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Review

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Chemical synthesis of small-ring cyclic oligosaccharides

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Respectfully dedicated to Professor Horst Kunz on the occasion of his 80th Birthday

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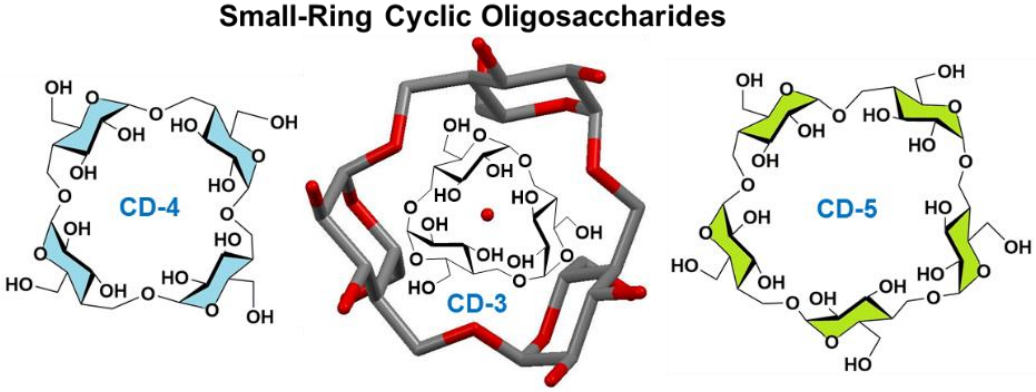
Abstract

Immense interest on studies and applications of naturally-occurring cyclic oligosaccharides has attracted novel methods and ingenuities in their chemical synthesis. The conformation of the monosaccharides constituting the macrocyles is important, in order to permit cyclization and facilitate the macrocyclic supramolecular properties. Synthesis of small-ring cyclic oligosaccharides combining the structural and functional features continues to be a challenge. This review article assesses the current chemical methods for the synthesis of small-ring cyclic oligosaccharides, particularly, macrocycles that possess five or fewer monomer units constituting the macrocycle. Methods to retain the stable conformation of individual sugar units on small-ring macrocyles and the benefits to supramolecular properties are discussed.



Keywords: Cyclodextrins, Cyclo-oligomerization, Cyclic oligosaccharides, Glycosylation, Small-ring macrocycles

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Acknowledgments

References

1. Introduction

Cyclic oligosaccharides attract an interest and importance as a result of their distinct macrocyclic structural and functional features.[1-4] The cylindrical structures that are comprised of a sugar wall, decorated further with polar hydroxy groups at the top and bottom of the wall. The structural features of the cylindrical macrocycles are characterized further by regions of apolar and polar surfaces. Prominent among the cyclic oligosaccharides is the oligo-cyclo-glucosides, generically called as cyclodextrins, wherein glucopyranoside oligomers cyclize with the aid of interglycosidic bonds and form all-sugar macrocycles. The naturally-occurring cyclodextrins are the enzymatic degradation products of starch, the amylose component of which undergoes degradations and enzyme-mediated cyclizations as one of the end-products. The enzymatic syntheses are streamlined largely.[5] The exquisite selectivities of enzyme reactions lead to cyclic oligomers with well-defined number of sugar units constituting the macrocycle, without enforcing structural constraints that would alter the stable chair conformation of the sugar moieties, the interglycosidic bond, torsion angles, the hydroxy functionalities occupying upper, lower rims of the cylindrical structure and the cavity sizes and shapes. Importance of these characteristics in naturally-occurring cyclodextrins is analyzed in great detail by Lichtenthaler and co-workers, through systematic molecular dynamics studies.[6] Further studies reveal that oligosaccharide macrocycles composed of fewer glucopyranosyl moieties than that of the smallest naturally-occurring macrocycle, namely, α-cyclodextrin possessing 6 glucopyranosyl units, would be constrained. Penalties arise due to shrinking of the macrocycle size, the largest being the inability to retain the favorable chair conformation of the individual glucopyranoside ring. Rings with fewer than 6 glucopyranosides would undergo conformational changes towards distorted chair, skew and envelop conformations of individual sugar units, referring to the number of atoms forming the plane and the associated steric constraints encountered by the substituents of the pyranoside moiety. As a result, formation of cyclic oligosaccharides containing 2 to 5 glucopyranosyl units is thought not feasible during the enzymatic synthesis of macrocycles with 6 and more glucopyranosyl units in the ring.[7] On the other hand, the benefits of the supramolecular properties of cyclic oligosaccharide macrocycles continue to be exploited in a number of disparate chemical, biological and materials studies.[8-11] Chemical synthesis of cyclic oligosaccharides has been of great interest too, as a result of the manifold structural and functional features of cyclic oligosaccharides.[12-17] Presence of multiple hydroxy groups and the requirements to retain the regio- and stereoselectivities in glycosidic bond formation warrant judicious synthetic designs. Cyclic oligosaccharide syntheses remain a challenge, further complicated by the requirement to retain favorable conformation of the sugar moieties, particularly in small ring cyclic oligosaccharides. The theme of this article is to discuss the major synthetic approaches to prepare the small ring cyclic oligosaccharides, with either native glycosidic bond or heteroatoms linking the individual sugar

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residues in such all sugar macrocycles. The structural and functional properties of these newer types small ring un-natural cyclic oligosaccharides are also presented wherever available in original reports.

2. Chemical Synthesis of Native Cyclodextrins and Small-Ring Cyclic Oligosaccharides

Chemical synthesis of native cyclodextrins, produced naturally by enzymatic reactions on starch, was an early feat awaiting to be demonstrated. The first chemical synthesis of α-cyclodextrin was reported by Ogawa and co-workers in 1987.[18-20] This pioneering work had given the necessary impetus to achieve chemical synthesis of cyclic oligosaccharides through non-enzymatic routes. The synthesis relied on building blocks approach, wherein a convergent assembly of smaller building blocks and an intramolecular cyclization were adopted to secure the first fully synthetic cyclodextrin. As many as 21 steps were involved in the course of the synthesis, initiated from maltose as the substrate, with a good yield of individual synthetic steps. The stepwise synthesis of the linear hexasaccharide precursor **5** and the final step of the ring closing cyclization to afford α-cyclodextrin **6** are shown in Scheme 1. Maltose derivatives **1** and **2** were the key intermediates for the preparation of the target cyclic oligosaccharide. The Mukaiyama glycosylation between disaccharide fluoride donor **1** and disaccharide acceptor alcohol **2**, in the presence of $SnCl_2$ and AgOTf, afforded the protected tetrasaccharide, which upon *O*-deacetylation furnished tetrasaccharide **3**, having a free hydroxy functionality at the reducing end. Iteration of the glycosylation of **3** with the disaccharide donor **1**, followed by *O*-deacetylation led to the formation of linear hexasaccharide **4**, possessing an allyl moiety at the reducing end and a hydroxy moiety at the non-reducing of the hexasaccharide. A 5-step synthetic manipulation of **4** was undertaken, namely, (i) protection of primary hydroxy group at the non-reducing end as a chloroacetate; (ii) deprotection of the allyl moiety at the reducing-end; (iii) conversion of the hemiacetal to the corresponding chloride, upon treatment with SO_2Cl_2; (iv) transformation of chloride to fluoride using AgF and (v) removal of labile chloroacetyl moiety under the Zemplén condition to secure linear hexasaccharide **5** (Scheme 1). Treatment of the linear hexasaccharide fluoride precursor **5** with $SnCl_2$ and AgOTf afforded the protected derivative of **6**, as a result of cyclo-glycosylation reaction. Subsequent *O*-debenzylation by hydrogenolysis led to the isolation of α-cyclodextrin, in an overall yield of 0.3% from maltose.

The successful demonstration of the chemical synthesis of a cyclodextrin led to queries on the preparation of different types of constitutionally varied cyclodextrin analogues. Among these analogues, synthesis of small-ring cyclic oligosaccharides is of prime interest. In the following sections, preparation of macrocycle with less than six sugar units is discussed.

Synthesis of a cyclic oligosaccharide with five sugar units was reported by Nakagawa and co-workers.[21] The stereoselective synthesis of cyclo-maltopentaose was achieved by intramolecular cyclization of the linear pentasaccharide precursor. Preparation of the precursor was initiated with glycosylation of 1,6-anhydromaltose derived disaccharide acceptor **7** with monosaccharide thiol donor **8** to afford protected derivative **9**, which upon *O*-deacetylation afforded trisaccharide **9** (Scheme 2). Glycosylation of **9** with maltose derived disaccharide thioglycoside donor **10** led to the formation of linear pentasaccharide **11**. The anhydro-sugar moiety at the reducing end was converted to a thioglycoside and subjected further to secure the linear pentasaccharide **12**.

