JOC Article

Functionalization of Cyclodextrins via Reactions of 2,3-Anhydrocyclodextrins†

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Three types of reactions of 2,3-anhydro-β-cyclodextrins, namely nucleophilic ring-opening, reduction to 2-enopyranose, and reduction to 3-deoxypyranose, have been investigated to regio- and stereoselectively functionalize the secondary face of β-cyclodextrin. Upon treatment with various nucleophiles, both 2,3-mannoepoxy and 2,3-alloepoxy-β-cyclodextrins are found to undergo nucleophilic ring-opening reaction generating 3- and 2-modified cyclodextrin derivatives. In each case, the 3-position is more easily accessible than the 2-position. By using these ring-opening reactions, imidazolyl, iodo, azido, and benzylmercapto groups are selectively introduced to the secondary face of β-cyclodextrin in place of the 2- or 3-hydroxyl groups. The functionalized cyclodextrins have either modified glucosidic subunits or modified altrosidic subunits that make the hydrophobic cavity slightly distorted from that of native β-cyclodextrin. Thiourea also reacts with the cyclodextrin epoxides. In this case, thiirane and olefin species are generated instead of any ring-opening products. By ameliorating the reaction condition, cyclodextrin olefin, diene, and triene derivatives are prepared in moderate to good yields. Reduction of per[6-(*tert*-butyldimethyl)silyl]-β-cyclodextrin permannoepoxide with lithium aluminum hydride produces the per(3-deoxy)-β-cyclomannin. All these chemically modified cyclodextrins are structurally well characterized and most of them are expected to serve as versatile scaffolds for diverse purposes such as the construction of catalysts and development of synthetic receptors and molecular containers.

Introduction

Cyclodextrins (CDs) are natural cyclic maltooligosaccharides. The three best characterized forms are α-, β-, and γ-CDs consisting of six, seven, and eight α-(1→4)-D-glucopyranose units, respectively.[1] They take the shape of a hollow truncated cone with the wider side formed by the secondary 2- and 3-hydroxy groups and the narrower side by the primary 6-hydroxy groups, and the intramolecular crossed-subunit hydrogen bonds between 2-OH and 3-OH help to keep the symmetrical and rigid shape. Their interior cavity is as hydrophobic as dioxane, and possesses the ability to accommodate various guest molecules yielding inclusion complexes. This property has made CDs very popular building blocks for supramolecular structures and their derivatives are widely used in a variety of research fields, including microencapsulation of sensitive or active compounds, chromatography (mainly for the purpose of chiral discrimination), drug delivery, catalysis, molecular recognition, and sensing, to mention a few.[2] In practice, the binding properties required to perform these functions differ widely. In chiral discrimination, for example, enantioselective binding is crucial. In a drug delivery system, the drug−host binding should be strong enough to ensure that the complex reaches safely the target site before its dissociation, while in enzyme mimetics, strong binding of the transition state rather than the ground state or product is important for the catalyst to demonstrate large rate acceleration and turnover. Therefore it becomes necessary to modify or functionalize CDs to meet the requirements of diverse purposes.

The shape and hydrophobic area of the CD cavity, the introduction of additional interaction sites, and their cooperation with the cavity are undoubtedly among the most important factors that have to be taken into account in CD-based molecular design. It has already been demonstrated that replacement of the hydroxyl groups

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(1) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743−1753. Saenger, W.; Jacob, J.; Gessler, K.; Steiner, T.; Hoffmann, D.; Sanbe, H.; Koizumi, K.; Smith, S. M.; Takaha, T. *Chem. Rev.* **1998**, *98*, 1787−1802. Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer: Berlin, Germany, 1978.

(2) Stainer, C. A.; Alderman, S. J.; Claridge, T. D. W.; Anderson, H. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 1769−1772. Juvancz, Z.; Szejtli, J. *TrAC, Trends Anal. Chem.* **2002**, *21*, 379−388. Cardin, D. J. *Adv. Mater.* **2002**, *14*, 553−563. Mellet, C. O.; Defaye, J.; García Fernández, J. M. *Chem. Eur. J.* **2002**, *8*, 1983−1990. Harada, A. *Acc. Chem. Res.* **2001**, *34*, 456−464. Nepogodiev, S. A.; Stoddart, J. F. *Chem. Rev.* **1998**, *98*, 1959−1976. Uekama, K.; Hirayama, F.; Irie, T. *Chem. Rev.* **1998**, *98*, 2045−2076.

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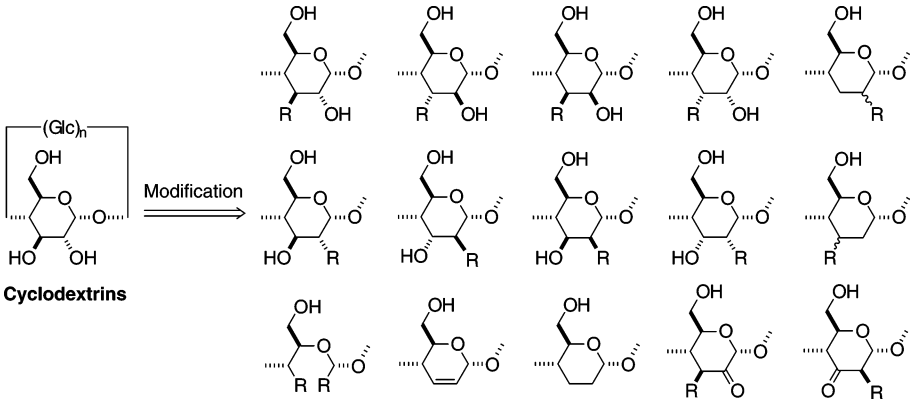
SCHEME 1. Some of the Various Subunit Structures That Can Be Potentially Derived from the Modification of the Secondary Face of CDs



of CDs with other functional moieties can improve remarkably the binding and catalytic ability of CDs or even result in the finding of novel functions,[3] and this has led to extensive investigation on the selective chemical modification of CDs.[4]

Taking advantage of the greater reactivity of the chemically equivalent C-6 hydroxyl groups, it has been relatively facile to perform selective mono-, di-, or monofacial functionalization at the primary face, although overall yields are often unsatisfactory.[5] The secondary hydroxyl groups are more acidic than the primary ones, and this feature has been utilized to effect selective functionalization of the secondary face under basic conditions.[6] However, this process is relatively less facile and has been limited to a much smaller selection of pendent groups because of the competitive reaction of the primary face and/or the reaction complexity of the secondary face itself. The 2-OH group is readily accessible to direct alkylation or sulfonylation, usually generating a mixture of heterologous (with different degrees of substitution) and homologous (regio-) isomers.[7] On the other hand, the 3-OH group is very difficult to access directly. Up to now only a couple of reagents have been reported to directly react at that site in a selective manner.[8,9]

Modification of the secondary face of CDs, though very difficult as mentioned above, has the potential to provide a great diversity in variegating the shape and size of the hydrophobic cavity and tuning the interplay between the cavity and additional recognition sites. For example, simple replacement at the secondary face may result in either modified glucoside units or other modified sugar units such as altrosides, allosides, and mannosides, while redox reactions can further build the vocabulary (cf. Scheme 1), and most of them may possess a cavity different from each other. Development of generally applicable methods for the modification of a specific position to generate desired sugar types still represents a major challenge. Since the various CD 2,3-epoxides **1**−**8** (Scheme 2)[6,9,11−17] have become available, we herein report the reactions of these CD epoxides with various nucleophiles and reducing reagents, and their use in producing CD derivatives containing a 3-iodoglucoside, 2- or 3-aminoglucoside, 2- or 3-thioglucoside, 2- or 3-iodoaltroside, 2- or 3-aminoaltroside, 2- or 3-thioaltroside,

(3) Yuan, D.-Q.; Kishikawa, N.; Yang, C.; Koga, K.; Kuroda, N.; Fujita, K. *Chem. Commun.* **2003**, 416−417. Liu, Y.; Fan, Z.; Zhang, H. Y.; Diao, C. H. *Org. Lett.* **2003**, *5*, 251−254. de Jong, M. R.; Knegtel, R. M. A.; Grootenhuis, P. D. J.; Huskens, J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1004−1008. Michels, J. J.; Huskens, J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2002**, *124*, 2056−2064. Breslow, R.; Yang, J.; Yan, J. M. *Tetrahedron* **2002**, *58*, 653−659. Yan, J.-M.; Atsumi, M.; Yuan, D.-Q.; Fujita, K. *Helv. Chim. Acta* **2002**, *85*, 1496−1504. Yuan, D.-Q.; Lu, J.; Atsumi, M.; Izuka, A.; Kai, M.; Fujita, K. *Chem. Commun.* **2002**, 730−731. Baugh, S. D. P.; Yang, Z.; Leung, D. K.; Wilson, D. M.; Breslow, R. *J. Am. Chem. Soc.* **2001**, *123*, 12488−12494. Berberan-Santos, M. N.; Choppinet, P.; Fedorov, A.; Jullien, L.; Valeur, B. *J. Am. Chem. Soc.* **2000**, *122*, 11876−11886. Yan, J.-M.; Atsumi, M.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **2000**, *41*, 825−828. Rizzarelli, E.; Vecchio, G. *Coord. Chem. Rev.* **1999**, *188*, 343−364. Yuan, D.-Q.; Dong, S. D.; Breslow, R. *Tetrahedron Lett.* **1998**, *39*, 7673−7676. Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997−2011.

(4) Yuan, D.-Q.; Yang, C.; Fukuda, T.; Fujita, K. *Tetrahedron Lett.* **2003**, *44*, 565−568. Maccarrone, G.; Rizzarelli, E.; Vecchio, G. *Polyhedron* **2002**, *21*, 1531−1536. Heck, R.; Dumarcay, F.; Marsura, A. *Chem. Eur. J.* **2002**, *8*, 2438−2445. Yuan, D.-Q.; Yamada, T.; Fujita, K. *Chem. Commun.* **2001**, 2706−2707. Wenz, G.; Höfler, T. *Carbohydr. Res.* **1999**, *322*, 153−165. Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977−1996. Coleman, A. W.; Zhang, P.; Parrot-Lopez, H.; Ling, C. C.; Miocque, M.; Mascrier, L. *Tetrahedron Lett.* **1991**, *32*, 3997−3998. Croft, A. P.; Bartsch, R. A. *Tetrahedron* **1983**, *39*, 1417−1474.

