bis-(4-fluorophenyl)boronic acid, reacted with the protected erythritol to form the product in high yield with β-selectivity. A library of mannosylerythritol biosurfactants were synthesized using this method (Scheme 12).[36,37] These examples are notable considering the realization of β-selectivity in the absence of the 4,6-*O*-benzylidene group.



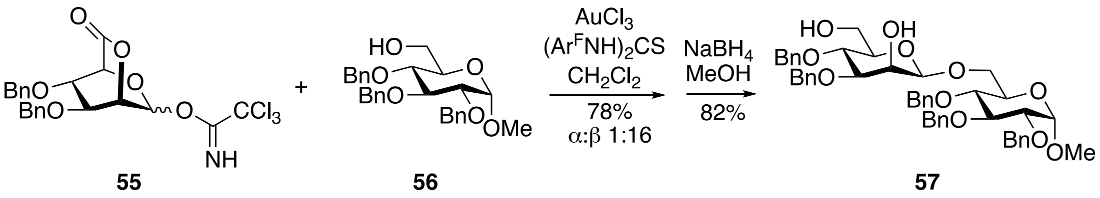
Scheme 12. β-Mannoside synthesis with 1,2-anhydromannose **48** catalyzed by boronic acid

Conformational changes of the donors by virtue of the presence of a bridging hydroxy group has been used for changing the stereoselectivity of glycosylation. Previously, it has been reported that the glycosylation stereoselectivity is influenced significantly by the conformation of the pyranosides. For instance, xylose with the restricted $^4C_1$ conformation gave the α-glycoside in both ionic and radical-mediated *C*-allylations, whereas the $^1C_4$ conformation gave the β-glycoside predominantly (Scheme 13).[38, 39]



Scheme 13. *C*-Glycoside stereoselectivity with conformationally-restricted donors **51** and **53**

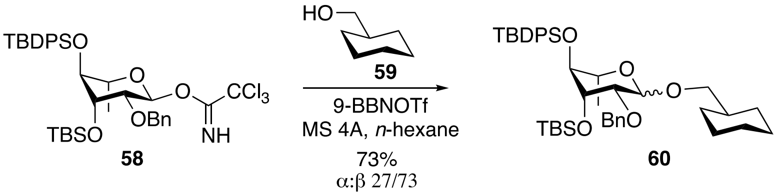
The formation of 2,6- or 3,6-lactone bridges in the mannose series was carried out using 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)/ (diacetoxyiodo)benzene (Scheme 14). The use of the conformationally-inverted mannosyl donor **55**, afforded β-selectivity.[40,41] Using the conformationally inverted mannose donor **55**, β-selectivity was observed.



Ar^F = 3,5-bis(trifluoromethyl)phenyl

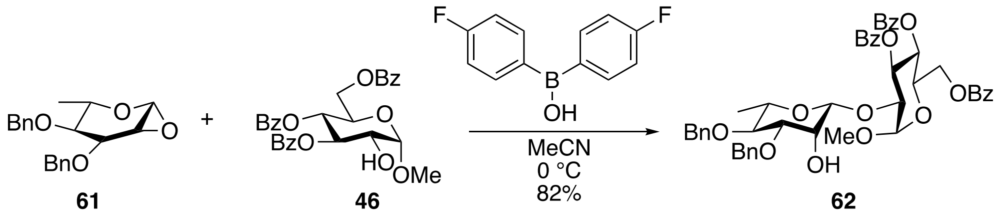
Scheme 14. β-Mannosylation with 2,6-lactone donor **55**

β-L-Rhamnose is often found in antigenic bacterial polysaccharides. The β-L-rhamnosylation is considered more difficult than β-mannosylation. The 4,6-*O*-benzylidene group, that is essential in the mannosylation chemistry, cannot be employed in the rhamnose series because of the 6-deoxy structure of rhamnose. The conformation of rhamnose is rather flexible, and the pyranose is easily flipped to the conformations other than the $^4C_1$. Protection of *O*3 by a TBS group and *O*-4 by a TBDPS of the rhamnoside leads to the facile change of the rhamnoside conformation to $^1C_4$. The rhamnoside donor with the axial substitution rich conformation **58** formed the β-glycoside preferentially (Scheme 15).[42]



Scheme 15. β-Rhamnosylation with conformationally flipped donor **58**

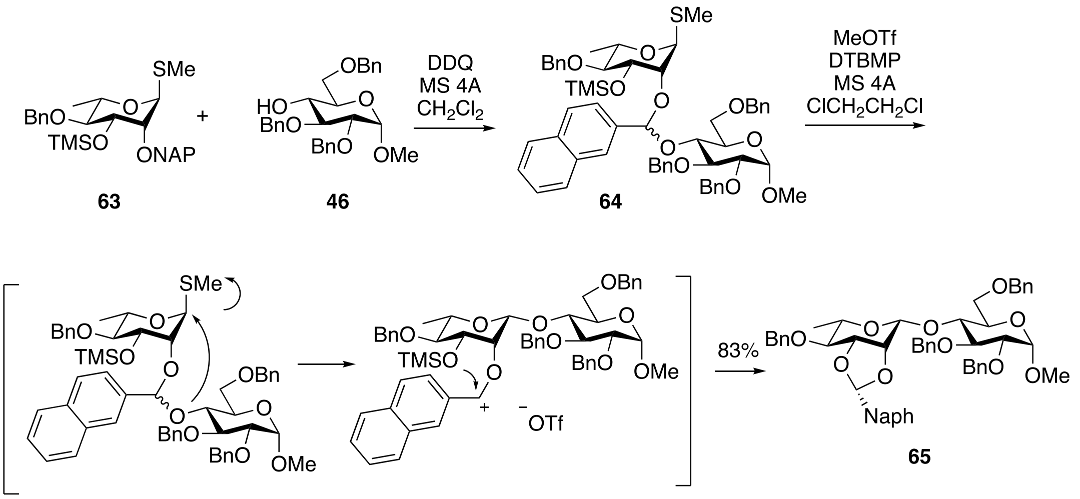
With the successful realization of β-mannosylation without the need for the 4,6-*O*-benzylidene group, a similar approach was attempted in the rhamnose series and the synthesis of the β-rhamnoside was successful using the 1,2-anhydride approach (Scheme 16).[43]



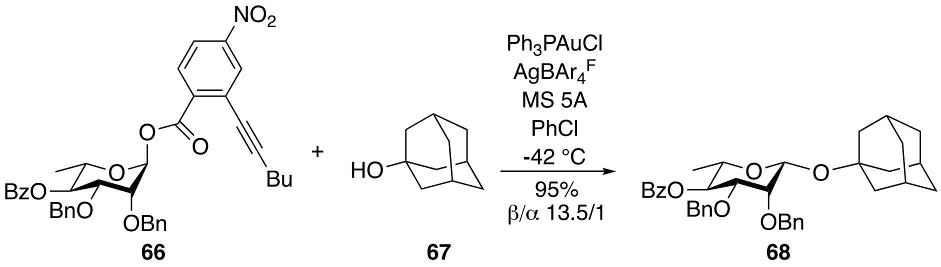
Scheme 16. β-Rhamnosylation with 1,2-anhydrorhamnoside with boronic acid

The 2-naphthylmethyl ether (NAP) mediated intramolecular aglycon delivery methodology also afforded β-rhamnosides in complete stereoselectivity (Scheme 17).[44] The benzylic cation of the NAP is trapped to afford the naphthyl ether when 2-hydroxy group is protected as TMS ether.

Direct β-rhamnosylation with the 2-alkynyl-4-nitrobenzoate leaving group **66** in the presence of the Au catalyst comprising a noncoordinating counter anion was reported (Scheme 18).[45] The β-stereoselectivity realized with this approach was up to 13.5/1 (β/α).