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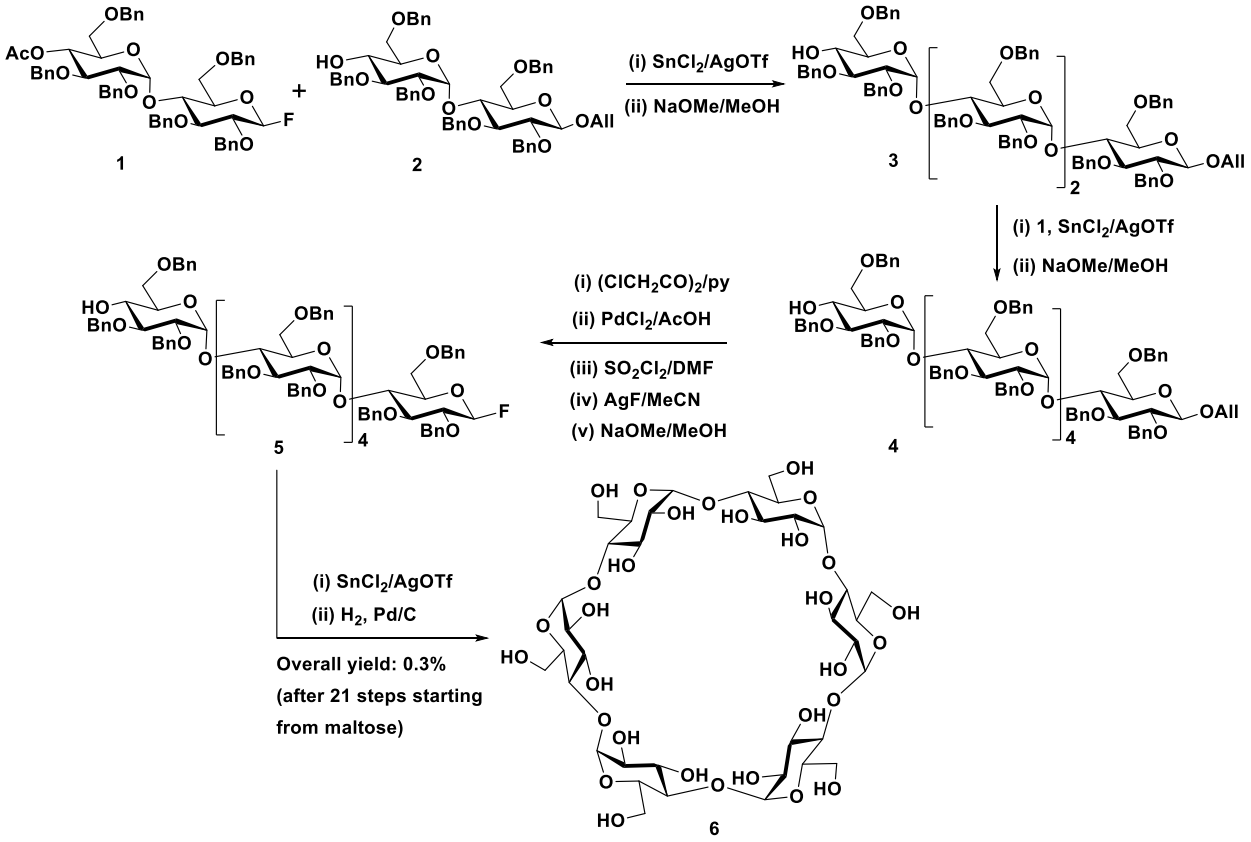
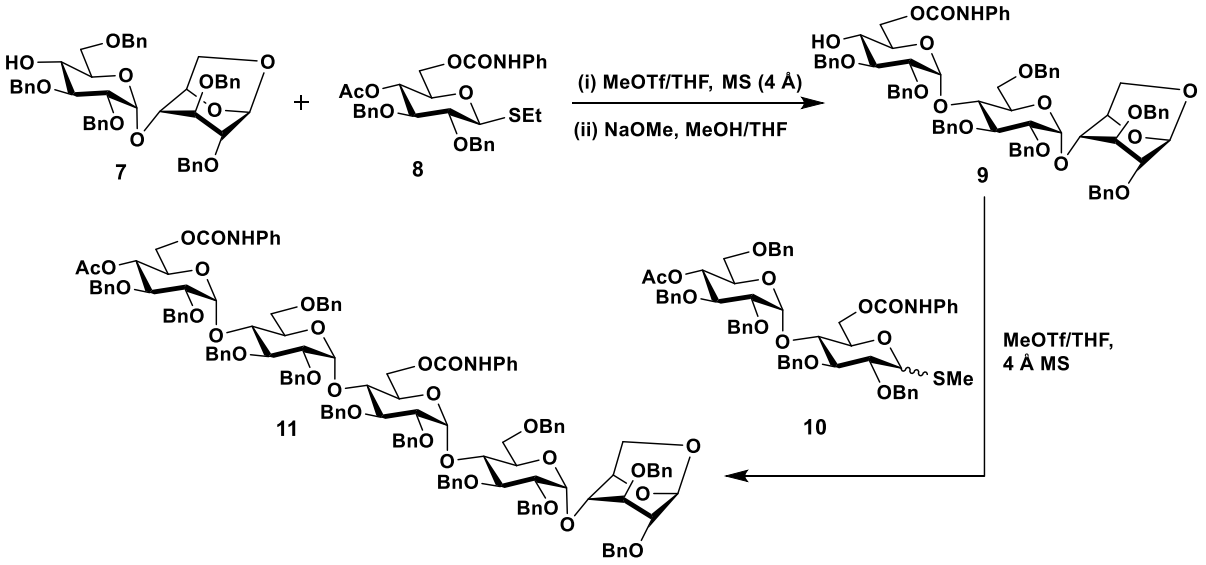


Scheme 1. Chemical synthesis of α-cyclodextrin.[18]



Scheme 2. Synthesis of linear pentasaccharide **11**.[21]

Intramolecular cyclization of **12**, under high dilution, in the presence of MeOTf promoter, followed by removal of *N*-phenyl- carbamoyl group and hydrogenolysis afforded cyclomaltopentose **13** (Scheme 3). Importantly, the presence of *N*-phenylcarbamoyl group at *O*-6 of each donor compounds **8**, **10**, **11** facilitated the α-selective glycosylations, including the final cyclization step.

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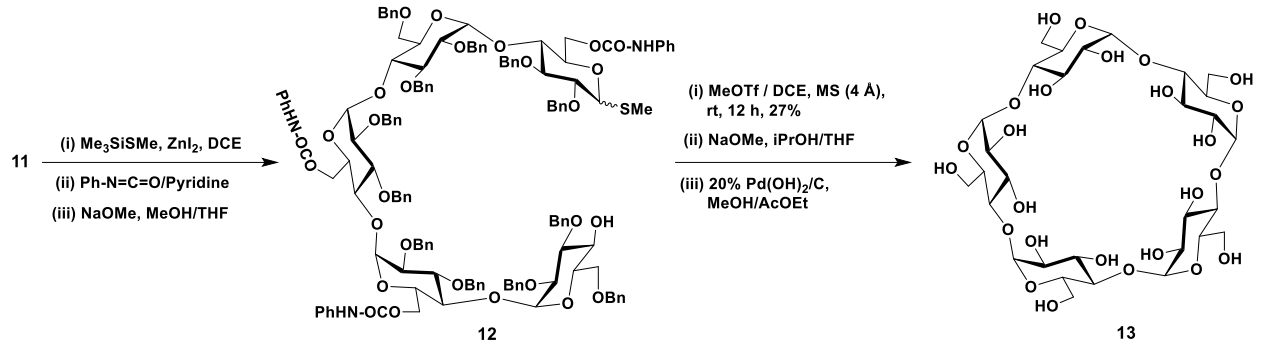
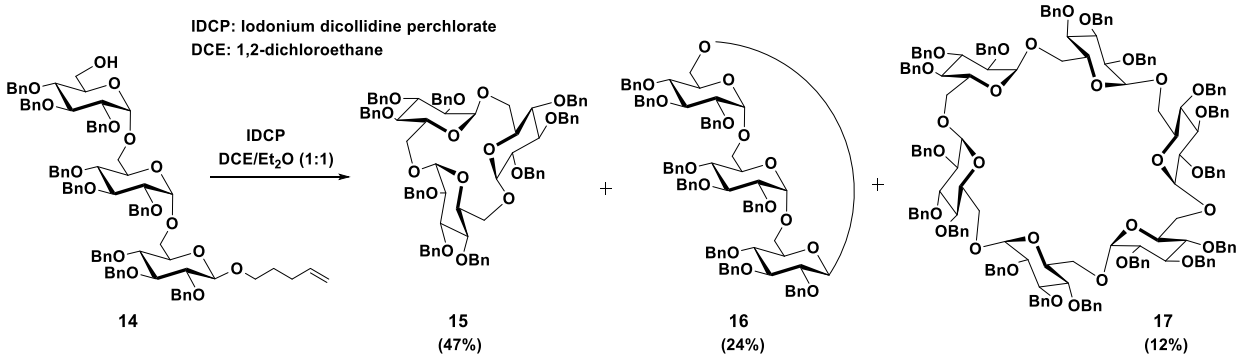


Scheme 3. Stereoselective synthesis of cyclomaltopentose.[21]

As opposed to the α-(1→4) glycosidic linkage, many efforts were devoted towards the preparation of small-ring cyclic oligosaccharides with α-(1→6) glycosidic linkages. Important developments on such macrocycles with α-(1→6) glycosidic linkage are summarized below.

Vottero and co-workers reported the synthesis of benzylated cycloisomaltotri- (**15**, **16**) and -hexaoside (**17**) from trisaccharide monomer **14**, functionalized with *O*-pentenyl moiety at the reducing end (Scheme 4).[22] The trisaccharide monomer **14** was prepared through stepwise synthesis, initiated from monomer building blocks, with *O*-pent-1-enyl moiety as the glycosyl donor component. Upon securing linear trisaccharide **14**, cycloglycosylation was conducted under high dilution condition (6.0 mM), in the presence of iodinium ion (I^+) promoter and the cyclic trimer **15** and **16** were obtained, in 47% and 24% yields, with α-and β-glycosidic linkages, respectively. Cyclic hexasaccharide **17** (12%) was also noticed in this cyclization reaction, as a result of initial intermolecular glycosylation and subsequent intramolecular cyclization. The formation of all α-anomeric cyclic hexaoside **17** indicated no ensuing steric strain upon cyclization, as opposed to both α- and β-glycosidic bond during the formation **15** and **16**.



Scheme 4. Synthesis of cycloisomalto-trisaccharide **15**, **16** and -hexasaccharide **17**.[22]

Skeletal modifications of cyclodextrin analogues with thioglycosidic linkages are important for reasons that the heteroatom binds selectively to metal ions and contribute to increase the hydrolytic and enzymatic degradation stabilities, as compared to the corresponding *O*-glycoside. In an approach, Hindsgaul first reported the synthesis of β-(1→6) thia-linked cyclic glucopyranoside dimer **21**, trimer **22** and tetramer **23** from the corresponding pre-formed linear thioglycoside precursor **18**, **19** and **20**, respectively (Scheme 5).[23] Linear monomers **18**-**20** were synthesized by utilizing 6-deoxy-6-iodo glucoside derivative and glucopyranosyl thiolate anion through iterative cross coupling reaction followed by stepwise extension. Intramolecular ring