(5) Atsumi, M.; Izumida, M.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **2000**, *41*, 8117−8120. Koga, K.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **2000**, *41*, 6855−6857. Byun, H.-S.; Zhong, N.; Bittman, R. *Org. Synth.* **2000**, *77*, 225−230. Vizitiu, D.; Walkinshaw, C. S.; Thatcher, G. R. J. *J. Org. Chem.* **1997**, *62*, 8760−8766. Gadelle, A.; Defaye, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 78−79. Tabushi, I.; Nabeshima, T.; Fujita, K.; Matsunaga, A.; Imoto, T. *J. Org. Chem.* **1985**, *50*, 2638−2643. Tabushi, I.; Yamamura, K.; Nabeshima, T. *J. Am. Chem. Soc.* **1984**, *106*, 5267−5270. Tabushi, I.; Kuroda, Y.; Yokota, K.; Yuan, L.-C. *J. Am. Chem. Soc.* **1981**, *103*, 711−712.

(6) Rong, D.; D'Souza, V. T. *Tetrahedron Lett.* **1990**, *31*, 4275−8. Law, H.; Baussanne, I.; García Fernández, J. M.; Defaye, J. *Carbohydr. Res.* **2003**, *338*, 451−453.

(7) Hanessian, S.; Benalil, A.; Laferriere, C. *J. Org. Chem.* **1995**, *60*, 4786−4797. Hanessian, S.; Benalil, A.; Simard, M.; Bélanger-Garipiépy, F. *Tetrahedron* **1995**, *51*, 10149−10158.

(8) Tian, S.; Forgo, P.; D'Souza, V. T. *Tetrahedron Lett.* **1996**, *37*, 8309−8312;

(9) Fujita, K.; Tahara, T.; Imoto, T.; Koga, T. *J. Am. Chem. Soc.* **1986**, *108*, 2030−2034.

(10) Chen, W.-H.; Yuan, D.-Q.; Fujita, K. *Tetrahedron Lett.* **1997**, *38*, 4599−4602. Yuan, D.-Q.; Ohta, K.; Fujita, K. *J. Chem. Soc., Chem. Commun.* **1996**, 821−822.

(11) Ueno, A.; Breslow, R. *Tetrahedron Lett.* **1982**, *23*, 3451−3452.

(12) Ohta, K.; Fujita, K.; Shimada, H.; Ikegami, Y.; Nogami, Y.; Koga, T. *Chem. Pharm. Bull.* **1997**, *45*, 631−635.

(13) Teranishi, K.; Watanabe, K.; Hisamatsu, M.; Yamada, T. *J. Carbohydr. Chem.* **1998**, *17*, 489−494.

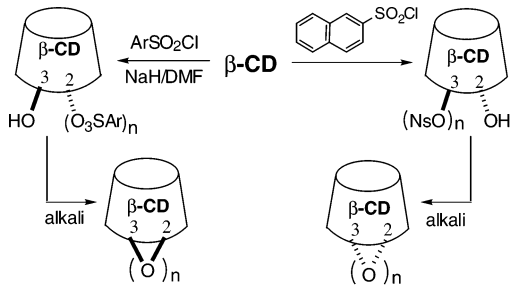
(14) Teranishi, K. *Tetrahedron Lett.* **2001**, *42*, 5477−5480. Teranishi, K. *Tetrahedron Lett.* **2000**, *41*, 7085−7088.

(15) Fujita, K.; Tahara, T.; Yamamura, H.; Imoto, T.; Koga, T.; Fujioka, T.; Mihashi, K. *J. Org. Chem.* **1990**, *55*, 877−880.

(16) Fujita, K.; Ishizu, T.; Oshiro, K.; Obe, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2960−2962. Fujita, K.; Nagamura, S.; Imoto, T.; Tahara, T.; Koga, T. *J. Am. Chem. Soc.* **1985**, *107*, 3233−3235.

(17) Breslow, R.; Czarnik, A. W. *J. Am. Chem. Soc.* **1983**, *105*, 1390−1391.

SCHEME 2. Syntheses of Cyclodextrin Epoxides[a]



1: n = 1, mannoepoxide
2: n = 2, AB-dimannoepoxide
3: n = 2, AC-dimannoepoxide
4: n = 3, AD-dimannoepoxide
5: n = 1, alloepoxide
6: n = 2, AC-diallooepoxide
7: n = 2, AD-dialloepoxide
8: n = 3, ACE-trialloepoxide

[a] In 1982, Breslow et al.[11] demonstrated the first successful sulfonylation of the 2-OH of β-CD by tosyl transfer from the *m*-nitrophenyl tosylate bound in the CD cavity, making a landmark in the selective functionalization of CDs. Years later, D'Souza et al.[6] sulfonylated the 2-OH by deprotonation with NaH and subsequent reaction with sulfonyl chloride or sulfonyl triazole. This method can be used to sulfonylate any two 2-OH groups of β-CD.[12] Teranishi[13,14] sulfonylated the 2-OH with sulfonyl imidazole in DMF, by utilizing molecular sieves rather than a base to promote the reaction. Fujita et al.[9,15] demonstrated the selective sulfonylation of up to three 3-OH groups of β-CD by reacting 2-naphthalenesulfonyl chloride with β-CD in 30% CH_3CN solution (pH 12). All these sulfonates can be easily transformed into their corresponding 2,3-epoxy-β-CDs **1**−**8** in alkaline condition.[9,15,16,17]

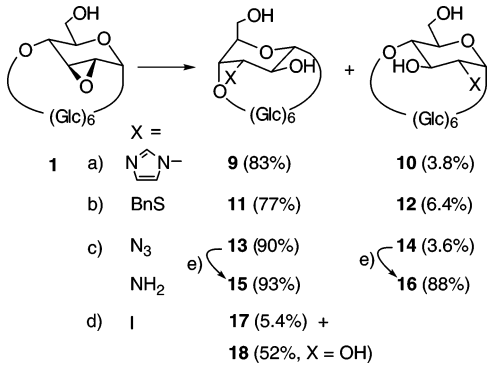
2-enopyranoside, and 3-deoxymannoside, respectively.[10] All these species can be used as important scaffolds for further functionalization.

Result and Discussion

(a) Ring-Opening of 2,3-Mannoepoxy-β-cyclodextrin: Abnormal Nucleophilic Attack at the C2. 2,3-Mannoepoxy-β-CD **1** was first utilized to react with a thiol to generate transaminase model.[17] The isolated product was proved to have the functional group attached to the C3, and its formation follows the *trans*-diaxial rule[18] that governs the ring-opening reaction of sugar epoxides. It should be noted that the attack of nucleophiles at C3 inverses the conformation of this position and the resultant functional CDs have one C3 modified altroside unit. The presence of an altrose residue within the CD macrocycle distorts the hydrophobic cavity from that of β-CD and engenders enhanced ability in restricting guest-orientation, but at the cost of a decrease in the binding strength.[19]

By heating 2,3-mannoepoxy-β-CD **1** in an imidazole−HCl buffer solution, we found that in addition to the expected 3^A-imidazolyl-*altro*-β-CD **9**, 2-imidazolyl-β-CD **10** was formed as a minor product (3.8%), and we succeeded in isolating and characterizing these products (Scheme 3). The result indicates that there exists an unprecedented attack of imidazole at the C2 of the 2,3-mannoepoxide. This *abnormal* reaction is of significance in that the glucosidic structure is recovered in the final

SCHEME 3. Nucleophilic Ring-Opening of 2,3-Mannoepoxy-β-cyclodextrin[a]



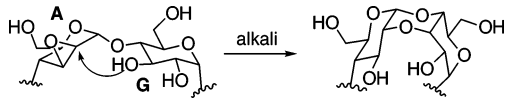
[a] Reagents and conditions: (a) imidazole−HCl buffer (pH 7)/75 °C/90 h; (b) $PhCH_2SH/Cs_2CO_3$/DMF/80 °C/6 h; (c) NaN_3/Me_3N·HCl/H_2O/80 °C/3 d; (d) LiI/Me_3N·HCl/H_2O/80 °C/10 d; (e) Ph_3P/DMF/40 °C/1 d, then aq NH_3/rt/1 d.

product. Various nucleophiles such as thiols, azide, etc. have been used to react with the epoxide, and similar results are obtained in each case. That is, the reaction of the mannoepoxide **1** always gives the corresponding 3-substituted *altro*-β-CDs in very high yields together with a few percent of the 2-substituted β-CDs. Benzylmercaptan reacts smoothly with **1** in DMF in the presence of Cs_2CO_3, affording 3-benzylmercapto-*altro*-β-CD **11** in 77% and the 2-glucosidic isomer **12** in 6.4% yields, respectively. Sodium azide reacts with **1** in aqueous solution, generating 3^A-azido-*altro*-β-CD **13** and 2-azido-β-CD **14** in 90% and 3.6% yields, respectively. Reduction of the azido β-CDs **13** and **14** by triphenylphosphine in DMF afforded the corresponding CD amines **15** and **16** in pretty high yields.

