JOC The Journal of Organic Chemistry

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Synthesis and Structure of Cyclic Trisaccharide with Expanded Glycosidic Linkages

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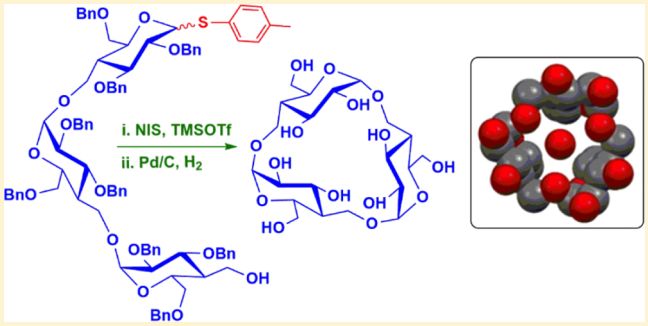
Supporting Information

ABSTRACT: A new cyclic trisaccharide is synthesized by cycloglycosylation of a linear trisaccharide, modified with hydroxymethyl moiety at C4 of glucopyranose moiety. The cyclic trisaccharide possesses a rarely observed perfect trigonal symmetry in the *P*3 space group, in a narrow cone shape, and a brick-wall type arrangement of molecules in the solid state, and exhibits a significantly enhanced binding affinity to 1-aminoadamantane in aqueous solution.



INTRODUCTION

Cyclodextrins, the most abundant naturally occurring cyclic oligosaccharides, are valuable synthetic hosts, primarily as a result of their properties to form inclusion complexes with guest molecules.[1−6] The host−guest relationship is exploited elegantly in a number of instances, a few among them are supra- and supermolecular assembly formation,[7−12] analytical separations and pharmacotherapies,[13] and pharmaceutical formulations.[14] In spite of voluminous literature on the application of cyclodextrins, through modifications of hydroxyl groups, modifications at the backbone continue to be a challenge, although such backbone modifications can be rewarding in order to alter their macrocyclic host properties.[15−20] Skeletal modifications using aromatic, triazole, diyne, thioether, thiourea, phosphate, and disulfide moieties, that replace the native glycosidic bond, were developed previously to alter the cavity properties of cyclodextrins.[21−31] For example, Davis, Bayley, and co-workers demonstrated a breadth in fine sensitivity and diversity of interactions of backbone disulfide modified *β*-cyclodextrins, analytes, and protein pores.[26] We recently reported a skeletal modification through incorporation of an additional methylene moiety at the glycoside linkages, so as to form backbone modified cyclic di- and tetrasaccharides. The cavity properties changed dramatically in the case of the cyclic tetrasaccharide, by which the cyclic oligomer became amphiphilic, a property so far unknown to a cyclic oligosaccharide retained fully with free hydroxyl groups. Due to amphiphilic nature, the host solubilizes both water-insoluble and organic solvent-insoluble guests in aqueous and organic solutions, respectively.[32] The study thus opened up possibilities to synthesize backbone modified cyclic oligosaccharides modified at the glycosidic linkage, yet retained with glycosidic oxygen at the backbone. Synthesis of a backbone modified cyclic oligosaccharide is achieved using a monomer wherein a one carbon insertion is conducted at *C*4 of a pyranose, such that the hydroxyl moiety at *C*4 is replaced with a hydroxymethyl moiety. In an approach, a linear trisaccharide monomer was anticipated to provide cyclic oligosaccharides in multiples of such a monomer.[33−36] In the event, a trisaccharide linear monomer was found to afford a cyclic trisaccharide as the major cyclo-oligomer. Subsequent solid-state structural studies show that the molecule confers a perfect trigonal symmetry in the *P*3 space group, such a geometry is hither-to unknown to a cyclic oligosaccharide. We further identify that the cyclic trisaccharide exhibits strong binding affinities to organic bases in aqueous solutions, as determined by isothermal measurements.

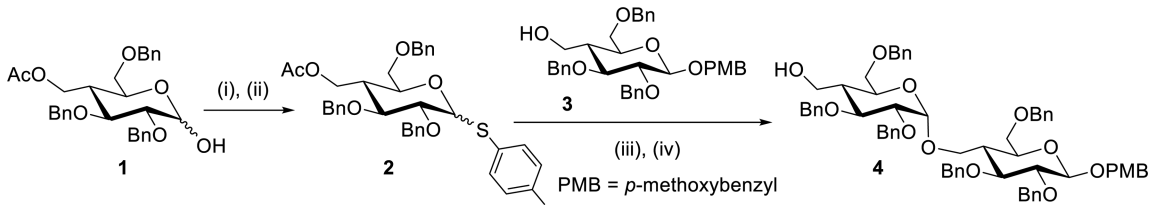
RESULTS AND DISCUSSION

Preparation of a disaccharide from a suitably modified monosaccharide **1** initiated the synthesis toward cyclic trisaccharide (Scheme 1). Monosaccharide **1** was synthesized from the alcohol **3**,[32,37] by performing two following steps (i) acetylation of the primary hydroxyl group and (ii) removal of *p*-methoxybenzyl alcohol group. Monosaccharide hemiacetal **1** was O-acetylated, followed by treatment with *p*-thiocresol in the presence of $BF_3{\cdot}OEt_2$, to afford thioglycoside donor **2** (*α*:*β* = 1:0.4). The activated thioglycoside donor[38] **2** was subjected to glycosylation with the glycosyl acceptor **3** in the presence of NIS/TfOH in PhMe at 0 °C, and a subsequent O-deacetylation provided disaccharide acceptor **4**, in a moderate yield. The *α*-anomeric configuration at the nonreducing end of **4** was inferred by the appearance of a peak at 4.77 ppm as a doublet (*J* = 3.2 Hz) for anomeric proton (H*α*-1′) and 97.8 ppm for