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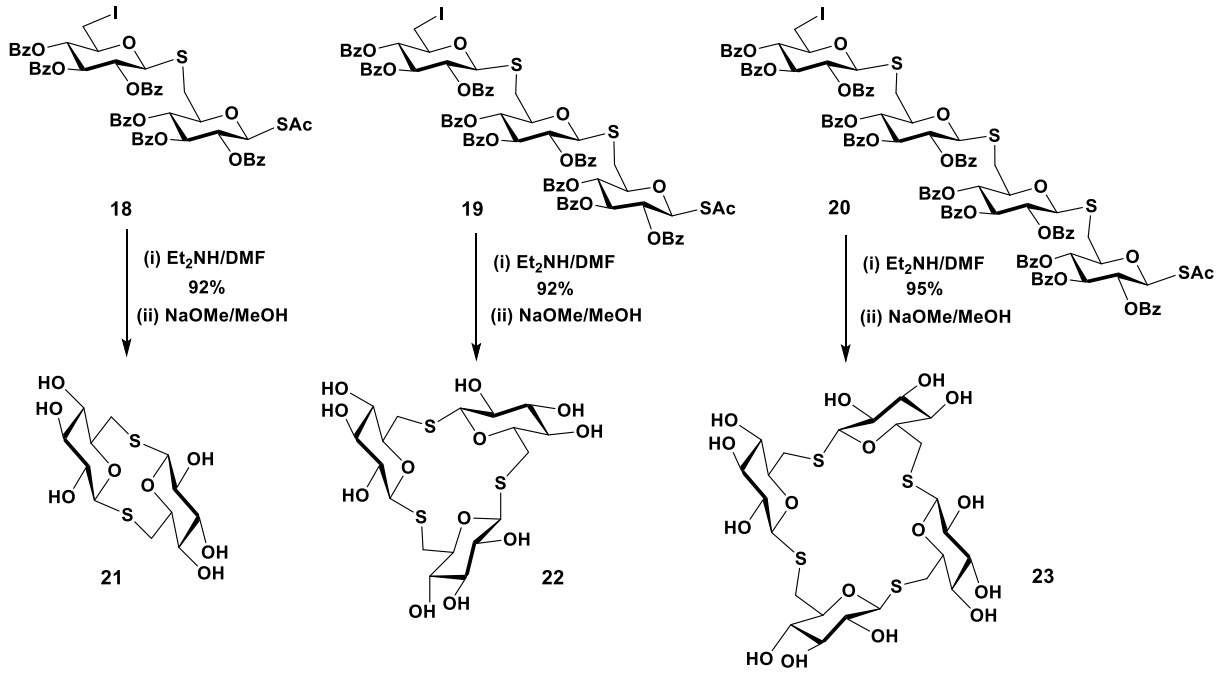
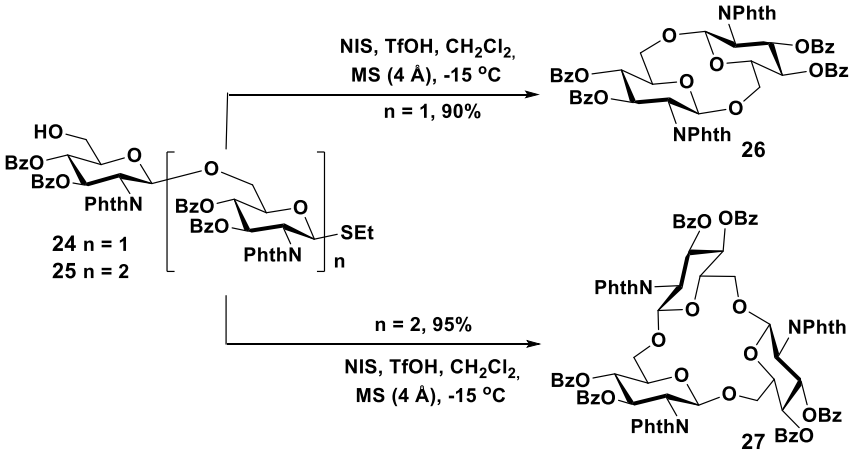
cyclization through S_N2-type glycosylation of 6-iodo thioacetate derivatives **18**-**20** was conducted in the presence of diethyl amine and subsequent removal of benzoyl protecting groups under Zemplén condition afforded β-(1→6) thio-linked cyclic oligomer **21**-**23**, in excellent yields with high stereoselectivities (Scheme 5).

D-Glucosamine-based cyclic oligosaccharides with up to seven units was demonstrated by Nifantiev and co-workers.[24,25] Syntheses of cyclic oligo-β-(1→6)-D-glucosamines, derived from the corresponding linear analogues, are shown in Scheme 6. Linear disaccharide **24** and trisaccharide **25**, constituted with thioethyl moiety at the reducing end and hydroxy functionality at the non-reducing end, underwent intramolecular cyclo-glycosylation, in the presence of NIS/TfOH, and afforded cyclic di- (**26**) and trisaccharide (**27**), in 90% and 95% yield, respectively, with β-glycosidic linkage. The presence of strongly participating 2-*N*-phthaloyl group led to high β-stereoselectivity of glycosylation (Scheme 6).



Scheme 5. Synthesis of β-(1→6) thio-linked cyclic di- to tetrasaccharides.[23]



Scheme 6. Synthesis of cyclo-di- and tri-β-(1→6)-D-glucosamines **26** and **27**.[24]

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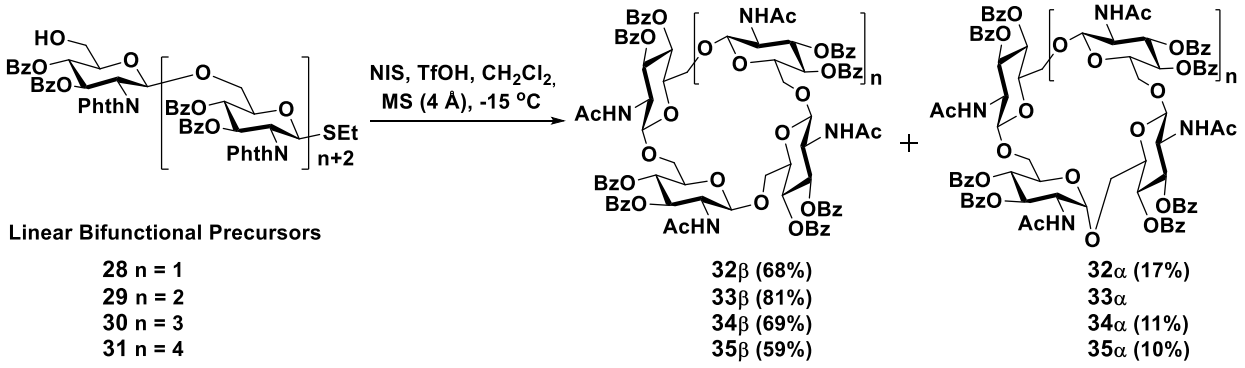
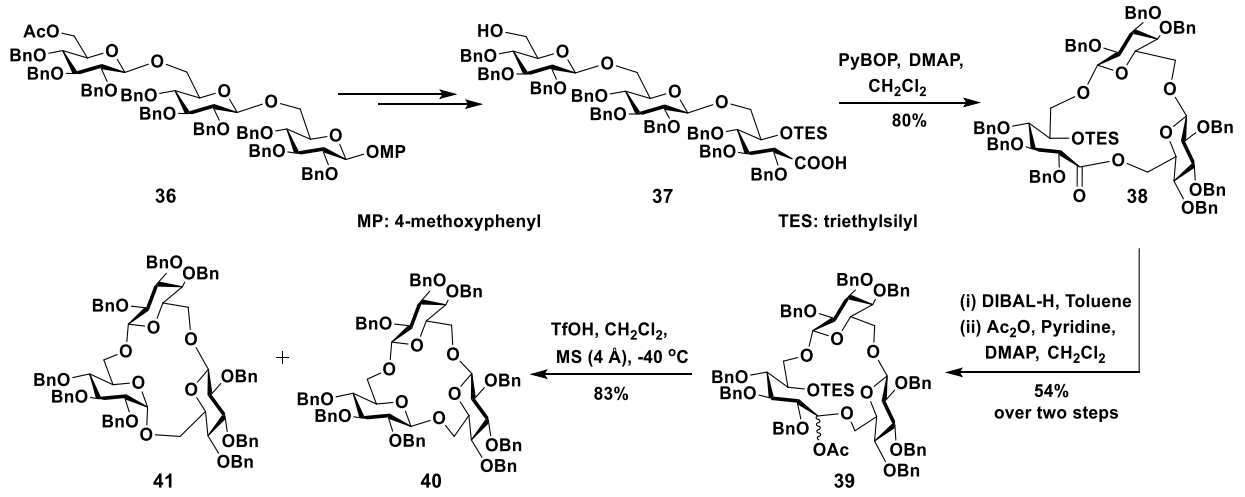
Similarly, one-pot cyclo-oligomerization of linear tetra- to heptasaccharides **28**-**31** led to the formation of the corresponding cyclic oligomers **32**-**35**, in moderate to good yields (Scheme 7). It was observed that except linear pentasaccharide **29**, precursors **28**, **30** and **31**, furnished both α- and β-anomers in the cyclic products, with β-product as the major isomer. Computer modeling studies revealed that a distinct hydrophobic cavity was absent in the cyclo-oligo glucosamines, in contrast to native cyclodextrins. These novel cyclic oligomers were used for designing vaccines and oligo-dentate glycoconjugates.

Liu and Li reported the synthesis of benzylated β-(1→6)-linked cyclo-gentiotrioses through an alternate route not involving the usual oxocarbenium ion intermediate during glycosylation.[26] In this study, linear trisaccharide **37** containing acyclic carboxylic acid moiety at the reducing end and a hydroxy functionality at the non-reducing end was utilized to prepare cyclic trisaccharides **40** and **41** (Scheme 8). Synthesis of *seco*-acid derivative **37** was achieved from trisaccharide **36**, having 4-methoxyphenyl group at the reducing end through following synthetic manipulations of: (i) removal of *p*-methoxyphenyl protecting group upon treatment with ceric ammonium nitrate (CAN), followed by deprotection of OAc at the non-reducing end; (ii) oxidation of lactal, followed by formation of amide using benzylamine; (iii) triethylsilyl (TES) protection of hydroxy groups; (iv) conversion of amide to an activated imide, followed by selective deprotection of TES at the primary hydroxy group and (v) hydrolysis of imide to acid by treatment with LiOH and H_2O_2 to secure carboxylic acid **37**.



Scheme 7. Synthesis of cyclic tetra- to hepta-β-(1→6)-D-glucosamines.[24]



Scheme 8. Synthesis of benzylated β-(1→6)-linked cyclo-gentiotrioses.[26]

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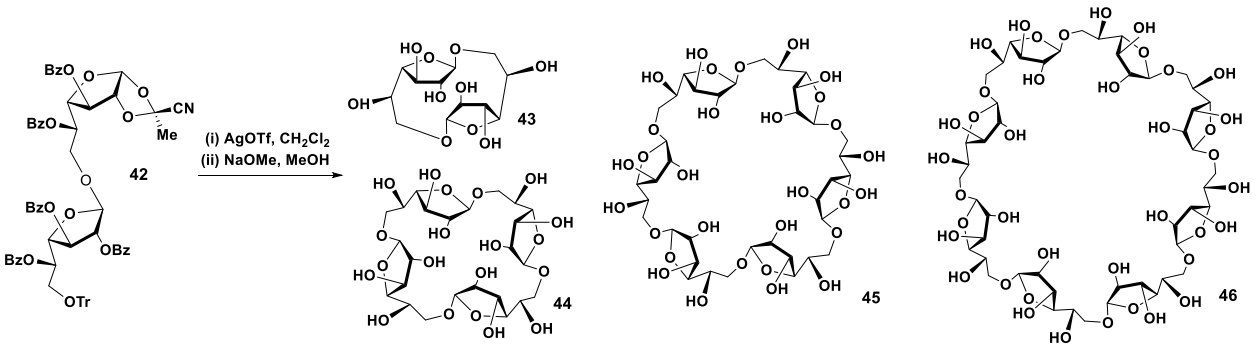
Macrolactonization of the acid derivative **37**, in the presence of benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) and 4-dimethylamino pyridine (DMAP), afforded macrocycle **38**, in 80% yield. Further, macrolactone **38** afforded α-acetoxy ether **39** upon reduction using DIBAL and Ac_2O. TfOH-mediated ring-closing cyclization of trisaccharide **39** furnished cyclo-gentiotriose **40**, as the major isomer and (α,α,β)-linked cyclic trisaccharide **41**, as a minor product (Scheme 8). This technique involving macrolactonization followed by intramolecular ring closing appears as a promising approach towards synthesis of small-ring cyclic oligosaccharides.