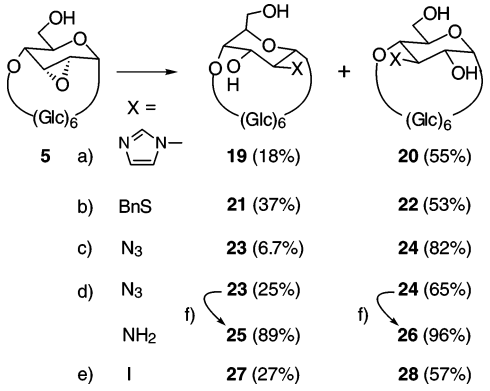
Although in very low yield, this method does afford the undistorted C2 functional CDs that are otherwise inaccessible at present. Attempts were made to improve the availability of the 2-substituted β-CD derivatives by varying the reaction conditions such as reaction temperature, solvent, and nucleophiles, but only very limited effects were observed. The reaction media exercise remarkable influence on the reaction rate but little influence on the product distribution. When DMF was employed as solvent, thiols reacted smoothly at 80 °C while neither imidazole nor sodium azide demonstrated obvious reaction even after being heated at an elevated temperature for a prolonged time. Buffered aqueous solutions seem to be the preferable choice as solvents for the reaction of mannoepoxide that requires the nucleophile to attack the reaction sites from inside the CD cavity. The reaction of iodide anion with **1** proceeds smoothly in water, but in this case, the products do not accumulate because of the reverse elimination reaction of the CD iodides and the irreversible competition reaction of water. When the trimethylamine-buffered aqueous solution of **1** and LiI is heated at 80 °C for 10 d, 3-iodo-*altro*-β-CD **17** is isolated only in low 5.4% yield while *altro*-β-CD **18** even amounts to 52% yield. Strong acidic or strong basic conditions should be avoided for the reaction in aqueous solution because the altrose-type products appear to be less acid-resistant than β-CD, and decompose significantly at pH <3, while in strong alkaline solution, the 3^G-OH adjacent to the epoxy group becomes ionized and

(18) Williams, N. R. *Adv. Carbohydr. Chem.* **1970**, *25*, 109−179.
(19) Chen, W.-H.; Fukudome, M.; Yuan, D.-Q.; Fujioka, T.; Mihashi, K.; Fujita, K. *Chem. Commun.* **2000**, 541−542. Fujita, K.; Chen, W.-H.; Yuan, D.-Q.; Nogami, Y.; Koga, T.; Fujioka, T.; Mihashi, K.; Immel, S.; Lichtenthaler, F. *Tetrahedron: Asymmetry* **1999**, *10*, 1689−1696. Fujita, K.; Okabe, Y.; Ohta, K.; Yamamura, H.; Tahara, T.; Nogami, Y.; Koga, T. *Tetrahedron Lett.* **1996**, *37*, 1825−1828.

SCHEME 4. Intramolecular Crossed-Subunit Reaction of 2,3-Mannoepoxy-β-cyclodextrin



SCHEME 5. Nucleophilic Ring-Opening of 2,3-Alloepoxy-β-cyclodextrin[a]



[a] Reagents and conditions: (a) imidazole/DMF/90 °C/5 d; (b) $PhCH_2SH/Cs_2CO_3$/DMF/80 °C/6 h; (c) NaN_3/DMF/95 °C/18 h; (d) $NaN_3/Me_3N{\cdot}HCl/H_2O$/80 °C/3 d; (e) LiI/$Me_3N{\cdot}HCl$/DMF/80 °C/1 d; (f) Ph_3P/DMF/40 °C/1 d, then aq NH_3/rt/1 d.

undergoes an intramolecular crossed-subunit attack at the epoxide (Scheme 4).[20]

(b) Nucleophilic Ring-Opening of 2,3-Alloepoxycyclodextrins: The Abnormal Reaction Predominates. With the reaction information of the CD mannoepoxide in hand, we elected to investigate the reactivity of 2,3-alloepoxy CD, which is expected to generate pairs of modified CDs complementary to those from the corresponding mannoepoxide. 2,3-Alloepoxide **5** reacts smoothly with various nucleophiles (Scheme 5). An altrose unit with a functional group at C2 was expected to be generated from this reaction based on the general *trans*-diaxial rule.[18] Indeed this altrose unit does form in each case, but only as a minor product! The *abnormal* 3-modified glucosidic species are always generated as major products. Alloepoxide **5** reacts with imidazole in DMF, affording the *normal* product 2^A-imidazolyl-*altro*-β-CD **19** (expected from the *trans*-diaxial ring-opening) in 18% isolated yield and the *abnormal* product 3-imidazolyl-β-CD **20** in 55% isolated yield. Benzylmercaptan and LiI react similarly with **5**, each affording a pair of 3-substituted β-CD and 2^A-substituted *altro*-β-CD in a ratio of ∼2. A much higher "abnormal/normal" ratio (up to 12) was obtained by heating sodium azide and epoxide **5** in DMF at 95 °C. Solvent exhibits significant influence on the reaction of **5**. The "abnormal/normal" product ratio of the reaction of **5** with sodium azide decreased to 2.6 when water was used as solvent, although the total yield remained unaffected. In the reaction of LiI and **5**, water as solvent significantly decreases the yields of the CD iodides. Strong alkaline solution should always be avoided because of the possible intramolecular attack of the 6-OH leading to the formation of 3,6-anhydro species.[21]

The dialloepoxy-β-CDs **6** and **7** and trialloepoxy-β-CD **8** also react well with these nucleophiles (Scheme 6). It is quite interesting to note that in this case, each epoxy unit seems to react independently and with quite similar "abnormal/normal" selectivity to that of monoepoxide **5**. That is, all-glucose type species are always generated as the main product although three other isomers from a dialloepoxide or seven minor products from the trialloepoxide are expected to be generated. Careful reversed-phase column chromatography allows the effective isolation of the all-glucose type species from the reaction mixtures although the separation of the other altrose-bearing isomers from each other still relies upon the development of new strategy. This method enables the regiospecific introduction of two or three functional groups onto the C-3 positions of β-CD without a net alteration of their stereochemistry.

Imidazole reacts smoothly with epoxides **6**, **7**, and **8** in DMF, affording the diimidazolyl-β-CDs **29** and **30** and triimidazolyl-β-CD **31** in 37%, 32%, and 21% isolated yields, respectively. In the reaction of polyepoxy-β-CDs in DMF, a proton source seems to be important to protonate the generated CD oxylates. Otherwise, the latter may cause serious side reactions such as the formation of 3,6-anhydro units. Imidazole itself can provide this proton and therefore reacts well with all the alloepoxides in DMF. In the case of azide salt, however, the proton source becomes an important issue. We even failed in isolating any pure product of triazide **34** from the reaction of NaN_3 and **8** in DMF under anhydrous condition. The utilization of β-CD as the proton source enabled the formation of triazide **34** in 28% yield. A comparable yield of **34** is obtained when the reaction is carried out in buffered aqueous solution. By a similar procedure, diazides **32** and **33** are also obtained from diepoxides **6** and **7**. It appears that water is the convenient medium for this reaction. Reduction of azides **23**, **24**, and **32**−**34** with triphenylphosphine afforded the corresponding CD amines **25**, **26**, and **35**−**37** in very high yields.

(c) Identification and Structural Assignment of Ring-Opening products. The ring-opening reaction of the monoepoxy-β-CDs usually demonstrates complete conversion to one pair of isomeric products, giving a very simple final reaction mixture. The two isomers exhibit retention behavior significantly different from each other on reversed-phase ODS column. The altrose-type isomer elutes much faster than its glucose-type counterpart, and this relationship holds well in each pair of isomers hitherto generated from CD epoxides. This difference is supposed to be a reflection of their different binding affinity to the ODS alkyl chain. The glucose-type isomer retains the regular cavity of native CD and binds the ODS alkyl groups more strongly than the altrose-type isomer whose cavity is slightly distorted. This feature enables an efficient separation of each pair of isomeric products and also affords a convenient empirical identification of the two isomers. The general appearance of conventional 1D NMR spectra may also afford very useful information for the differentiation of the altrose-type and glucose-type isomers. The altrose-type isomer always demonstrates much more complicated spectra than the glucose-type (cf. Figure 1).

Detailed structural assignments of CD derivatives

(20) Fujita, K.; Tahara, T.; Sasaki, H.; Egashira, Y.; Shingu, T.; Imoto, T.; Koga, T. *Chem. Lett.* **1989**, 917−920.
(21) Fujita, K.; Yamamura, H.; Imoto, T.; Tabushi, I. *Chem. Lett.* **1988**, 543−546.

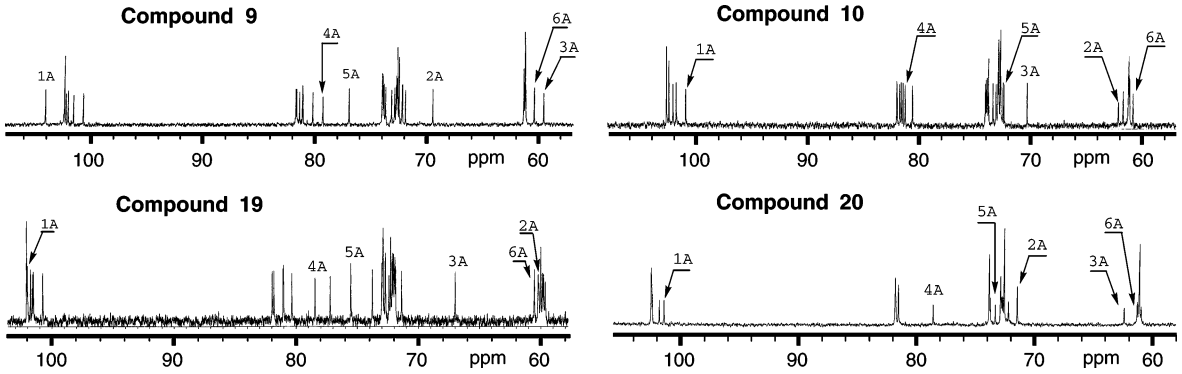
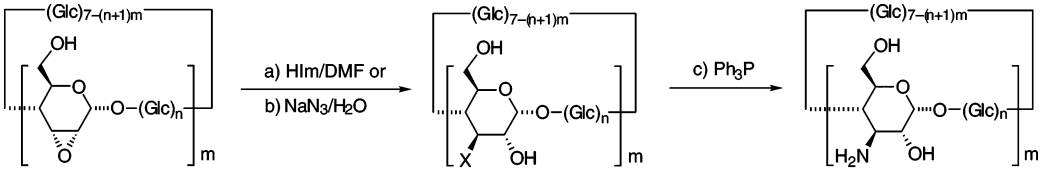


FIGURE 1. ^{13}C NMR (125 MHz) spectra of **9**, **10**, **19**, and **20**.

