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DOI: 10.1039/D4CC04877F

FEATURE ARTICLE

Recent Advancements in Synthesis of Cyclic Oligosaccharides

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

The development of synthetic methods for chemical glycosylation enables the synthesis of various oligosaccharides, including nonnatural cyclic oligosaccharides. Electrochemical glycosylation is an enabling technology not only for automated solution-phase synthesis of linear oligosaccharides and the chemical synthesis of cyclic oligosaccharides. In this review, recent syntheses of nonnatural cyclic oligosaccharides are also introduced, and glycosylation methodologies are focused on.

Introduction

Macrocyclic molecules including cyclodextrins

Chemistry is a field of science and technology that enables the manipulation of substances at the atomic and molecular levels. To achieve this goal, chemists have created a variety of macrocyclic molecules, such as crown ether,[1] calixarene,[2] pillar[n]arene,[3] cyclodextrin (**CD**),[4] cucurbit[n]uril,[5] cyclophane,[6] cycloparaphenylene,[7] and carbon nanobelt (Fig. 1).[8] These macrocyclic molecules are used as host molecules with internal cavities that enclose guest molecules through hydrogen bonding, hydrophobic interactions, electrostatic interactions, and specific molecular shapes or size compatibility. The respective components and their numbers determine the inner and outer diameters of macrocyclic systems.[9] Generally, **CD** and cucurbit[n]uril are easy to obtain or synthesize, and the cavity depths are constant at 0.78 and 0.91 nm, respectively. Contrary, the cavity depth of calixarene ranges from 1.2 to 2.2 nm.

Sugars are renewable biological resources that exert their structure and function in the form of oligosaccharides and polysaccharides. Oligosaccharides are generally water soluble and flexible; however, **CDs** are structurally rigid oligosaccharides with a nanosized hydrophobic interior. The reason for this is that, in addition to being a cyclic structure, intramolecular hydrogen bonds reinforce the structure. Such structures have been reproduced by artificial host molecules with advantages such as easy chemical modification; however, they are inferior in terms of biocompatibility and sustainability to **CDs**.

Cyclodextrins as sustainable macrocyclic molecules with various applications

It has been more than 130 years since Villers discovered **CDs**,[12] however, the large-scale industrial production of **β-CD** had to be waited until 1980's (Fig. 2A). In the early stages of **CD** history, researchers experienced impurities and a lack of structural information, so-called "the period of doubt".[4] By the middle of the last century, significant progress had been made in structural determination,[13,14] molecular recognition,[15] and enzymatic production.[16] Many scientists have been attracted to the unique properties of **CDs** as water-soluble macrocyclic molecules. The first chemical synthesis of **CDs** had to wait until 1985 because analytical techniques, such as high-resolution NMR and MS, which are crucial for structural determination in modern chemical synthesis, were not common by the 1980s.[17] Since then, many cyclic oligosaccharides have been synthesized as macrocyclic compounds with many applications in supramolecular chemistry. Although various types of nanomaterials have been reported so far, **CDs** are highly appreciated because of their unique properties derived from the D-glucose repeating unit, which is one of the most sustainable natural resources (Fig. 2B). **CDs** are safe nanomaterials at reasonable prices.[18] **CDs** are soluble in water but are equipped with a hydrophobic interior that encapsulates hydrophobic molecules.[19] Thermal stability has been an important property of **CDs** since their discovery, and chiral recognition has also been a distinctive function of **CDs**.[20]

The applications of **CDs** and their derivatives have expanded throughout various fields of daily life (Fig. 2C).[21] In the pharmaceutical industry, **CDs** improve the solubility and stability of active pharmaceutical ingredients (APIs).[22] By multiplying the function of sustained release, it is possible to adjust the location and concentration of APIs for drug delivery. In the food business, based on the biological safety of **CDs**, the quality and appearance of food products can be maintained by encapsulating flavour and colouring agents that are vulnerable to light and oxidation.[23] In addition, by encapsulating ingredients that are the source of unpleasant odours

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and bitterness, **CDs** can mask the odour and bitterness by inhibiting binding to their receptors. This effective anti-odour property allows **CDs** to be used commercially as deodorants. Using **CDs** that have been pre-incrusted with fragrance components, it is also possible to release the fragrance components and encapsulate and remove the odour components. **CDs** are also used for separation.[24] For example, β-cyclodextrin-linked silica gels can be used for the optical resolution of organic compounds. Cyclodextrin polymers are new materials that have the properties of **CDs** but is insoluble in water and organic solvents.[25] They can be used as water purification agents because environmental pollutants such as VOCs and dioxins can be encapsulated.

CDs have been important molecules in academic research for many years. The contribution of **CDs** to supramolecular chemistry is significant, and various derivatives of **CDs** have been synthesized to date.[26] Therefore, the structure and function of cyclic oligosaccharides composed of monosaccharides other than D-glucose are also of interest, and various cyclic oligosaccharides have been synthesized; however, unexplored cyclic oligosaccharides remain due to the underdevelopment of chemical synthesis technology.

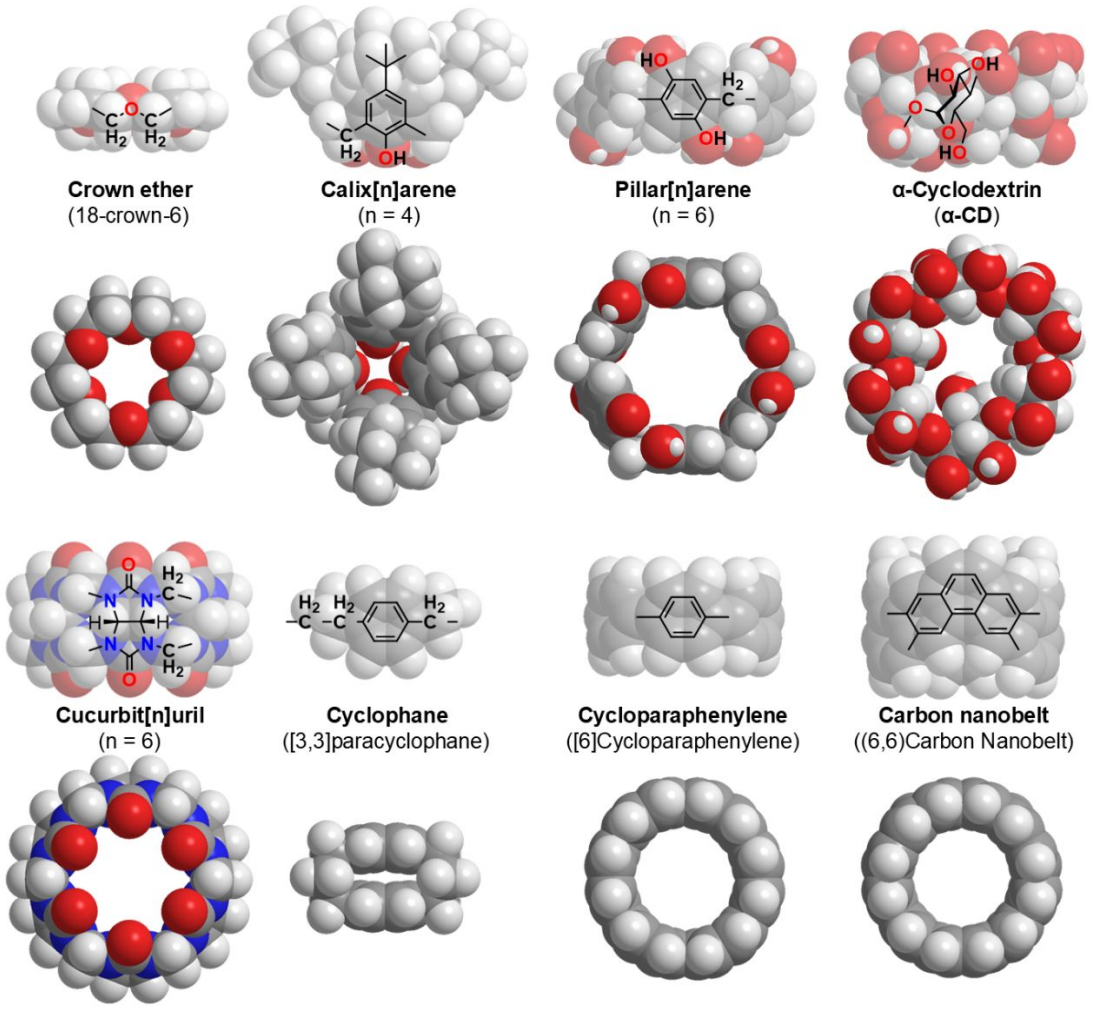

Figure 1 Selected macrocyclic molecules.[10,11]

