ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2022, **58**, 7948

Received 22nd April 2022,
Accepted 6th June 2022

DOI: 10.1039/d2cc02287g

rsc.li/chemcomm

Synthesis of cyclic α-1,4-oligo-*N*-acetylglucosamine 'cyclokasaodorin' *via* a one-pot electrochemical polyglycosylation–isomerization–cyclization process†

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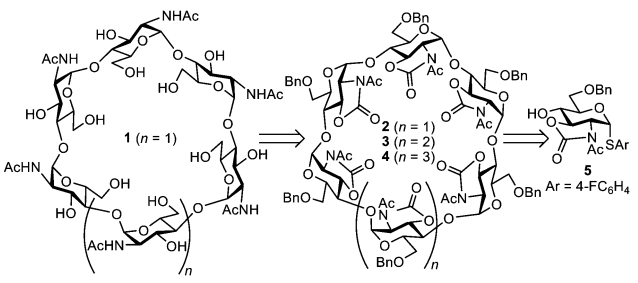
Electrochemical synthesis of unnatural cyclic oligosaccharides composed of *N*-acetylglucosamine with α-1,4-glycosidic linkages has been accomplished. A thioglycoside monomer equipped with the 2,3-oxazolidinone protecting group was used to prepare linear oligosaccharides by electrochemical polyglycosylation. In the same pot, isomerization of the linear oligosaccharides and intramolecular electrochemical glycosylation for cyclization were also conducted sequentially to obtain the precursor of the cyclic α-1,4-oligo-*N*-acetylglucosamine 'cyclokasaodorin'.

Electrochemical transformations of organic molecules have attracted significant attention over the last decade.[1] Both anodic oxidation and cathodic reduction can generate highly reactive chemical species, including strong acid and base under mild reaction conditions, and their amount can be precisely controlled under the constant current condition. These beneficial properties of electrochemical methods enable unique molecular transformations that are difficult to achieve using conventional chemical methods.[2]

We have been interested in the synthesis of oligosaccharides under electrochemical conditions.[3] Cyclic oligosaccharides are one example of electrochemically synthesized oligosaccharides; however, it required the preparation of linear oligosaccharides to convert them to the corresponding cyclic oligosaccharides.[4] Chemical synthesis of a variety of cyclic oligosaccharides has already been reported; however, multiple-step synthesis had to be performed using conventional methods of glycosylation.[5] Thus, an ideal approach to synthesizing cyclic oligosaccharides is glycosylation polymerization (*i.e.*, polyglycosylation). Indeed, the synthesis of cyclic oligosaccharides under the polyglycosylation conditions has already been reported; however, it is limited to β-1,6-glycosidic linkages.[6]

Based on this background, we planned the retrosynthesis of the unnatural cyclic α-1,4-hexa-*N*-acetylglucosamine **1** (n = 1) which has never been reported previously (Scheme 1). Cyclic oligosaccharides **2** (n = 1), **3** (n = 2), and **4** (n = 3) with protecting groups will be precursors of the desired cyclic hexasaccharide **1** (n = 1) and larger oligosaccharides. These precursors might be synthesized by polyglycosylation of thioglycoside **5**, which is a monosaccharide derived from glucosamine hydrochloride (Scheme 1). Thioglycoside **5** was chosen as a monomer because thioglycosides with the 2,3-oxazolidinone protecting group have been used extensively for the α-selective synthesis of glucosamines *via* acid-catalysed isomerization.[7] We assumed that the polyglycosylation of thioglycoside **5** might be achieved using a one-pot three-step process including two steps of electrochemical oxidation and an isomerization step (Scheme 2). *In situ* generation of linear oligosaccharides **6–10** with α-1,4-glycosidic bonds are crucial for the success of this process. Here, we report the first total synthesis of cyclic α-1,4-hexa-*N*-acetylglucosamine **1**.

We initiated our study for the development of the novel one-pot electrochemical process from the optimization of



Scheme 1 Retrosynthesis of cyclic α-1,4-oligo-*N*-acetylglucosamine.