SCHEME 6. Nucleophilic Ring-Opening of *β*-Cyclodextrin Di- and Trialloepoxides



6	m = 2, n = 1: AC	**29** (37%)	**32** (34%)	**35** (91%)
7	m = 2, n = 2: AD	**30** (32%)	**33** (30%)	**36** (92%)
8	m = 3, n = 1: ACE	**31** (21%)	**34** (28%)	**37** (93%)

TABLE 1. 125-MHz ^{13}C NMR Chemical Shift Differences and 500-MHz ^{1}H NMR Coupling Constants for the Imidazolyl Sugar Units in Compounds 9, 10, 19, and 20[a]

	chemical shift differences ($\delta_{funct} - \delta_{norm}$, ppm)					coupling constants (Hz)			assignment	
compd	C1	C2	C3	C4	C5	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	position of Im	sugar type
9	1.6	−3.4	−14.4	−2.6	4.4	7.3	11.2	3.7	C3	altrose
10	−1.7	−10.8	−3.7	−0.7	−0.4	3.7	11.2	8.7	C2	glucose
19	0.2	−12.1	−5.9	−3.0	3.6	∼6.4		∼3.0	C2	altrose
20	−1.2	−1.4	−11.6	−3.3	0.7	3.4	10.8	10.5	C3	glucose

[a] δ_{funct} and δ_{norm} denote the chemical shifts for the imidazolyl sugar units in **9**, **10**, **19**, and **20** and those for *β*-CD, respectively. Compound **19** was detected in $(CD_3)_2SO$ (TMS int.), while **9**, **10**, and **20** were detected in D_2O (MeCN int.), and *β*-CD was measured under both conditions. All the NMR spectra were assigned based on $^{1}H-^{1}H$ and $^{13}C-^{1}H$ COSY NMR experiments.

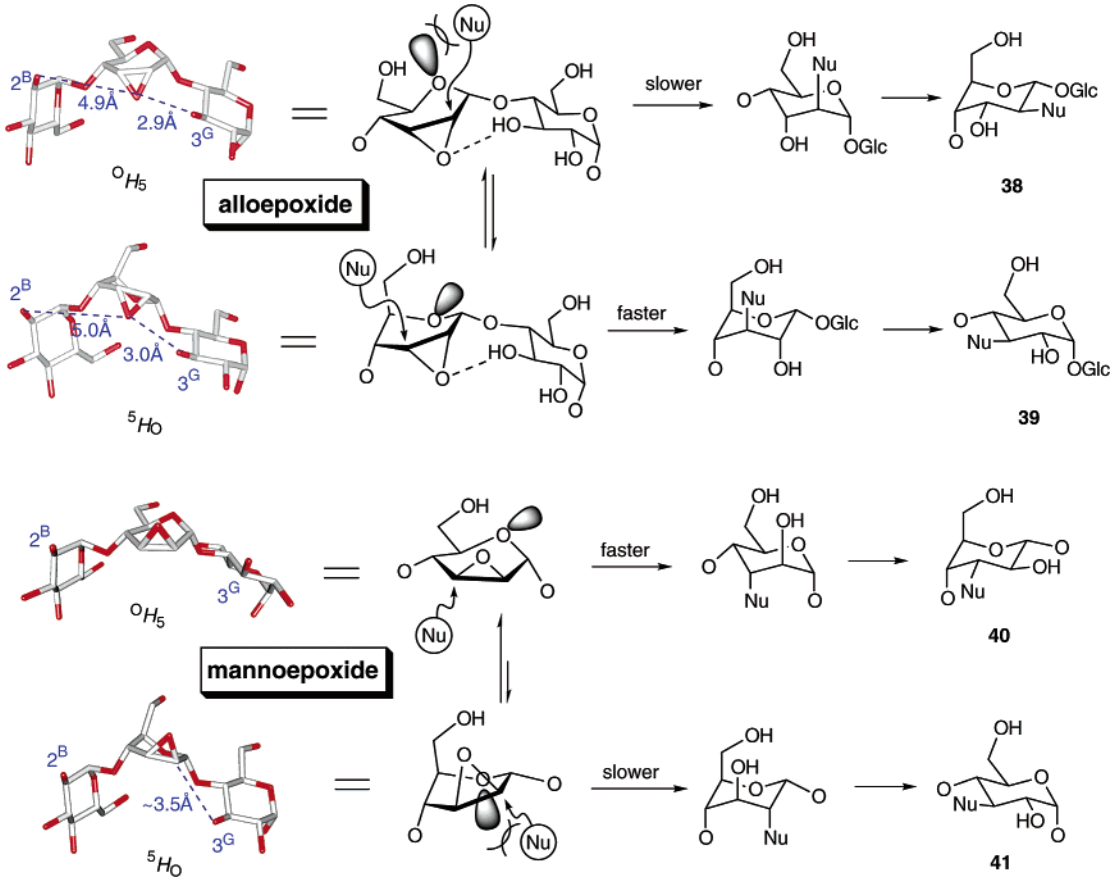
usually need intensive NMR experiments including the utilization of advanced techniques.[22] The problem in the present case is greatly simplified since the C2 and C3 of the modified sugar unit are the only two positions in question during the structural investigation of the ring-opening products. First of all, the most remarkably shifted signal can easily be recognized from the normal ones in the ^{13}C NMR spectrum and that signal corresponds to the modified position since an introduced substituent always has a different inductive effect from that of OH. Then COSY, HSQC, and/or TOCSY experiments[22] allow us to determine whether that signal comes from C2 or C3. As long as the modified position is determined, the proper sugar type can be drawn based on the stereochemistry of the reaction and further confirmed by the examination of the corresponding spin−spin coupling constants $^{3}J_{x,y}$.

The imidazolyl CDs are taken as examples for the illustration of the structure assignment since the ring-current effect shifts the protons of the modified unit from the corresponding region of unmodified sugar units, allowing the extraction of necessary $J_{x,y}$ values. The position of the imidazole moiety can be convincingly determined by ^{13}C NMR, since there is a large upfield shift for the nitrogen-attached carbon (α-carbon) but a much smaller upfield shift for the *β*-carbon.[23] Figure 1 and Table 1 demonstrate that both **10** and **19** exhibited these large upfield shifts of C2 but much smaller upfield shifts of the neighboring C1 and C3. While in **9** and **20** great upfield shifts were observed for C3, but much smaller upfield shifts for C2 and C4 were observed. Therefore, we assign the imidazolyl moiety to C2 for **10** and **19**, but to C3 for **9** and **20**. Examination of the proton NMR spectra gives a clue to the stereochemistry of the functional sugar units. Compound **9** showed axial−axial couplings for H2 with both H1 ($J_{1,2}$ = 7.3 Hz) and H3 ($J_{2,3}$ = 11.2 Hz), indicating that H1, H2, and H3 are all axial. The axial−equatorial coupling between H3 and H4 ($J_{3,4}$ = 3.7 Hz) indicated an equatorial orientation of H4. Therefore, the imidazolyl sugar unit in **9** is most likely

(22) Schneider, H.-J.; Hacket, F.; Ruediger, V.; Ikeda, H. *Chem. Rev.* **1998**, *98*, 1755−1785.

(23) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293−297. Walker, T. E.; Barker, R. *Carbohydr. Res.* **1978**, *64*, 266−270.

SCHEME 7. Mechanistic Consideration of the Ring-Opening Reactions of CD Epoxides[a]



[a] The models on the left are generated by energy minimization using MM2 force field to show the geometries of the trioses consisting of the anhydrosugar unit and the two units on both sides with the hydrogen atoms being omitted for clarity.

to be of an altroside type with a predominant conformation of $^1C_4$. In the case of **10**, the coupling constants suggested the axial orientation of H2, H3, and H4 ($J_{2,3}$ = 11.2 Hz, $J_{3,4}$ = 8.7 Hz) and the equatorial orientation of H1 ($J_{1,2}$ = 3.7 Hz), implying a glucoside type unit having a $^4C_1$ conformation. In the same way, a glucoside type unit with a $^4C_1$ conformation can also be evaluated for the imidazole-modified unit in **20**, but an altroside type unit takes $^1C_4$ as the predominant conformation for **19**.

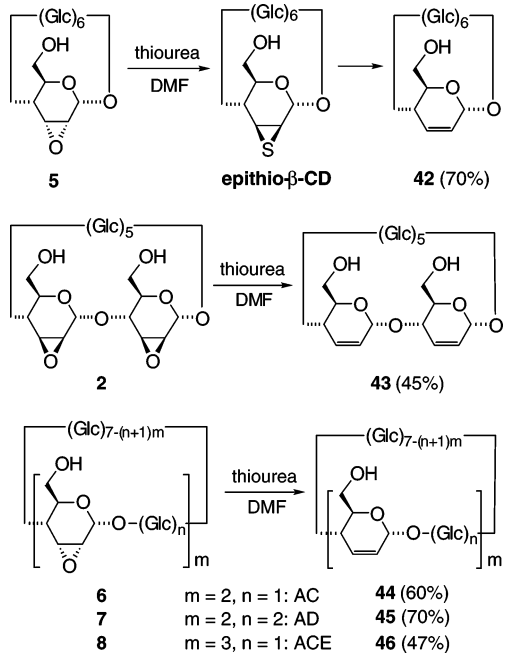
For the CD derivatives bearing substituents other than imidazolyl, structural assignments are similarly performed. The modified carbons are found to be shifted 20−25 ppm upfield by the benzylmercapto group (**11**, **12**, **21**, and **22**), ∼7 ppm upfield by the azido group (**13**, **14**, **23**, **24**, and **32**−**34**), ∼15 ppm upfield by the amino group (**15**, **16**, **25**, **26**, **35**−**37**), and 35−38 ppm upfield by the iodo atom (**17**, **27**, and **28**). A predominant $^4C_1$ conformer is always derived for modified glucose residues, and a $^1C_4$ conformer for altrose residues.

(d) On the Product Distribution. This ring-opening reaction is interesting because it provides a possibility to substitute secondary hydroxyl groups, either with or without the conformational inversion of both the C2 and C3. In principle, this methodology can afford CD derivatives with functionality either on C2 or on C3 of a glucosidic or altrosidic sugar unit. In addition, the ring-opening takes place predominantly at the C3 position of both the manno and alloepoxides regardless of whether it is expected from the normal *trans*-diaxial rule. Obviously, this result implies that the factors that govern the nucleophilic ring-opening of epoxy-*β*-CDs may be different from those in ordinary sugar epoxides.