Received: March 2, 2016
Published: May 16, 2016

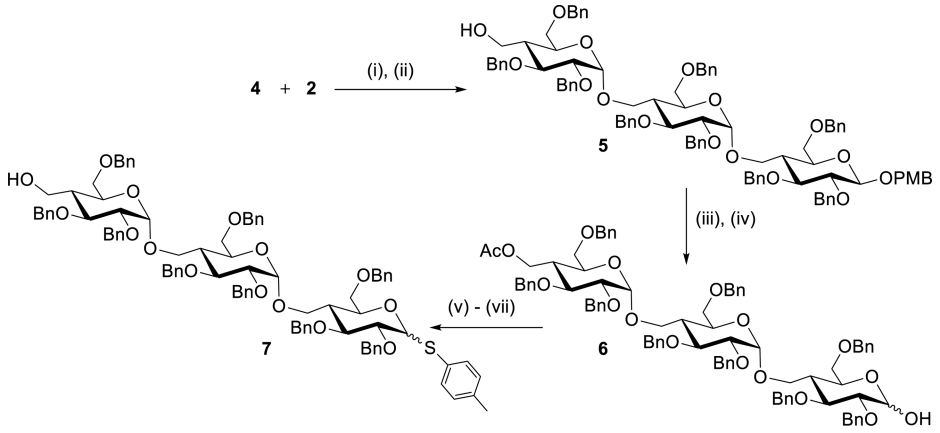
DOI: 10.1021/acs.joc.6b00462
J. Org. Chem. 2016, 81, 4616−4622

Scheme 1[a]



[a]Reagents and conditions: (i) Ac_2O, pyridine, DMAP, 0 °C to rt, 4 h; (ii) *p*-thiocresol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 4 h (85%, 2 steps); (iii) NIS, TfOH, PhMe, MS (4 Å), 0 °C, 1 h; (iv) NaOMe, MeOH, rt, 6 h (67%, 2 steps).

Scheme 2[a]



[a]Reagents and conditions: (i) NIS, TfOH, PhMe, MS (4 Å), 0 °C, 1 h; (ii) NaOMe, MeOH, rt, 6 h (68%, 2 steps); (iii) Ac_2O, pyridine, DMAP, 0 °C to rt, 3 h; (iv) CF_3COOH, CH_2Cl_2/H_2O, 0 °C to rt, 4 h (74%, 2 steps); (v) Ac_2O, pyridine, DMAP, 0 °C to rt, 4 h; (vi) *p*-thiocresol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 4 h; (vii) NaOMe, MeOH, rt, 6 h (75%, 3 steps).

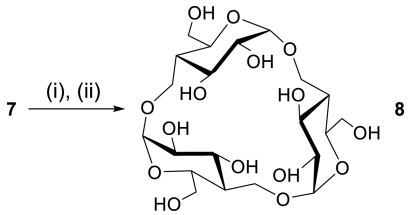
anomeric carbon (Cα-1′) in ^{1}H and ^{13}C NMR spectrum, respectively.

Glycosyl acceptor **4** and donor **2** on treatment with NIS/TfOH in toluene at 0 °C underwent glycosylation to form trisaccharide which was further O-deacetylated to afford **5** (Scheme 2).

The O-deacetylation to afford **5** and an O-acetylation to afford **6** were conducted in order to facilitate purification by column chromatography (SiO_2, PhMe/EtOAc linear gradient). In ^{1}H NMR spectrum of **5**, the appearance of chemical shift at 4.83 ppm (d, J = 3.6 Hz) for H-1 and in ^{13}C NMR spectrum, resonance at 98.5 ppm for anomeric carbon C-1 suggested α-anomeric configuration of the newly formed glycosidic linkage at the nonreducing end. Acetylation of primary hydroxyl group followed by removal of *p*-methoxybenzyl group in **5**, using TFA at 0 °C to rt, afforded trisaccharide hemiacetal **6**, as an anomeric mixture (α:β = 1:0.9). Lactal **6** was converted further to an activated trisaccharide monomer **7** (Scheme 2), using the following three steps sequence (i) acetylation (Ac_2O/Py) of the anomeric hydroxyl group; (ii) installation of thioglycoside (*p*-thiocresol/$BF_3{\cdot}OEt_2$); and (iii) O-deacetylation using NaOMe/MeOH at the nonreducing end.

Cyclo-glycosylation of **7** (20 mM) was performed in the presence of NIS/TMSOTf in PhMe for 12 h to afford a crude product, which was subjected to a purification (SiO_2, PhMe/EtOAc, linear gradient). A major product was isolated, which was subjected to O-debenzylation (H_2/Pd−C). The resulting crude product was purified (SiO_2, $CHCl_3$/MeOH, linear gradient) to afford a major product. From a series of subsequent analyses, the major product was identified to be the cyclic trisaccharide **8** (Scheme 3). Changes in the glycosylation reaction conditions, such as the reagent or solvent, did not markedly improve the product formation. The fully functionalized cyclic trisaccharide (**8**) was readily soluble in aqueous solution, whereas weekly soluble in organic solvents (e.g., $CHCl_3$).

Scheme 3[a]



[a]Reagents and conditions: (i) NIS, TMSOTf, PhMe, MS (4 Å), 0 °C to rt, 12 h; (ii) H_2, Pd/C (10%), EtOAc/MeOH (1:1), rt, 12 h (52%, 2 steps).

The constitution and configuration of cyclic trisaccharide **8** was ascertained by ^{1}H, ^{13}C NMR spectroscopies and mass spectrometry. The molecular ion peak at 551.1967 $[M+ Na]^+$ corresponds to the major peak in the ESI-mass spectrum of **8**. In ^{1}H NMR spectrum of **8**, anomeric proton resonated at 4.93 ppm, as a doublet (J = 4 Hz), whereas anomeric carbon resonated at 98.6 ppm in ^{13}C NMR spectrum, concluding the α-configuration of the glycosidic linkage. Further, a J_{C1-H1} of 169 Hz conformed to an α-anomeric configuration of the glycosidic linkage in **8**. The assignments were confirmed further