Synthetic methods for preparing cyclic oligosaccharides

There are several methods for synthesizing cyclic oligosaccharides, including conventional enzymatic and chemical methods. The enzymatic production of **CDs** remains one of the most practical methods for producing specific cyclic oligosaccharides.[16] For example, cyclodextrin glycosyltransferase (CGtase) produces **α-**, **β-**, and **γ-CDs** from amylose. Due to its selectivity and efficiency, enzymatic synthesis has been industrialized; however, the scope and ratio of cyclic oligosaccharides depend on the enzymes involved. The template-based enzymatic synthesis overcomes the limitations of conventional enzymatic methods. The enzymatic synthesis of larger cyclic oligosaccharides, such as **γ-** and **δ-CDs**, is still challenging because of their low yields and difficulty in purification. Zimmerman improved the selectivity for larger cyclic oligosaccharides using engineered CGtases and isolated these products in a single step.[27]

Beeren reported the selective enzymatic synthesis of **δ-CD** by introducing a bolaamphiphile template.[28]

Conventional chemical synthesis greatly expands the variety of cyclic oligosaccharides by assembling intentionally protected mono- or disaccharide units. Since Ogawa's first report on the chemical synthesis of **α-CD**,[17] numbers of artificial cyclic oligosaccharides have been synthesized.[29] Although the number of synthetic cyclic oligosaccharides has continued to increase, achieving these syntheses often involve lengthy synthetic routes. Electrochemical glycosylation[30,31,32] is an alternative to conventional chemical glycosylation for synthesizing cyclic oligosaccharides.[33] The electrochemical method offers the advantages of controlling reactions and generating highly reactive glycosylation intermediates at low temperatures. Multiple synthetic protocols for producing cyclic oligosaccharides have been developed across diverse research areas; however, each method presents its own advantages and limitations. Therefore, it is crucial to select an appropriate synthetic approach for the desired cyclic oligosaccharides.

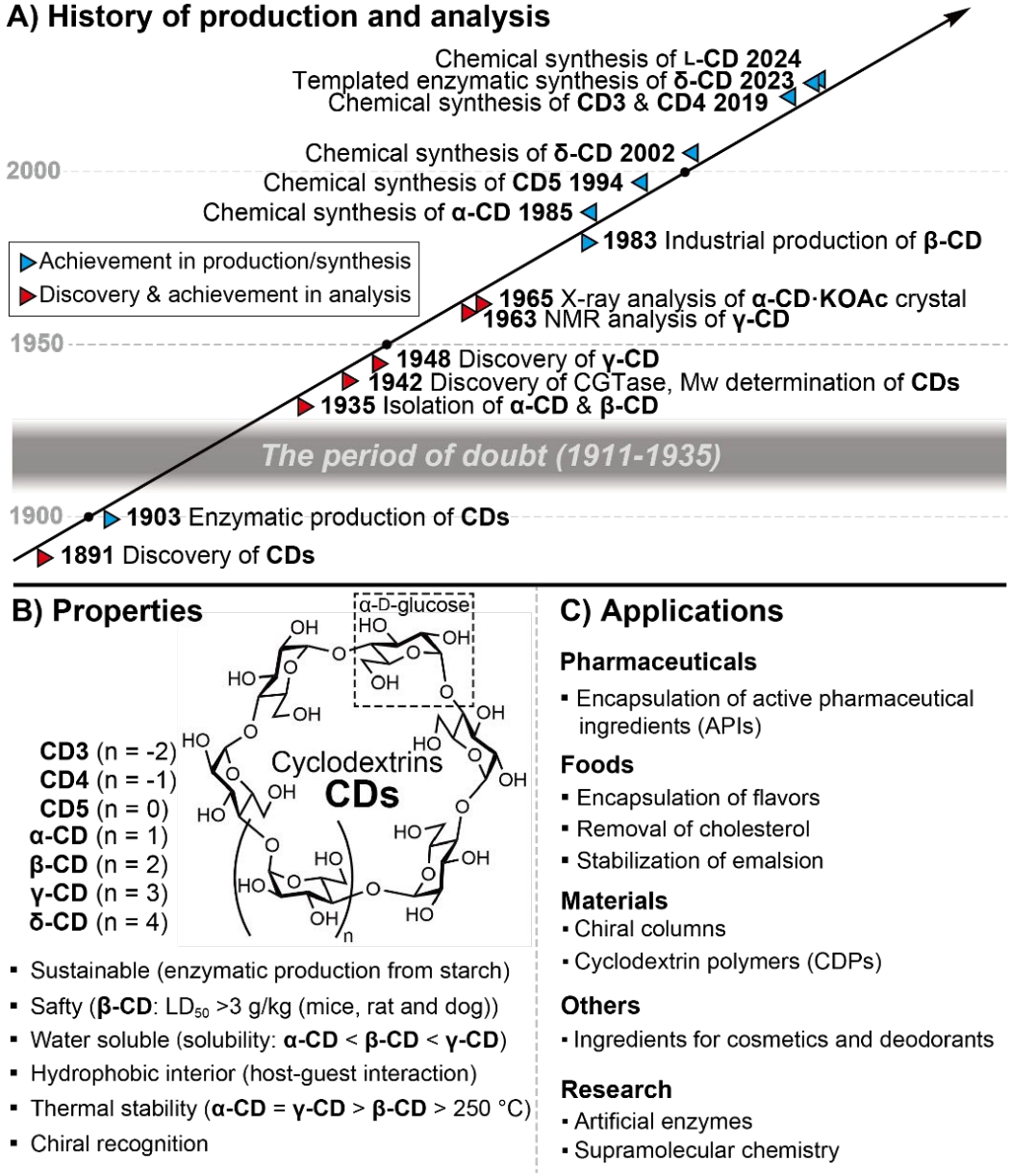

Figure 2 History, properties, and applications of cyclodextrin.

Selected synthesis of cyclodextrin analogues

New methodologies are needed for synthesizing cyclodextrin analogues (Fig. 3). After the chemical synthesis of **α-CD** (**1**), a cyclic oligosaccharide consisting of L-rhamnose 'Cycloawaodorin' (**2**) was reported by Nishizawa and co-workers, and this is the first example of a cyclic oligosaccharide swapping normal D-sugars for L-sugars.[34,35] The mirror-image **CD** (**α-L-CD**) (**3**),[36] which is the C-6 deoxy and C-2 epimer of **2**, had never been reported, although **CDs** have received considerable attention for many years. 'Cyclokasaodorin' (**4**) is also a

nonnatural cyclic oligosaccharide with *N*-acetyl-D-glucosamine as a repeating unit.[37] Although the structural differences between **α-CD** (**1**) and **4** are only the substituents at C-2 positions, it is difficult to convert all the C-2 hydroxyl groups of **α-CD** (**1**) into acetamide groups. Therefore, **4** must be prepared from D-glucosamine as a starting material. Recent advances in chemical glycosylation enable the synthesis of unique nonnatural cyclic oligosaccharides. **CD3** (**5**) and **CD4** (**6**) are the smallest **CDs**.[38] In this article, we also focus on recent glycosylation methodologies that enable the synthesis of nonnatural cyclic oligosaccharides. Although there are some interesting analogues such as thio-linked or glycosidic bond expanded small-ring cyclic oligosaccharides,[39,40] these are beyond the scope of this article.