The 2,3-anhydropyranose unit may adopt $^OH_5$ and ^5H_O half-chair conformations that equilibrate with each other (Scheme 7). Ring-opening of the $^OH_5$ conformers directs the nucleophiles to the C2 position of the alloepoxide and C3 of the mannoepoxide, generating the altroside units (**38** and **40**). Reaction of the ^5H_O conformers requires the axial attack of nucleophiles at the C3 of the alloepoxide and C2 of the mannoepoxide, recovering the glucoside structure (**39** and **41**). Since the NMR spectra suggest a predominant $^4C_1$ conformation for the modified glucose unit but a $^1C_4$ conformation for the altroside unit in each case, a chair flip should have subsequently taken place after the ring-opening.

Molecular model inspection reveals important information that may account for the product distribution. In the case of the alloepoxide, the C3^G-OH of the adjacent glucose on the clockwise side of the epoxide is in close vicinity of the epoxy oxygen and can act as a hydrogen donor to form a crossed-unit H-bond with the epoxy oxygen whereas the C2^B-OH on the counterclockwise side is located too far away to form a crossed-unit H-bond with the epoxy oxygen (Scheme 7, left). Nucleophilic attack at the C3 of the ^5H_O conformer, though it confronts steric repulsion from the hydroxymethyl group, leads to the formation of an energetically favored transition state by

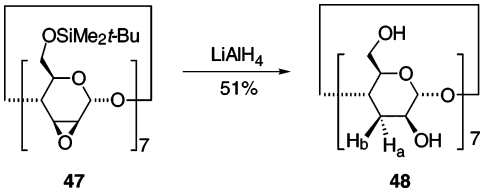
SCHEME 8. Syntheses of *β*-Cyclodextrin Olefins



intensifying this H-bonding interaction. In contrast, nucleophilic attack at the C2 of the $^{O}H_5$ conformer will break this H-bond. In addition, the possible electronic repulsion between the incoming nucleophile and the lone-pair electrons of the endo O5 oxygen may also play a role in suppressing **38** to a minor product. In the case of mannoepoxide, the steric and electronic effects together with the conformational factor may play an important role in governing the regiochemistry of the reaction since the crossed-unit H-bonding of the epoxy oxygen is not likely to occur in both conformers. First, the $^{O}H_5$−$^{5}H_O$ equilibrium favors the $^{O}H_5$ conformer, which was actually found to be the only conformer in the solid structure of 2,3-anhydro-α-cyclomannin.[24] Second, the C3^{G}-OH blocks the C2^{A} carbons from the rear side of the epoxy oxygen.[25] Finally, the electronic repulsion between the nucleophile and the endo-O5 and glycosidic oxygen appears to be much stronger in the $^{5}H_O$ conformer than in the $^{O}H_5$ one. As a result, all the conformational steric and electronic factors favor the reaction of the $^{O}H_5$ conformer, and the C3 modified altrose-type products **40** are therefore generated almost exclusively.

(e) Reaction of Cyclodextrin 2,3-Epoxides with Thiourea. Both manno- and alloepoxy-*β*-CDs react with thiourea in DMF. Instead of ring-opening products, the reaction produces 2,3-epithio-*β*-CDs and olefinic species (Scheme 8). We focused on the syntheses of the olefin compounds and succeeded in ameliorating the reaction conditions for producing these species. By using thiourea in excess and prolonging the reaction time, the reaction of both manno- and alloepoxy-*β*-CDs proceeds well and affords the olefin as the predominant product, which can be precipitated with acetone and then purified by reversed-phase column chromatography. The isolated yield of olefin **42** from the reaction of alloepoxy-*β*-CD **5** amounts to 70%. Similarly, the dimannoepoxides **2**−**4**, dialloepoxides **6** and **7**, and trialloepoxide **8** all react with thiourea to give the corresponding dienes **43**−**45** and triene **46** in moderate yields. In general, the mannoepoxides take much longer time than the corresponding alloepoxides for the reactions to reach a completion, and therefore the alloepoxides were employed in the preparation of the corresponding olefins except for the AB-dimannoepoxide **2** whose allo-isomer is unavailable.

SCHEME 9. Reduction of *β*-Cyclodextrin Permannoepoxide



In the NMR spectra of all the olefinic CD derivatives, the olefinic units demonstrated H1, H2, H3, and H4 around *δ* 5.21, 5.90, 6.04, and 4.12 ppm, and C1, C2, C3, and C4 around *δ* 97, 127, 131, and 72.5 ppm. All the glucose units showed basically the ordinary chemical shift patterns in the normal region of native *β*-CD.

Despite the enormous effort devoted to the chemical modification of CDs, derivatives bearing subunits other than glucose or altrose are very rare. The above and other possible olefinic derivatives of CDs should afford an interesting approach to access novel cyclooligosaccharides consisting of sugar units other than the conventional glucose and altrose.

(f) Reduction of Cyclodextrin Per(2,3-manno-epoxide). Since the *β*-CD permannoepoxide has become available,[26] and nucleophiles such as H_2O and NH_3 tend to selectively attack the C-3 generating *β*-cycloaltrin and per(3-amino)-*β*-cycloaltrin,[27] it is reasonable to deduce that the hydride anion would react similarly to produce per(3-deoxy)cyclomannin (Scheme 9). Compared to native *β*-CD, the number of secondary hydroxyl groups in per-(3-deoxy)-*β*-cyclomannin is half. If all the 3-deoxymannoside units take the $^{4}C_1$ conformation to form a cavity, all the 2-OH groups are axially located outside the cavity and a crossed-unit hydrogen bond would not be likely to occur for the secondary hydroxyl side. Therefore, the cavity of per(3-deoxy)-*β*-cyclomannin, if it can form, is expected to have more flexibility and stronger hydrophobicity which are very important for bio-receptors or biocatalysts.

During the course of our research on this transformation, Kelly et al.[28] reported the reduction of persilyl permannoepoxy-*β*-CD to persilyl per(3-deoxy)-*β*-cyclomannin with Super-Hydride as reducing agent. With $LiAlH_4$ or $AlH(i\text{-}Pr)_2$ as reducing agent they only obtained a complex mixture. We succeeded in a one-pot conversion

(24) Immel, S.; Lichtenthaler, F. W.; Lindner, H. J.; Fujita, K.; Fukudome, M.; Nogami, Y. *Tetrahedron*: *Asymmetry* **2000**, *11*, 27−36.

(25) Immel, S.; Fujita, K.; Fukudome, M.; Bolte, M. *Carbohydr. Res.* **2001**, *336*, 297−308.

(26) Zhang, P.; Coleman, A. W. *Supramol. Chem.* **1993**, *2*, 255−263. Kahn, A. R.; Barton, L.; D'Souza, V. T. *J. Chem. Soc., Chem. Commun.* **1992**, 1112−1114.

(27) Khan, A. R.; Tong, W.; D'Souza, V. T. *Supramol. Chem.* **1995**, *4*, 243−246. Groaning, M. D.; D'Souza, V. T. *Supramol. Chem.* **1996**, *8*, 5−8. Fujita, K.; Shimada, H.; Ohta, K.; Nogami, Y.; Nasu, K.; Koga, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1621−1622.

(28) Kelly, D. R.; Mish'al, A. K. *Tetrahedron*: *Asymmetry* **1999**, *10*, 3627−3648.

of persilyl permannoepoxy-β-CD to per(3-deoxy)-β-cyclomannin with $LiAlH_4$ as reducing agent. Persilyl permannoepoxy-β-CD **47** was heated with excess $LiAlH_4$ in DMF, and the process of the reaction was traced by TLC. The reaction mixture was worked up with water when no further changes were observed on TLC. Chromatography on a reversed-phase column of the reaction mixture afforded the desired per(3-deoxy)-β-cyclomannin **48** in 51% yield.

NMR spectra of **48** demonstrated a C_7 symmetry. Two protons were found to be attached to each C3 and they resonated at very high field (δ 2.06 ppm), while only one proton was found for each C2 in the much lower field (δ 3.92 ppm). The H4 proton also showed a large downfield shift to δ 4.01 ppm, while H1, H5, and H6 protons resonated in regions (at δ 4.80, 4.01, and 3.88 ppm, respectively) quite similar to those of β-CD. The result indicated that the reduction occurred at the C3 position. On the basis of the *trans*-diaxial rule that governs the ring-opening reaction of sugar epoxides, the C2 should retain the stereochemistry of mannoside. In agreement with this assignment, the ^{13}C NMR spectrum demonstrated a signal at δ 32.3 ppm for the deoxygenated C3. In addition, the C2 and C4 carbons were subjected to significant upfield shift to δ 67.5 and δ 72.3 ppm, respectively, while the C1, C5, and C6 carbons were not obviously affected by comparison with those of β-CD.

The deoxygenated cyclooligosaccharide is very soluble in water and its proton signals are obviously broader than those of β-CD. This may imply that the inter-unit hydrogen bond is not likely to occur for the secondary hydroxyl side, and the whole molecule is more flexible than β-CD. Further work is needed to evaluate the existence of the hydrophobic cavity and its binding property.

Conclusion

In summary, we have described three types of reactions of 2,3-anhydro-β-CDs, the very important intermediates for the modification of the secondary face of β-CD. First, nucleophilic opening of the epoxy rings was intensively investigated with various nucleophiles. It has been clarified that the reaction of mannoepoxides basically follows the *trans*-diaxial rule that governs the reaction of sugar epoxides, generating predominantly the 3-modified altrose structure, while the counterpart 2-modified glucose-type species are only formed in a small percent yield. However, this is the only method hitherto established to incorporate functionalities directly to the C3 carbons of CDs. On the contrary, the reaction of alloepoxides demonstrates reversed regioselectivity from that expected based on the *trans*-diaxial rule, affording the 3-modified glucose species and the 2-modified altrose species in a ratio of ca. 2−3 to 1. The possible H-bond formation between the epoxy oxygen and the $C3^G$-OH together with the electronic repulsion from the endo-O5 oxygen may account for this inversion of the regioselectivity. Second, conversion of the epoxides to the corresponding olefins was effected with good yields by using thiourea as the deoxygenation reagent. Finally, reduction of permannoepoxy-β-CD succeeded and the per(3-deoxy)-β-cyclomannin was efficiently synthesized. Most of the chemically modified cyclodextrins reported herein are expected to serve as versatile scaffolds for diverse purposes such as construction of catalysts and development of synthetic receptors and molecular containers.