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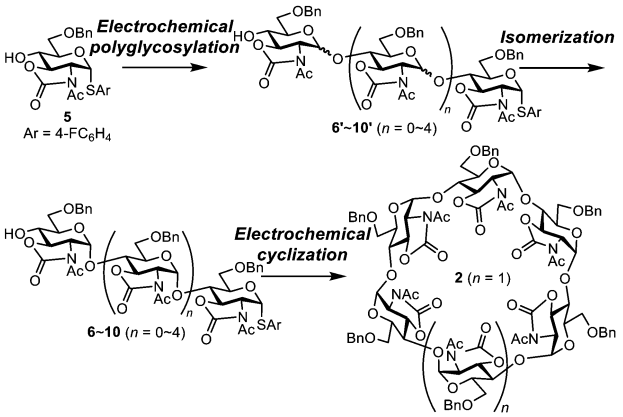
† Electronic supplementary information (ESI) available: Experimental procedures and spectral data of new compounds. See DOI: https://doi.org/10.1039/d2cc02287g

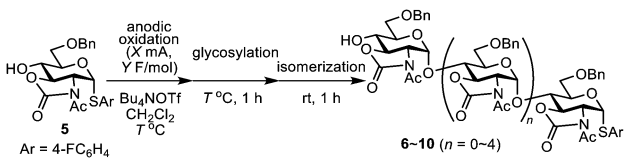


Scheme 2 Electrochemical polyglycosylation–isomerization–cyclization for the synthesis of cyclic oligosaccharides.

electrochemical polyglycosylation to prepare linear oligosaccharides **6–10** with α-1,4-glycosidic bonds (Table 1). Our previous study has already had shown that the isomerization from the β-isomer to α-isomer of glycosides occurred within 1 h above 0 °C.[7f] This isomerization process was promoted by *in situ*-generated triflic acid (TfOH) using tetrabutylammonium triflate (Bu_4NOTf) as an electrolyte. Thus, we decided to raise the reaction temperature from *T* °C to room temperature (rt) after electrochemical polyglycosylation to accelerate the isomerization process, although it took time to control the temperature of the reaction.

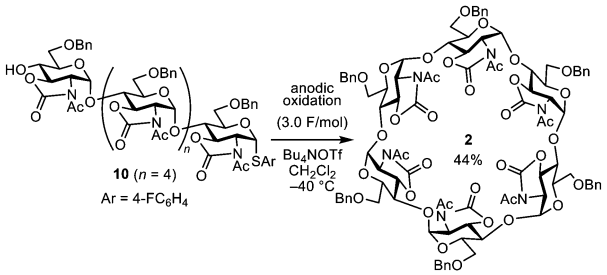
The reaction temperature for electrochemical polyglycosylation was examined from −20 °C to −60 °C (entries 1–5). Yields of linear oligosaccharides **6–10** (*n* = 0 to 4) were determined after isolation by preparative gel permeation chromatography (GPC). Yields of oligosaccharides were better at higher reaction temperatures, such as −20 °C and −30 °C (entries 1 and 2); however, oligosaccharides of hydroxy sugars, which have a hydroxy group instead of the thioaryl (SAr) group at the anomeric carbon, were

Table 1 Electrochemical polyglycosylation and isomerization



	Conditions			Yields of oligosaccharides				
Entry	*X* mA	*Y* F mol^{-1}	*T* °C	**6** *n* = 0 (%)	**7** *n* = 1 (%)	**8** *n* = 2 (%)	**9** *n* = 3 (%)	**10** *n* = 4 (%)
1	8	0.6	−20	14	21	16	11	7.4
2[a]	8	0.6	−30	21	24	16	7.5	7.2
3[a]	8	0.6	−40	21	18	13	8.7	7.7
4	8	0.6	−50	18	20	11	11	6.6
5	8	0.6	−60	17	20	13	8.9	4.6
6	8	0.7	−40	13	18	15	8.3	7.6
7	4	0.6	−40	22	19	13	8.9	6.3
8	12	0.6	−40	25	22	14	8.1	5.5

[a] Average of 2 runs.