Polycondensation strategy of suitably decorated linear di- and trisaccharides was another successful approach to obtain cyclic oligosaccharides with the sugar units in multiples of its monomer. Kochetkov and co-workers first explored this method to achieve cyclo-[(1→6)-β-D-galactofurano]-oligosaccharides **43** to **46** from disaccharide monomer **42** (Scheme 9).[27] Monomer **42**, equipped with cyanoethylidene moiety at the reducing end and tritylated moiety at the non-reducing end, was synthesized judiciously from cyanoethylidene protected D-galactofuranosyl derivative. One-pot polycondensation of tritylated 1,2-*O*-(1-cyanoethylidene) disaccharide derivative **42** in the presence of silver trifluoromethanesulfonate, followed by removal of ester functionalities, afforded cyclic di- (**43**), tetra- (**44**), hexa- (**45**) and octa- (**46**) β-D-galactofuranosaccharides, respectively (Scheme 9). In a similar approach, trisaccharide monomer provided cyclic tri-, hexa- and nona- β-D-galactofurano-oligosaccharides. The cyclo-glycosylation involved the formation of free hydroxy group upon *O*-detritylation by AgOTf and subsequent glycosylation involving cyanoethylidene donor at *C*-1. Notably, mixtures of cyclic oligosaccharides were well-separated by column chromatography, due to large differences in their molecular weights. Stoddart and co-workers later expanded this polycondensation strategy to achieve various types of cyclic oligosaccharides in an elegant manner. Several large ring cyclic oligosaccharides were synthesized and their structural properties, including solid state structures, were established.[28-30]



Scheme 9. Synthesis of cyclo-(1→6)-β-D-galactofurano)-oligosaccharides by a polycondensation strategy.[27]

3. Chemical Synthesis of the Smallest Cyclodextrin

Cyclodextrins, discovered in 1891 by Antoine Villiers,[31] have occupied most interest, mainly on three cyclic oligomers, namely, α-, β- and γ-CD, consisting of six, seven and eight sugar units connected through α-(1→4) glycosidic linkages, respectively. Chemical synthesis of cyclodextrins with less than six sugar units is challenging, due to conformational instability and steric overlap in individual sugar moieties constituting the macrocycle. Existence of cyclodextrins with three and four sugars was considered nearly impossible until Yamada and co-workers achieved the synthesis of 3 and 4 monosaccharide-containing cyclodextrins, using conformationally supple glucose monomers.[32]

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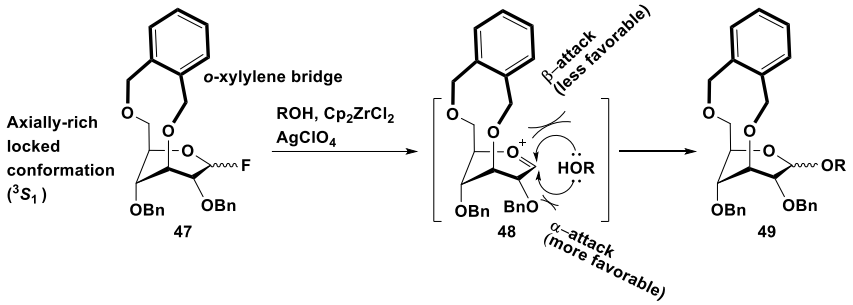
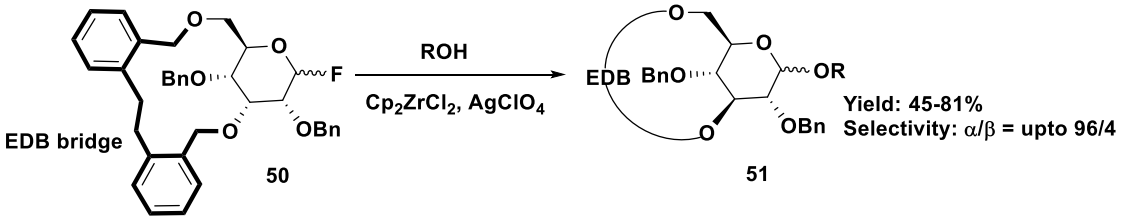
Constraining the conformation of the glycosyl donor is a valuable route to enforce stereoselectivities in glycosidic bond formation. Conformationally-constrained 3,6-*O*-*o*-xylylene-bridged glucosyl fluoride **47** as a donor was developed in order to conduct glycosylation with high α-anomeric selectivity (Scheme 10).[33,34] The *o*-xylylene aids to block the β-face of the pyranose ring and facilitates the approach of the nucleophile from α-face to form α- anomeric product selectively, under kinetically-controlled reaction conditions. The presence of 2-*O*-benzyl group at C-2 in **48** hinders the α-face in the locked pyranose ring system in skew conformation ($^3S_1$) and resulted in a low yield of **49**, with poor α-selectivity in glycosylation with sterically hindered alcohol.



Scheme 10. Glycosylation approach involving conformationally-constrained glycosyl donor, constituted with *o*-xylylene bridge.[33]

In order to overcome the loss of stereoselectivity, the authors identified the possibility of increasing the length of the bridge and fulfil two important factors, namely, (i) increase the steric hindrance at the β-face and (ii) reduce steric hindrance arising from 2-*O*-benzyl group on the α-face. With these considerations, (1,1'-(ethane-1,2-diyl) dibenzene-2,2'-bis(methylene) (3,6-*O*-EDB) bridged glycosyl fluoride donor **50** was chosen over 3,6-*O*-*o*-xylene bridged conformer for glycosylation. The attempts resulted in glycoside products with excellent α-selective product formation (**51**), under Suzuki glycosylation condition at room temperature (Scheme 11).[33,34]

Following the ability to enforce the reaction to afford glycosidic bond with excellent α-selectivity, the concept was extended to synthesize strained cyclodextrins rings. A supple pyranose system, attached with EDB bridge between two distant oxygen atoms on the pyranose, forms a bicyclic ring which can modulate the conformations of pyranose intermediates during the glycosylation reactions. The EDB bridge was assumed to be perfect in length to modulate the conformations between an equatorial-rich $^4C_1$ form and an axial-rich $^1C_4$ conformation.



Scheme 11. Conceptualization of the EDB bridge glycosyl fluoride donor in a glycosylation.[33]

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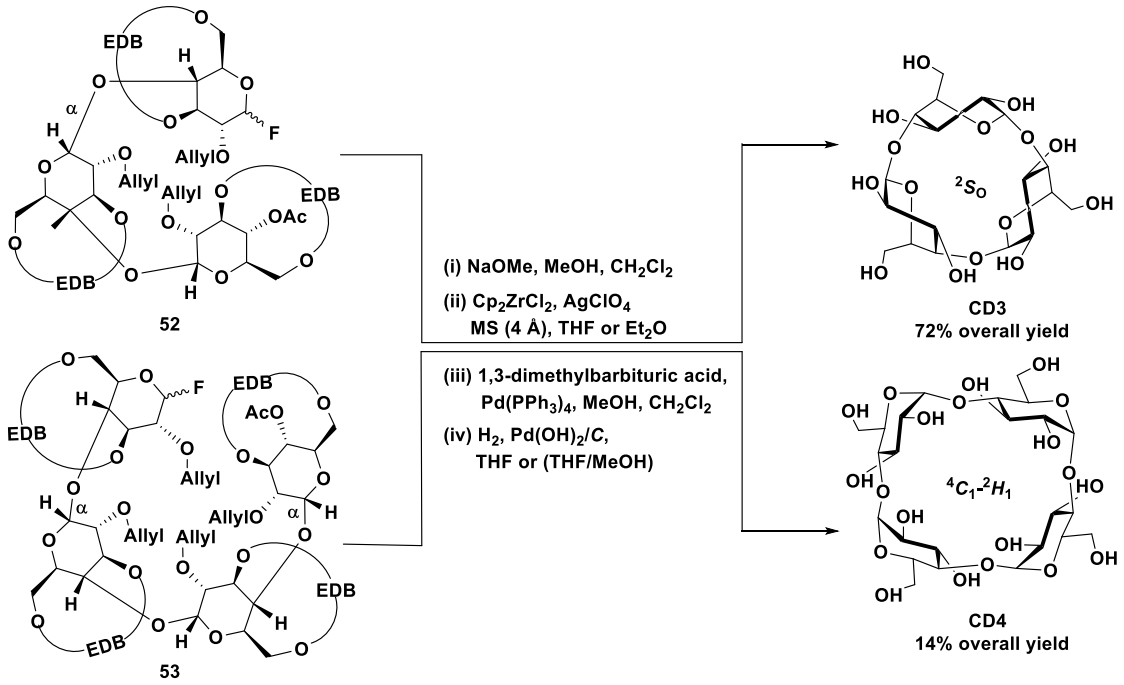
The target cyclodextrin analogues CD3 and CD4 were prepared from 1,2,4-orthoacetylglucose monosaccharide in a convergent manner. Linear precursors **52** and **53** were synthesized by α-selective glycosylation, using a common disaccharide acceptor, monosaccharide and disaccharide donors, respectively.



Scheme 12. Synthesis of small ring cyclodextrins CD3 and CD4 by Yamada and co-workers.[32]

The incorporation of sterically less-hindered allyl group, compared to benzyl group, at C-2 carbon afforded high α-selectivity during the glycosylations. Intramolecular cyclization of the trisaccharide **52** and tetrasaccharide **53** glycosyl fluoride donors under Suzuki glycosylation condition and subsequent global deprotections afforded the desired small ring cyclic oligosaccharides CD3 and CD4, in 72% and 14% overall yields, respectively (Scheme 12). The synthesis illustrated that small ring cyclodextrins could indeed be formed and made a record at a time when it was considered nearly impossible that such products could ever exist, for reasons of unfavorable conformations on individual sugar units in these macrocycles.

As anticipated, NMR studies showed that the conformation of CD4 tended to be between $^4C_1$ and $^2H_1$, wherein pyranose rings were distorted, and flattened, when compared to that of the larger ring cyclodextrins. Further, the three sugar-containing CD3 was found to adopt $^2S_0$ conformation in each sugar units in D_2O solution, as adjudged in early molecular simulation studies of Lichtenthaler and co-workers.[6] Single crystal X-ray diffraction studies further reiterated the skew conformation in one of the sugar units ($^5S_1$) in CD3, with remaining two sugar units retained in between $^4C_1$ and $^0H_1$ conformations in the solid state, much away from the stable $^4C_1$ conformation of naturally-occurring and large ring cyclodextrins.