Experimental Section

General Methods. Reversed-phase column chromatography was performed on Merck prepacked Lobar columns (LiChroprep RP-18, 40−63 μm, 25 × 310 mm^2 (Size B) or 37 × 440 mm^2 (Size C)). Thin-layer chromatography (TLC) was carried out with Merck aluminum-backed 0.2-mm silica gel 60F-254 plates. Mixed solvents of *n*-propanol/ethyl acetate/water in volume ratios of 7/7/5 (solvent A), 7/7/6 (solvent B), 7/3/6 (solvent C), and 7/3/7 (solvent D) were used as the mobile phase for TLC development. Spot detection was done with a staining solution of 0.1% 1,3-dihydroxynaphthalene in EtOH/H_2O/H_2SO_4 (200/157/43, v/v/v).

General Procedure A: Reaction of β-Cyclodextrin Epoxides with Sodium Azide. A β-CD epoxide (0.2 mmol), NaN_3 (1 mmol), and trimethylammonium chloride (1 mmol) were dissolved in water (15 mL) and the resulting solution was stirred at 80 °C for 3−6 d. After diluted with water, the reaction mixture was chromatographed on a reversed-phase Lobar column (Size B). Elution of the column with a gradient from water (1 L) to 40% methanol (1 L) afforded the corresponding β-CD azides.

General Procedure B: Reduction of β-Cyclodextrin Azides. A β-CD azide (0.95 mmol) and triphenylphosphine (5.3 mmol) were added to DMF (5 mL) and the mixture was stirred at 40 °C for 1 d. Concentrated ammonia (8 mL) was then added and stirring was continued for 1 d. The reaction mixture was slowly added to acetone (600 mL) and the precipitates were collected by filtration and purified by ion-exchange column chromatography (Bio-Rad AG 50W-X2, 100−200 mesh, ϕ-SO_3H type, washed with a gradient of 0−5% aq ammonia solution) to afford the corresponding β-CD amine.

General Procedure C: Reduction of β-Cyclodextrin Epoxides to β-Cyclodextrin Olefins. A β-CD epoxide (0.40 mmol) and thiourea (1.53 g, 20 mmol) were dissolved in water (30 mL) and the solution was stirred at 80 °C for 1 d. After being cooled to room temperature, the reaction mixture was slowly added to acetone (300 mL). The resultant white precipitates were collected by filtration of the clear solution and purified by chromatography on a reversed-phase Lobar column (Size B) with a gradient from H_2O (500 mL) to 40% methanol (500 mL) to furnish the corresponding β-CD olefin as a colorless solid.

3^A-Deoxy-3^A-imidazolyl-*altro*-β-cyclodextrin (9) and 2^A-Deoxy-2^A-imidazolyl-β-cyclodextrin (10). β-CD mannoepoxide **1** (200 mg, 0.18 mmol) was heated for 90 h at 75 °C in a pH 7.0 imidazole−HCl buffer solution (10 mL, containing 680 mg of imidazole, 10 mmol). The reaction mixture was diluted to 100 mL with water and chromatographed on a reversed-phase Lobar column (Size B) with H_2O (500 mL) and a gradient system from H_2O (1 L) to 25% methanol (1 L) as sequential eluents. The saccharides were identified by TLC. The fractions containing the second saccharide species (eluted out at around 18% methanol) were combined, evaporated, and lyophilized to give **10** (8 mg, 3.8%) as a colorless solid. Rechromatography of the fractions containing the faster eluting CD species (around 7% methanol) with a gradient elution from H_2O (1 L) to 20% methanol (1 L) afforded **9** (eluted out at around 8% methanol, 177 mg, 83%) as a colorless solid.

Data for **9**: R_f 0.06 (solvent B). ^{13}C NMR (125 MHz, D_2O, CH_3CN int.) δ 139.3, 128.0, 120.2 104.3, 102.5, 102.4, 102.2, 101.7, 100.9; 81.8, 81.7, 81.5, 81.3, 81.2, 80.3, 79.4, 77.0, 74.1, 74.0, 73.9, 73.8, 73.2, 73.0, 72.8, 72.7, 72.3, 72.3, 72.2, 72.0, 69.5, 61.3, 61.2, 60.4, 59.6. ^1H NMR (500 MHz, D_2O, CH_3CN int.) δ 7.88 (s, 1H), 7.30 (d, ^3J = 1.1 Hz, 1H), 7.00 (d, ^3J = 1.1 Hz, 1H), 5.11 (d, ^3J = 4.1 Hz, 1H), 5.08 (d, ^3J = 4.1 Hz, 1H), 4.98−4.95 (m, 4H), 4.77 (d, ^3J = 3.9 Hz, 1H), 4.57 (dd, ^3J = 11.2, 3.7 Hz, 1H), 4.37 (m, 1H), 4.24 (dd, ^3J = 11.2, 7.3 Hz,

1H), 4.04 (dd, ^3J = 3.7, ~2.5 Hz, 1H), 3.93−3.72 (m, 26H), 3.70−3.38 (m, 12H). FAB-MS *m/z* 1185 (M + H).

Data for **10**: R_f 0.06 (solvent B). ^{13}C NMR (125 MHz, D_2O, CH_3CN int.) δ 139.3, 126.9, 121.1, 102.7, 102.4, 102.1, 101.8, 100.9, 82.0, 81.8, 81.6, 81.5, 80.6, 81.3, 74.0, 73.9, 73.8, 73.7, 73.3, 73.0, 72.9, 72.8, 72.7, 72.6, 72.4, 72.3, 70.3, 62.1, 61.7, 61.2, 60.1, 60.8. ^{1}H NMR (500 MHz, D_2O, CH_3CN int.) δ 8.00 (s, 1H), 7.35 (s, 1H), 7.07 (s, 1H), 5.21 (d, ^3J = 3.7 Hz, 1H), 5.07 (d, ^3J = 3.7 Hz, 1H), 5.01−4.97 (m, 4H), 4.91 (d, ^3J = 3.9 Hz, 1H), 4.50 (dd, ^3J = 11.2, 8.7 Hz, 1H), 4.38 (dd, ^3J = 11.2, 3.7 Hz, 1H), 3.93−3.74 (m, 28H), 3.60−3.31 (m, 12H). FAB-MS *m/z* 1185 (M + H).

3^A-Benzylmercapto-3^A-deoxy-*altro*-β-cyclodextrin (11) and 2^A-Benzylmercapto-2^A-deoxy-β-cyclodextrin (12). β-CD mannoepoxide **1** (1.0 g, 0.9 mmol), benzylmercaptan (500 μL, 4.2 mmol), and Cs_2CO_3 (580 mg, 1.8 mmol) were added to DMF (5 mL) and the resultant mixture was stirred at 80 °C for 6 h. After being cooled to room temperature, the reaction mixture was added to acetone (300 mL). The precipitates were collected by filtration and applied to chromatography on a reversed-phase Lobar column (Size C). Elution of the column with a gradient from 10% CH_3OH (0.5 L) to 20% methanol (0.5 L) followed by a second gradient from 20% CH_3OH (1 L) to 40% methanol H_2O (500 mL) afforded **11** (eluted faster, 859 mg, 77%) and **12** (eluted slower, 71 mg, 6.4%) as colorless solids.

Data for **11**: R_f 0.70 (solvent C). ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 138.4, 128.9, 128.3, 126.8, 103.4, 102.2, 102.0, 101.8, 101.5, 100.8, 82.1, 81.8, 81.4, 81.0, 79.9, 73.4, 73.2, 73.1, 73.0, 72.9, 72.8, 72.4, 72.3, 72.0, 71.9, 71.7, 60.2, 59.9, 59.8, 59.7, 49.0, 36.5. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int.) δ 7.39−7.28 (m, 5H), 5.75−5.32 and 4.56−4.25 (m, 20H), 4.94−4.81 (m, 6H), 4.61 (d, ^3J = 5.8 Hz, 1H), 3.95 (s, 2H), 3.73−3.48 (m, 27H), 3.42−3.24 (m, 14H), 3.11 (br s, 1H). FAB-MS *m/z* 1241 (M + H).

Data for **12**: R_f 0.70 (solvent C). ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 137.9, 128.8, 128.3, 126.9, 102.2, 102.0, 101.9, 101.6, 101.1, 100.6, 82.4, 81.7, 81.4, 81.3, 80.9, 73.6, 73.0, 72.8, 72.5, 72.4, 72.3, 72.1, 71.9, 71.8, 60.4, 60.0, 59.7, 51.5, 35.8. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 7.36−7.24 (m, 5H), 4.94 (d, ^3J = 3.3 Hz, 1H), 4.87−4.83 (m, 6H), 3.94 (s, 2H), 3.77 (dd, ^3J = 11.2, ~8.7 Hz, 1H), 3.75−3.50 (m, 27H), 3.42−3.29 (m, 13H), 2.69 (dd, ^3J = 11.2, 3.3 Hz, 1H). FAB-MS *m/z* 1241 (M + H).

3^A-Azido-3^A-deoxy-*altro*-β-cyclodextrin (13) and 2^A-Azido-2^A-deoxy-β-cyclodextrin (14). General procedure A was used starting with β-CD mannoepoxide **1** to give **13** (eluted faster, 90%) and **14** (eluted slower, 3.6%).

Data for **13**: R_f 0.48 (solvent C). ^{13}C NMR (125 MHz, D_2O, CH_3CN int.) δ 103.8, 102.6, 102.3, 102.2, 102.0, 101.5, 81.9, 81.6, 81.4, 80.6, ca. 78.2, ca. 75.8, 74.0, 73.8, 73.7, 73.2, 72.9, 72.7, 72.6, 72.3, 70.6, 62.3, 61.2, 61.1, 60.5. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 5.06 (m, 2H), 4.98−4.95 (m, 4H), 4.84 (d, ^3J = 6.0 Hz, 1H), 4.18 (m, 1H), 4.03 (t, ^3J = ~3.9 Hz, 1H), 3.93−3.68 (m, 28H), 3.60−3.47 (m, 12H). FAB-MS *m/z* 1160 (M + H), 1182 (M + Na).

