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Conformationally supple glucose monomers enable synthesis of the smallest cyclodextrins

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Cyclodextrins (CDs) are cyclic oligomers of α-1–4-D-glucopyranoside and are mainly known as hexamers to octamers. The central cavity of these molecules can retain small molecules, enabling diverse applications. The smallest members, CD3 and CD4, have ring sizes too small to permit the most stable conformations of glucopyranose and have not been accessible synthetically. In this study, we present methods to chemical synthesize both CD3 and CD4. The main factor in the successful synthesis is the creation of a glucopyranose ring conformationally counterbalanced between equatorial- and axial-rich forms. This suppleness is imparted by a bridge between O-3 and O-6 of glucose, which enables the generation of desirable, albeit deformed conformers when synthesizing the cyclic trimer and tetramer.

CDs are cyclic polymers of D-glucose (*1*), and CD6 to CD8 (**1**) (Fig. 1A) are produced enzymatically in bulk (*2*) making them easily available and non-toxic (*3*–*5*). These properties, along with the ability of CDs to capture small molecules within their hydrophobic central cavity, have permitted diverse applications in industry, medicine, and consumer products. Larger CDs, up to CD35, have been characterized (*6*). Conversely, the smallest known CD formed through chemical synthesis is CD5 (**2**) (*6*). The cyclodextrins CD3 (**3**) and CD4 (**4**) have been discussed without the actual compounds being known. French said, in 1957, that space-filling models of **3** to CD-infinity could be constructed when the glucose units had conformational flexibility, and that the smallest CD produced by treatment of a glycogen with *Bacillus macerans* amylase was most likely CD6 (*8*). In 1970, Sundararajan reported, based on computational calculations, that CDs having fewer than six glucoses could not be cyclized because of steric overlap (*9*). However, Nakagawa synthesized **2** in 1994 (*7*). In the following year, Immel indirectly concluded the difficulty of the synthesis of **3** and **4** due to the strained glucose units (*10*). Despite synthesis of CD-like molecules with smaller rings (*11*–*14*), synthesis of **3** and **4** remains an unmet goal. Here, we present chemical syntheses of these small cyclodextrins.

In our synthesis of **3** and **4**, one of the decisive factors for success was the adoption of the 3,6-*O*-EDB bridge (Fig. 1B), which was introduced to improve α-selective glycosylation using **5** (*15*, *16*). The bridge in **5** arches over the β-face of the pyranose ring, and hinders the β-face approach of an alcohol to produce the corresponding product with high α-selectivity under kinetic conditions using Cp_2ZrCl_2 and $AgClO_4$ in the presence of 4 Å molecular sieves (MS) (Suzuki glycosylation) (*17*). However, the bridge locked the pyranose ring into the $^3S_1$ form, which directed the 2-*O*-benzyl group axially toward the α-face, thus inducing adverse steric hindrance as in **6**. The α-selectivity and the yield of glucosides **7** therefore decreased using elevated reaction temperatures and more sterically hindered alcohols. We suspected this issue could be resolved by increasing the steric hindrance at the β-face and reducing the overhang of the 2-*O*-benzyl group on the α-face. To satisfy both of these requirements, we planned to modify the pyranose conformation by introducing a longer bridge than the *o*-xylylene group. With this consideration in mind, we chose an EDB group. The glycosylation reaction using the EDB-bridged glucosyl fluoride **8** afforded the corresponding glucosides with α-selectivity even at room temperature [supplementary material sections 2 and 19–24 (SM-2 and 19–24)]. The reaction proceeded through the corresponding oxocarbenium ion intermediate, as similar α-selectivity was observed using both **8**-α and **8**-β (SM-15, 16).