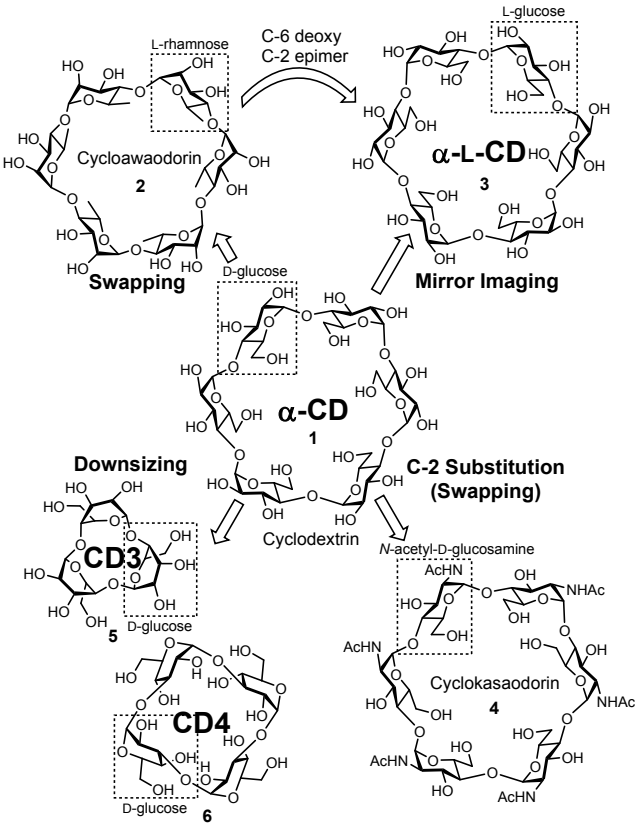

Figure 3 Selected analogues of **α-CD**.

Clockwise from bottom left: Hirofumi Endo, Yu-Cong Sun, Norihiko Sasaki, Toshiki Nokami.

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Recent Examples from Other Groups

The smallest CDs

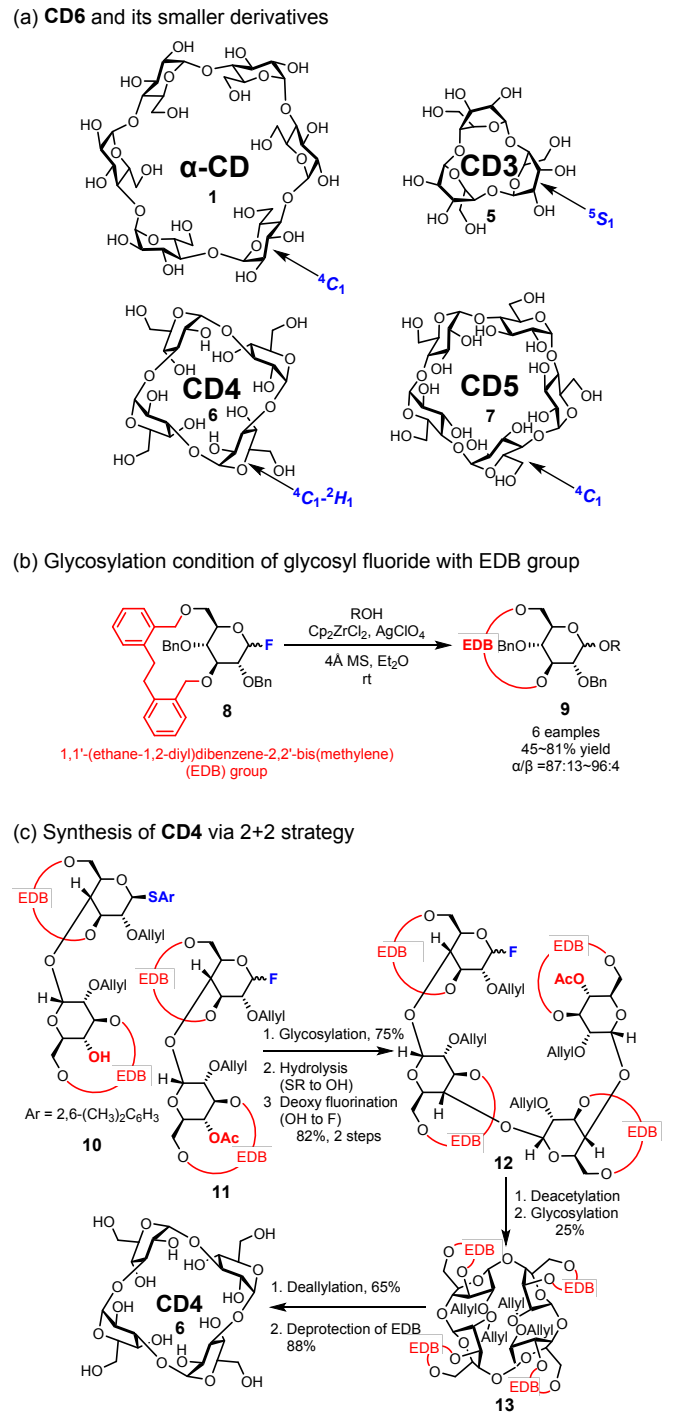


Figure 4 Structures of **α-CD** to **CD3** and the synthetic protocol of **CD4**.

In 1970, Sundararajan and co-workers reported that **CDs** bearing fewer than six glucose molecules could not be cyclized due to their steric hindrance based on computational analysis.[41] After 24 years, Nakagawa and co-workers synthesized a **CD** composed of five D-glucose units called **CD5** (**7**);[42] however, smaller and more strained CDs remained difficult to synthesize for another 25 years. In 2019, Yamada and co-workers reported the first synthesis of smaller CDs, specifically **CD3** (**5**) and **CD4** (**6**), using conformationally supple glucose monomers (Fig. 4).[38] These monomers contain a benzyl-type protecting group named, [1,1'-(ethane-1,2-diyl)dibenzene-2,2'-bis(methylene)] (EDB) on 3-OH and 6-OH of D-glucose. The EDB group on the D-glucose monomer enables not only α-selective glycosylation, which is crucial for the synthesis of CDs, but also increases the conformational flexibility of pyran rings, which is also pivotal for synthesizing smaller CDs.[43] Both **CD3** (**5**) and **CD4** (**6**) were synthesized via Mukaiyama-Suzuki glycosylation[44,45] using the 2+1 and 2+2 strategies, respectively. **CD3** (**5**) and **CD4** (**6**) were successfully deprotected by removing the allyl groups at 2-OH of the pyranose ring and the EDB groups at 3-OH and 6-OH. The structure of **CD3** (**5**) was also revealed through single-crystal X-ray structural analysis and NMR spectroscopy, and its stable structure of **CD3** (**6**) in D_2O is the $^5S_1$ skew-boat conformation. This is an example of how the protecting group influences the conformation of the pyran ring, and the flexible glucose units enable the formation of **CD3** (**5**) and **CD4** (**6**).