Data for **14**: R_f 0.48 (solvent C). ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 101.8, 101.7, 101.5, 101.2, 99.8, 81.6, 81.3, 81.2, 80.9, 72.8, 72.7, 72.0, 71.9, 71.7, 70.7, 63.4, 61.2, 59.8, 59.7. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 5.01 (d, ^3J = 3.6 Hz, 1H), 4.88−4.83 (m, 6H), 3.87 (dd, ^3J = 10.2, 8.9 Hz, 1H), 3.73−3.55 (m, 27H), 3.51 (t, ^3J = ~9.1 Hz, 1H), 3.41−3.31 (m, 13H). FAB-MS *m/z* 1160 (M + H), 1182 (M + Na).

3^A-Amino-3^A-deoxy-*altro*-β-cyclodextrin (15). General procedure B was used starting with azide **13** to give amine **15** (93%). R_f 0.39 (solvent D). ^{13}C NMR (125 MHz, D_2O, CH_3CN int.) δ 104.4, 102.6, 102.5, 102.2, 101.9, 101.8, 81.8, 81.7, 81.6, 81.3, 80.5, 79.6, 76.6, 74.0, 73.9, 73.8, 73.5, 73.2, 73.1, 72.8, 72.7, 72.6, 72.5, 72.3, 72.0, 61.2, 61.1, 60.5, 53.0. ^{1}H NMR (500 MHz, D_2O, CH_3CN int.) δ 5.06−4.92 (m, 6H), 4.74 (d, ^3J = 6.7 Hz, 1H), 4.15 (m, 1H), 3.92−3.66 (m, 27H), 3.61−3.4 (m, 13H), 2.93 (dd, ^3J = 9.8, 3.7 Hz, 1H). FAB-MS: *m/z* 1134 (M + H), 1156 (M + Na).

2^A-Amino-2^A-deoxy-β-cyclodextrin (16). General procedure B was used starting with azide **14** to give amine **16** (88%). R_f 0.39 (solvent D). ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 102.2, 101.8, 101.7, 101.6, 81.8, 81.6, 81.5, 81.4, 81.3, 72.9, 72.4, 72.2, 71.9, 59.8, 55.9. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 4.84−4.80 (m, 7H), 3.70−3.54 (m, 28H), 3.39−3.29 (m, 13H), 2.65 (dd, ^3J = 10.3, 3.2 Hz, 1H). FAB-MS *m/z* 1134 (M + H), 1156 (M + Na).

3^A-Deoxy-3^A-iodo-*altro*-β-cyclodextrin (17) and Mono-*altro*-β-cyclodextrin (18). β-CD mannoepoxide **1** (100 mg, 0.09 mmol), lithium iodide dihydrate (356 mg, 2.1 mmol), and trimethylammonium chloride (126 mg, 1.3 mmol) were dissolved in water (2 mL) and the resultant solution was stirred at 80 °C. After 10 days, the reaction mixture was diluted with water, desalted on an electrolytic desalting system (IE-Labo, Tosoh), and chromatographed on a reversed-phase Lobar column (Size B). Elution of the column with water (100 mL) followed by a gradient elution from water (500 mL) to 40% methanol (500 mL) afforded **17** (eluted slower, 6 mg, 5.4%) and **18** (eluted faster, 53 mg, 52%) as colorless solids.

Refluxing **1** in pure water afforded mono-*altro*-β-CD **18** almost in quantitative yield.[29]

Data for **17**: R_f 0.2 (solvent A). ^{13}C NMR (100 MHz, D_2O, CH_3CN int.) δ 102.2, 101.9, 101.7, 101.4, 101.0, 100.5, 81.0, 80.9, 80.8, 80.7, 80.4, 80.1, 76.8, 73.2, 73.1, 73.0, 72.4, 72.3, 72.1, 71.9, 71.8, 71.4, 60.3, 59.3, 30.8. ^{1}H NMR (400 MHz, D_2O, CH_3CN int.) δ 5.00−4.87 (m, 6H), 4.73 (d, ^3J = 7.0 Hz, 1H), 4.34 (dd, ^3J = 10.6, ~3.2 Hz, 1H), 4.18 (br s, 1H), 3.93−3.56 (m, 28H), 3.55−3.43 (m, 12H). FAB-MS *m/z* 1245 (M + H), (neg) *m/z* 1243 (M − H).

2^A-Deoxy-2^A-imidazolyl-*altro*-β-cyclodextrin (19) and 3^A-Deoxy-3^A-imidazolyl-β-cyclodextrin (20). A solution of imidazole (500 mg, 7.4 mmol) and β-CD alloepoxide **5** (100 mg, 0.09 mmol) in DMF (3 mL) was stirred at 90 °C for 5 d. The reaction mixture was dissolved in 500 mL of water, filtered, and chromatographed on a reversed-phase Lobar column (Size B) with H_2O (500 mL) and a gradient system from H_2O (1 L) to 25% methanol (1 L) as sequential eluents. The fractions containing the second sugar species (eluted out around 4% CH_3OH) were combined and evaporated, furnishing **20** (59 mg, 55%) as a colorless solid. Fractions containing the first sugar species (eluted out with H_2O, overlapping with imidazole) were rechromatographed on the same column with a gradient elution from H_2O (1 L) to 20% methanol (1 L) giving **19** (eluted out around 10% CH_3OH, 20 mg, 18%) as a colorless solid.

Data for **19**: R_f 0.06 (solvent B). ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 137.5, 127.8, 118.4, 102.0, 102.1, 101.8, 101.6, 101.5, 100.8, 82.0, 81.8, 81.0, 80.3, 77.2, 78.5, 75.6, 73.8, 73.0, 72.9, 72.7, 72.4, 72.3, 73.2, 72.1, 72.0, 71.9, 71.4, 67.0, 60.5, 60.2, 60.0, 59.9, 59.8, 59.6. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int.) δ 7.75 (s, 1H), 7.29 (s, 1H), 6.90 (s, 1H), 5.83−5.26, 5.01−4.94, and 4.45−4.36 (m, 20H), 5.13 (d, ^3J = ca. 6.4 Hz, 1H), 4.91−4.75 (m, 6H), 4.09 (m, 2H), 3.97−3.92 (m, 2H), 3.73−3.54 (m, 26H), 3.42−3.10 (m, 12H). FAB-MS *m/z* 1185 (M + H).

Data for **20**: R_f 0.06 (solvent B). ^{13}C NMR (125 MHz, D_2O, CH_3CN int.) δ 139.8, 129.2, 118.4, 102.6, 102.5, 101.9, 101.5, 81.9, 81.6, 78.7, 73.9, 73.8, 73.4, 72.9, 72.8, 72.7, 72.6, 72.2, 71.5, 62.4, 61.3, 61.1, 60.9. ^{1}H NMR (500 MHz, D_2O, CH_3CN int.) δ 7.81 (s, 1H), 7.30 (s, 1H), 7.03 (s, 1H), 5.10 (d, ^3J = 3.4 Hz, 1H), 5.01−4.97 (m, 5H), 4.62 (d, ^3J = 3.7 Hz, 1H), 4.46 (t, ^3J = 10.8 Hz, 1H), 4.05−3.99 (m, 2H), 3.96−3.70 (m, 26H), 3.65 (t, ^3J = 9.6 Hz, 1H), 3.59−3.47 (m, 10H), 3.43 (t, ^3J = 9.4 Hz, 1H), 3.21 (dd, ^3J = 10.1, 3.7 Hz,1H). FAB-MS *m/z* 1185 (M + H).

2^A-Benzylmercapto-2^A-deoxy-*altro*-β-cyclodextrin (21) and 3^A-Benzylmercapto-3^A-deoxy-β-cyclodextrin (22). β-CD

(29) Fujita, K.; Ohta, K.; Ikegami, Y.; Shimada, H.; Tahara, T.; Nogami, Y.; Koga, T.; Saito, K.; Nakajima, T. *Tetrahedron Lett.* **1994**, *35*, 9577−9580.

alloepoxide **5** (500 mg, 0.45 mmol), benzylmercaptan (300 μL, 2.5 mmol), and Cs_2CO_3 (730 mg, 2.2 mmol) were added to DMF (5 mL) and the resultant mixture was stirred at 80 °C. After 6 h, the reaction mixture was added to water (40 mL) and extracted with diethyl ether to remove the excess thiol. The aqueous solution was evaporated to dryness and the residue was applied to reversed-phase chromatography (Lobar column, Size C). Elution of the column with a gradient from 10% CH_3OH (0.5 L) to 20% methanol (0.5 L) followed by a second gradient from 20% CH_3OH (1 L) to 40% methanol−H_2O (500 mL) afforded **21** (eluted faster, 208 mg, 37%) and **22** (eluted slower, 293 mg, 53%) as colorless solids.

Data for **21**: R_f 0.17 (solvent A). ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 138.0, 129.2, 128.2, 126.8, 102.5, 102.1, 102.0, 101.8, 101.7, 101.3, 101.0, 81.9, 81.8, 81.3, 81.2, 80.5, 77.0, 78.5, 74.2, 74.2, 73.1, 73.0, 72.9, 72.6, 72.4, 72.3, 72.2, 72.1, 72.0, 71.9, 71.4, 68.9, 60.9, 60.2, 60.0, 59.9, 59.8, 59.7, 47.3, 34.8. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 7.41−7.24 (m, 5H), 5.03 (d, ^3J = 6.8 Hz, 1H), 4.90 (d, ^3J = 3.6 Hz, 1H), 4.87 (d, ^3J = 3.7 Hz, 1H), 4.84−4.79 (m, 4H), 4.02 (d, ^3J = 12.6 Hz, 1H), 3.88 (d, ^3J = 12.6 Hz, 1H), 3.82 (dd, ^3J = 5.8, −5.1 Hz, 1H), 3.75−3.49 (m, 28H), 3.44−3.26 (m, 12H), 2.87 (dd, ^3J = ∼10.5, 6.8 Hz, 1H). FAB-MS *m*/*z* 1241 (M + H).

Data for **22**: R_f 0.17 (solvent A). ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 137.3, 129.3, 128.3, 126.9, 102.0, 101.9, 101.8, 101.7, 101.0, 100.8, 81.8, 81.5, 81.3, 81.1, 76.0, 73.7, 73.3, 73.1, 73.0, 72.9, 72.5, 72.4, 72.3, 72.1, 72.0, 71.9, 60.1, 60.0, 59.8, 50.5, 35.0. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 7.39−7.24 (m, 5H), 4.91−4.83 (m, 7H), 3.98 (d, ^3J = 12.0 Hz, 1H), 3.91 (d, ^3J = 12.0 Hz, 1H), 3.72−3.47 (m, 29H), 3.45−3.23 (m, 12H), 2.85 (t, ^3J = 10.6 Hz, 1H). FAB-MS *m*/*z* 1241 (M + H).