The other key element for synthesizing **3** and **4** was the discovery of the supple pyranose system. The most stable conformation of D-glucopyranose is $^4C_1$. On the other hand, attachment of a bridge between the two discontiguous oxygen atoms on the pyranose ring produces a bicyclic skeleton in which the newly-formed ring modulates the conformation of the pyranose scaffold. A short bridge locks the conformation into a motif with more axial substituents, as seen in **5** and **7** (*18*) and others (*19*–*23*). In contrast, when the O-3 and O-6 atoms were bridged by the EDB group, the pyranose conformation was modified by subtle structural alteration (Fig. 1C), revealed by ^{1}H NMR coupling constants of **8** to **12** (SM-8–14). Thus, although the difference between the diols **9**-α and **9**-β relates only to the anomers, the conformations

of the pyranose moieties were in $^1C_4$ and $^4C_1$ forms, respectively. In the case of dibenzylated compounds **8** and **10 to 12**, where the anomeric substituents were varied, the conformations of the pyranose systems were widely distributed, as displayed on a map of conformations that puts $^1C_4$ and $^4C_1$ forms on both poles (Cremer-Pople-Stoddart coordinates) (*24*, *25*). We propose the length of the EDB bridge is appropriate to equally balance the innate preference of glucose for the equatorial-rich $^4C_1$ form and the tendency of the bridge to transform the pyranose ring into axial-rich forms. The α-selectivity featured in the reaction using **8** and supple pyranose ring set the stage for synthesis of strained cyclodextrins.

As **3** and **4** repeat α-1,4-linkages, we protected oxygen atoms other than the bonding sites in their synthesis. The EDB group already protected the O-3 and O-6 (Fig. 2A, box), so we added protection for O-2 (P^2). Full deprotection of **13** yielded the desired product **4**. We obtained the cyclized intermediate **13** by intramolecular glycosylation of a linear tetramer (**a**) produced by glycosylation of **15** and **16**, alteration of protecting circumstances, and addition of a leaving group (L). The dimers **15** and **16** derived from starting monomers **18** and **19**. To equip the EDB-bridge of **18** and **19**, the synthesis began with 1,2,4-orthoacetylglucose (**20**) (*26*), the O-3 and O-6 of which are locked in the same direction to ease construction of the bridge. The precursor of **3** was **21**, which was produced by intramolecular glycosylation of a linear trimer (**b**) formed from **15** and **19**. The suppleness caused by the EDB-bridge enabled the cyclizations leading to **13** and **21**, which we suggest are not possible when the glucopyranosyl moieties are in the $^4C_1$ form. Because α-selectivity is essential for synthesizing CDs (*27*, *28*), we apply the fluorine atom for the leaving group based on the glycosylation of **8** (Fig. 1B).

Points in synthesis of the disaccharide **17** (Fig. 2B) (SM-25–33) are as follows. Bisetherification of **20** with 2,2′-bis-(bromomethyl)-dibenzyl (*29*) furnished the EDB-bridged **23**. Keeping the concentration of **20** lower than 10 mM assured reproducibility. The indium bromide promoted cleavage of orthoester of **23** accompanying β-specific introduction of the arylthio groups followed by deacetylation provided **24** and **9**-β, which were converted to **18** and **19**, respectively. The glycosylation using **18** and **19** provided the dimer **17** with perfect α-selectivity. We speculate that the higher selectivity observed in the use of **19** than that in the use of **8** (Fig. 1B) is attributed to reduction of steric hindrance at the α-face by alteration of the P^2, which tends to overhang on the α-face, from the benzyl group to the sterically smaller allyl group. We confirmed the α-stereochemistry of **17** by transformation to **25**, whose pyranoses were $^4C_1$ (SM-3).

We synthesized **4** (Fig. 2C) from dimers **15** and **16**, derived from **17** (SM-37–43). The stereochemistry of the formed glycosidic bond in tetramer **14** was undetermined because of the overlapped NMR signals (SM-61). However, the ^{1}H and ^{13}C NMR spectra of cyclized **13** (SM-60) were in agreement with the pattern of a monosaccharide indicating the unified stereochemistry of the four anomeric positions. These linkages were α- because **13** integrated **17** whose 1'-α-stereochemistry was confirmed. The reproducibility and yield of the intramolecular glycosylation was poor (6/17 successes/failures). Removal of the allyl (*30*) and EDB groups from **13** afforded **4** through **27**, demonstrating successful removability of the EDB group by hydrogenolysis. Mass spectrometry of **4** indicated the desired molecular ion peak for the cyclic tetramer (SM-50). ^{1}H NMR spectra revealed that the conformations of the pyranose ring of **13** and **4** were $^2H_1$ and between $^4C_1$ and $^2H_1$ (see **4** in Fig. 1A), respectively (SM-41, 43). The pyranose in these compounds is distorted and flatter than that of larger CDs (*31*–*33*).