DOI: 10.1021/acs.joc.6b00462
J. Org. Chem. 2016, 81, 4616−4622

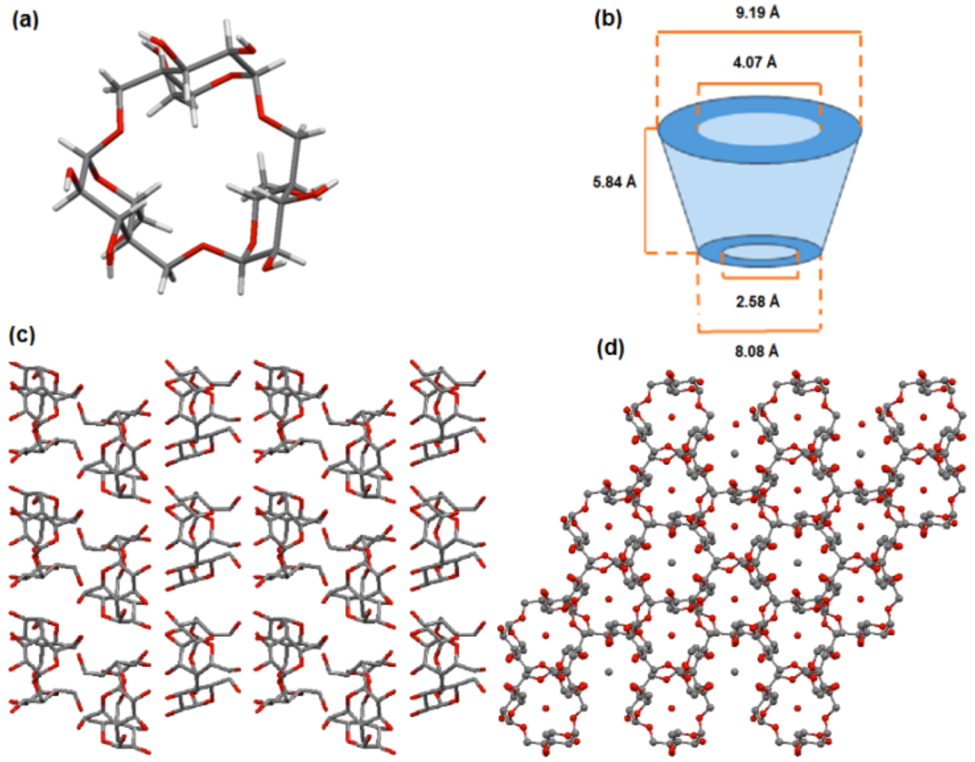


Figure 1. (a) Stick model of the crystal structure of **8**, as viewed along the crystallographic *c*-axis. (b) Cartoon representation provided with molecular dimensions. (c) Packing diagram crystal lattice, as viewed along the crystallographic *b*-axis, and without solvent inclusion. (d) Packing diagram included with methanol (gray) and water (red) solvents, as viewed along the crystallographic *c*-axis. Hydrogen atoms are omitted for clarity in (c and d).

by COSY and HMQC NMR spectroscopies. In addition to **8**, cyclic oligosaccharides in multiples, corresponding to cyclic hexa- and nona-saccharides, were also observed in the mass spectrum of the crude product of cyclo-glycosylation reaction, however, such higher cyclic oligosaccharides could not be isolated in a pure form at present. In this respect, reaction conditions remain to be identified that promote an intermolecular cyclo-glycosylation, which was observed in our previous report using disaccharide monomer leading to cyclic tetrasaccharide as a major product,[32] overtaking the intramolecular reaction when trisaccharide is the monomer for cyclo-glycosylation.

Solid-State Structure of 8. Crystals, suitable for single crystal X-ray structural determination, were secured by vapor diffusion of acetone into a methanolic aqueous solution of **8**. The structural determination revealed that the molecule crystallized in the *P*3 space group, with a perfect trigonal symmetry and with three molecules in the unit cell. Crystallographic parameters of **8** can be found in the Supporting Information[39] Bond lengths are in the range of 1.28−1.53 Å (C−O) and 1.49−1.56 Å (C−C), and bond angles are largely in the range of 107−125°. Dihedral angles of primary hydroxymethyl substituent (C6) conformed to *gauche*−*gauche* (−67 and 55°) conformation. Primary and secondary hydroxyl groups are seen to be residing away from the macrocyclic cavity and the hydrogen atoms at *C*-3 and *C*-5 moieties are directed inward the cavity.

Further analysis show that the molecule possesses a bowl-shape, with primary hydroxyl groups placed in the narrower side, whereas secondary hydroxyl groups located in the wider face of the bowl, similar to that in cyclodextrin.[6] Figure 1a shows the crystal structure diagram of **8**, included with approximate locations of methylene and methine hydrogens. Cremer−Pople puckering parameter[40,41] analysis shows that the glucose units adopted nearly a $^4C_1$ conformation, with set of polar coordinate values: $Q = 0.559 \pm 0.027$ Å, $\theta = 4 \pm 3.5°$, and $\phi = 176 \pm 33°$ for the individual sugar ring in **8**. The observed ϕ value indicates that there is a small deviation of the pyranose ring from perfect $^4C_1$ conformation toward the direction of a skew conformation.

A perfect three-fold symmetry exists with the glycosidic oxygen and other exocyclic substituents. The inner cavity diameter of the bowl at the wider face is 4.07 Å, whereas the narrow lower rim diameter is 2.58 Å. The height of the torus is 5.84 Å, and the glycosidic oxygens are equi-distant, at 4.46 Å from one another. A cartoon representation showing the structural dimensions is given in Figure 1b. The ratio of upper-to-lower rim cavity diameter in **8** is 1.58, implying a rather sharp cone shape of **8**. Similar in the case of CDs, the wider upper rim is constituted by the secondary hydroxyl groups, whereas the narrow lower rim is occupied by the primary hydroxyl groups of the sugar moieties. A packing diagram of the molecules of **8** is presented in Figure 1c. A wider rim-to-wider rim and narrow rim-to-narrow rim arrangement of a block of three molecules form repeating units in the crystal lattice. In a "brick-wall" type arrangement of the block of three molecules, one molecule is translationally and rotationally correlated to two neighboring molecules. Thus, the arrangement of the molecules in the crystal lattice appears to provide a space for one molecule within the block to undergo translational and rotational transition. Such a brick-type arrangement wherein one molecule of the trimeric block retaining wider rim-to-wider rim and narrow rim-to-narrow rim positioning with the adjacent molecules is rather unusual to a cyclic oligosaccharide