Scheme 3 Electrochemical cyclization of linear hexasaccharide.

observed as by-products. Desired linear hexasaccharide **10** (*n* = 4), which was a potential precursor of cyclic oligosaccharide **2**, was obtained up to 7.7% at temperatures below −40 °C (entries 3–5). Increasing electricity from 0.6 F mol^{-1} to 0.7 F mol^{-1} did not improve the yields of oligosaccharides (entry 6) and further investigation of the current value was not effective to obtain oligosaccharides in better yields (entries 7 and 8). Although the corresponding peaks of linear heptasaccharide and octasaccharide were observed using matrix assisted laser desorption/ionization time of flight mass spectroscopy (MALDI-TOF MS), they were very difficult to isolate in high purity. Unreacted thioglycoside **5** was recovered, and formation of 1,4-anhydrosugar, which must be generated by intramolecular glycosylation, was not observed in this reaction.

Conversion of linear hexasaccharide **10** (*n* = 4) to cyclic hexasaccharide **2** (*n* = 1) was also investigated under the anodic oxidation conditions at −40 °C (Scheme 3). Although it required an excessive amount of electricity (3.0 F mol^{-1}), linear hexasaccharide **10** (*n* = 4) was completely consumed (>99%). Furthermore, the corresponding cyclic hexasaccharide **2** was obtained in 44% yield. This was an important result for the development of the one-pot electrochemical process because the reaction conditions of the electrochemical cyclization were almost the same as those of electrochemical polyglycosylation (Table 1).

The isomerization step after electrochemical polyglycosylation is crucial to obtaining the precursor of a cyclic oligosaccharide with α-glycosidic linkages. The ^{1}H NMR spectrum of linear hexasaccharide **10′** obtained without the isomerization step is shown in Fig. 1b together with thioglycoside **5**, linear hexasaccharide **10**, and cyclic hexasaccharide **2**. The peaks between 4.8 and 5.5 ppm (▲) indicate the presence of β-glycosidic linkages in linear hexasaccharide **10′**. The complexity of the peaks may stem from the difference in the number and position of β-glycosidic linkages of linear hexasaccharide **10′**. After the isomerization of **10′** the corresponding peaks of the β-glycosidic linkages disappeared as shown in the spectrum of linear hexasaccharide **10**, and two sets of peaks at 6.07 ppm (doublet, *J* = 4.4 Hz, 1 H, ▼) and 6.03–6.00 ppm (multiplet, 5 H, ▼) were observed around 6.0 ppm (Fig. 1c). The peak at 6.07 ppm was assigned to the anomeric proton of the reducing end of the oligosaccharide **10** because it was in good agreement with the anomeric proton of thioglycoside **5** at 6.05 ppm (doublet, *J* = 4.5 Hz, 1 H, ▼). After cyclization of **10**, no peaks