The simplest approach towards cyclic oligosaccharides

The chemical synthesis of cyclic oligosaccharides often involves a lengthy process, including two glycosylation steps, the elongation of linear oligosaccharides, and their cyclization (cycloglycosylation).[46] In 2020, Aoki and co-workers reported the one-pot synthesis of cyclic oligosaccharides **15**-**20** bearing β-1,6-glycosidic bonds from thiogalactoside **14** as a monomer (Fig. 5a).[47] Although the formation of anhydro sugars is a substantial problem to prevent the formation of larger cyclic oligosaccharides, this strategy is the simplest synthesis of cyclic oligosaccharides by integrating the elongation and cyclization of linear oligosaccharides into a single step. Thioglycosides of D-galactose and D-glucose can be used as monomers **14** and **21**, each equipped with benzoyl groups at 2, 3, and 4-OH. For this one-pot synthesis, 3.0 equivalents of NIS and 1.5 equivalents of Me_3SiOTf in CH_2Cl_2 provide optimal conditions. In the case of D-glucose, the concentration of the initiating thioglycoside **21** is crucial for successful cyclization; at a low concentration of **21** (0.01 M), linear oligosaccharides, indicating incomplete cyclization, are observed. However, under more concentrated conditions of **21** (0.1 M), complete conversion to cyclic oligosaccharides was achieved (Fig. 5b). In this one-step synthesis, cyclic tetrasaccharides **17** and **25** are the major products of both D-glucose and D-galactose. This polyglycosylation approach works very well because cyclization is slower than intermolecular glycosylation, although it is difficult to predict relative reaction rate of these competitive glycosylations.

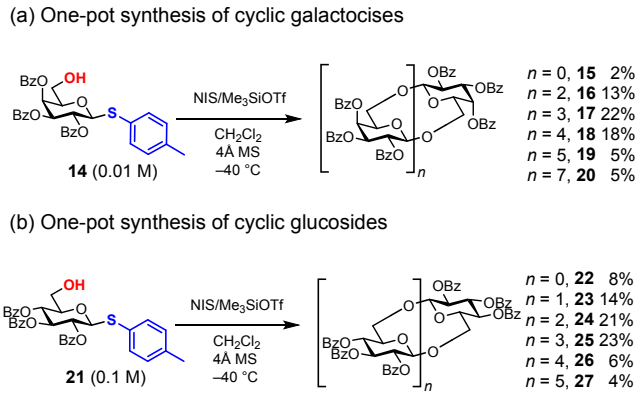


Figure 5 Synthesis of cyclic oligosaccharides under polyglycosylation conditions.

The largest synthetic cyclic oligosaccharides

The major challenge in the construction of cyclic oligosaccharides is the cycloglycosylation of linear oligosaccharides prepared using multistep elongation sequences. Since the first synthesis of **α-CD** (**1**) by Ogawa,[17] various cyclic oligosaccharides have been synthesized based on this strategy. The synthesis of ultra-large cyclic polysaccharides remains challenging because of the constrained conformational spaces of the precursors. Recently, Yang and co-workers reported the synthesis of cyclic mannoside of various sizes by promoter-controlled cycloglycosylation using oligosaccharide thioglycosides and (*Z*)-ynenoates (Fig. 6).[48,49] Particularly noteworthy is the synthesis of ultra-large cyclic polymannosides (16-mer **38**, 32-mer **39**) via cycloglycosylation under high-dilution conditions (0.001 M). Cycloglycosylation is highly dependent on the promoters. In small and middle-sized cyclic oligosaccharides, with the elongation of the linear oligosaccharides (4-mer **28**, 8-mer **29**), the more effective promoters for the cycloglycosylation of thioglycoside precursors are IBr/AgOTf rather than NIS/Me_3SiOTf. Furthermore, excess amounts of promoters are found to dramatically accelerate the cycloglycosylation of the linear oligosaccharides **28** and **29**. In contrast, activation of oligosaccharide (*Z*)-ynenoates by a stoichiometric amount of a gold(I) complex is more effective for the cycloglycosylation of ultra-large linear oligosaccharides **34** and **35** by proper preorganization of the ultra-large cyclic transition state. The stabilizing effect of the oxocarbenium ions also led to higher yields when using toluene as the solvent compared with CH_2Cl_2. The global deprotection of precursors **34** and **35** afforded the corresponding cyclic oligosaccharides **38** and **39** in reasonable yields. Although the demonstrated monomer is limited to mannoside with β-1,6-glycosidic bonds, the importance of the anomeric leaving groups and their promoters were clearly demonstrated by this study.

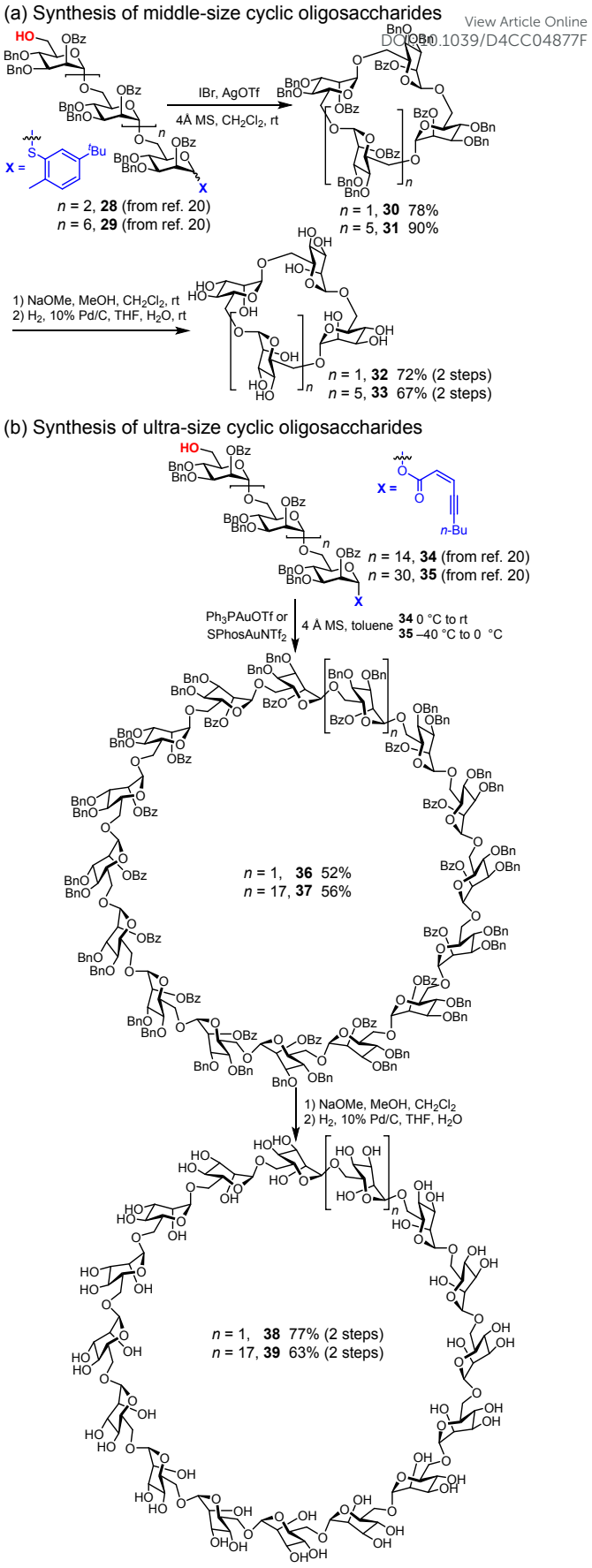


Figure 6 Synthesis cyclic oligomannosides.