In the synthesis of **3** (Fig. 2D) (SM-44–48), the intramolecular glycosylation was more efficient than that of **4**, with yield of **21** reaching 88%. The ^{1}H and ^{13}C NMR, HRMS (SM-49), and X-ray diffraction study of a single crystal (SM-48) confirmed that **3** was the cyclic trimer. The NMR spectra of **21** and **3** (SM-68, 49) were consistent with equivalent sugar units and averaged pyranose conformations were E_1 in acetone-d_6 and ^2S_O in D_2O (see **3** in Fig. 1A), respectively (SM-46, 48). The X-ray diffraction study of a single crystal of **3** indicated that the conformations of the three pyranoses were different (2 × $^5S_1$ and between $^4C_1$ and $^OH_1$) in the crystal lattice (figs. S7 to S9). The interatomic distances among three O-4s, O-5s, and H-5s (figs. S10 to S12) suggest that there is essentially no cavity in the center of the molecule when considering the robes of lone pairs on the O-5s. The lower field shift of H-5 in the ^{1}H NMR spectrum of **3** than those of CD6–8 (fig. S5) may be a result of a deshielding effect induced by the O-5s.

The use of glucose monomers with conformational flexibly, which we term supple, allowed for the syntheses of the strained CDs **3** and **4**. The creation of suppleness in sugars by addition of another ring is potentially applicable to the synthesis of other strained compounds or where function requires flexible structure. The averaged C3 and C4 symmetry observed in NMR spectra of **3** and **4**, where multiple stereocenters exist, could be useful in construction of molecular catalysts or metal-organic frameworks. CDs have general applications which take advantage to hold of molecules within the central cavity. We expect the smaller cavity of **4** may permit selective inclusion of molecules smaller than those accommodated in currently available CDs.

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SUPPLEMENTARY MATERIALS
www.sciencemag.org/cgi/content/full/science.aaw3053/DC1
Materials and Methods
Supplementary Text
Figs. S1 to S12
Tables S1 and S2
References (*34*–*41*)