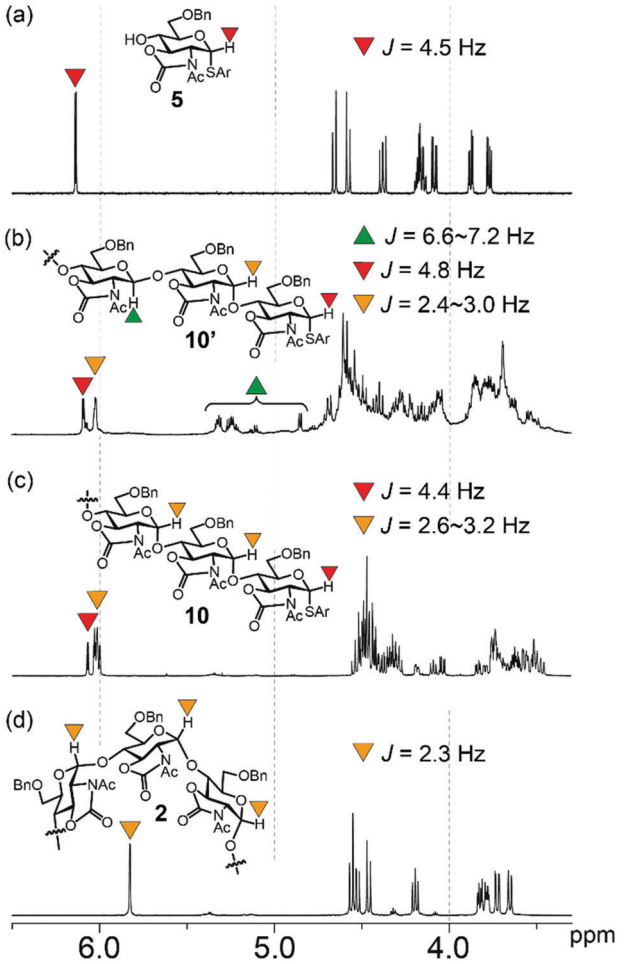


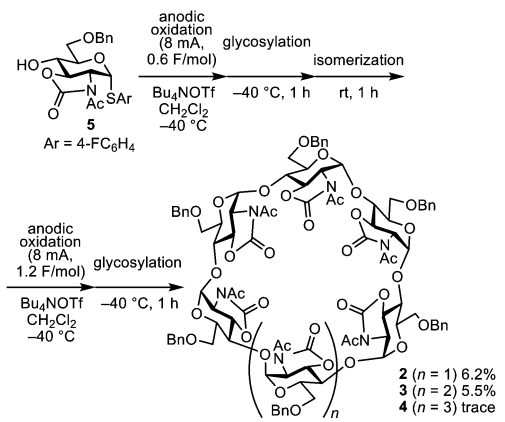
Fig. 1 Comparison of ^{1}H NMR spectra. (a) thioglycoside **5**, (b) linear hexasaccharide without isomerization **10′**, (c) linear hexasaccharide **10**, (d) cyclic hexasaccharide **2**.

were observed at 6.0 ppm, and the doublet peak at 5.80 ppm (J = 2.3 Hz, 6 H, ▼) was assigned to the α-glycosidic linkage of cyclic hexasaccharide **2** (Fig. 1d).

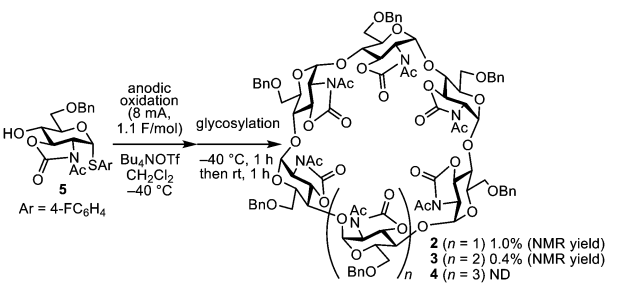
Based on these results, we performed a one-pot electrochemical polyglycosylation–isomerization–cyclization (*e*PIC) process using our automated electrochemical synthesizer (Scheme 4).[8] Electrochemical polyglycosylation starts at −40 °C, and the reaction mixture was stirred for another 1 h at the same temperature (−40 °C). In the second step, isomerization was promoted at rt for 1 h. The final electrochemical cyclization was again performed at −40 °C under the same anodic oxidation conditions. Under the optimized conditions of each step of the process, the targeted cyclic oligosaccharides **2** (n = 1) and **3** (n = 2) were obtained in yields of 6.2% and 5.5%, respectively, together with a trace amount of **4** (n = 3). Although the size difference of cyclic oligosaccharides **2**-**4** was difficult to distinguish by NMR spectra, molecular ion peaks in MALDI-TOF MS spectra clearly showed 319 Da difference which was the molecular weight of the repeating unit. Larger cyclic oligosaccharide **4** (n = 3) was more polar than smaller oligosaccharides **2** (n = 1) and **3** (n = 2) as determined by TLC; however, we used a preparative GPC for purification.