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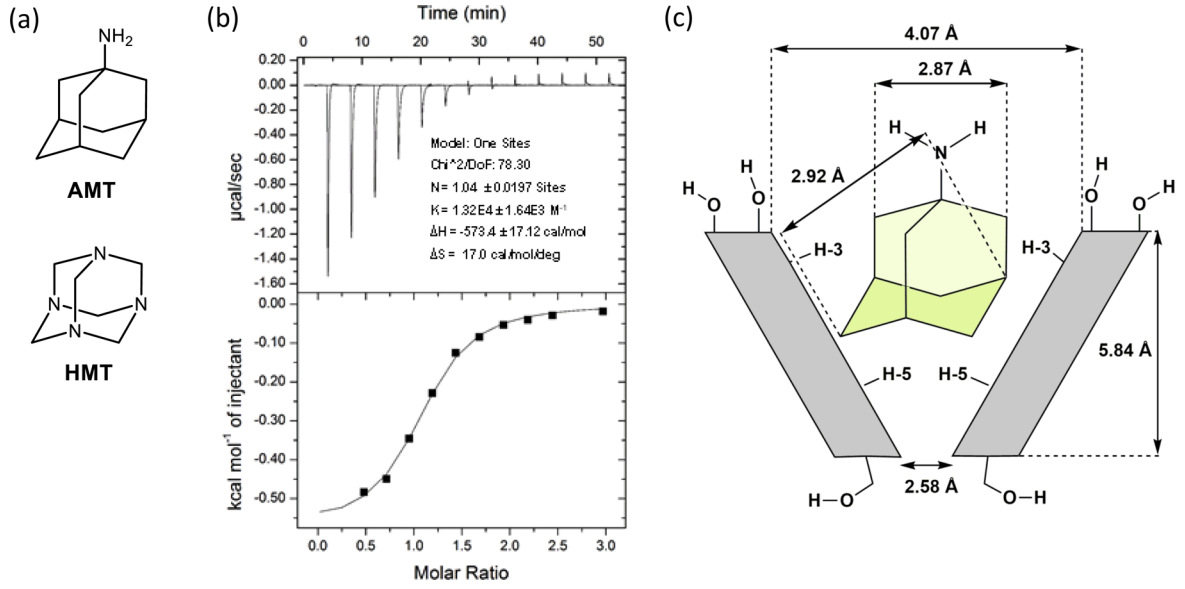

Figure 2. (a) Molecular structures of AMT and HMT. (b) ITC isotherm of the interaction of **8** (1 mM) and AMT (15 mM) at 30 °C in water. (c) A cartoon of the binding of AMT with **8**, without measuring solvent accessible surface area.

Table 1. Binding Parameters of the Interaction of 8 and *β*-CD with AMT and HMT

host	guest	stoichiometry (N)	binding constant (K, M^{-1})	ΔH (cal/mol)	$T\Delta S$(kcal/mol)	ΔG (kcal/mol)
8	AMT	1.04 ± 0.02	13,200 ± 1640	−573.4 ± 17.1	5.15	−5.71
	HMT	0.51 ± 0.01	2,020 ± 388	95.24 ± 7.23	4.67	−4.57
β-CD	AMT	1.12 ± 0.02	5,210 ± 384	−1522 ± 30.60	3.64	−5.15
	HMT	0.98 ± 0.02	9,090 ± 1470	−1715 ± 65.1	3.79	−5.50

molecular packing. In this arrangement, the channel running through the macrocyclic interior cavity is partially blocked. Yet, solvents in a ratio of one water and one methanol molecules to one molecule of **8** occupy the channels and voids in the lattice (Figure 1d). A network of hydrogen-bonding interactions[42,43] are observed among hydroxyl groups of the sugar within the trimer blocks of the lattice. Two- and three-center, bifurcated hydrogen-bonding interactions are observed in an intermolecular fashion, involving wider and narrower rim hydroxyl groups. Within donor−acceptor (D−A) bond length limits of 3.2 Å, hydrogen-bonding interactions with solvents are also seen from analysis. In addition, intramolecular hydrogen-bonding interactions within a macrocycle exist in the crystal lattice.

Host−Guest Interactions of 8 with Organic Bases. In order to evaluate encapsulation properties of new glycosidic bond expanded cyclic trisaccharide **8**, inclusion complexation with a few guest molecules was conducted. After an initial screening of alcohols, amines, carboxylic acids, and polyaromatic guest molecules, amines were chosen to identify the host−guest properties of **8**. A preliminary evaluation in aqueous solution showed that amines possessed higher binding affinities, in comparison to other types of guest molecules. Two amines, namely, 1-aminoadamantane (AMT) and hexamethylene tetramine (HMT), as shown in Figure 2a, were studied, and the associated thermodynamic parameters were evaluated by isothermal titration calorimetry (ITC) in aqueous solutions.[44] Amines are known to bind with *β*-cyclodextrin (*β*-CD) in water, as assessed by calorimetry.[45] ITC titrations of **8** with amines were performed at 30 °C, resulting thermograms were corrected for dilution effects and analyzed. Binding isotherm for AMT with cyclic trisaccharide is shown in Figure 2b. Analysis of the thermodynamic parameters revealed that binding followed an one-site binding stoichiometry (Table 1). The binding constant was 13,200 M^{-1}, with negative binding enthalpy and free energy changes. Interaction of *β*-CD with AMT was undertaken as a comparison.[46,47] The binding parameters are given in Table 1. The comparison shows that the binding of AMT with **8** was about 2.5 times stronger than to the binding with *β*-CD.

We premise that AMT occupies the upper rim of **8**, with the adamantane moiety occupying the macrocycle cavity and amine moiety exposed to the hydroxyl groups and water molecules of the aqueous environment, as in the case of AMT binding to CDs.[46,47] Lengths of AMT[48] and **8**, as derived from crystal structure analysis, are given in Figure 2c. Enhanced binding strength of AMT with **8**, when compared to AMT binding to *β*-CD, might prove to be useful, as AMT is an antiviral drug[49] and its slow release when complexed with CD is beneficial.

A binding study of **8**-HMT complexation was undertaken further. The binding in this instance was promoted by a much weaker enthalpy change, and the stoichiometry of host−guest was found to be ∼2:1 in this instance. Positive enthalpy and entropic changes indicated that the binding was favored by hydrophobic interaction-mediated host−guest complexation. This observation was distinctly different from that of the *β*-CD-HMT complexation, in which the binding interaction was favored by a large negative enthalpic change. The resulting binding constants were also significantly different, with *β*-CD binding having close to 4.5 times higher binding affinity than HMT with **8** (Table 1). The 2:1 host−guest complexation was verified through monitoring the ^{1}H NMR resonance shift as a function of the host−guest mole fraction. A bell-shaped curve was observed in the Job plot when the mole fraction was

DOI: 10.1021/acs.joc.6b00462
J. Org. Chem. 2016, 81, 4616−4622

plotted against the product of change in chemical shift and host concentration. A nearly matching host−guest 2:1 stoichiometry was observed in the Job plot, in agreement with the results from ITC studies.