Scheme 17. NAP-mediated IAD strategy for β-rhamnosylation



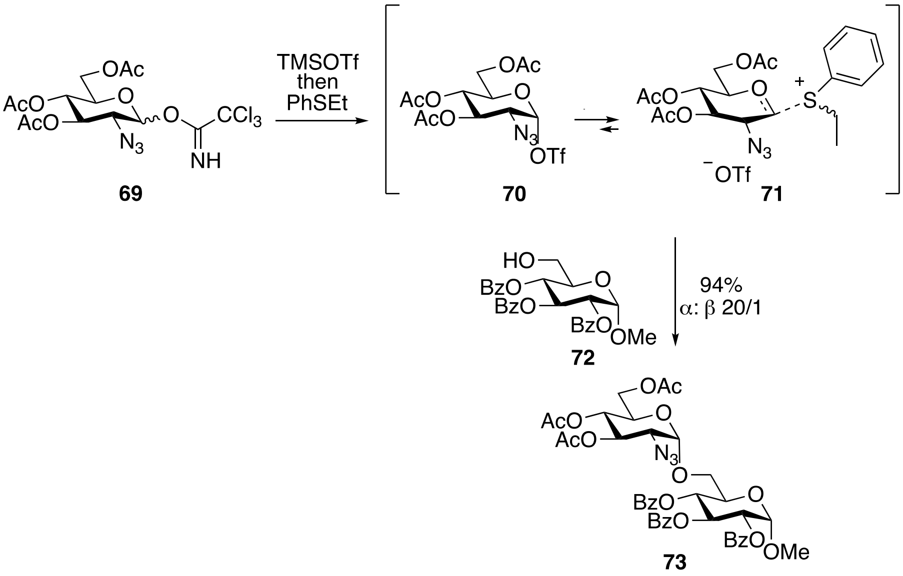
BAr^F = tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate

Scheme 18. β□Rhamnosylation by Au catalyst

5. 1,2-*cis*-2-AMINO-2-DEOXY SUGAR SYNTHESIS

For 1,2-*cis*-aminoglycoside formation, the azide protection of the amino group has been used for over 40 years.[46,47] Unfortunately, the 1,2-*cis* selectivity is moderate when donors carrying the 2-azide moiety are used.[48] Similar to that in the glucose donor, the external sulfide coordinates to an oxacarbenium ion, and afford the α-glycoside exclusively (Scheme 19).[49] The glycosyl intermediates **70** and **71** of this reaction were observed by NMR, and the α-triflate **70**, generated from the imidate **69**, was identified (δ 6.50, $J_{1,2}$ = 3.5 Hz). After the addition of PhSEt, two diastereomeric β-sulfonium ions of **71** were observed with large coupling constants (δ□5.95 and 5.48, $J_{1,2}$ = 10.0 Hz each). The acceptor attacks the sulfonium ion in a stereo-conversion manner to give the α-glycoside **73**.

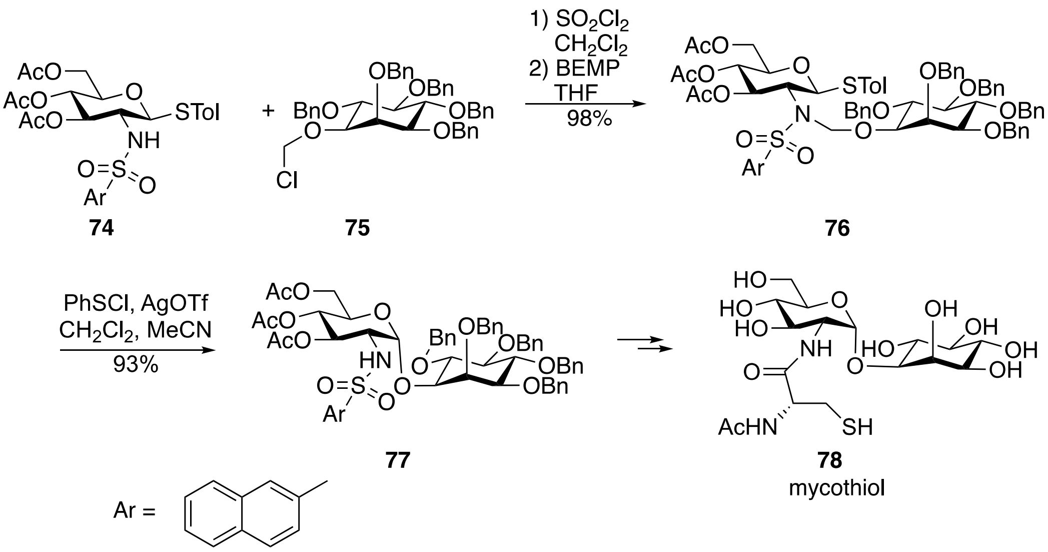
The IAD strategy is not very common in 2-amino-2-deoxy sugars. However, the (*N*-arylsulfonyl)glucosamine donor comprising a methylene linker was reported, and the strategy was successfully applied for the synthesis of mycothiol **78** (Scheme 20).[50]



Scheme 19. Additive effects in glycosylation reactions of 2-azide-2-deoxy sugars

To overcome the challenges in the formation of the 1,2-*cis*-glycosylation products in the 2-deoxy series, Kerns reported the use of pyranosides **79** carrying the 2,3-*trans*-carbamate group, which showed high selectivity in the 1,2-*cis*-glycosylation reaction (Figure 2).[51] While high 1,2-*cis* selectivity was realized with Kerns' donor, the approach still has some disadvantages. For instance, the reagent or the activated glycosyl cation are added to the nitrogen atom of the carbamate group.[52] To address this limitation, we proposed the use of a 2,3-*trans*-carbamate group with a benzyl-protected amine moiety as the glycosyl donor **80**.[53] In addition, the Ac protected pyranoside congener **81** has also been reported.[54,55] The unique character of the *N*-Ac carbamate-containing pyranosides will be described later.

The prepared donor **82** showed high 1,2-*cis* selectivity with a broad scope of acceptors under various glycosylation conditions at temperatures ranging from 0 °C to room temperature (Scheme 21).[56] The GlcNAc-α1,4-glucronic acid/GlcNAc-α1,4-iduronic acid saccharide is a repeating unit of heparin/heparan sulfate. High stereoselectivity was observed when the protected iduronic acid **83** was used as the acceptor. In addition, high stereoselectivity was again observed with protected glucuronic acid. This donor was also applied to short poly(ethylene glycol) methyl ether (MPEG)-supported acceptor, and the disaccharide was obtained in high yield with complete stereoselectivity. The observed high 1,2-*cis* selectivity was determined kinetically, and the anomerization did not occur under the conditions. The β-disaccharide was recovered unchanged under the glycosylation reaction conditions.



Scheme 20. Mycothiol **78** synthesis via IAD strategy

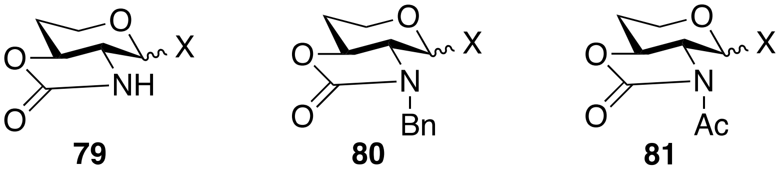
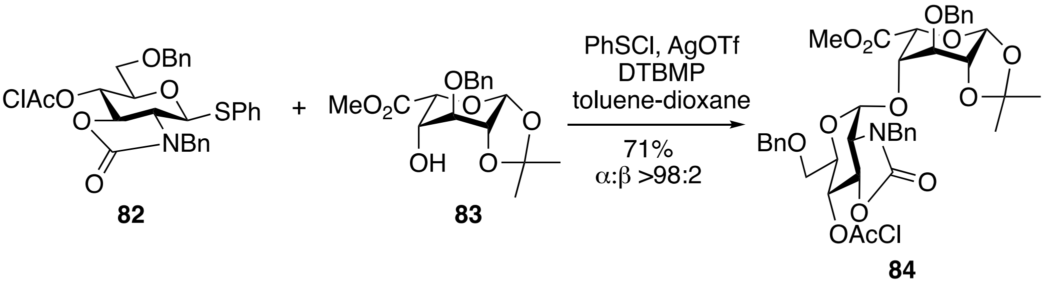


Figure 2. 2,3-*trans*-Carbamate carrying pyranosides



Scheme 21. α-Glycosylation of GlcNAc using 2,3-*trans*-carbamate

6. SYNTHESIS OF ANTI-*HELICOBACTER PYLORI* OLIGOSACCHRIDE

N-Acetylglucosamine capped core-2 branched-type *O*-linked glycan **85a** oligosaccharide is known to inhibit the growth of *Helicobacter pylori* (Figure 3).[57] The α-1,4-GlcNAc group at the non-reducing terminus is essential for the growth inhibition of *H. pylori*, and the antibiotic activity of **85a** is believed to inhibit the synthesis of the cholesteryl-α-glucoside, which is an important component of the cholesteryl-α-glucoside.