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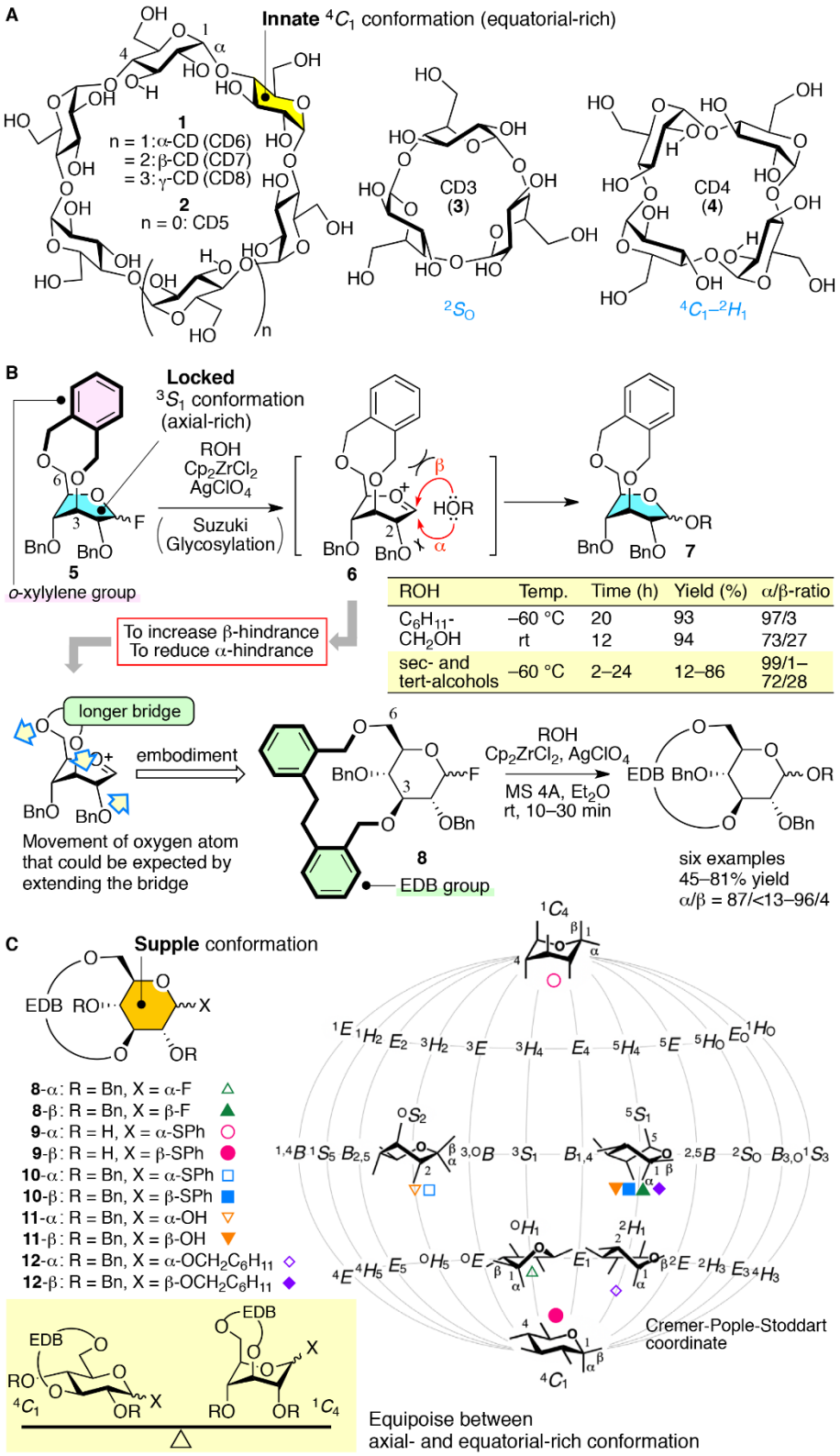

ROH	Temp.	Time (h)	Yield (%)	α/β-ratio
C_6H_{11}-CH_2OH	–60 °C	20	93	97/3
	rt	12	94	73/27
sec- and tert-alcohols	–60 °C	2–24	12–86	99/1–72/28

Fig. 1. Structures of CDs and key elements enabled synthesis of 3 and 4. (**A**) Because of the strained glucopyranose-rings in **3** and **4**, their existence was considered implausible. (**B**) Conception of the EDB bridge and the α-selective glycosylation attributed to the EDB bridge. The α-selective glycosylation using **5**, which possesses the 3,6-*O*-*o*-xylylene bridge, lacked clarity and effectiveness. A desire to improve the reaction led to the 3,6-*O*-EDB-bridged **8**. Glycosylation reaction with **8** proceeded efficiently with α-selectivity. (**C**) Supplied pyranose by formation of the 3,6-*O*-EDB bridge. Because the conformation of the EDB-bridged compounds is not constant, we hesitated to adopt the conventional notation of carbohydrates based on the chair form. For the synthesis of **8** to **12**, see SM-9–14. For the determination of each conformation, see SM-8–14. Cp, cyclopentadienyl; EDB, 1,1′-(ethane-1,2-diyl)dibenzene-2,2′-bis(methylene); MS, molecular sieves.