CONCLUSION

In conclusion, the present work illustrates that the cyclo-oligomerization strategy of a linear monomer is a valuable approach to mitigate existing major challenges in the backbone modification of the general class of cyclic oligosaccharides, as modifications at each sugar moiety are conducted at the linear monomer level, prior to cyclization, through synthetic manipulations of the monomer moiety. The present study demonstrates cyclization of a linear trisaccharide monomer in which the intersugar glycosic bonds are expanded with an additional methylene moiety. Resulting newly formed cyclic trisaccharide conforms elegantly to structural features of the naturally occurring CDs, even when the glycosidic bond with nonreducing end of the sugar is expanded with an extra methylene moiety. The cyclic trisaccharide adopts a perfect trigonal symmetry in the *P*3 space group, a more sharp-cone than CDs and a brick-wall-type arrangement of a block of three molecules in a wider rim-to-wider rim and narrow rim-to-narrow rim packing in the crystal lattice. Such a symmetry and molecular packing are hitherto unknown to a CD derivative. The molecule hosts solvent and water molecules in its cavity and at the interstitial void spaces, and hydrogen-bonding interactions are abound. The cyclic trisaccharide shows preferential binding to AMT and HMT in aqueous solution in a 1:1 and 2:1 host−guest ratio, with binding constant significantly higher than β-CD in the case of AMT.

EXPERIMENTAL SECTION

General Information. Solvents were dried and distilled according to literature procedures. All chemicals were purchased from commercial sources and were used without further purification. Silica gel (100−200 and 230−400 mesh) was used for column chromatography, and TLC analysis was performed on commercial plates coated with silica gel 60 F_{254}. Visualization of the spots on TLC plates was achieved by UV radiation or spraying 5% sulfuric acid in ethanol. High-resolution mass spectra were obtained from Q-TOF instrument by electrospray ionization (ESI). ^{1}H and ^{13}C NMR spectral analyses were performed on a spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts are reported with respect to tetramethylsilane (TMS) for ^{1}H NMR and the central line (77.0 ppm) of $CDCl_3$ for ^{13}C NMR. Coupling constants (*J*) are reported in Hz. Standard abbreviations s, d, t, dd, br s, m, and app t refer to singlet, doublet, triplet, doublet of doublet, broad singlet, multiplet, and apparent triplet. For disaccharide and trisaccharide derivatives, H and C denote the proton and carbon of reducing sugar moiety, whereas H′ and C′ denote the proton and carbon of nonreducing pyranose moiety. H-7 and C-7 denote proton and carbon of 4-*C*-hydroxymethyl moiety of the pyranose ring.

*2,3,6-Tri-O-benzyl-4-C-acetoxymethyl-α/β-D-glucopyranose (**1**).* Acetic anhydride (0.46 mL, 4.93 mmol) was added to a solution of **3** (2.4 g, 4.11 mmol) in pyridine (15 mL) and DMAP (0.05 g, 0.41 mmol) at 0 °C and stirred for 2 h at room temperature. The reaction mixture was diluted with water (50 mL), extracted with $CHCl_3$ (3 × 70 mL), washed with aq. HCl (2 N) and satd. aq. $NaHCO_3$ (2 × 50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Trifluoroacetic acid (0.61 mL, 7.98 mmol) was added to a solution of crude residue (2.5 g) in aq. CH_2Cl_2 (10 mL) at 0 °C and stirred for 4 h at room temperature. The reaction mixture was diluted with water (50 mL), washed with aq. $NaHCO_3$ (10% w/v, 2 × 50 mL), extracted with CH_2Cl_2 (3 × 70 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified (SiO_2) (hexane/EtOAc = 3:2) to afford **1** (1.35 g, 65%, α/β = 2:1), as a colorless oil. R_f = 0.2 (hexane/EtOAc = 3:2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38−7.25 (m, 24 H), 5.30 (d, *J* = 3.2 Hz, 1 H), 5.01 (d, *J* = 10.8 Hz, 0.5 H), 4.93 (d, *J* = 11.2 Hz, 1 H), 4.90 (d, *J* = 10.8 Hz, 0.5 H), 4.76 (d, *J* = 6.8 Hz, 0.5 H), 4.73 (d, *J* = 7.2 Hz, 1 H), 4.69 (d, *J* = 12 Hz, 1 H), 4.64 (d, *J* = 11.6 Hz, 1 H), 4.60 (d, *J* = 10.8 Hz, 1.5 H), 4.56 (app s, 1 H), 4.50 (d, *J* = 12.4 Hz, 0.5 H), 4.46 (d, *J* = 12 Hz, 1 H), 4.30 (dd, *J* = 2.8 Hz, 11.6 Hz, 1 H), 4.25 (dd, *J* = 2.8 Hz, 12 Hz, 0.5 H), 4.17−4.13 (m, 1 H), 4.05−4.00 (m, 1.5 H), 3.94 (d, *J* = 9.2 Hz, 0.5 H), 3.91 (d, *J* = 9.6 Hz, 0.5 H), 3.64−3.55 (m, 5 H), 3.44−3.40 (m, 0.5 H), 2.07−2.00 (m, 1.5 H), 1.92 (s, 3 H), 1.90 (s, 1.5 H); ^{13}C NMR ($CDCl_3$, 100 MHz): 170.7, 170.5, 140.8, 138.3, 138.2, 138.0, 137.8, 137.7, 137.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 126.8, 97.5, 91.3, 84.6, 81.4, 75.2, 75.0, 74.6, 74.2, 73.4, 73.3, 72.6, 72.4, 69.6, 68.0, 65.0, 60.1, 42.4, 42.2, 20.6, 20.5; HRMS (ESI/TOF-Q) *m*/*z*: [M + Na]$^+$ calcd for $C_{30}H_{34}O_7Na$, 529.2202; found 529.2207.