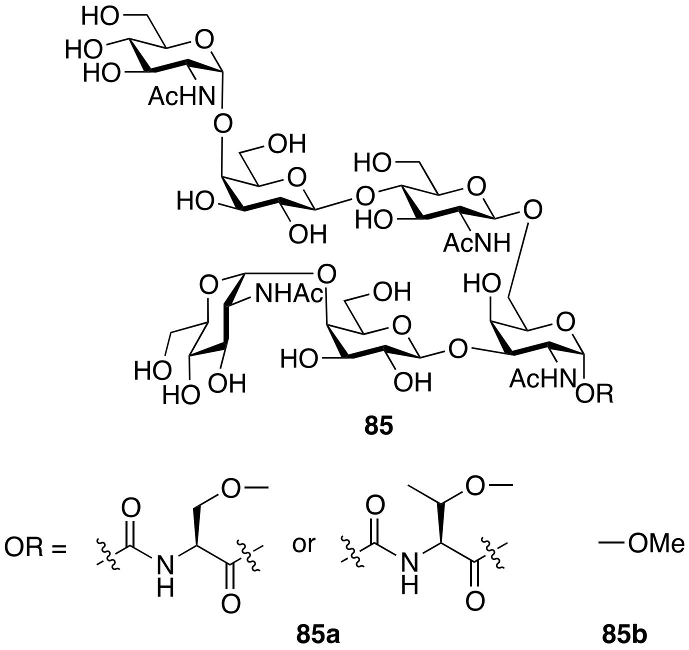
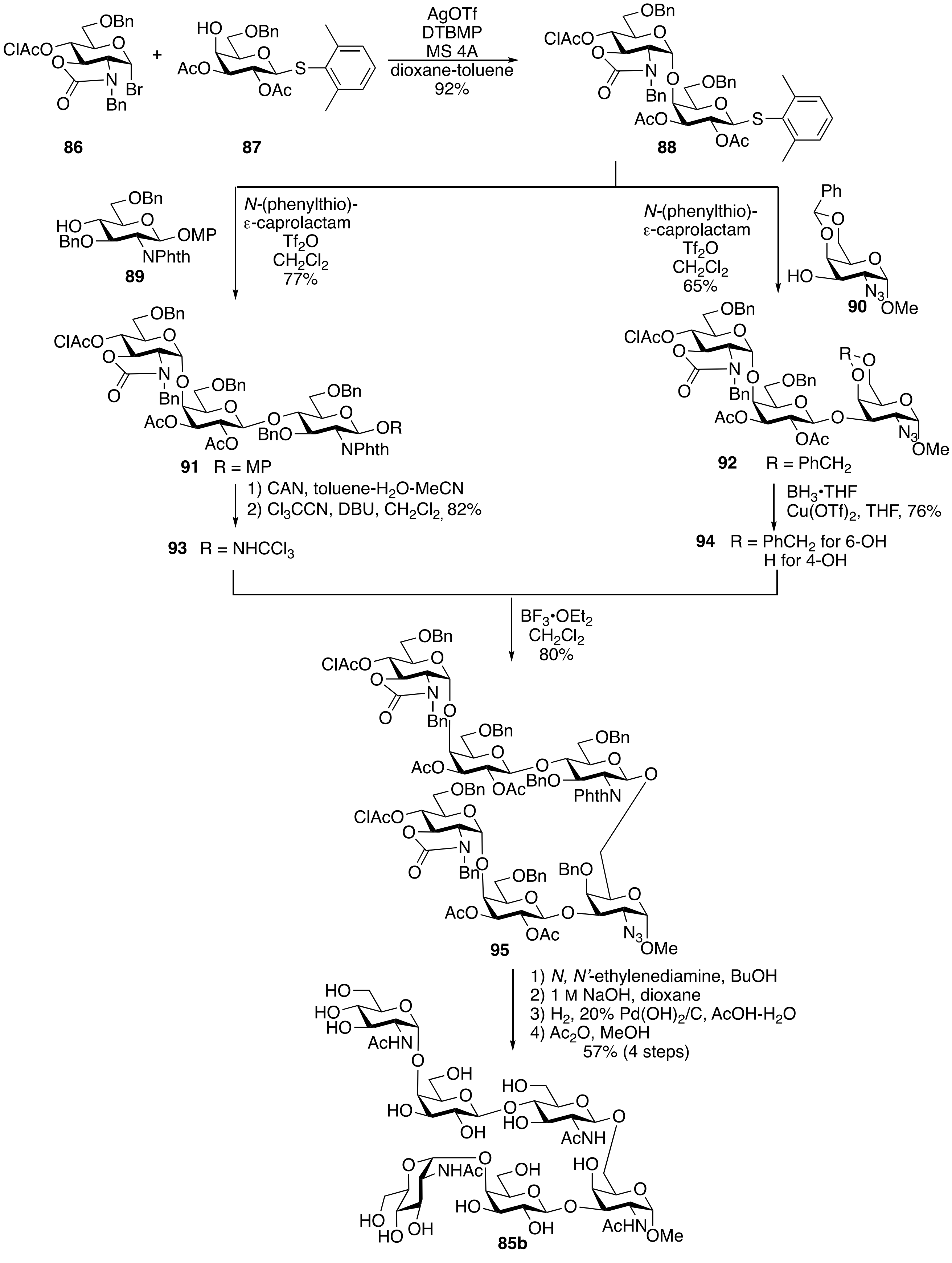


Figure 3. Structure of anti-*Helicobacter pylori* oligosaccharide

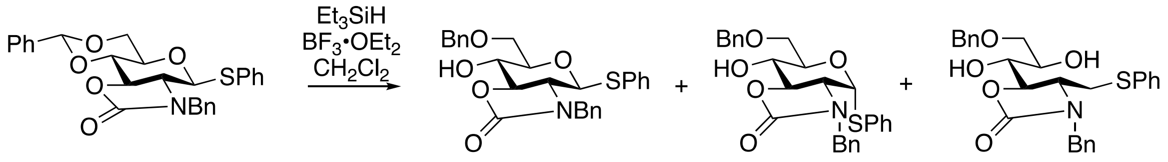
Using our *N*-benzylcarbamate donor, we achieved the synthesis of the corresponding methyl glycoside **85a** for the first time.[58] The bromide **86** was activated in the presence of AgOTf and reacted with the thioglycoside acceptor **87** to furnish the disaccharide **88** with complete 1,2-*cis* stereoselectivity in 92% yield (Scheme 22). The disaccharide **88** was then directly activated using *N*-(phenylthio)-ε-caprolactam-Tf_2O[59] to prepare the trisaccharides **92** and **93**. The trisaccharides were transformed to the donor **93** and acceptor **94**, respectively. A [3+3] glycosylation reaction between **93** and **94** mediated by BF_3•OEt_2 gave the hexasaccharide **95** in 80% yield. The hexasaccharide **85b** was obtained after sequential deprotection reactions.