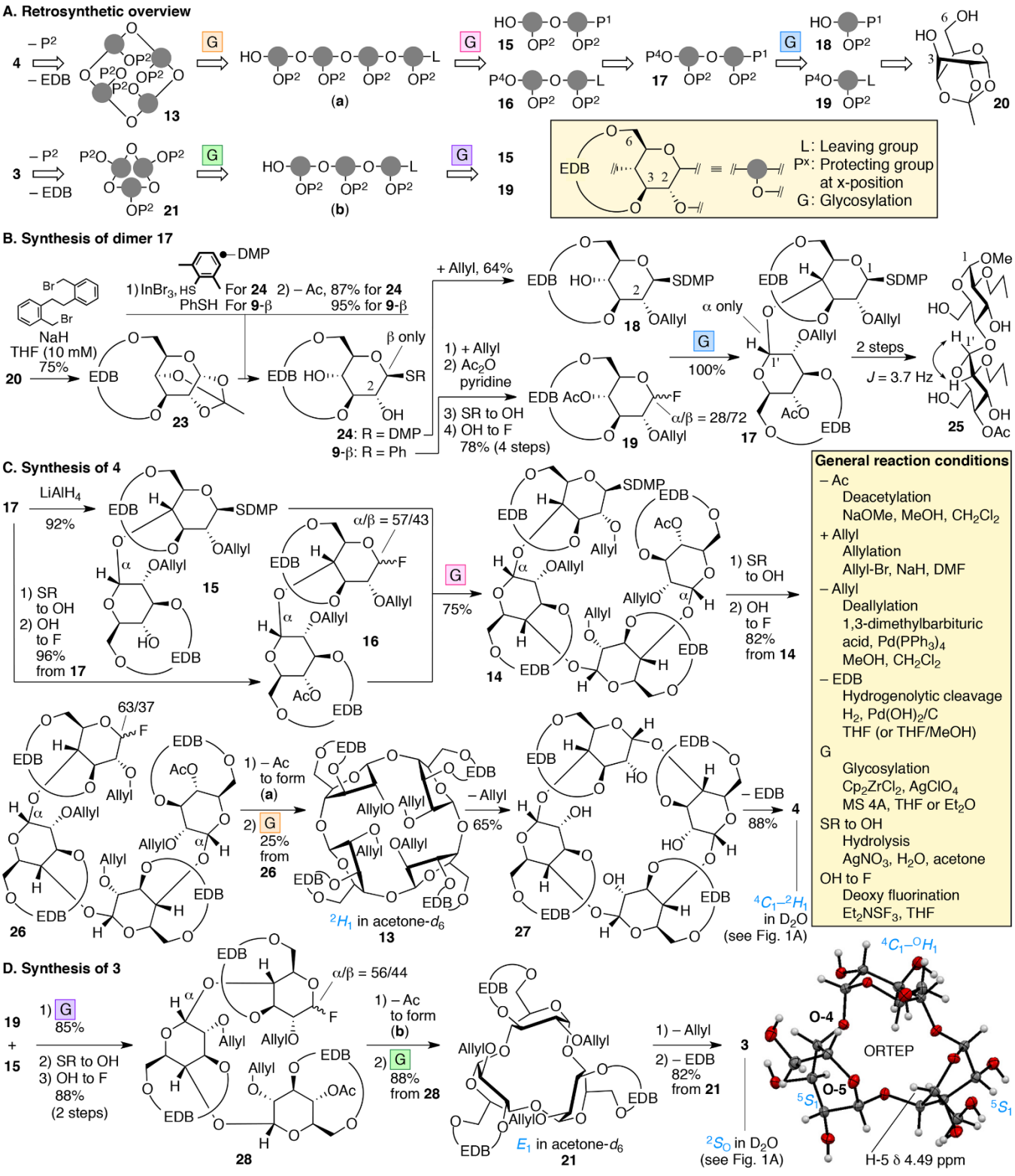

Fig. 2. Synthesis of 3 and 4. The colors in the frame around "G" indicate the corresponding reactions in (**A** to **D**). The pyranose conformations of **3**, **4**, **13**, **21**, and **25** were determined on the basis of ^{1}H NMR coupling constants (SM-48, 43, 41, 46, and 35, respectively). In the ORTEP drawing, waters of crystallization were omitted. For description of protecting groups, P^x, see SM-5. DMP, 2,6-dimethylphenyl.

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