To confirm the advantage of the *e*PIC process, we demonstrated the single-step anodic oxidation under the optimized reaction temperature with 1.1 F mol^{-1} of electricity for comparison (Scheme 5). Although we could isolate cyclic hexasaccharide **2** (n = 1) and heptasaccharide **3** (n = 2), the yields were determined using ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard because of the low yield and purity of the products. The formation of cyclic octasaccharide **4** (n = 3) was not detected (ND), even when using MALDI-TOF MS. We also performed the anodic oxidation with an increasing amount of electricity (1.8 F mol^{-1}); however, the corresponding cyclic oligosaccharides **2**–**4** were not obtained. These results suggested that the *e*PIC process has an advantage over the conventional single-step electrochemical polyglycosylation in obtaining the target cyclic oligosaccharides.

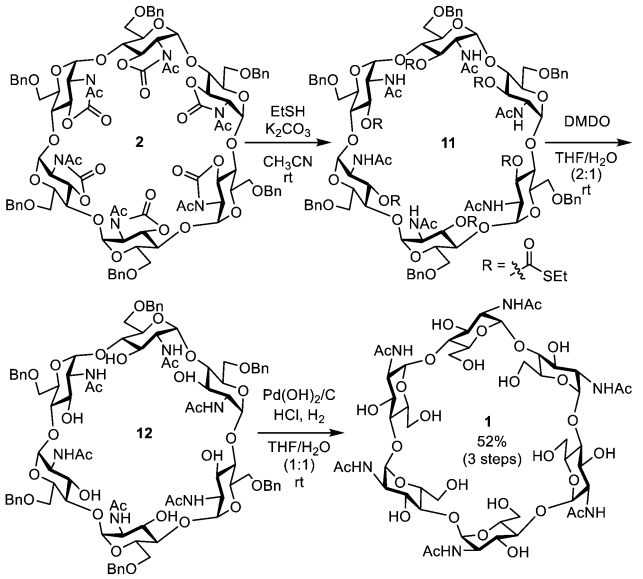
Global deprotection of cyclic hexasaccharide **2** was started with 2,3-oxazolidinone ring-opening using ethanethiol (EtSH) in the presence of K_2CO_3 (Scheme 6).[9] The subsequent oxidative removal of the thioester of **11** was achieved by the reaction of an acetone solution of dimethyldioxirane (DMDO) selectively, and the final deprotection of the benzyl group at the 6-position (6–OH) of intermediate **12** was achieved under the conventional hydrogenation reaction conditions using $Pd(OH)_2$/C as a catalyst. The global deprotection of precursor **2** afforded the desired cyclic oligosaccharide **1** in 52% total yield (three steps). Further optimization of reaction conditions is in progress to achieve global deprotection of precursors **3** and **4**.



Scheme 4 Preparation of cyclic oligosaccharides *via* the ePIC process.



Scheme 5 Electrochemical polyglycosylation with increasing amount of electricity as a control experiment.



Scheme 6 Global deprotection of the protected cyclic oligosaccharide.

In conclusion, we have achieved the first total synthesis of cyclic-α-1,4-hexa-*N*-acetylglucosamines, which are the 2-deoxy-2-acetoamide analogues of α-cyclodextrin and a cyclic variant of chito-oligosaccharides. We call these cyclic oligoglucosamines 'cyclokasaodorin' which was inspired by the unnatural cyclic oligosaccharide 'cycloawaodorin'[10] reported from the Nishizawa group in Tokushima and the traditional umbrella dance 'Kasaodori' in Tottori. Further optimization and modification of the synthetic process for large-scale synthesis of cyclokasaodorin to investigate their physical properties are in progress in our laboratory.

We acknowledge financial supports from the JSPS (No. JP19K05714). This paper is dedicated to the late Professor Hidetoshi Yamada of Kwansei Gakuin University.

H. E. and T. N. organized the research; H. E., M. O., and A. R. synthesized and characterized compounds; T. H. and T. K. developed the automated electrochemical synthesizer; H. E. and T. N. principally wrote the manuscript according to the suggestion and discussions with all authors.

Conflicts of interest

There are no conflicts to declare.

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