*p-Tolyl 4-deoxy-4-C-acetoxymethyl-2,3,6-tri-O-benzyl-1-thio-α/β-D-glucopyranoside (**2**).* Acetic anhydride (0.25 mL, 2.6 mmol) and dimethylamino pyridine (0.026 g, 0.217 mmol) were added to a solution of **1** (1.1 g, 2.17 mmol) in pyridine (5 mL) at 0 °C and stirred for 4 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with dil. aq. HCl (2 × 50 mL), satd. aq. $NaHCO_3$ (1 × 50 mL), and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was co-evaporated with PhMe (2 × 5 mL) to afford a diacetate intermediate (1.1 g), as a gum. *p*-Thiocresol (0.29 g, 2.4 mmol) was added to a solution of diacetate intermediate (1.1 g, 2.0 mmol) in CH_2Cl_2 (10 mL), and $BF_3{\cdot}OEt_2$ (0.25 mL, 2 mmol) was added dropwise at room temperature and stirred for 1 h under N_2 atmosphere. The reaction mixture was quenched with Et_3N (0.5 mL), filtered, concentrated in vacuo, and purified (SiO_2) (pet. ether/EtOAc = 9:1) to afford **2** (1.13 g, 85%, α/β = 1:0.4); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40−7.23 (m, 24 H), 7.06 (d, *J* = 8 Hz, 2 H), 7.03 (d, *J* = 8 Hz, 0.8 H), 5.67 (d, *J* = 5.2 Hz, 1 H), 5.00 (d, *J* = 8 Hz, 0.4 H), 4.97 (d, *J* = 10.8 Hz, 1 H), 4.89 (d, *J* = 11.2 Hz, 0.4 H), 4.78 (d, *J* = 11.6 Hz, 1 H), 4.76−4.71 (m, 0.8 H), 4.65 (d, *J* = 13.2 Hz, 2 H), 4.60 (d, *J* = 4.8 Hz, 1.4 H), 4.55 (d, *J* = 12.4 Hz, 1.4 H), 4.50−4.46 (m, 1.4 H), 4.43 (d, *J* = 12 Hz, 1 H), 4.34 (dd, *J* = 2.8 Hz, 12 Hz, 1 H), 4.10 (dd, *J* = 2 Hz, 12 Hz, 0.4 H), 4.06 (dd, *J* = 2 Hz, 12 Hz, 1 H), 3.93 (dd, *J* = 5.2 Hz, 9 Hz, 1 H), 3.81 (t, *J* = 9.8 Hz, 1 H), 3.75 (dd, *J* = 2 Hz, 10.8 Hz, 0.4 H), 3.69−3.64 (m, 2.8 H), 2.31 (s, 3 H), 2.30 (s, 1.2 H), 2.14−2.04 (m, 1.4 H), 1.98 (s, 3 H), 1.91 (s, 1.2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.5, 138.2, 138.1, 138.0, 137.9, 137.8, 137.7, 137.6, 137.1, 133.1, 132.5, 131.7, 131.0, 130.1, 129.6, 129.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 88.1, 87.6, 82.2, 81.1, 79.5, 75.3, 75.2, 75.1, 74.8, 73.5, 73.4, 71.9 70.2, 69.6, 69.0, 60.1, 42.7, 42.1, 21.0, 20.7, 20.6; HRMS (ESI/TOF-Q) *m*/*z*: [M + Na]$^+$ calcd for $C_{37}H_{40}O_6SNa$, 635.2443; found 635.2443.

*p-Methoxybenzyl 2,3,6-tri-O-benzyl-4-deoxy-4-C-methyl-α-D-glucopyranosyl-(1 → 4)-2,3,6-tri-O-benzyl-4-deoxy-4-C-methyl-β-D-glucopyranoside (**4**).* *N*-Iodosuccinimide (0.22 g, 0.98 mmol) was added to a mixture of **2** (0.5 g, 0.817 mmol) and **3** (0.38 g, 0.654 mmol) and MS (4 Å) (1.6 g) in PhMe (5 mL) at 0 °C and stirred for 10 min. TfOH (7 μL, 0.082 mmol) was added and stirred for 1 h under N_2 atmosphere. The reaction mixture was neutralized with Et_3N, filtered, extracted with EtOAc, washed with aq. $Na_2S_2O_3$ (2 × 50 mL), satd. aq. $NaHCO_3$ (2 × 50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo, purified (SiO_2) (pet. ether/EtOAc = 4:1) to afford acetyl protected disaccharide derivative. NaOMe in MeOH (1 M, 0.2 mL) was added to a solution of disaccharide derivative in MeOH, stirred for 6 h at room temperature, neutralized with Amberlite resin (H$^+$), filtered, and concentrated in vacuo. Purification (SiO_2) (pet. ether/EtOAc = 3:1) afforded **4** (0.45 g, 67%), as a gum. $[\alpha]_D$ −3.13 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33−7.14 (m, 32 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 4.96 (dd, *J* = 4 Hz, 10.8 Hz, 2 H), 4.91 (dd, *J* = 3.2 Hz, 11.2 Hz, 2 H), 4.77 (d, *J* = 3.2 Hz, 1 H), 4.72−4.56 (m, 8 H), 4.51 (d, *J* = 8 Hz, 1 H), 4.49−4.41 (m, 2 H), 3.91−3.86 (m, 2 H), 3.82 (d, *J* = 4.8 Hz, 1 H), 3.79 (d, *J* = 2.8 Hz, 1 H), 3.78 (s, 3 H), 3.77−3.70 (m, 4 H), 3.67 (dd, *J* = 4.4 Hz, 10.8 Hz, 2 H), 3.55 (dd, *J* = 3.2 Hz, 9.6 Hz, 1 H), 3.52−3.48 (m, 3 H),

DOI: 10.1021/acs.joc.6b00462
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2.01−1.96 (m, 1 H), 1.84−1.80 (m,1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3, 138.8, 138.7, 138.4, 138.3, 138.1, 137.7, 129.8, 129.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 113.8, 102.5, 97.8, 83.6, 81.4, 78.4, 75.3, 75.0, 74.9, 74.7, 73.6, 73.4, 73.2, 72.7, 70.7, 70.5, 70.4, 68.7, 63.7, 59.2, 55.2, 45.8, 43.9; HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ calcd for $C_{64}H_{70}O_{12}Na$, 1053.4765; found 1053.4763.