Scheme 22. Synthesis of anti-*Helicobacter pylori* oligosaccharide using *N*-benzyl-2,3-*trans*-donor **86**

7. ENDOCYCLIC CLEAVAGE REACTION

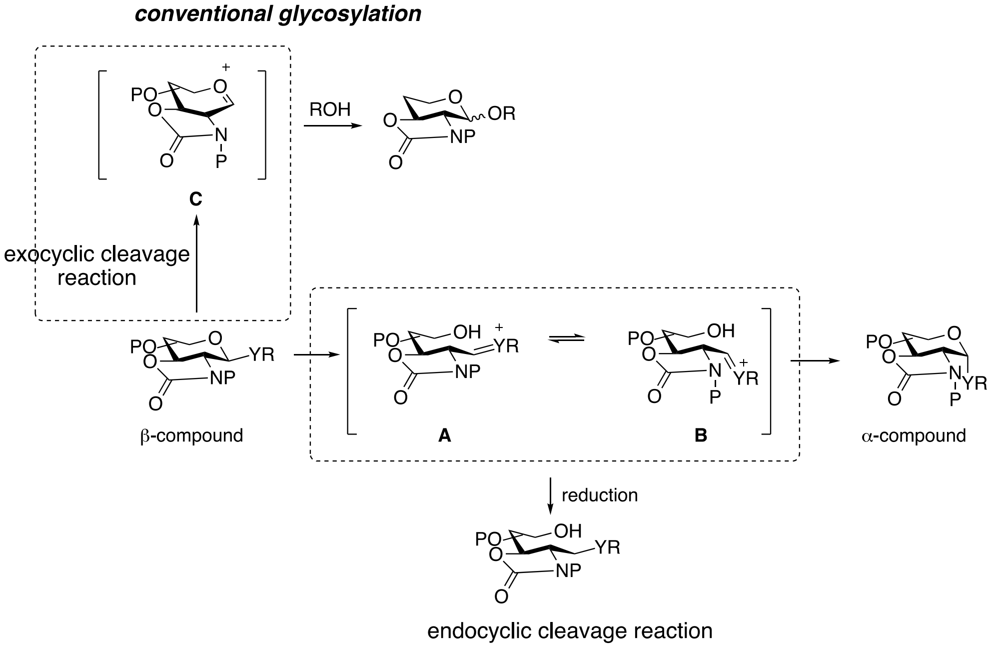
We noticed that the introduction of the 2,3-*trans*-carbamate group causes significant anomerization in the presence of Lewis acids.[60] During the benzylidene acetal cleavage of compound **96**, the α-thioglycoside **98** was obtained in 53% yield together with diol **99** in 11% yield, instead of the expected β-glycoside **97** (Scheme 23). The formation of compound **99** is caused by the reduction of the acyclic cation A and B generated by the Lewis acid (Scheme 24). The recyclization of cation A and B afforded the α-anomer. Since Emil Fischer's first report on the glycosylation reaction,[61] conventional glycosylation reactions have proceeded though the cyclic oxacarbenium ion intermediate C.



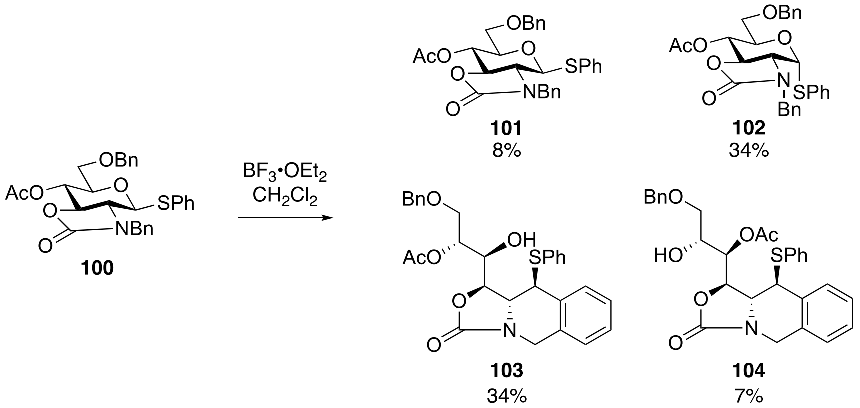
96 **97** 0% **98** 53% **99** 11%

Scheme 23. Anomerization reaction of pyranoside bearing 2,3-*trans*-carbamate **96** in the presence of Lewis acid

Another evidence of the endocyclic cleavage is the intramolecular Friedel-Crafts reaction (Scheme 25). Treatment of the β-thioglycoside **100** with BF_3•OEt_2 gave the corresponding α-thioglycoside **102** together with the intramolecular Friedel-Crafts reaction products **103** and **104**.



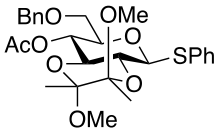
Scheme 24. Exocyclic and endocyclic cleavage reactions



Scheme 25. Evidence of endocyclic cleavage-intramolecular Friedel-Crafts reaction

Although efforts to prove the endocyclic cleavage have been reported in the late 1980s, it was concluded that endocyclic cleavage reaction is a minor component of the reaction. Through our work, we clearly showed the evidence for endocyclic cleavage reaction by capturing the acyclic cation.

The endocyclic cleavage reaction is often discussed in terms of stereoelectronic effects.[62-65] Considering the stereoelectronic effect theory, it is necessary for the $^4C_1$ conformation of the β-anomer to change before the hydrolysis to maximize the overlap of the oxygen lone pair. If the stereoelectronic effect is dominant in our endocyclic cleavage reaction system, the rigid, conformationally locked $^4C_1$ structure of compound **105** should undergo anomerization, which was never the case (Figure 4). Computational analysis revealed that the strain caused by the presence of the 2,3-*trans*-carbamate group is the major factor for the endocyclic cleavage reaction, and stereoelectronic effects are secondary factors, as revealed in our case by the quantum-mechanical calculations.[66]



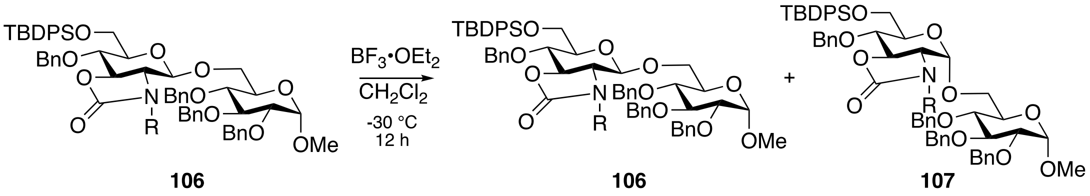
105

Figure 4. Endocyclic cleavage-free $^4C_1$ locked pyranosides

Endocyclic cleavage of glycosides has been reported as early as 1941,[67] and normally strong Lewis acids such as $SnCl_4$ and Me_2BBr are required to carry out this reaction.[68] Inspired by our results, several groups reported endocyclic cleavage in several systems. Murphy reported that glucuronic acid and galacturonic acid anomerized in the presence of $TiCl_4$ and $SnCl_4$, respectively.[69,70]

Sulfated and sialylated pyranosides also undergo endocyclic cleavage, and the rearrangement from pyranosides to furanosides has also been reported.[71-73]

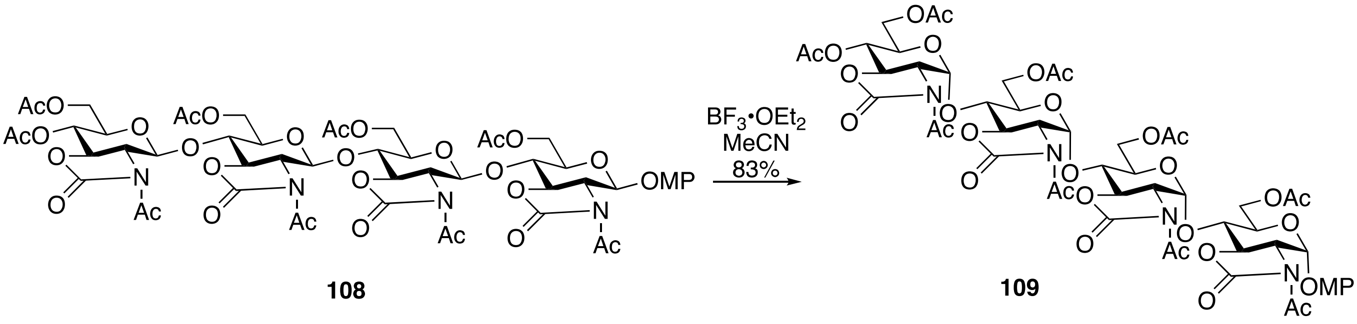
For complete anomerization towards the α-anomer, we investigated the relationship between groups employed for the substitution of the nitrogen in the 2,3-*trans*-carbamate to study their influence on the anomerization tendency (Table 2). The presence of alkyl groups, such as Bn (entry 1), gave minor anomerization, whereas the methoxycarbonyl group shifted anomerization toward the α-compound (entry 3). The acetyl group gave the most feasible and rapid anomerization reaction (entry 4).