Synthesis of mirror-image CDs

Naturally occurring **CDs** exhibit chirality originating from their component D-glucose units.[50] As mentioned above, Nishizawa and co-workers synthesized the nonnatural cyclic oligosaccharides 'Cycloawaodorin' consisting of L-rhamnose, which is a natural L-sugar. Recently, Stoddard and co-workers reported three mirror images of **CDs** (**α-L-CD**) (**3**), **51**, and **52** consisting of nonnatural L-glucose (Fig. 7).[37] To this end, they employ L-glucose building blocks **41** and **42** bearing benzyl groups (Bn), benzoyl groups (Bz), *tert*-butyldimethylsilyl groups (TBDMS), and *p*-toluene thiol (STol). For the diastereoselective formation of α-1,4-glycosidic bonds with L-glucose, they devised a strategy combining the solvent effect of Et_2O[51] and remote anchimeric assistance originating from the Bz group at 6-OH.[52] As an activator of glycosylation, *p*-toluenethionyl chloride (*p*-PhMeSCl) and AgOTf were used, resulting in the desired disaccharide **43** with 86% yield and complete α-selectivity (Fig. 7a). The cyclic hexasaccharide precursor **45** was synthesized in 65% yield by donor preactivation-based one-pot glycosylation,[53-57] reducing the need for intermediate purification steps. They extended the linear hexasaccharide **45** to synthesize linear heptasaccharide **46** and octasaccharide **47** in 55% and 45% yields, respectively (Fig. 7b). Cyclization was achieved using the corresponding lengths of linear oligosaccharides **48**, **49**, and **50**, NIS or *p*-PhMeSCl activators, and CH_2Cl_2, resulting in yields of 84%, 75%, and 54%, respectively. They investigated the chiral properties of deprotected **α-L-CD** (**3**) and found that **α-L-CD** (**3**) exhibit opposite chiral properties to those of natural **CDs**. The preactivation strategy is a powerful method for preparing linear oligosaccharides equipped with reactive anomeric leaving groups and protecting-group-free hydroxyl groups.

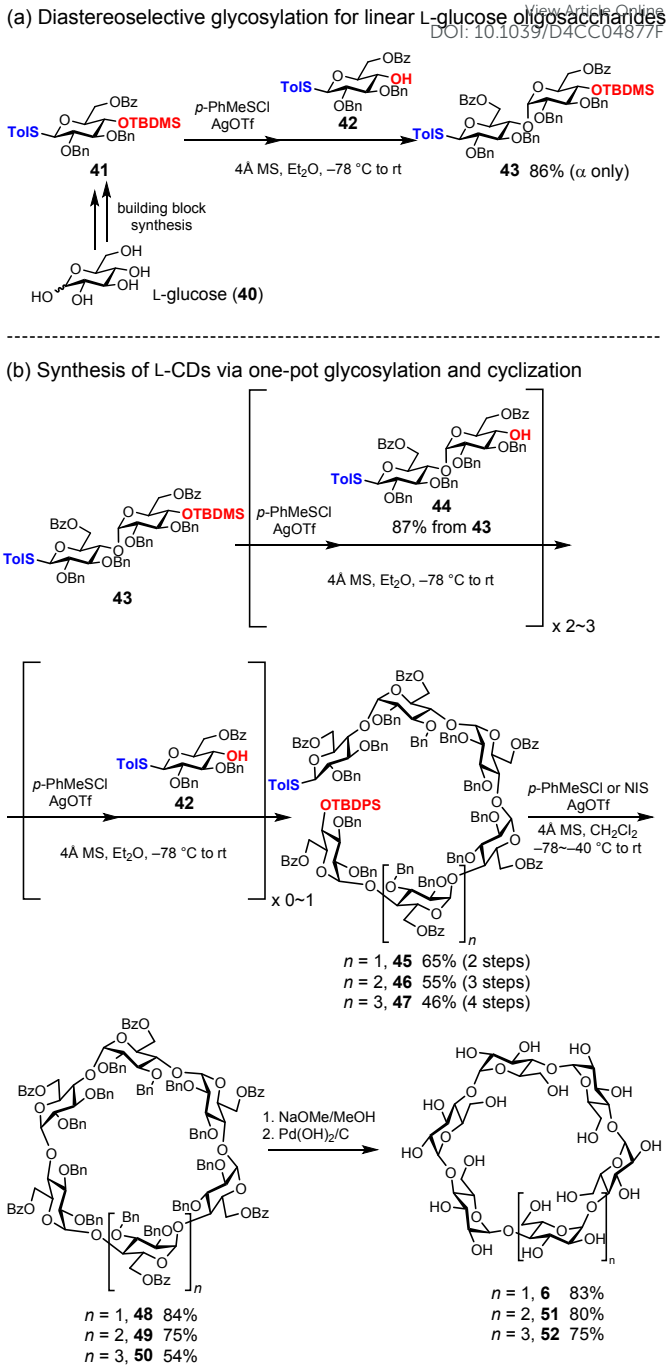


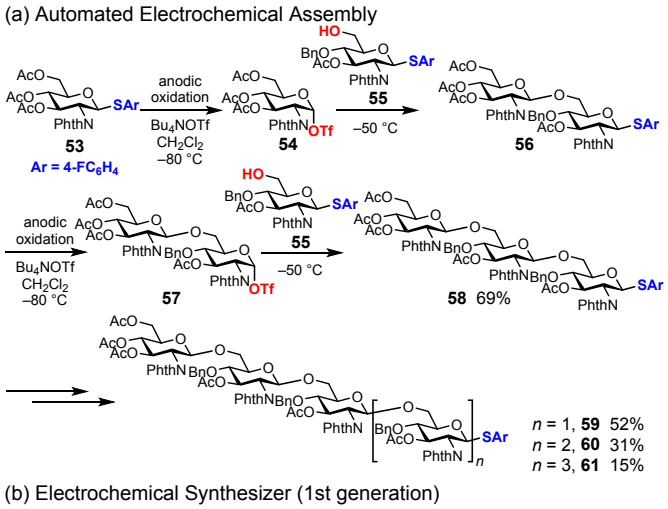
Figure 7 Total synthesis of L-CDs.

Synthesis of Cyclic Oligosaccharides via Intramolecular Electrochemical Glycosylation

Automated electrochemical assembly

Similar to automated synthesis of oligonucleotides and oligopeptides, automated synthesis of oligosaccharides is developed based on solid-phase synthesis.[58,59] In contrast, we have been interested in the solution-phase synthesis of oligosaccharides and inspired by the 'preactivation method' and

'the 'cation pool method'.[60,61] The preactivation method is a two-step process based on the generation of a highly reactive glycosylation intermediate in the absence of nucleophiles; thus the generated intermediate reacts with nucleophiles, which are sugar hydroxyl groups. This method allows the elongation of oligosaccharides multiple times in one pot without the need for deprotection. The cation pool method is based on the electrochemical generation of carbocations in the absence of nucleophiles. Thus, the generated carbocations can react with various nucleophiles with low oxidation potentials because the nucleophiles are not exposed to anodic oxidative conditions. The 'Automated electrochemical assembly' developed by the authors is an electrochemical solution-phase synthesis to produce oligosaccharides in a one-pot automated manner (Fig. 8a).[62,63] For example, thioglycoside **53** is used as a starting material, which is converted to the corresponding glycosyl triflate **54** via anodic oxidation at low temperatures. Thus, the generated glycosyl triflate **54** is sufficiently reactive to couple with the sugar hydroxyl group of **55** in one pot, affording disaccharide **56**. Oligosaccharides with the desired chain length can be obtained by repeating this two-step process. To conduct this process in an automated manner, we developed an electrochemical synthesizer equipped with an electrolysis cell, DC power supply, chiller, syringe pump, and PC (Fig. 8b). The synthesis of poly-*N*-acetylglucosamine (PNAG) oligosaccharides was demonstrated using an electrochemical synthesizer, and PNAG oligosaccharides up to hexasaccharide **61** (n = 3) were obtained.[62] Automated electrochemical assembly can be used to synthesize other linear oligosaccharides, including TMG-chitotriomycin[64,65] and Myc-IV(C16:0, S).[66] There are several benefits to automated synthesis using an electrochemical synthesizer, such as reproducibility, observability, and controllability; however, productivity (time, scale, yield) has to be improved for further applications of this method.