4. Preparation of Glycosidic Bond Expanded Small-Ring Cyclic Oligosaccharides

It became imperative to retain the $^4C_1$ conformation in the individual sugar units, in order to achieve the sugar wall constituting the cyclic oligosaccharides as that in native CDs and to benefit from attendant molecular, supramolecular properties. Small ring cyclic oligosaccharide analogues were conceived with changes in the

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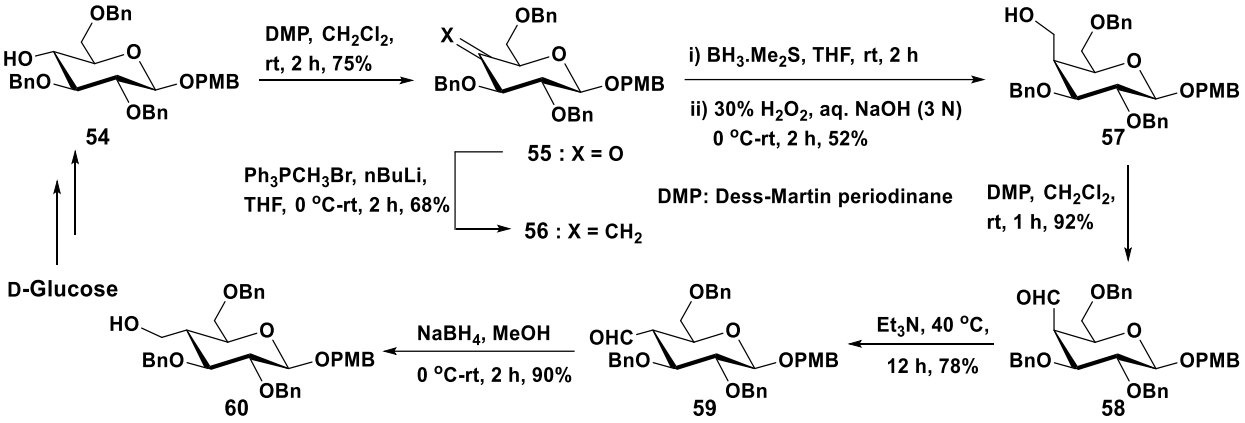
glycosidic bond linking the individual sugar units. Important to a modification is to (i) retain the glycosidic oxygen in the α-anomeric configuration and (ii) involve *C*-1 and *C*-4 carbons of the sugar units in the cyclic oligomers. Reducing the conformational instability warranted changes in the glycosidic bond linkage beyond that present in native cyclodextrins. A one-atom extension between the glycosidic oxygen and *C*-4 carbon was thought invaluable, in order to meet the above requirements. Thus, the glycosidic bond linkage would be extended with a methylene moiety. With this motivation, early studies focused on synthesis and studies of a disaccharide constituted with the extended glycosidic bond linkage.

Synthesis of this *C*-4 methylene attached D-glucopyranoside derivative **13** was achieved by using D-glucose as starting material, as shown in Scheme 13.[35] At first D-glucose was converted to orthogonally protected derivative **54**, possessing a free hydroxy moiety at *C*-4 carbon. Dess-Martin periodinane (DMP) oxidation of **54** afforded ketone **55**, in a good yield. In order to introduce one carbon at *C*-4 of **55,** Wittig methylidenation reaction was performed to furnish olefin **56**.



Scheme 13. Synthesis of 4-deoxy-4-*C*-hydroxymethyl glucopyranoside **13**.[35]

Hydroboration-oxidation of olefin **56** afforded monosaccharide **57**, with *galacto*-configuration. The reaction also led to the tertiary alcohol, an anti-Markovnikov addition side product, in 10-15% yield. The *galacto*-alcohol **57** was taken through: (i) DMP oxidation to form aldehyde **58**; (ii) epimerization of **58** in the presence of Et_3N to afford thermodynamically stable aldehyde **59** and (iii) reduction in the presence of $NaBH_4$ in MeOH to afford **60**, installed with the hydroxymethylene functionality at *C*-4 carbon (Scheme 13).

An effort was undertaken to synthesize the disaccharide constituted with the new monomer **60**. The corresponding imidate monomer **61** was prepared through deprotection of *p*-methyoxybenzyl protecting group in **60** with trifluoracetic acid and reaction of the resulting hemiacetal with trichloroacetonitrile (Cl_3CCN), in the presence of K_2CO_3, which served as the glycosyl donor. Glycosylation of acceptor **60** and acetimidate donor **61**, in the presence of TMSOTf, afforded disaccharide **62**, with α-anomeric configuration, in 66% yield. The β-anomer was also obtained in ~30% yield. Further, the disaccharide **62** was converted to active thioglycoside disaccharide monomer **63** by (i) removal of *p*-methoxybenzyl group in the presence of trifluoroacetic acid and (ii) *O*-acylation of the resulting lactal; (iii) reaction with EtSH in the presence of $BF_3.OEt_2$ and (iv) *O*-deacetylation at the non-reducing end (Scheme 14).[35]

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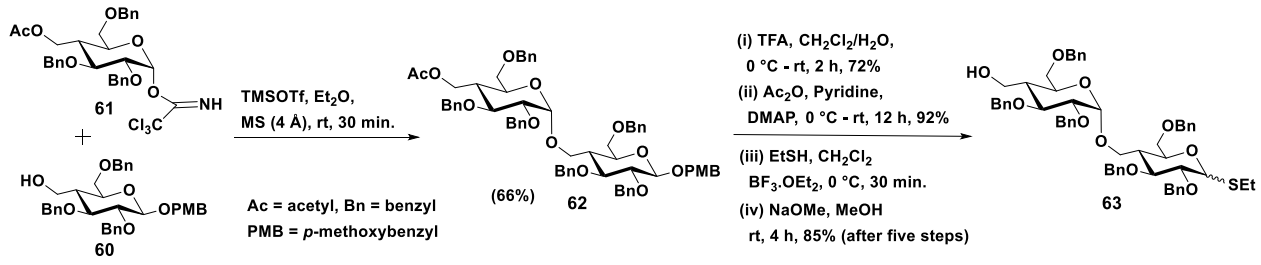
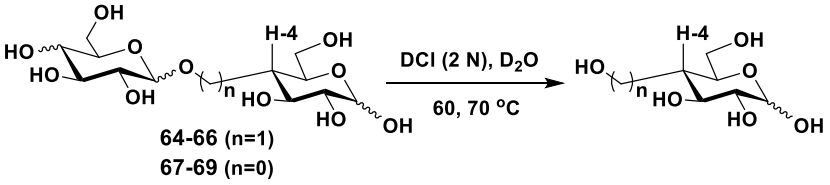


Scheme 14. Synthesis of disaccharide **62** and the corresponding thioglycoside donor **63**.[35]

It was of interest to evaluate the hydrolytic stabilities of the disaccharides constituted with the new monosaccharide monomer **60**. For this purpose, 3 disaccharides possessing 4-deoxy-4-*C*-hydroxymethyl pyranose moiety were synthesized. The corresponding naturally-occurring disaccharides were used for the comparison of the hydrolytic stabilities. An acid-catalyzed hydrolysis was conducted on 6 disaccharides, in the presence of DCl (2 N) in D_2O, at 60 and 70 °C (Scheme 15). Rate of inter-glycosidic bond hydrolysis was monitored by the appearance of new H-4 in 4-deoxy-4-*C*-hydroxymethyl D-glucopyranose through ^1H NMR spectroscopy.



Scheme 15. Acid-catalyzed hydrolysis of disaccharides **64 – 69**.[35]

The hydrolysis data was plotted as a function of time and the observed kinetic data was compared with that of native disaccharide analogues, for example, cellobiose (**67**), lactose (**68**) and maltose (**69**), as shown in Table 1. These experiments showed that 4-deoxy-4-*C*-hydroxymethyl glucopyranose-containing disaccharides possessed increased hydrolytic stability in comparison to the naturally-occurring disaccharide **67**-**69**. Protonation of the glycosidic bond being the first step in the acid hydrolysis, increased hydrolytic stabilities of glycosidic bond expanded disaccharides appeared to undergo slower protonation in these disaccharides than in the case of native disaccharides.

Encouraged by the increased hydrolytic stabilities of glycosidic bond involving 4-deoxy-4-*C*-hydroxymethyl glucopyranosides, synthesis of new cyclic oligosaccharides constituted with this new glycoside was undertaken and properties of the resulting macrocycles were investigated. For this purpose, disaccharide monomer **63** turned out to be superior for cyclization reactions than the corresponding monosaccharide monomer. A one-pot cyclo-oligomerization was carried out by utilizing thioglycoside monomer **63**, in the presence of NIS/TMSOTf or AgOTf (Scheme 16). The cycloglycosylation reaction led to the formation of fully benzyl protected cyclic di- **70** and tetrasaccharide **71**, in 11% and 64% yields, respectively, through intra- and intermolecular cyclization reaction.

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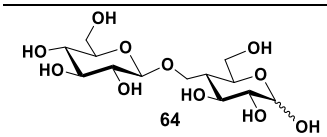
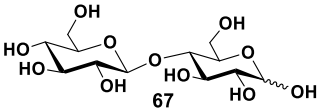
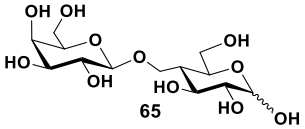
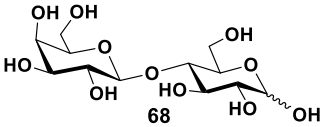
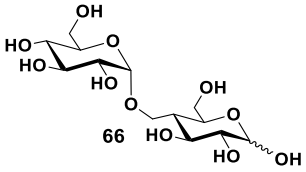
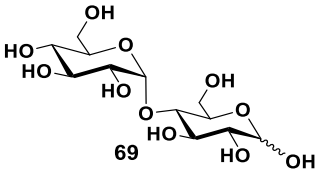
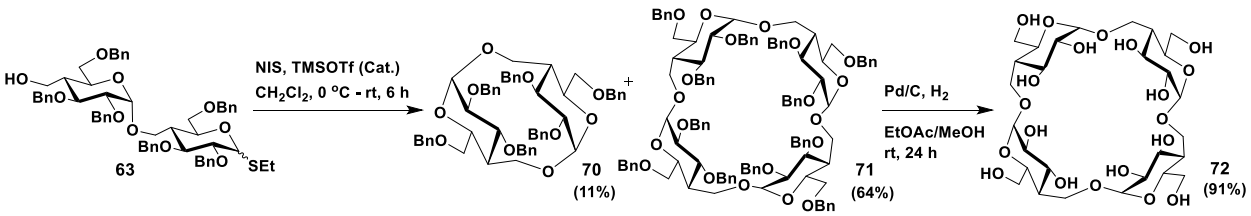
Table 1. A comparison of the rate of hydrolysis of disaccharides

Compound	(k)[a] (60 °C)	(k)[a] (70 °C)	Compound	(k)[a] (60 °C)	(k)[a] (70 °C)
 64	0.25	1.08	 67	4.39	19.20
 65	1.37	4.78	 68	7.85	35.80
 66	0.49	2.10	 69	16.20	61.15

[a] Rate of hydrolysis (k) x 10^5 $s^{-1}mol^{-1}$



Scheme 16. Cyclo-glycosylation of disaccharide monomer **63** and synthesis of cyclic disaccharide (**70**) and tetrasaccharide (**71**), possessing the expanded glycosidic bond linkage.[36]

By varying the promoter from TMSOTf to AgOTf, as well as, changing the monomer concentration of **63** from 3 mM to 20 mM did not improve the yield of benzyl protected cyclic tetrasaccharide **71** considerably. After purification, cyclic tetrasaccharide **71**, *O*- debenzylation was performed by hydrogenolysis, which led to the formation of fully free hydroxy group containing cyclic tetramer **72**, in 58% overall yield.[36]

Energy minimized structure obtained through molecular modeling studies showed that cyclic tetramer **72** possessed an ellipsoid structure, in which all pyranoside moieties adopted $^4C_1$ conformation with primary hydroxy groups at the wider side of the rim and secondary hydroxy groups at the narrower side of the rim, respectively. The molecular dynamics simulation revealed (i) such a small ring cyclic oligosaccharide fully adopts the stable chair conformation and (ii) the location of primary and secondary hydroxy groups differed with that present in native CDs.