*p-Methoxybenzyl 2,3,6-tri-O-benzyl-4-deoxy-4-C-methyl-α-D-glucopyranosyl-(1 → 4)-2,3,6-tri-O-benzyl-4-deoxy-4-C-methyl-α-D-glucopyranosyl-(1 → 4)-2,3,6-tri-O-benzyl-4-deoxy-4-C-methyl-β-D-glucopyranoside (**5**).* *N*-Iodosuccinimide (0.14 g, 0.629 mmol) was added to a mixture of **2** (0.32 g, 0.524 mmol) and **4** (0.45 g, 0.437 mmol) and MS (4 Å) (1 g) in PhMe (4 mL) at 0 °C and stirred for 10 min. TfOH (5 μL, 0.052 mmol) was added and stirred for 1 h under N_2 atmosphere. The reaction mixture was neutralized with Et_3N, filtered, extracted with EtOAc, washed with aq. $Na_2S_2O_3$ (2 × 50 mL), satd. aq. $NaHCO_3$ (2 × 50 mL), and brine (50 mL), dried (Na_2SO_4), concentrated in vacuo, and purified (SiO_2) (pet. ether/EtOAc = 5.6:1) to afford acetyl protected trisaccharide derivative. NaOMe in MeOH (1 M, 0.15 mL) was added to a solution of trisaccharide derivative in MeOH, stirred for 6 h at room temperature, neutralized with Amberlite resin (H^+), filtered, and concentrated in vacuo. Purification (SiO_2) (pet. ether/EtOAc = 4:1) afforded **5** (0.43 g, 68%), as a gum. $[\alpha]_D$ +0.26 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28−7.10 (m, 47 H), 6.77 (d, *J* = 8.4 Hz, 2 H), 4.91 (d, *J* = 10.4 Hz, 3 H), 4.87 (d, *J* = 5.6 Hz, 1 H), 4.83 (d, *J* = 3.6 Hz, 1 H), 4.78 (d, *J* = 3.2 Hz, 1 H), 4.72 (d, *J* = 10.8 Hz, 1 H), 4.69−4.52 (m, 12 H), 4.49−4.42 (m, 2 H), 4.38 (dd, *J* = 4.2 Hz, 12.2 Hz, 2 H), 4.00−3.94 (m, 2 H), 3.86−3.78 (m, 3 H), 3.76 (s, 3 H), 3.75−3.70 (m, 5 H), 3.64−3.53 (m, 6 H), 3.49−3.38 (m, 4 H), 3.30 (d, *J* = 10 Hz, 1 H), 2.11−2.00 (m, 2 H), 1.82−1.77 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): 159.1, 138.9, 138.6, 138.5, 138.4, 138.3, 138.2, 137.9, 129.9, 129.3, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 113.6, 102.9, 98.5, 97.6, 83.6, 81.2, 81.1, 78.3, 75.4, 75.3, 75.2, 74.6, 73.6, 73.5, 73.4, 73.3, 72.8, 72.5, 70.8, 69.9, 69.6, 69.4, 68.8, 68.3, 65.6, 64.6, 63.8, 55.2, 44.8, 43.8, 43.3; HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ calcd for $C_{92}H_{100}O_{17}Na$, 1499.6858; found 1499.6859.

*2,3,6-Tri-O-benzyl-4-deoxy-4-C-acetoxymethyl-α-D-glucopyranosyl-(1 → 4)-2,3,6-tri-O-benzyl-4-deoxy-4-C-methyl-α-D-glucopyranosyl-(1 → 4)-2,3,6-tri-O-benzyl-4-deoxy-4-C-methyl-α/β-D-glucopyranose (**6**).* Acetic anhydride (33 μL, 0.35 mmol) and dimethylamino pyridine (0.004 g, 0.029 mmol) were added to a solution of **5** (0.43 g, 0.29 mmol) in pyridine (2 mL) at 0 °C and stirred for 3 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (80 mL), washed with dil. aq. HCl (2 × 30 mL), satd. aq. $NaHCO_3$ (1 × 30 mL), and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product (0.44 g) was dissolved in aq. CH_2Cl_2 and stirred at 0 °C, and then trifluoroacetic acid (0.045 mL, 0.58 mmol) was added and stirred for 4 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (80 mL), washed with H_2O (2 × 30 mL), satd. aq. $NaHCO_3$ (2 × 30 mL), and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo, purified (SiO_2) (pet. ether/EtOAc = 3:1) to afford **6** (0.30 g, 74%, α/β = 1:0.91); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31−7.17 (m, 86 H), 5.23 (d, *J* = 2.8 Hz, 1 H), 4.94−4.83 (m, 10 H), 4.78 (d, *J* = 3.2 Hz, 1 H), 4.70−4.35 (m, 33 H), 4.21−4.08 (m, 6 H), 3.82−3.69 (m, 14 H), 3.62−3.55 (m, 12 H), 3.41−3.39 (m, 3 H), 2.20−2.01 (m, 6 H), 1.84 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 170.7, 138.9, 138.7, 138.6, 138.4, 138.3, 138.2, 138.1, 138.0, 137.9, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 98.1, 98.0, 97.9, 97.7, 91.5, 84.6, 81.6, 81.4, 81.2, 81.0, 78.2, 75.6, 75.4, 75.2, 75.1, 75.0, 74.9, 74.6, 73.6, 73.4, 72.7, 72.6, 72.5, 70.3, 70.1, 70.0, 69.9, 69.8, 69.7, 69.5, 69.1, 69.0, 64.8, 64.7, 64.4, 64.2, 61.2, 60.8, 60.4, 43.5, 43.4, 43.3, 43.2, 42.1, 41.9, 20.7; HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ calcd for $C_{86}H_{94}O_{17}Na$, 1421.6389; found 1421.6387.