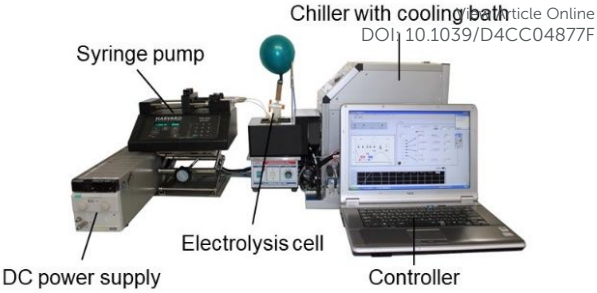


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Figure 8 Automated electrochemical assembly for the synthesis of oligosaccharides.

Electrochemical synthesis of cyclic oligoglucosamines

Cyclic oligoglucosamines are nonnatural cyclic oligosaccharides. Nifantiev and co-workers have been achieved the synthesis of cyclic oligo-1,6-β-D-glucosamines using thioglycosides as building blocks and *N*-iodosuccinimide (NIS) and triflic acid (TfOH) as the promoter system.[67,68] However, in the case of linear oligosaccharides containing four, six, and seven glucosamine units, the control of stereochemistry is not perfect, even in the presence of a strongly participating 2-*N*-phthaloyl group to control β-glycosylation. In contrast, the electrochemical method enabled the stereoselective synthesis of cyclic oligoglucosamines.[33] Linear oligoglucosamines (the precursors of the cyclic oligoglucosamines) are readily prepared using an automated electrochemical synthesizer (Fig. 9a). In the cyclization process, stereoselective electrochemical glycosylation afforded the corresponding cyclic oligoglucosamines in high yields (cyclic tetrasaccharide **67**: 81%; cyclic pentasaccharide **68**: 93%; cyclic hexasaccharide **69**: 78%) (Fig. 9b). We also performed the cyclization of linear tetrasaccharide **63** under conventional chemical glycosylation conditions using the NIS/TfOH system. The reaction afforded both α- and β-isomers of cyclic oligoglucosamine **67**. Therefore, electrochemical glycosylation is a powerful tool for synthesizing cyclic oligosaccharides, allowing for complete stereoselectivity by optimizing the electrochemical glycosylation conditions, such as temperature, electrolyte, and reaction time.

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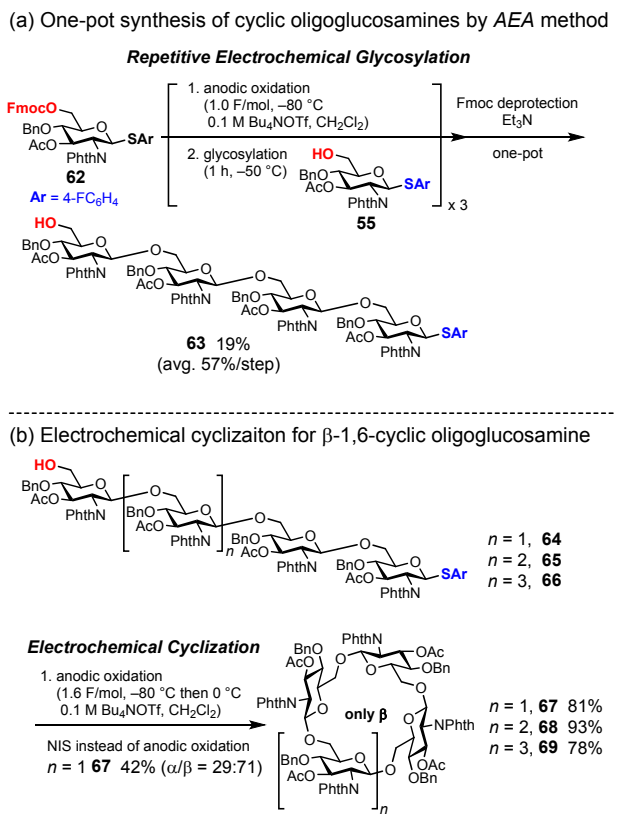

Figure 9 Synthesis of cyclic oligoglucosamines.

Electrochemical synthesis of cyclic β-glucans

β-glucan is a polysaccharide consisting of glucose repeating units linked by β-glucosidic bonds. Among them, cyclic β-glucans play various roles. For example, they exhibit biological activities such as osmotic regulation,[69] rhizogenesis,[70] and antioxidant activity,[71] and the ability to encapsulate target compounds.[72] Cyclic β-glucans have a variety of different structures, and we are particularly interested in the chemical synthesis of naturally occurring cyclic (1,3;1.6)-β-glucans **70** with two different glycosidic linkages (Fig. 10).[73,74]

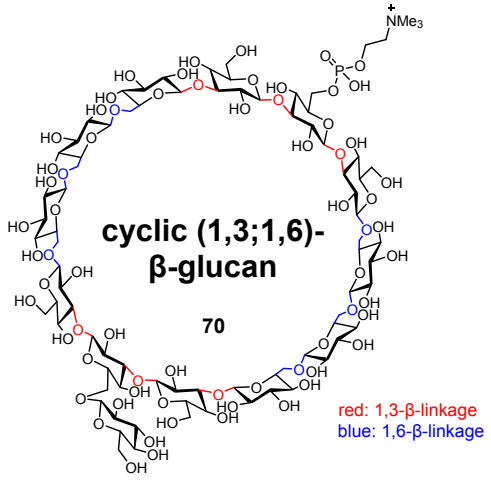

Figure 10 Structure of cyclic (1,3;1,6)-β-glucan tridecasaccharide.

Initially, we synthesized a linear hexasaccharide **74** as the target cyclic oligosaccharide (Fig. 11). We synthesized three disaccharide building blocks **71**-**73** by electrochemical glycosylation, and the linear hexasaccharide **74** was the synthesized by assembling disaccharide **71** and the tetrasaccharide obtained from the remaining two disaccharide building blocks **72** and **73**. During these processes, ionic liquid 1-butyl-1-methylpyrrolidinium ($[P_{14}]OTf$) instead of tetrabutylammonium triflate (Bu_4NOTf) was used as an electrolyte to improve yields of oligosaccharide building blocks. Thus, $[P_{14}]OTf$ is used for dimerization and cyclization as well. Next, we synthesized the protected cyclic (1,3;1,6)-β-glucan dodecasaccharide **75** via a one-pot synthesis under electrochemical dimerization-cyclization conditions;[48] however, the yield of **75** was only 3%. This low yield was due to the intramolecular cyclization of linear hexasaccharide **74** and excessive reactions of hexasaccharide **74** with each other to form smaller and larger cyclic oligosaccharides, which are not desired compounds. To suppress these side reactions, stepwise synthesis via intramolecular glycosylation of linear dodecasaccharide **76b** was also performed. As a result, the yield of **75** increased from 3% (1 step) to 10% (3 steps).[75] Further optimization of the reaction conditions and global deprotection of cyclic oligosaccharide **75** is currently underway.