Interestingly, the new cyclic tetramer **72** is amphiphilic in nature, soluble in both organic solvents, as well as, in aqueous solutions. As a result, water insoluble pyrene can be solubilized in aq. solutions containing **72**. Pyrene was admixed with aqueous solution of cyclic tetramer **72** in varying concentrations and its extent of solubilization was determined by UV-Vis spectroscopy. It was found that a concentration of up to 14.7 µM pyrene can be solubilized in 0.9 mM of cyclic host **72** in aqueous medium. Further, it was found that organic solvent insoluble L-tyrosine can be solubilized in organic solutions of **72**. A 1:1 molar ratio of cyclic tetramer **72**

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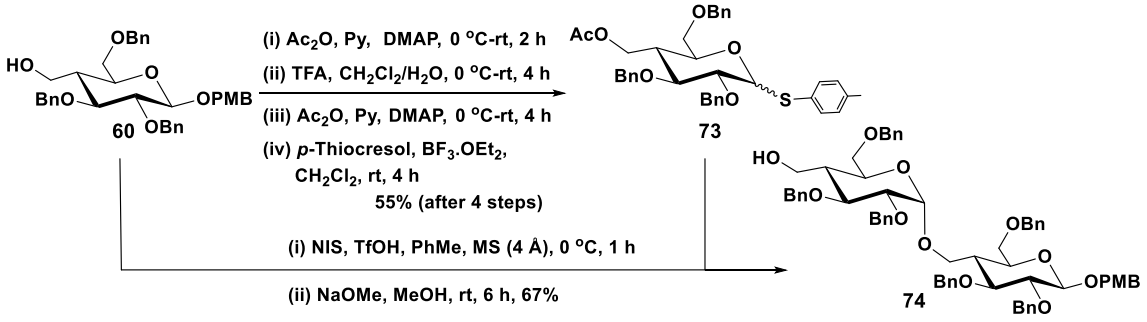
to L-tyrosine was determined from integration values of ^{1}H NMR spectrum of the inclusion complex. The amphiphilic character of the glycosidic bond expanded cyclic tetrasaccharide **72**, with free hydroxy groups in the pyranoside, is un-common in cyclic oligosaccharide macrocycles at large, and opens a new direction for host-guest studies.[36]

A glycosidic bond expanded linear trisaccharide monomer **77** constituted with hydroxy acceptor site at the non-reducing end and thiocresyl donor moiety at the reducing end was synthesized from 4-deoxy-4-*C*-hydroxymethyl D-glucopyranose **60**. Derivative **60** was converted to a thioglycoside monomer **73** by performing: (i) *O*-acetylation at the non-reducing end; (ii) selective removal of *p*-methoxybenzyl group; (iii) acetylation of anomeric lactal and (iv) thioglycosylation using *p*-thiocresol, as shown in Scheme 17.[37]

Glycosylation of acceptor **60** with thioglycoside **73**, in the presence of NIS and TfOH, afforded protected derivative of **74**, which upon *O*-deacetylation condition facilitated isolation of the α-anomer **74** (Scheme 17).



Scheme 17. Synthesis of disaccharide acceptor **74**.[37]

Towards synthesis of the trisaccharide monomer **77**, further glycosylation of disaccharide **74** and thioglycoside **73**, in the presence of NIS/TfOH, followed by *O*-deacetylation at the non-reducing end afforded trisaccharide **75**, in 68% yield (Scheme 18). Finally, trisaccharide **75** was converted to active trisaccharide thioglycoside monomer **77**, through formation of lactal **76**. First, *O*-acetylation at the non-reducing end in the presence of Ac_2O in pyridine, followed by removal of *p*-methoxybenzyl group using trifluoroacetic acid afforded lactal **76**. Further, *O*-acetylation of anomeric lactal **76** and subsequent thioglycosylation using *p*-thiocresol, in the presence of $BF_3.OEt_2$, led to the formation of thioglycoside **77** (Scheme 18).

Trisaccharide monomer **77** was subjected to one-pot cyclo-glycosylation in dilute condition (20 mM) by the treatment of NIS/TfOH. The crude reaction mixture was taken through *O*-debenzylation to furnish intra-molecular cyclized hydroxy groups containing cyclic trisaccharide **78**, in 52% yield after these two steps (Scheme 18). In addition to the cyclic trimer, the crude reaction mixture also revealed the presence of cyclic hexamer and nonamer, as adjudged through mass spectral analysis. However, these higher cyclic oligosaccharide species could not be isolated upon chromatographic purifications.

The new cyclic trimer **78** is highly soluble in aqueous medium, whereas weekly soluble in organic solvents, such as, $CHCl_3$. Further structural studies of **78** became feasible through single crystal X-ray diffraction. Single crystal suitable for the analysis was obtained by slow vapor diffusion of acetone in aqueous solution of the cyclic trimer. Several structural features were identified in the solid state structures. (i) The presence of complete symmetry of the molecule was revealed by the molecule adopting a perfect trigonal symmetry, with *P*3 space group (Figure 1a). (ii) The pyranoside adopts a perfect $^4C_1$ conformation, even when the macrocycle is constituted only with 3 sugar units. (iii) The primary hydroxy groups are located at the

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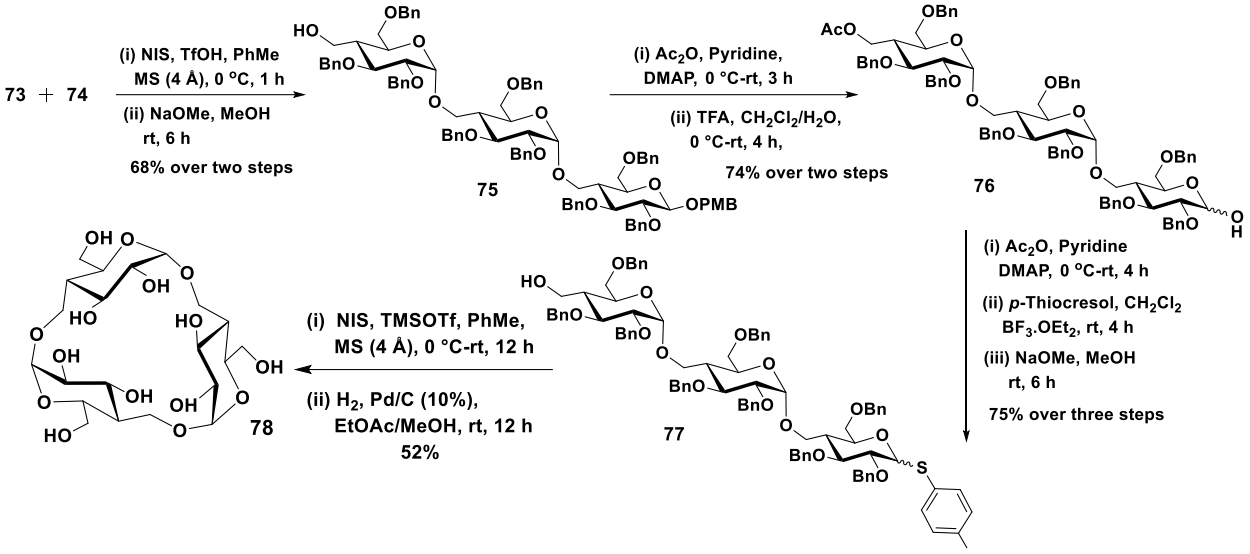
narrower side of the cone, whereas secondary hydroxy groups are situated at the wider side of the rim, respectively, similar to that of native CDs. (iv) The structure presents a sharper cone shape than native CDs (Figure 1b). (v) A brick wall type arrangement of molecular packing occurs in the solid state, a feature not observed in the native CDs, as shown in Figures 1c and 1d.



Scheme 18. Synthesis of glycosidic bond expanded trisaccharide **78**.[37]

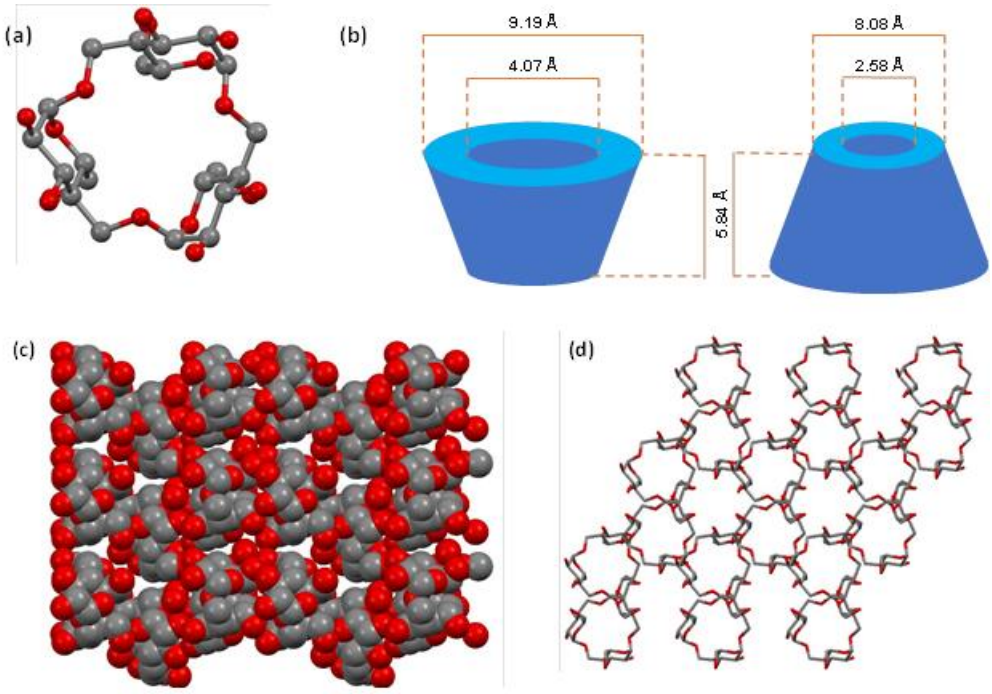


Figure 1. (a) ORTEP diagram of cyclic trimer **78**; (b) cartoon representation of cyclic trimer with molecular dimensions; (c) CPK model and (d) gauss views of the packing in the solid state.[37]

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A comparison between this backbone modified cyclic trimer **78** and smallest cyclic CD3 was of interest to address their conformational dissimilarities. There are two distinct features related to their X-ray crystal structures and microenvironments created by these macrocycles: (i) although suppleness of the linear monomeric unit allowed the synthesis of highly strained CD3, the sugar units in CD3 turned into a distorted $^{5}S_{1}$ and between $^{4}C_{1}$ and $^{0}H_{1}$ conformations deviated from $^{4}C_{1}$ conformation, whereas each sugar unit in cyclic trimer **78** possessed a perfect $^{4}C_{1}$ conformation in its single crystal lattice; (ii) The interatomic distances in CD3 revealed almost no cavity inside the macromolecule suggesting its ability to form inclusion complex would be almost nil, whereas trimer **78** contained a micro-cavity which could encapsulate guest molecule (1-aminoadamantane) with higher efficacy than native β-CD.