*p-Tolyl 2,3,6-tri-O-benzyl-4-deoxy-4-C-methyl-α-D-glucopyranosyl-(1 → 4)-2,3,6-tri-O-benzyl-4-deoxy-4-C-methyl-α-D-glucopyranosyl-(1 → 4)-2,3,6-tri-O-benzyl-4-deoxy-4-C-methyl-1-thio-α/β-D-glucopyranoside (**7**).* Acetic anhydride (24 μL, 0.258 mmol) and dimethylamino pyridine (0.003 g, 0.021 mmol) were added to a solution of **6** (0.3 g, 0.214 mmol) in pyridine (2 mL) at 0 °C and stirred for 4 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (80 mL), washed with dil. aq. HCl (2 × 30 mL), satd. aq. $NaHCO_3$ (1 × 30 mL), and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was co-evaporated with PhMe (2 × 2 mL) to afford diacetate intermediate (0.305 g), as a gum. *p*-Thiocresol (0.032 g, 0.254 mmol) was added to a solution of diacetate intermediate (0.305 g, 0.212 mmol) and MS (4 Å) (0.4 g) in CH_2Cl_2 (5 mL), and $BF_3{\cdot}OEt_2$ (26 μL, 0.212 mmol) was added dropwise at room temperature and stirred for 1 h under N_2 atmosphere. The reaction mixture was quenched with Et_3N (0.1 mL), filtered, extracted with CH_2Cl_2 (80 mL), washed with satd. aq. $NaHCO_3$ (1 × 30 mL) and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product (0.31 g) in MeOH (2 mL) was subjected to deacetylation using NaOMe in MeOH (1 M, 0.1 mL) for 6 h at room temperature, neutralized with Amberlite resin (H^+), filtered, concentrated in vacuo, and purified (SiO_2) (pet. ether/EtOAc = 5.2:1) to afford **7** (0.23 g, 75%, α/β = 1:1.4); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, *J* = 8 Hz, 5 H), 7.31−7.18 (m, 108 H), 6.96 (d, *J* = 8.4 Hz, 2 H), 6.91 (d, *J* = 7.6 Hz, 3 H), 5.63 (d, *J* = 4.8 Hz, 1 H), 4.96−4.80 (m, 14 H), 4.74−4.47 (m, 36 H), 3.95−3.69 (m, 26 H), 3.66−3.39 (m, 24 H), 2.26 (s, 3 H), 2.22 (s, 4.4 H), 2.08−2.03 (m, 7 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.2, 138.8, 138.7, 138.5, 138.4, 138.3, 138.2, 138.1, 138.0, 137.7, 137.5, 136.9, 133.0, 132.6, 132.1, 131.7, 129.6, 129.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 98.7, 98.3, 97.8, 97.3, 87.8, 87.3, 81.9, 81.5, 81.2, 81.1, 81.0, 80.9, 80.3, 77.6, 77.2, 75.9, 75.7, 75.6, 75.4, 75.3, 75.2, 75.1, 74.9, 73.5, 73.4, 73.3, 73.2, 73.1, 73.0, 72.8, 72.6, 72.4, 71.8, 71.2, 70.4, 70.2, 70.1, 69.8, 69.7, 69.6, 68.4, 65.3, 64.7, 64.2, 58.4, 57.9, 44.8, 44.7, 43.8, 43.5, 43.4, 43.1, 21.1, 21.0; HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ calcd for $C_{91}H_{98}O_{15}SNa$, 1485.6524; found 1485.6525.

*Cyclo[(1 → 4)-4-deoxy-4-C-methyl-α-D-glucopyranosyl-(1 → 4)-4-deoxy-4-C-methyl-α-D-glucopyranosyl-(1 → 4)-4-deoxy-4-C-methylenyl]-α-D-glucopyranoside (**8**).* Linear trisaccharide **7** (0.1 g, 0.068 mmol) was dissolved in PhMe (2 mL) and freeze-dried, and the process was repeated twice. *N*-Iodosuccinimide (NIS) (0.018 g, 0.0816 mmol) was added to a solution of freeze-dried **7** (20 mM) and MS (4 Å) (0.1 g) in PhMe (3.4 mL) at 0 °C and stirred for 10 min. Trimethylsilyltrifluoromethanesulfonate (TMSOTf) (1.2 μL, 0.0068 mmol) was added to it and stirred for 12 h under N_2 atmosphere. The reaction mixture was neutralized with Et_3N, filtered, concentrated in vacuo, and purified (SiO_2) (pet. ether/EtOAc = 7:1) to afford protected derivative of cyclic trisaccharide. A solution of benzyl group protected cyclic trisaccharide (0.059 g, 0.022 mmol) in MeOH and EtOAc (1:1, 10 mL) was subjected to hydrogenolysis over H_2/Pd (10%, 0.11 g) under positive pressure of H_2 gas for 12 h at room temperature. The reaction mixture was filtered through Celite, concentrated in vacuo, and purified (SiO_2) ($CHCl_3$/MeOH = 4:1) to afford **8** (0.018 g, 80%); $[\alpha]_D$ +3.78 (c 0.05, MeOH); ^{1}H NMR (D_2O, 400 MHz): δ 4.93 (d, *J* = 3.6 Hz, 3 H, H-1), 4.10 (d, *J* = 10.4 Hz, 3 H, H-3), 4.07−4.05 (m, 3 H, H-7a), 3.93 (d, *J* = 11.2 Hz, 3 H, H-5), 3.84−3.76 (m, 6 H, H-6a, H-6b), 3.71 (d, *J* = 10 Hz, 3 H, H-7b), 3.58 (dd, *J* = 3.6 Hz, 10 Hz, 3 H, H-2), 1.78 (app t, *J* = 10.6 Hz, 3 H, H-4); ^{13}C NMR (D_2O, 100 MHz): δ 98.6 (C-1), 72.4 (C-2), 70.1 (C-5), 66.1 (C-3), 64.3 (C-7), 61.0 (C-6), 43.1 (C-4); HRMS (ESI/TOF-Q) m/z: $[M + Na]^+$ calcd for $C_{21}H_{36}O_{15}Na$, 551.1962; found 551.1967.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00462.

^{1}H and ^{13}C NMR spectra of all new compounds and details of host−guest binding studies (PDF)

crystallographic analysis of **8** (CIF)

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DOI: 10.1021/acs.joc.6b00462
J. Org. Chem. 2016, 81, 4616−4622

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Department of Science and Technology and Council of Scientific and Industrial Research (CSIR), New Delhi, for a financial support of the work. CSIR is acknowledged for a research fellowship to K.M. We thank Mr. Prodip Howlader, Department of Inorganic and Physical Chemistry, IISc., for his help with single crystal X-ray structural analysis. N.J. acknowledges a J.C. Bose Fellowship of the DST, India.

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DOI: 10.1021/acs.joc.6b00462
J. Org. Chem. 2016, 81, 4616−4622