entry	R	β-compound	yield (%)	α-compound	yield (%)
1	H	**106a**	86	**107a**	0
2	Bn	**106b**	90	**107b**	5
3	CO$_2$Me	**106c**	21	**107c**	73
4	Ac	**106d**	0	**107d**	88

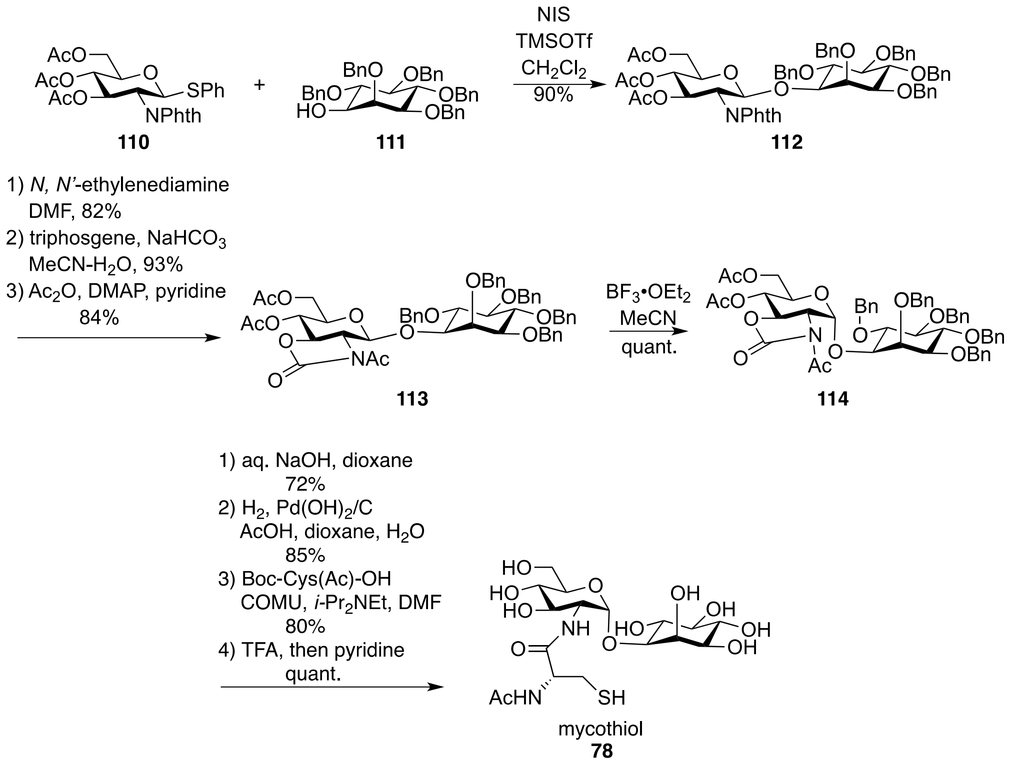
Table 2. Relationship between anomerization and substituent on the nitrogen of 2,3-*trans*-carbamate group

In conventional glycosylation reactions, the reaction proceeds through the formation of the cyclic cation via the exocleavage reaction. Further, in conventional glycosylation reactions, the configuration at the anomeric center is always established step-by-step after each glycosyl bond formation. On the other hand, in the endocyclic cleavage reaction, the configurations at the multiple anomeric centers can be changed post glycosylation. We demonstrated this unique reactivity by changing the configuration at four anomeric centers in a single transformation. The chemically-synthesized tetrasaccharide **108** with β-configuration at all anomeric centers was transformed to the corresponding tetrasaccharide **109** in the presence of BF$_3$•OEt$_2$ in 83% yield (Scheme 26). The α-configuration at anomeric centers was confirmed by ^{1}H-NMR, as evidenced by the small coupling constants. Further, solvent effects were significantly observed in the anomerization reaction.[74]

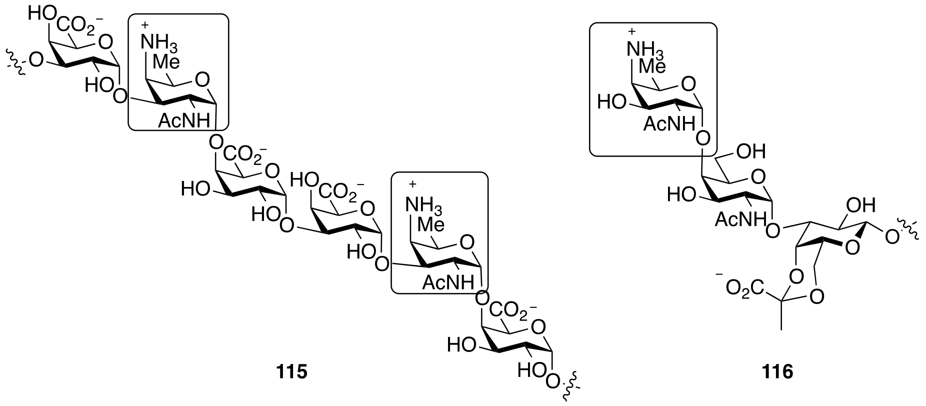


Scheme 26. Anomerization of tetrasaccharide **108** to **109**

Mycothiol **78** is a low-molecular-weight thiol found as a major component in most actinomycetes, including *Mycobacteria* and *Streptomycetes*, and is necessary for maintaining a reducing intracellular environment for protection against foreign electrophilic agents (e.g., oxidants, radicals, and drugs) in Gram-positive bacteria. While several synthetic approaches to this molecule have been reported,[75-79] we attempted the synthesis of mycothiol **78** by applying the endocyclic cleavage approach (Scheme 27). The glycosylation reaction with the optically-resolved tetra-*O*-benzyl-protected inositol **111**[80] and the phthalimide protected donor **112** gave the glycosylation product **118** with β-selectivity through neighboring group participation. After the removal of the phthalimide group and subsequent introduction of the *N*-acetylcarbamate moiety, the anomerization reaction was conducted with BE_3•OEt_2. Finally, acetyl group migration afforded mycothiol **78**.



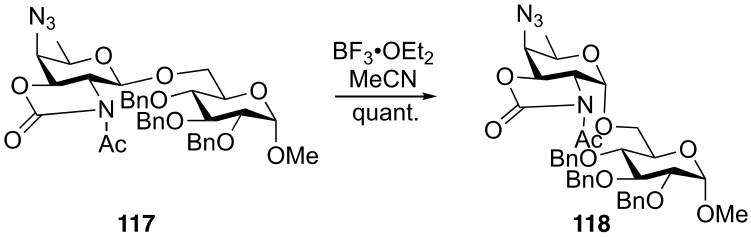
Scheme 27. Mycothiol **78** synthesis via endocyclic cleavage reaction



115 **116**

Figure 5. AAT-containing oligosaccharide in bacterial capsular polysaccharide glycans

The 2-acetamido-4-amino-2,4,6-trideoxy-α-D-galactopyranoside, known as ATT, is often found in bacterial capsular polysaccharide glycans as an α-glycoside (Figure 5).[81] We also applied the endocyclic cleavage reaction strategy for carrying out anomerization to prepare ATT. The 4-azide containing disaccharide **117** was similarly anomerized in the presence of $BF_3•OEt_2$ in a quantitative fashion (Scheme 28).[82]