An avenue of immense importance of CDs is their supramolecular properties in aqueous solutions, attendant with their high affinities to hydrophobic guest molecules. The macrocyclic cavity of CDs, possessing the $^{4}C_{1}$ conformation of individual sugar units, confers a hydrophobicity, attenuated further by the polar hydroxy-substituents firmly located at the peripheries and away from the cavities. A number of applications has been developed and practiced as a result of the host-guest complexation property suitable to such applications.[38-40] Having realized a perfect chair conformation in the case of the new cyclic trisaccharide, a study of the host-guest complexation property became pertinent and important. For this purpose, two guest molecules, namely, 1-aminoadamatane (AMT) and hexamethylene tetramine (HMT), were chosen and the thermodynamics of the complexation were studied by isothermal titration calorimetry (ITC). Figure 2 shows thermograms of complexation of **78** and β-CD with AMT as guest molecule.

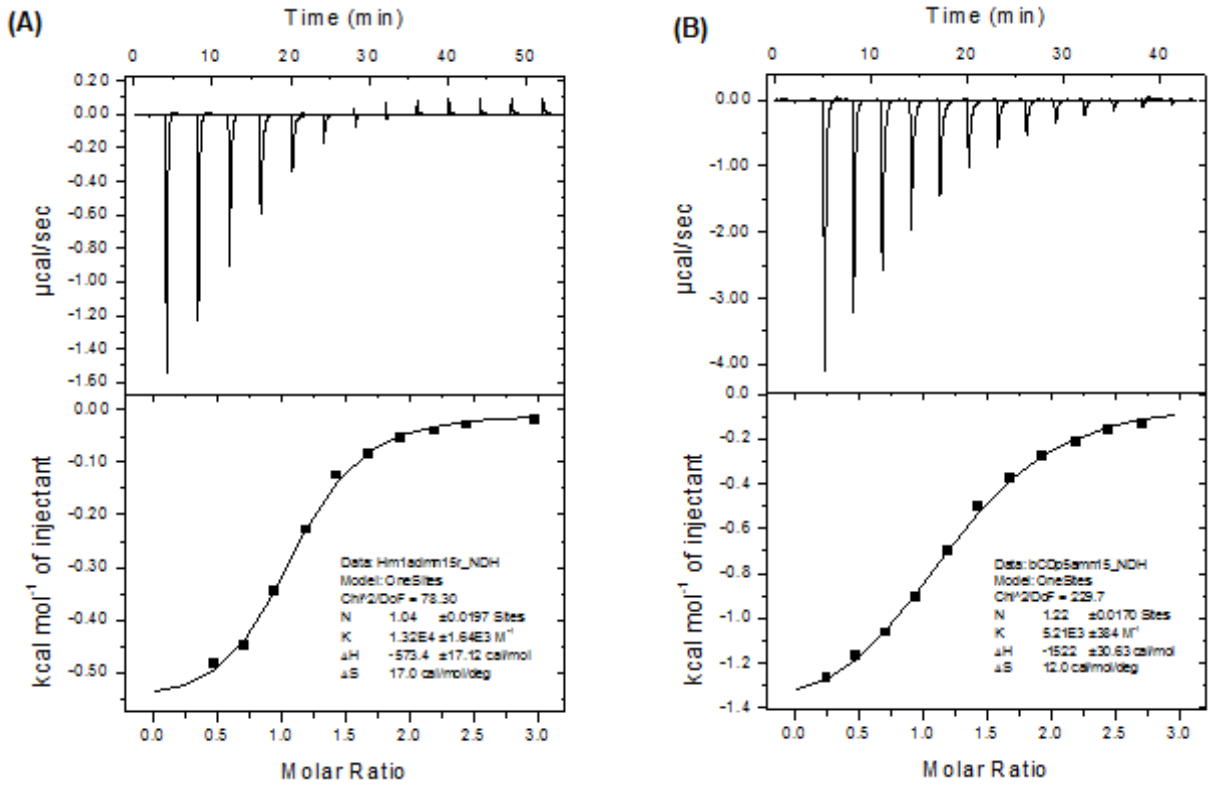

Figure 2. ITC profile for binding interaction of (a) trimer **78** with AMT at 30 °C in water; (b) β-CD with AMT in water.[37]

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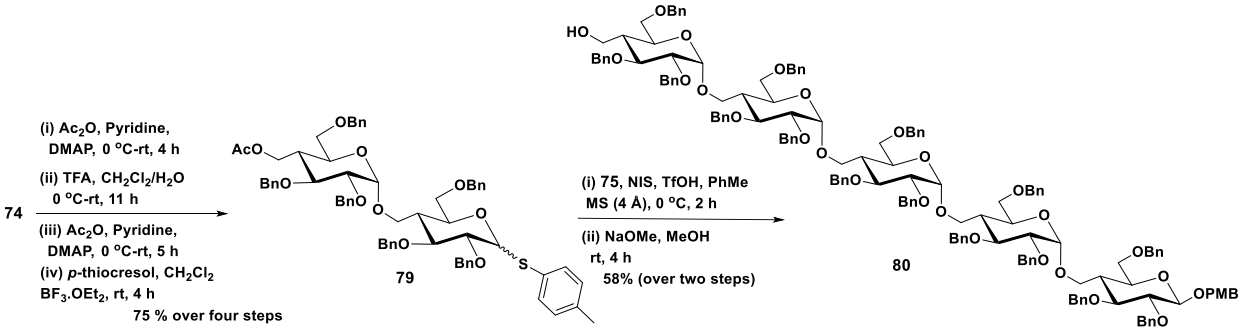
The encapsulation studies were performed in aq. medium at a cyclic trimer **78** or β-CD to AMT of 1:15 molar ratio. ITC studies showed that cyclic trimer **78** binds to AMT in a 1:1 host-guest ratio with binding constant (K_a) 13,200 M^{-1}, comparatively higher than β-CD, where formation of 1:1 host-guest complexation occurred with K_a 5,400 M^{-1}. The 1:1 complexation appeared to occur at the wider rim of the macrocycle with both synthetic cyclic trisaccharide **78** and β-CD. The higher binding constant with **78** could be attributed to the higher hydrophobicity of this host, which, in turn, is a consequence of the perfect $^4C_1$ conformation of individual glucopyranoside units constituting the macrocycle.[37]

The glycosidic expanded cyclic oligosaccharides with 3 and 4 glucopyranoside units showed that these small ring macrocycles compare well with native cyclodextrins in terms of their sizes, shapes and host-guest binding abilities. It became pertinent further to assess formation of 5 sugar containing glycosidic bond expanded cyclic oligomer and to assess the microenvironment offered by such a macrocycle. Towards this aim, an effort was undertaken to synthesize glycosidic bond expanded linear pentasaccharide **80**.[41] In order to synthesize linear pentasaccharide **80**, thioglycoside derivative **79** was prepared at first from disaccharide **74**, by performing four consecutive reactions of: (i) acetyl protection of free hydroxy group; (ii) deprotection of *p*-methoxybenzyl group; (iii) anomeric *O*-acetylation and (iv) anomeric glycosylation using *p*-thiocresol and $BF_3.OEt_2$, in an overall 75% yield, as shown in Scheme 19.



Scheme 19. Synthesis of linear pentasaccharide monomer **80**.[41]

Glycosylation of trisaccharide **75** with thioglycoside **79**, in the presence of *N*-iodosuccinimide and triflic acid in toluene at 0 °C, afforded protected pentasaccharide, which upon *O*-deacetylation led to the formation of linear pentasaccharide **80**, in 58% yield (Scheme 19). Along with α-anomeric configuration of the newly formed glycosidic linkage, corresponding β-anomer also formed at the newly generated glycosidic bond. Further, *O*-deacetylation reaction enabled separation of the α, β-anomeric linear pentasaccharides.

The linear pentasaccharide **80** was taken through multiple steps in order to equip it with an acceptor functionality at the nonreducing end and an activated thioglycoside functionality at the reducing end (Scheme 20). (i) *O*-Acylation of primary hydroxy group at the non-reducing end; (ii) deprotection of *p*-methoxybenzyl moiety at the anomeric carbon; (iii) *O*-acylation at anomeric lactal functionality; (iv) reaction with *p*-thiocresol and (v) *O*-deacetylation at the non-reducing end finally afforded the pentasaccharide monomer **81** (Scheme 20).

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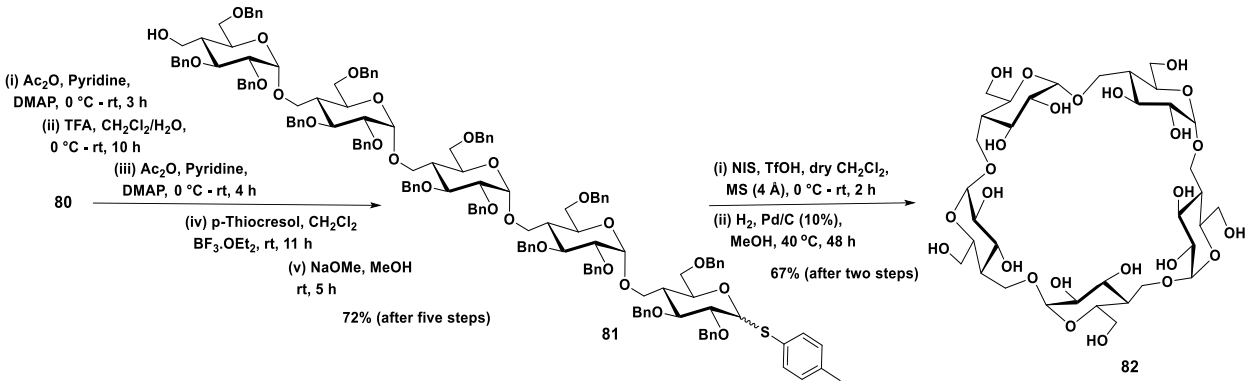

Scheme 20. Cycloglycosylation of linear pentasaccharide to the corresponding macrocycle.[41]

Upon synthesizing active thioglycoside monomer **81**, one-pot cyclo-glycosylation was performed with the concentration of **81** at 20 mM, in the presence of NIS/TfOH, followed by *O*-debenzylation, using H_2/Pd-C, which led to the formation of cyclic pentasaccharide **82**, in 67% yield (Scheme 20). The newly synthesized cyclic pentasaccharide was freely soluble in aqueous solution and weakly soluble in EtOH and $CHCl_3$.