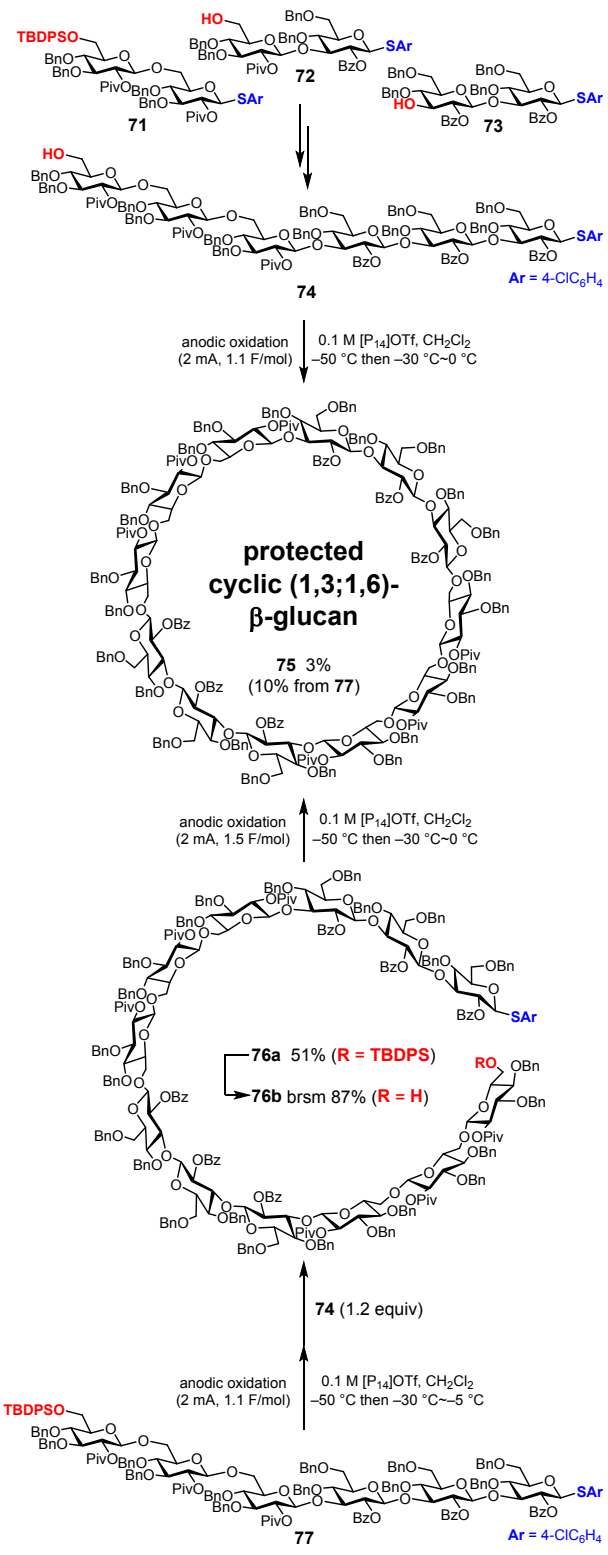

Figure 11 Synthesis of the protected precursor cyclic (1,3;1,6)-β-glucan dodecasaccharide.

Synthesis of Cyclic Oligosaccharides via Electrochemical Polyglycosylation

Electrochemical polyglycosylation of linear oligosaccharides

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Although polyglycosylation is not very useful for synthesizing oligosaccharides with specific chain lengths, it is a practical method for simultaneously preparing oligosaccharides with different chain lengths. The first report on polyglycosylation was published by Yoshimura in 1988.[76] After this work, the protocol for the polyglycosylation was explored; however, controlling the degree of polymerization of products remained difficult with conventional chemical reagents,[77] which often caused insufficient reactivity for polymerization or overreaction. In 2022, our group reported the electrochemical polyglycosylation of linear oligoglucosamine with β-1,4-glycosidic bonds consisting of D-glucosamine monomers, and this method enabled the control of the degree of polymerization of the product by simply changing the reaction conditions for the reaction (Fig. 12).[78] We investigated various conditions such as the temperature of anodic oxidation and glycosylation, leaving groups, and the number of electrolysis cycles. By optimizing the reaction conditions for elongation, we successfully synthesized linear octasaccharide **80** (*n* = 6) in 3% yield, which was previously too long to be chemically synthesized.

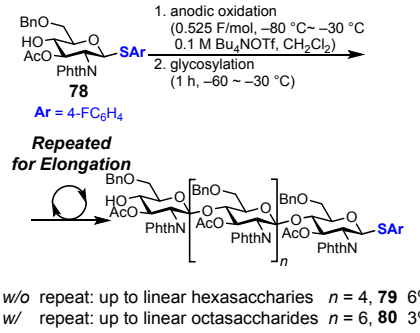


Figure 12 Synthesis of linear oligosaccharides under polyglycosylation conditions.

Based on these results, we reported the electrochemical polyglycosylation of cyclic oligoglucosamine with several D-glucosamine monomers in 2024.[79] Although polyglycosylation for cyclic oligosaccharides with D-glucose and D-galactose has already been reported by Aoki, the polyglycosylation with D-glucosamine has remained untouched due to the poor reactivity of D-glucosamine monomers, which often have electron-withdrawing protecting groups for the reactive amine. Consistent with this hypothesis, we report that the D-glucosamine building block bearing a phthalimide protecting group **81**, one of the most common electron-withdrawing protecting groups for amines, does not yield more than cyclic trisaccharides; instead, we obtained only anhydrosugar **82** exclusively (Fig. 13a). For the synthesis of cyclic oligoglucosamine, we used D-glucosamine monomer **84** equipped with a 2,3-oxazolidinone protecting group that suppressed inversion of the pyranose ring, which is the major cause of the generation of anhydrosugar **86** (Fig. 13b). By employing D-glucosamine bearing 2,3-oxazolidinone groups, we

exclusively obtained cyclic disaccharide **85** in 62% yield. We also tried a D-glucosamine monomer protected with azide groups (Fig. 13c). In the case of the azide group, the stereoselectivity of glycosylation could be a problem because it does not have any acryl groups, which are crucial for neighboring group participation; however, we obtained the cyclic disaccharide **88a** in 49% with perfect β-selectivity. In the same reaction, cyclic trisaccharide **89a** was also obtained; however, it contains both α- and β-glycosidic linkages. Although the mechanistic details of the formation of cyclic trisaccharide **89a** was not clear, the formation of α-glycosidic linkage at the first glycosylation may be crucial to obtain **89a**. Therefore, a better strategy for the synthesis of larger cyclic oligosaccharide with α-selective glycosylation has to be developed to β-1,6-glycosidic linkages of glucosamine via the polyglycosylation approach.