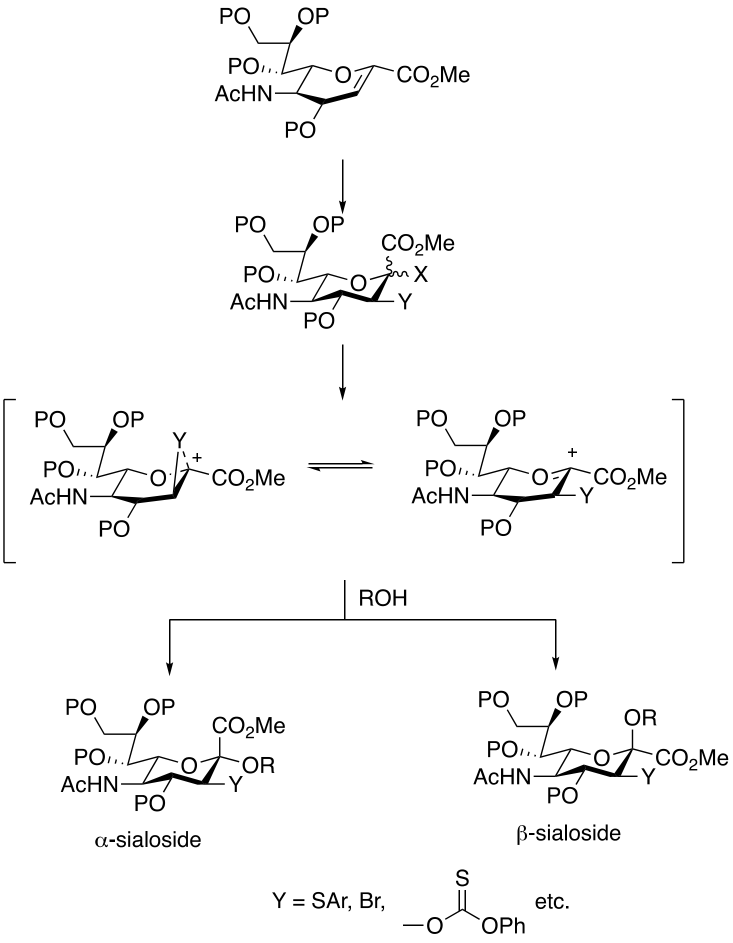


117 **118**

Scheme 28. Anomerization reaction of ATT-containing disaccharide

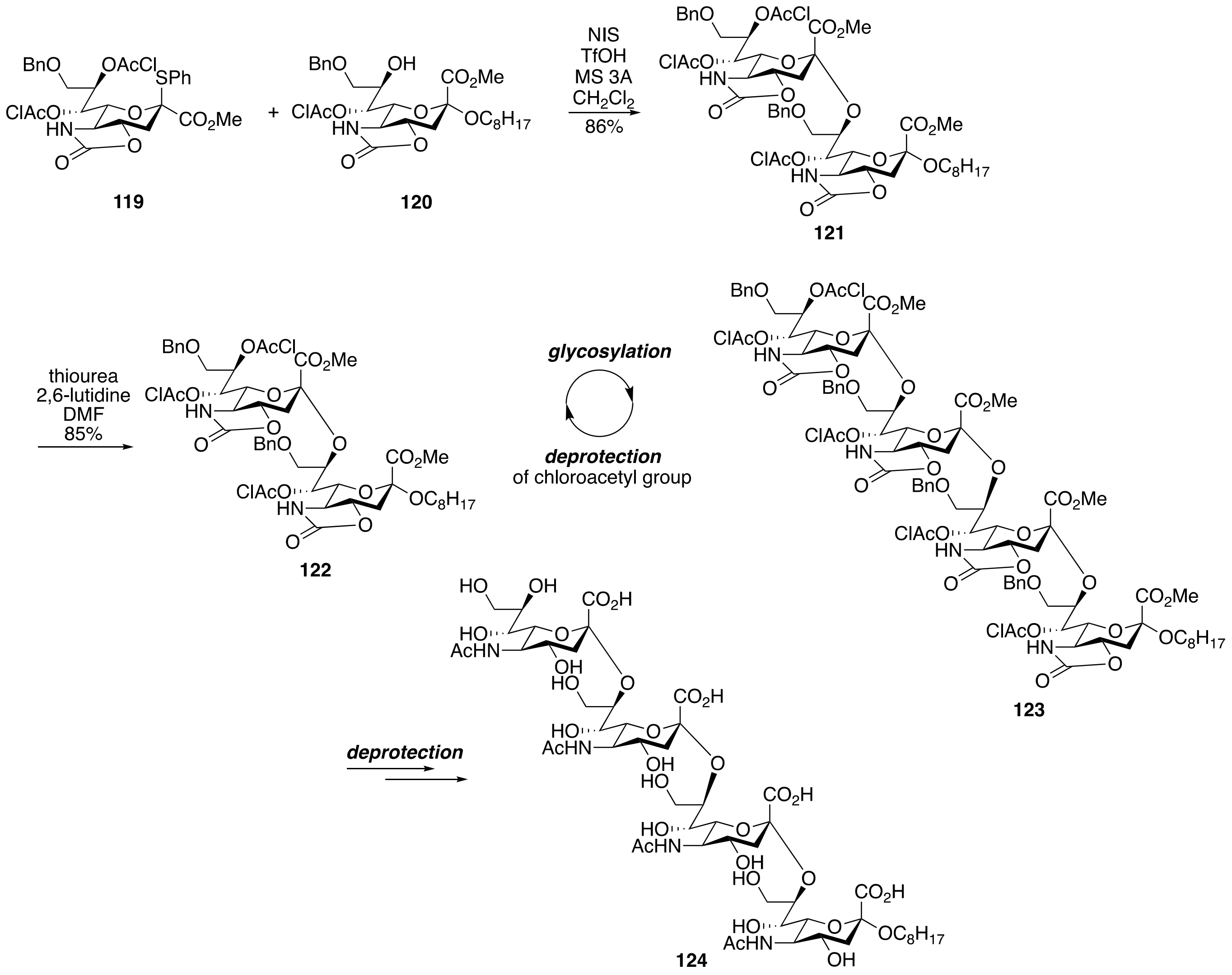
8. α-SIALIC ACID (*N*-ACETYLNEURAMINIC ACID) SYNTHESIS

Sialic acids are usually found in the terminal positions of oligosaccharides. The most abundant of these linkages include the α-(2,3) linkage to galactose, α-(2,6) linkages to galactose and *N*-acetylgalactosamine, and the α-(2,8) linkage to sialic acid. Stereoselective α-glycosylation is also one of the most difficult glycosylations, because of the 3-deoxy-2-ketoaldonic acid structure of the glycan. Further, the electron-withdrawing carboxyl group reduces the glycosylation reactivity, and the anomeric effect produces the β-isomer. In the conventional sialidation methods, the acetonitrile solvent effect has been employed for α-sialidation.[83] Previously, α-sialidations were reported mainly based on anchimeric assistance by auxiliaries at C3 (Scheme 29),[84-86] wherein the acceptor approaches from the opposite face of the group participating in the anchimeric assistance.



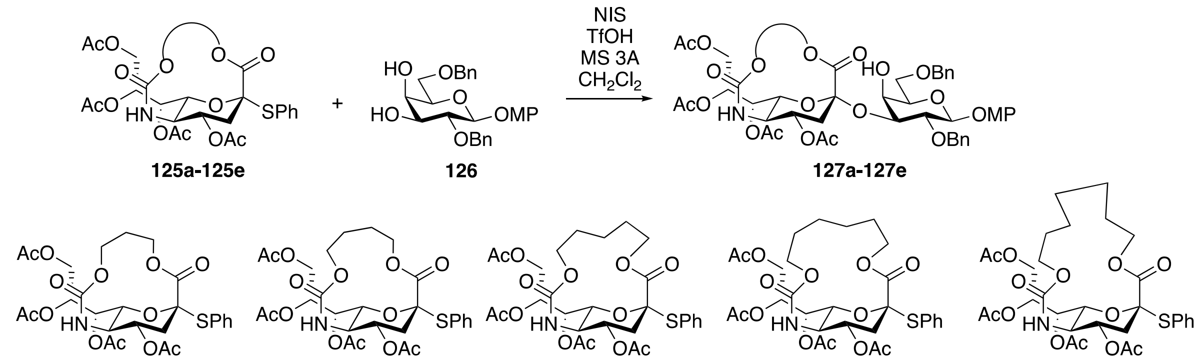
Scheme 29. Outline of α-sialidation by anchimeric assistance from C-3

Another approach for α-sialidation is the conversion of the acetamide group at the C5 position of the sialyl donor.[87-91] The most successful among such modifications is the synthesis of the *O*4,*N*5-carbonyl protected donor (Scheme 30). The donor **119** gave the sialyl disaccharide **121** in 86% with complete α-selectivity.[92] Notably, the high α-selectivity is achieved even in the absence of acetonitrile in the reaction medium. Furthermore, the high yield was also remarkable because the C8 hydroxy group is known to be less reactive. Importantly, the formation of the *O*4,*N*5-carbonyl group reduces the steric hindrance around the C8 hydroxy group to a minimum. Using the donor **119**, α(2,8)-linked sialyl tetrasaccharide **124** was synthesized by iterative glycosylation and the deprotection of the tentative chloroacetyl group sequence, and final deprotection.