In order to determine the structure of cyclic pentamer **82**, molecular modeling studies was performed using Gaussian 09 software at the (B3LYP)/6-311g level. Modeling studies showed that cyclic pentamer **82** possessed a distorted ellipsoid structure, with all the pyranoside residues retaining in $^4C_1$ conformation, in which size of lower rim is ~86% to that of upper rim (Figures 3a,b). Further, primary and secondary hydroxy groups are positioned at the wider and narrower face of the rim, respectively, similar to that of cyclic tetramer **72**, and in reverse manner as that of cyclic trimer **78** and β-CD.

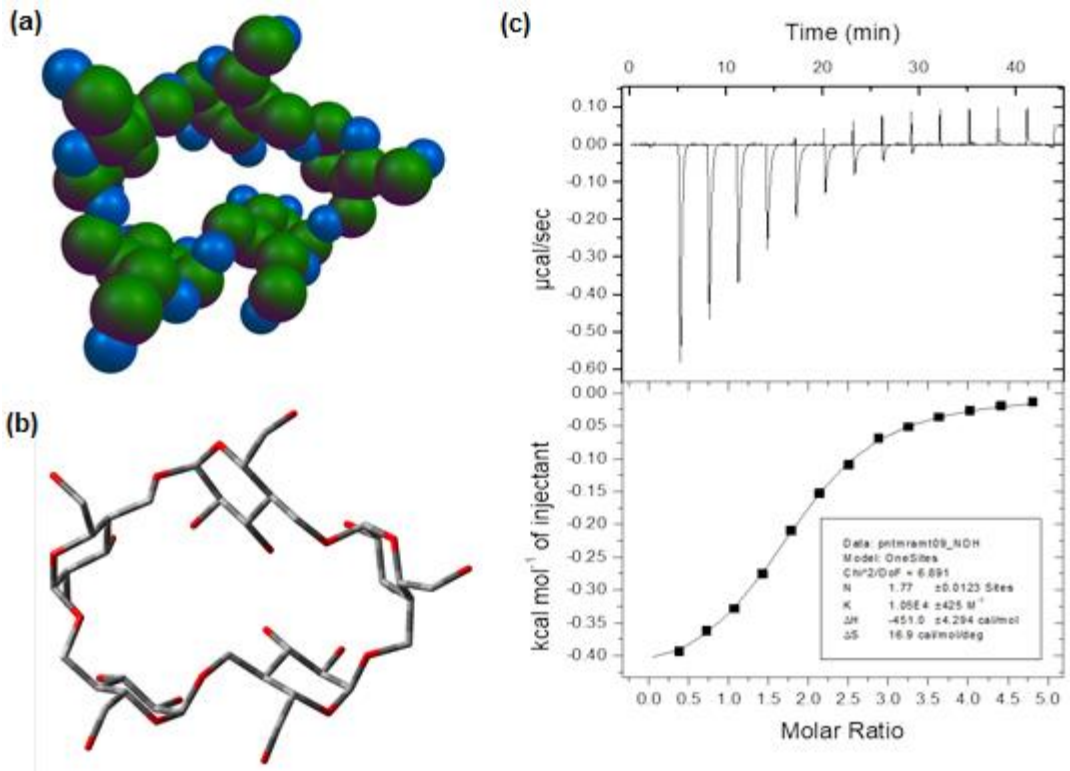

Figure 3. Energy minimized molecular modeling structures of cyclic pentamer **82**: (a) the CPK model exposing the inside cavity; (b) gauss view mode from the top; (c) ITC profile of AMT and cyclic pentamer **82** interaction.[41]

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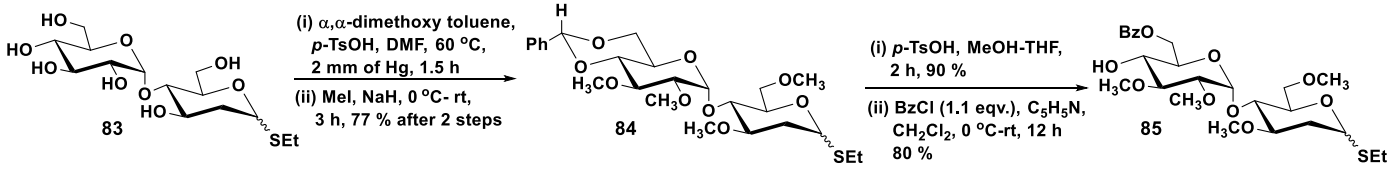
Similar to cyclic trimer **78**, encapsulation properties of cyclic pentamer **82** was assessed in aq. solution. Thermodynamic study was conducted in aq. medium using AMT as the guest, at a host-to-guest ratio of 1:20, at 30 °C (Figure 3c). Thermodynamic parameters revealed that cyclic pentamer **82** binds AMT in a 1:2 host-guest ratio, with binding affinity of 10,500 M^{-1}. Cyclic pentamer **82** exhibited binding interactions with two molecules of AMT either from the same face or from the opposite face of the rim, due to marginal difference in size between upper and lower faces. The ellipsoid geometry of **82** compared to regular cone shape structure of cyclic oligomer facilitated 1:2 of host-guest complexation, which is not common in cyclodextrin chemistry.

Synthesis of small ring cyclic oligosaccharide constituted with 2-deoxy glucopyranoside was also demonstrated.[42,43] A polycondensation approach was followed in this instance. A 2-deoxyglucopyranoside-containing disaccharide was synthesized as the cyclo-condensation monomer. The 2-deoxy sugar containing monomer was prepared from maltose, through a series of conversions, leading to the formation of the precursor. (i) A protection of 4′-OH and 6′-OH of **83**[44] with benzylidene to secure derivative **84**; (ii) methylation of hydroxy groups ; (iii) removal of the benzylidene moiety and (iv) selective protection of the primary 6′-OH group as benzoate afforded the required monomer **85** for cyclo-oligomerization (Scheme 21).



Scheme 21. Synthesis of 2-deoxy glucopuyranoside containing disaccharide monomer **85**.[42]

The monomer **85** was thus equipped with an active thioglycoside moiety at the reducing end and the acceptor functionality at *C*-4 of the non-reducing end. The cyclo-oligomerization was conducted in the subsequent step, at three different monomer concentrations, 2, 10 and 25 mM, in the presence of either NIS/TfOH or AgOTf as the promoter (Scheme 22). MALDI-TOF mass spectrometry and the HPLC analyses of the crude reaction mixture revealed the presence of the cyclic tetrasaccharide **86** and the cyclic hexasaccharide **87**, in addition to the linear di- and tetrasaccharides **88** and **89**, respectively. With 2 mM and 10 mM concentrations of **85α**, the linear saccharides **88** and **89** were isolated in larger amount (**88**: 40%; **89**: 30%). The cyclic products **86** and **87** were obtained in 15% and 7% yields, respectively. Better yields of the cyclic products **86** (40%) and **87** (25%) were isolated when the monomer concentration was 25 mM. The symmetrical structure of **86** was ascertained from their NMR spectra. Only one set of signal was observed in both ^{1}H NMR and ^{13}C NMR spectra. In the ^{1}H NMR spectrum, the signal for H-1 at the 2-deoxy sugar moiety was observed at 4.86 ppm, as a doublet with $J_{1,2a}$ = 3.3 Hz; whereas H-1 corresponding to non-reducing end sugar moiety resonated at 5.89 ppm, as a doublet with $J_{1,2}$ = 3.6 Hz. In the ^{13}C NMR spectrum, the *C*-1 carbon, corresponding to the 2-deoxy sugar moiety, appeared at 98.4 ppm and *C*-1 carbon, corresponding to the non-reducing end sugar moiety appeared at 95.6 ppm. The *C*-2 of the 2-deoxy sugar moiety resonated at 33.9 ppm. Benzoyl-deprotected cyclic hexamer **87** formed an inclusion complex with *p*-nitrophenol, as adjudged by ^{1}H NMR titration method.

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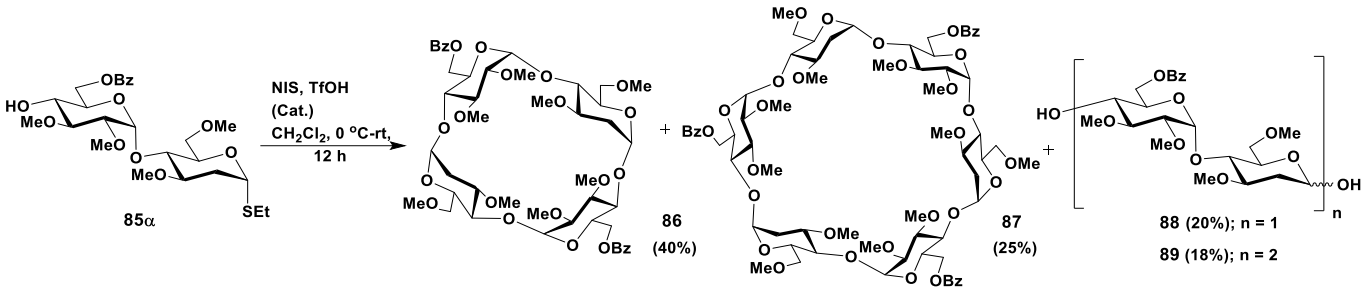

Scheme 22. Cyclo-glycosylation of 2-deoxy sugar-containing disaccharide monomer **85**.[44]

5. Conclusions

Foregoing illustration on synthetic methods exemplifies the challenges to prepare small-ring cyclic oligosaccharides. Some of the rigid requirements are in placing the glycosyl donor-acceptor sites judiciously on the monomers undergoing cyclo-oligomerization and in enabling the macrocyclic structures with functional properties. The synthetic strategies can be expected to undergo further developments incorporating contemporary ideas of conformational constraints as a source to conduct stereoselective glycosylation and cyclo-oligomerization. The sought-after functional properties are demonstrated to outweigh the naturally-occurring cyclodextrins with respect to the host-guest interactions, in few instances. The challenges to synthesize tailor-made macrocycles for defined application purposes, with minimal synthetic manipulations and more, can be expected to be the continuing themes on studies of these small-ring cyclic oligosaccharides.

Acknowledgements

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