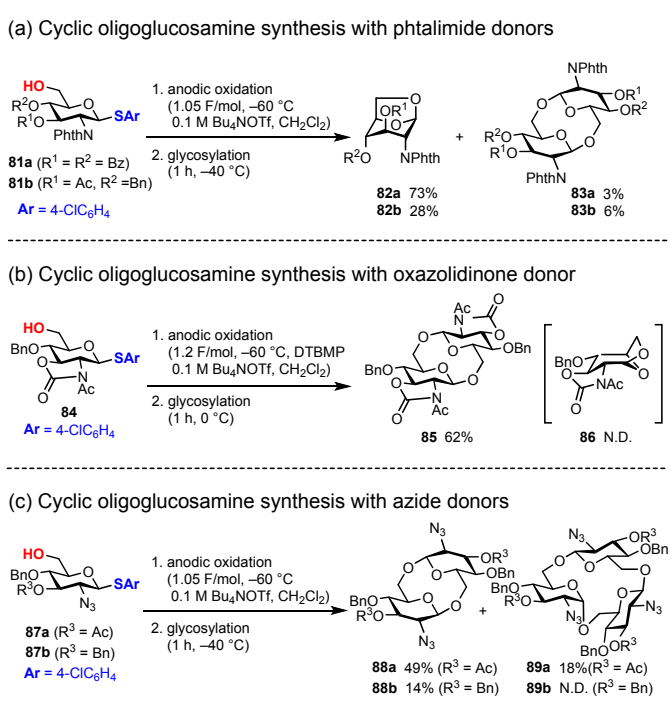
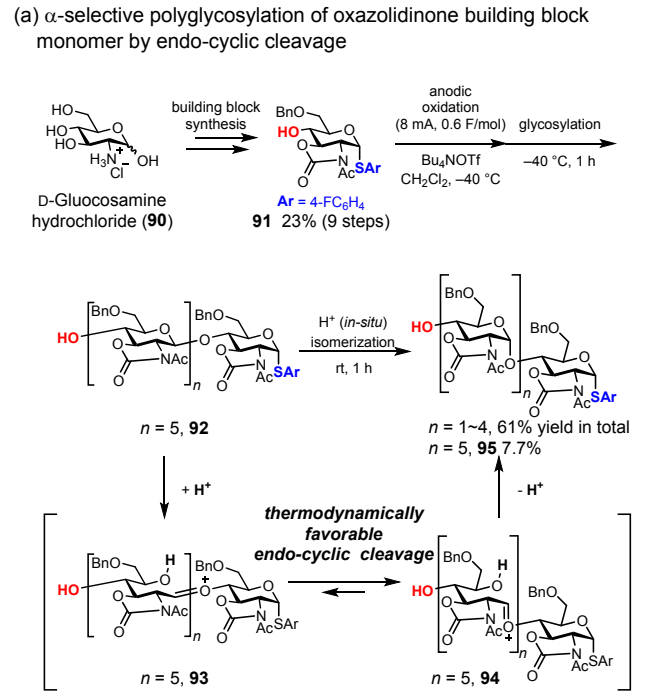


Figure 13 Synthesis of cyclic oligosaccharides under polyglycosylation conditions.

Synthesis of Cyclokasaodorin

Although D-glucose exhibits structural variety, including amylose (linear α-1,4-glycosidic bonds), cellulose (linear β-1,4-glycosidic bonds), and **CD** (cyclic α-1,4-glycosidic bonds), D-glucosamine, which is an aminated form of D-glucose at the 2-position of the pyranose ring, occurs in nature exclusively as chitin and chitosan, which have linear β-1,4-glycosidic bonds. In 2022, we achieved the first total synthesis of unnatural cyclic oligosaccharides composed of *N*-acetylglucosamine with α-1,4-glycosidic bonds, naming it cyclokasaoddorin (**4**),[36] inspired by the synthesis of cycloawaodorin (**2**) reported by Nishizawa.[34,35] Synthesis of cyclodextrin-shaped cyclic oligoglucosamine requires exclusive 1,2-*cis* selectivity at the anomeric position and 2,3-oxazolidinone protection, which enables α-selective glycosylation via endo-cyclic cleavage induced by the internal strain of the oxazolidinone ring.[80-84] We designed and prepared a D-glucosamine-based thioglycoside donor **91** bearing 2,3-oxazolidinone and Bn groups. Then, we establish a polyglycosylation protocol to convert monosaccharides into oligosaccharides via anodic oxidation. Electrochemical glycosylation provided control over the degree of polymerization, and we determined that 0.6 F/mol of electricity was optimal for polymerization of the monomer (Fig. 14a). After electrolysis, the reaction temperature is increased as isomerization from β-glycosidic bonds to α-glycosidic bonds, driven by in situ generated acid. Subsequently, we demonstrate the cyclization of a linear α-1,4-hexasaccharide **95** (*n* = 5) into the corresponding cyclic oligosaccharide, achieving a 44% yield of the desired cyclic hexasaccharide **98** (*m* = 1). By integrating polyglycosylation and cyclization into a one-pot process, we developed a synthetic protocol for cyclic hexasaccharide, heptasaccharide, and octasaccharide. We named this process *e*PIC, standing for 'Electrochemical Polyglycosylation, Isomerization, and Cyclization'. After the initial electrochemical polyglycosylation and acid-induced thermodynamic isomerization, electrolysis was repeated with 1.0 F/mol of electricity to promote cyclization. This process enables the one-pot synthesis of cyclic oligoglucosamines, yielding cyclic hexasaccharide **98**, heptasaccharide **99**, and octasaccharide **100** in 6.2%, 5.5%, and trace amounts, respectively. Deprotection of hexasaccharide **5** was accomplished through the site-selective cleavage of carbonyl groups using ethanethiol,[85] oxidative removal of the thioester with dimethyl dioxirane, and deprotection of the benzyl groups (Fig. 14b). Although the desired cyclic oligosaccharide **5** was obtained, the yield of its linear oligosaccharide precursor **95** was moderate via the *e*PIC process. Therefore, a stepwise process using a disaccharide building block, as shown in the L-CD synthesis (Fig. 7b), might be a useful alternative for preparing linear oligosaccharide precursors **95**-**97**.



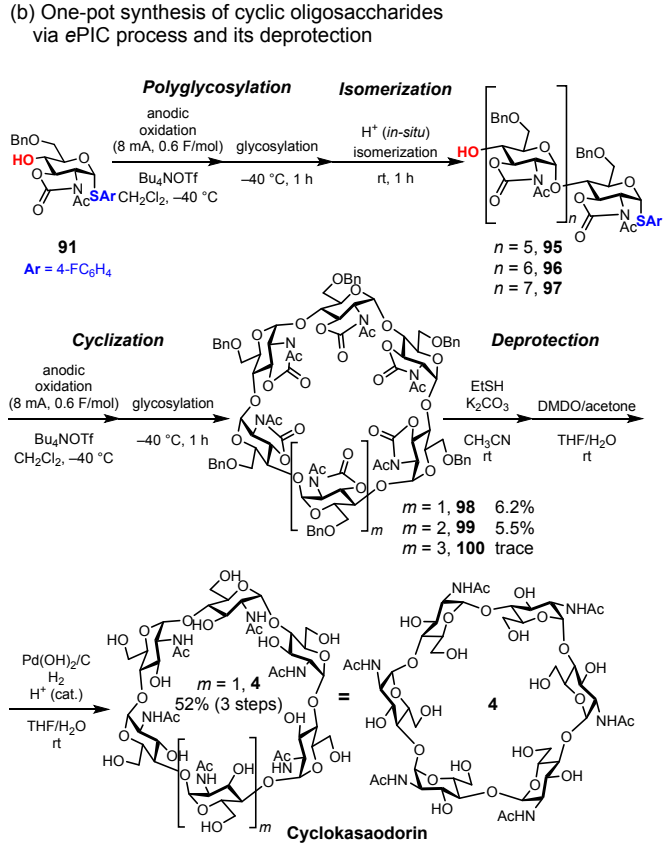


Figure 14 Synthesis of 'Cyclokasaodorin' via electrochemical polyglycosylation.

Conclusion

In this feature article, we introduce electrochemical approaches to cyclic oligosaccharides, with recent reports from other groups. Although it is still not clear why the electrochemical method is useful for converting linear oligosaccharides into cyclic oligosaccharides, the generation of reactive intermediates under low-temperature conditions may play a pivotal role. The development of synthetic protocols, protecting groups, and leaving groups with their activation system have lead to the synthesis of novel cyclic oligosaccharides. Thus, further advancements in the synthetic methods of complex oligosaccharides, including cyclic oligosaccharides, will allow the development of synthetic approaches toward unique oligosaccharide-based structures and materials.

Acknowledgements

We acknowledge financial support from the JSPS (grant Nos. JP25410115, JP19K05714, and JP23K26654) and the MEXT (grant No. JP15H05844). We thank Koganei Corporation for developing the second-generation electrochemical synthesizer and their continuous support.

Data availability statements

No primary research results, software, or code have been included and no new data were generated or analyzed as part of this feature article.

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