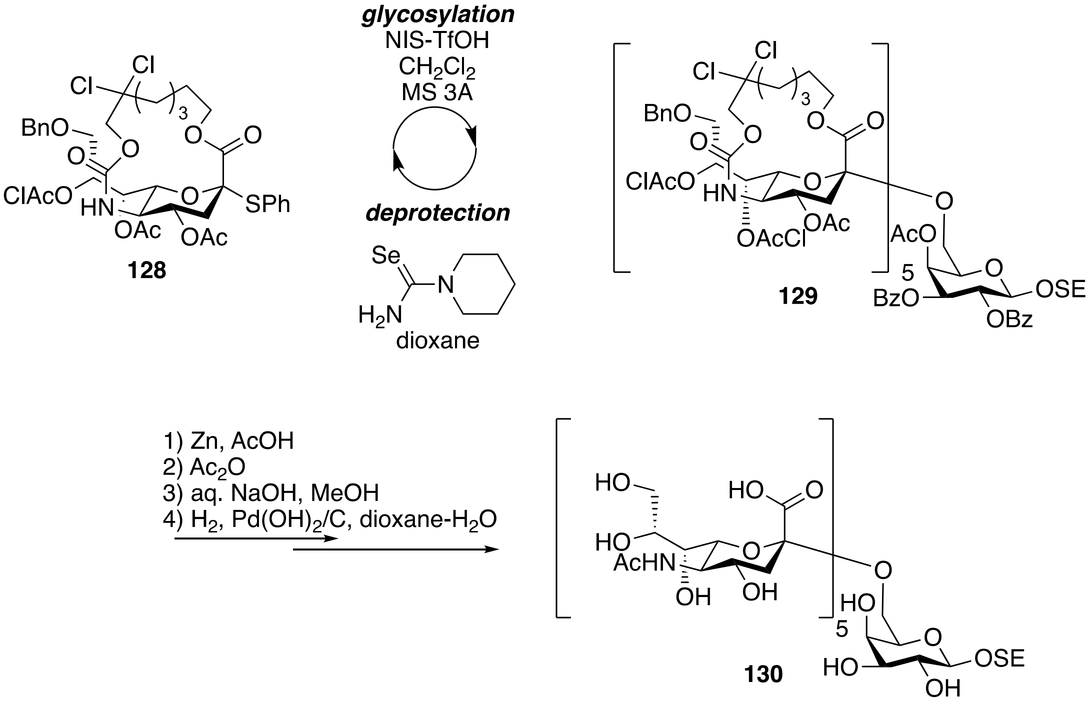
Scheme 30. Tetra-α-(2,8)-sialic acid synthesis by *O*4,*N*5-carbonyl protected sialyl donor **119**

In another approach to α-stereoselective glycosylation, the C5 amino group and C1 carboxylic acid of sialic acid were tethered using a medium-sized ring.[93] Both the bicyclo[8.2.2] **125a** and the bicyclo[9.2.2] system-donor **125b** could not be activated under the typical conditions, because the generation of the bridgehead carbocation is highly challenging, which is well-known as the Bredt's rule. However, as the ring-size increased, the bicyclo[12.2.2] donor **125d** could be activated at -40 °C and gave the disaccharide **127d** in 83% yield, likely due to the increased conformational flexibility (Scheme 31). The upper face of the oxacarbenium cation is blocked by the ring, due to which the acceptor approaches only from the α-side. The donor **127** was further modified by the introduction of a 2,2-dichloroethoxycarbonyl moiety in the tether to enable selective cleavage by Zn reduction (Scheme 32). The utility of donor **128** was demonstrated by the synthesis of the α-(2,8)-containing oligosialoside **130**.



donor	125a	125b	125c	125d	125e
product	127a	127b	127c	127d	127e
	no reaction 0 °C, 6 h	trace < 1% 0 °C, 6 h	18% 0 °C, 6 h	18% -20 °C, 24 h	83% -40 °C, 6.5 h

Scheme 31. Reactivity of alkyl chain-tethered sialic acid donors **125**



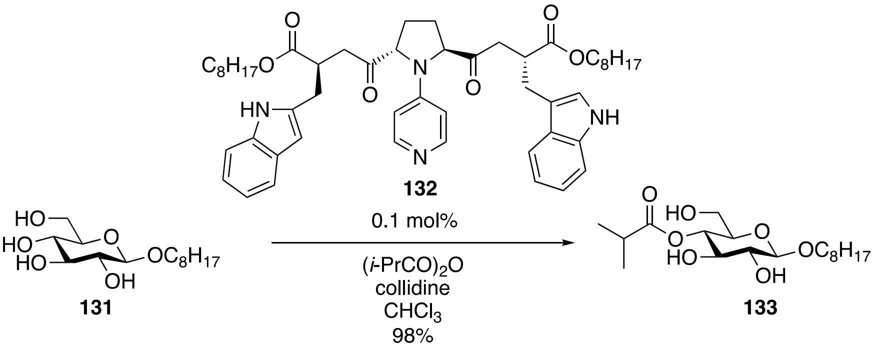
Scheme 32. Oligosialic acid synthesis using donor **128**

9. GLYCOSYLATION WITH MINIMALLY PROTECTED ACCEPTORS AND SITE-SPECIFIC ACYLATION METHODOLOGY

Carbohydrates comprise multiple hydroxy groups of similar activity. Thus, multi-step protection/deprotection is required for carrying out regioselective glycosylation. Recently, regioselective and stereoselective protection and glycosylation reactions with unprotected and partially protected carbohydrates as substrates have been reported.[94]

Site-selective protection of one of the multiple hydroxy groups of a sugar is useful. Kawabata developed a highly effective C2 symmetric organocatalyst **132** for such a purpose (Scheme 33).[95] The low 0.1 mol%

loading of the organocatalyst **132** was sufficient to prepare the 4-acylated glucose in 99% yield. Remarkably, the less reactive 4-OH is acylated in the presence of the highly reactive primary hydroxy group, probably because of the highly precise molecular recognition between the substrate and the acylated catalyst.



Scheme 33. Regioselective acylation with organocatalyst **132**

cis-Diols are activated by boronic acids, which enables site-selective acylations. Boronic esters of diols deactivate the reactivity of the diol; however, the tri-coordinated cyclic organoboronic esters attenuate the nucleophilicity of the boron-bound oxygen atoms by the flow of the electron lone-pairs of the oxygens into empty p-orbital of the boron atom (Figure 6). Taylor and Makino independently reported the organic borate-catalyzed site-selective acylation (Scheme 34).[96,97]

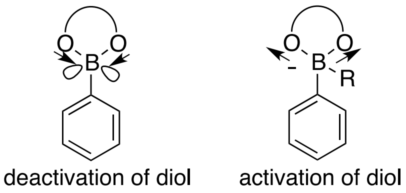
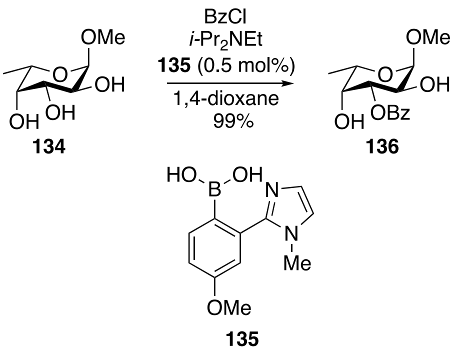
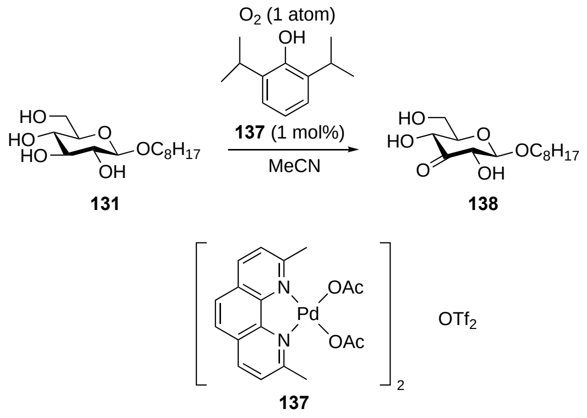


Figure 6. Activation and deactivation of diols



Scheme 34. Site-selective acylation catalyzed by boronic acid

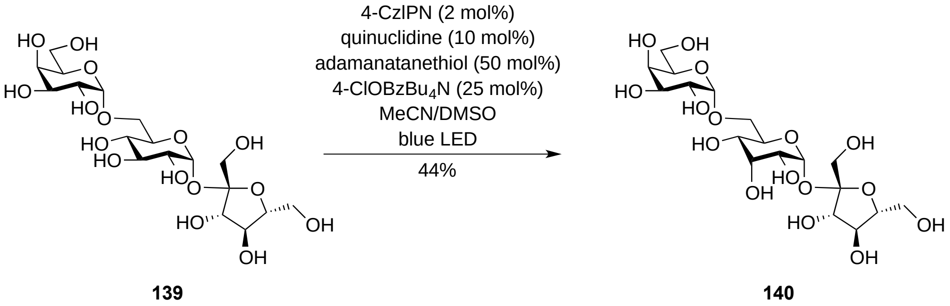
It is well known that TEMPO oxidizes less-hindered primary hydroxy group, namely 6-hydroxy group is selectively oxidized. Recently, several examples of site-selective oxidation of secondary hydroxy group in unprotecting sugar were reported.[98,99] For instance, catalytic oxidation of 3-hydroxy group of unprotected pyranosides with aerobic O_2 was possible (Scheme 35).[99] In the reported cases, hydroxy groups at 3-position were selectively oxidized.



Scheme 35. Pd-Catalyzed site-selective oxidation of glycoside

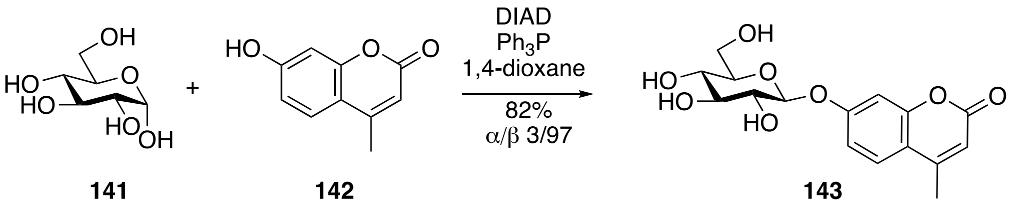
Site-selective C-3 epimerization of unprotected sugar under photo-irradiation conditions was reported.[100] The reaction proceeds though diastereoselective hydrogen-atom transfer reaction (Scheme 36). This system can be applied to oligosaccharides and glycoconjugates.

Initial attempts on the protecting group-free glycosylation reaction were reported recently. Kawabata reported the esterification of the anomeric position with the inversion of the stereochemistry under Mitsunobu reaction conditions in dioxane.[101] The SN2 reaction in 1,4-dioxane was supported by the ^{13}C kinetic isotope effect (1.028) (Scheme 35). In DMF, the stereoselectivity was reduced significantly, and the ^{13}C kinetic isotope effect was 1.001.



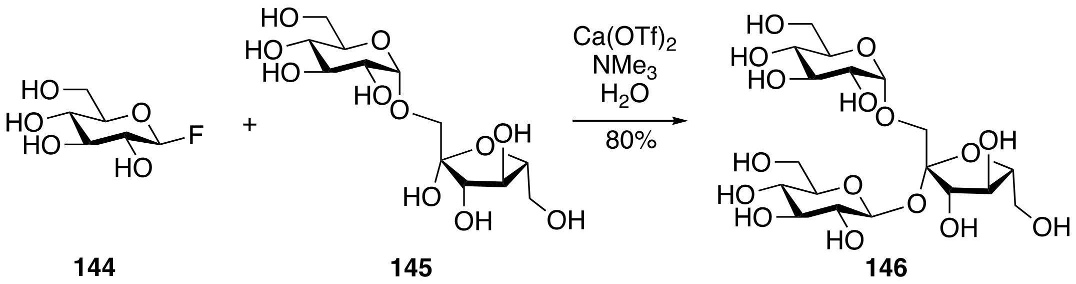
4-CzIPN = 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene

Scheme 36. Site-specific epimerization of unprotected oligosaccharide

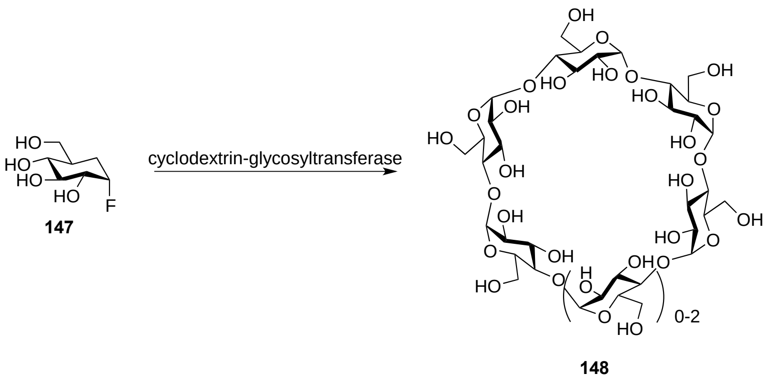


Scheme 37. Protecting group-free SN2 type glycosylation reaction

The glycosyl fluoride **144** gave the sucrosyl derivative **145** in 80% yield in the presence of $Ca(OTf)_2$ and trimethylamine (Scheme 36).[102] Although the structure of the acceptor is limited to sucrose derivatives, regio and stereoselective glycosylation was achieved without any hydroxy group protection. Glucosyl fluorides are often used as donors in enzymatic synthesis. For instance, cyclodextrin-α(1,4)glucosyltransferase accepts the glycosyl fluoride **147** as a donor and gave α, β, and γ-cyclodextrins (Scheme 39).[103] Chemo-enzymatic synthesis is a powerful strategy for oligosaccharide synthesis.[110]



Scheme 38. Protecting group-free glycosylation reaction using glycosyl fluoride **144**



Scheme 39. Chemo-enzymatic synthesis of cyclodextrin

CONCLUSION

Currently, sequence analysis and synthesis of glycans are still difficult compared to those of other biomolecules, such as peptides and nucleosides. However, synthetic endeavors to develop facile methods for producing large-quantity of glycans and the analytical methods for separating the heterogeneous natural glycans have been developed for decades. Synthetic oligosaccharides and glycoconjugates will aid the investigation and understanding of the biological functions of carbohydrates. Despite the numerous reports on various types of glycosylation reactions, the yield and selectivity are still not always predictable. The interplay between the glycosyl donor and acceptor, the protecting group pattern, and the reaction conditions, including solvent and reaction temperature, alter the outcome of the glycosylation event. In addition, the glycosylation reaction is not well-understood from a mechanistic point of view. Further, glycosyl intermediates are not stable, and multiple intermediates are present under equilibrium.

The relatively stable intermediates have been investigated using low-temperature NMR analyses.[104-106] Recently, identification of the reactive intermediates has been reported, and computational approaches were undertaken to gain insights into the conformations of oxacarbenium ions.[107-109] These novel approaches would contribute to the improvement of the understanding of the glycosylation mechanisms and will aid the development of highly efficient and predictable glycosylations.

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