2^A-Azido-2^A-deoxy-*altro*-β-cyclodextrin (23) and 3^A-Azido-3^A-deoxy-β-cyclodextrin (24). General procedure A was used starting with β-CD alloepoxide **5** to give **23** (eluted faster, 25%) and **24** (eluted slower, 65%).

An alternative procedure in DMF afforded the two products in a quite different ratio. Alloepoxide **5** (1.0 g, 0.9 mmol) and NaN_3 (580 mg, 8.9 mmol) were added to DMF (20 mL) and the mixture was stirred at 95 °C for 18 h. After being diluted with water (500 mL) and filtered, the clear solution was chromatographed on a reversed-phase Lobar column (Size C). Elution of the column with a gradient from H_2O (1 L) to 40% methanol (1 L) afforded **23** and **24** in 6.7% and 82% yields, respectively.

Data for **23**: R_f 0.48 (solvent C). ^{13}C NMR (125 MHz, D_2O, CH_3CN int.) δ 102.2, 102.3, 102.1, 101.7, 101.4, 101.1, 81.5, 81.1, 80.7, 79.5, 78.9, 76.3, 73.8, 73.6, 73.4, 73.2, 72.5, 72.4, 72.3, 72.2, 72.1, 71.9, 69.5, 64.1, 61.4, 61.0, 60.7, 60.1. ^{1}H NMR (500 MHz, D_2O, CH_3CN int.) δ 5.08 (d, ^3J = 3.8 Hz, 2H), 3.99−3.95 (m, 4H), 4.81 (d, ^3J = 7.3 Hz, 1H), 4.24 (m, 1H), 3.96−3.72 (m, 26H), 3.72−3.64 (m, 3H), 3.61−3.47 (m, 12H). FAB-MS *m*/*z* 1160 (M + H), 1182 (M + Na).

Data for **24**: R_f 0.48 (solvent C). ^{13}C NMR (125 MHz, D_2O, CH_3CN int.) δ 102.6, 102.4, 101.3, 101.6, 81.9, 81.7, 81.6, 78.9, 73.9, 73.8, 73.4, 73.0, 72.9, 72.7, 72.5, 72.3, 66.6, 61.3, 61.2, 61.1. ^{1}H NMR (500 MHz, D_2O, CH_3CN int.) δ 4.99 (m, 7H), 3.90−3.74 (m, 28H), 3.63 (dd, ^3J = 10.3, 3.6 Hz, 1H), 3.56−3.48 (m, 12H), 3.44 (t, ^3J = 9.3 Hz, 1H). FAB-MS *m*/*z* 1160 (M + H), 1182 (M + Na).

2^A-Amino-2^A-deoxy-*altro*-β-cyclodextrin (25). General procedure B was used starting with **23** to give amine **25** (89%) as a colorless solid. R_f 0.39 (solvent D). ^{13}C NMR (75 MHz, D_2O, CH_3CN int.) δ 105.3, 102.6, 102.5, 102.2, 101.9, 81.8, 81.6, 81.5, 81.3, 80.6, 79.6, 76.9, 73.9, 73.7, 73.6, 73.3, 72.9, 72.8, 72.6, 72.5, 72.4, 72.3, 72.1, 71.0, 61.1, 60.4, 54.7. ^{1}H NMR (500 MHz, D_2O, CH_3CN int.) δ 5.07−4.95 (m, 6H), 4.69 (d, ^3J = 7.5 Hz, 1H), 4.18 (ddd, ^3J = ca. 7.2, ca. 3.8, ca. 3.8 Hz, 1H), 3.92−3.66 (m, 27H), 3.63 (dd, ^3J = 10.5, 4.0 Hz, 1H), 3.60−3.47 (m, 12H), 2.99 (dd, ^3J = 10.5, 7.5 Hz, 1H). FAB-MS *m*/*z* 1134 (M + H), 1156 (M + Na).

3^A-Amino-3^A-deoxy-β-cyclodextrin (26). General procedure B was used starting with **24** to give amine **26** (96%) as a colorless solid. R_f 0.39 (solvent D). ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 102.0, 101.8, 101.2, 81.5, 81.4, 81.0 (4), 80.2, 73.0, 73.2, 72.9, 72.6, 72.5, 72.2, 72.1, 71.9, 60.0, 59.8, 55.3. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 4.87−4.82 (m, 7H), 3.71−3.55 (m, 27H), 3.40−3.23 (m, 14H), 2.79 (t, ^3J = ∼9.8 Hz, 1H). FAB-MS *m*/*z* 1134 (M + H), 1156 (M + Na).

2^A-Deoxy-2^A-iodo-*altro*-β-cyclodextrin (27) and 3^A-Deoxy-3^A-iodo-β-cyclodextrin (28). β-CD alloepoxide **5** (160 mg, 0.14 mmol), lithium iodide dihydrate (570 mg, 3.4 mmol), and trimethylammonium chloride (202 mg, 2.1 mmol) were dissolved in DMF (3.2 mL) and the resultant solution was stirred at 80 °C for 1 d. After diluted with water (5 mL), the reaction mixture was desalted on an electrolytic desalting system and chromatographed on a reversed-phase Lobar column (Size B). Elution of the column with water (100 mL) followed by a gradient elution from water (500 mL) to 40% methanol (500 mL) afforded **27 (**eluted faster, 49 mg, 27%) and **28** (eluted slower, 102 mg, 57%) as colorless solids.

Data for **27**: R_f 0.2 (solvent A). ^{13}C NMR (100 MHz, D_6O, CH_3CN int.) δ 102.9, 101.4, 101.3, 100.9, 100.8, 100.7, 100.3, 80.8, 80.4, 80.3, 80.0, 79.0, 77.4, 78.0, 74.3, 73.1, 73.0, 72.9, 72.8, 72.6, 72.4, 72.3, 71.9, 71.7, 71.6, 71.3, 70.5, 69.9, 60.3, 60.1, 59.9, 59.7, 59.5, 30.3. ^{1}H NMR (400 MHz, D_6O, CH_3CN int.) δ 4.99 (d, ^3J = 7.0 Hz, 1H), 4.81−4.68 (m, 6H), 3.94−3.88 (m, 2H), 3.72−3.40 (m, 28H), 3.32−3.20 (m, 12H). FAB-MS *m*/*z* 1245 (M + H), (neg) *m*/*z* 1243 (M − H).

Data for **28**: R_f 0.2 (solvent A). ^{13}C NMR (100 MHz, D_2O, CH_3CN int.) δ 101.5, 101.2, 100.2, 80.8, 80.7, 80.3, 80.1, 73.6, 72.8, 72.6, 72.4, 72.1, 71.9, 71.8, 71.7, 71.5, 70.5, 71.3, 60.3, 60.0, 59.8, 36.3. ^{1}H NMR (400 MHz, D_2O, CH_3CN int.) δ 5.01 (d, ^3J = 3.7 Hz, 1H), 4.91 (d, ^3J = 3.7 Hz, 1H), 3.90−3.84 (m, 4H), 4.78 (d, ^3J = 3.7 Hz, 1H), 4.13 (t, ^3J ≈ 10.4 Hz, 1H), 3.81−3.63 (m, 29H), 3.44−3.34 (m, 12H). FAB-MS *m*/*z* 1267 (M + Na).

3^A,3^C-Diazido-3^A,3^C-dideoxy-β-cyclodextrin (32). General procedure A was used starting with β-CD AC-dialloepoxide **6** to give diazide **32** (eluted last, 34%) as a colorless solid. ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 101.7, 101.5, 101.4, 100.4, 100.2, 81.4, 81.0, 80.8, 80.4, 77.5, 77.4, 72.8, 72.7, 72.3, 72.1, 71.9, 71.8, 71.7, 71.6, 71.4, 66.4, 66.3, 59.9, 59.8, 59.7, 59.5. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 4.89 (d, ^3J = 3.1 Hz, 2H), 4.85 (m, 5H), 3.75−3.54 (m, 28H), 3.47−3.28 (m, 14H). FAB-MS *m*/*z* 1185 (M + H), 1207 (M + Na).

3^A,3^D-Diazido-3^A,3^D-dideoxy-β-cyclodextrin (33). General procedure A was used starting with β-CD AD-dialloepoxide **7** to give diazide **33** (eluted last, 30%) as a colorless solid. ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 101.7, 101.5, 101.4, 100.4, 100.2, 81.2, 81.0, 80.9, 80.8, 80.4, 77.4, 72.8, 72.3, 72.2, 71.9, 71.7, 71.6, 71.5, 71.4, 66.6, 66.5, 60.0, 59.9, 59.7, 59.6, 59.5. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 4.89−4.85 (m, 7H), 3.71−3.54 (m, 28H), 3.48−3.28 (m, 14H). FAB-MS *m*/*z* 1185 (M + H), 1207 (M + Na).

3^A,3^C,3^E-Triazido-3^A,3^C,3^E-trideoxy-β-cyclodextrin (34). General procedure A was used starting with **8** to give triazide **34** (28%) as a colorless solid. ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 101.4, 100.3, 81.0, 80.6, 77.5, 77.3, 72.7, 72.3, 72.2, 72.0, 71.9, 71.7, 66.6, 66.5, 66.3, 59.9, 59.8, 59.6. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 4.91−4.85 (m, 7H), 3.86−3.52 (m, 28H), 3.47−3.28 (m, 14H). FAB-MS *m*/*z* 1210 (M + H), 1232 (M + Na).

3^A,3^C-Diamino-3^A,3^C-dideoxy-β-cyclodextrin (35). General procedure B was used starting with **32** to give diamine **35** (91%) as a colorless solid. R_f 0.15 (solvent D). ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 102.0, 101.8, 100.2, 100.1, 81.4, 81.1, 80.9, 80.2, 73.2, 72.8, 72.7, 72.6, 72.2, 71.9, 60.1, 59.8, 55.4, 55.3. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 4.86−4.82 (m, 7H), 3.72−3.54 (m, 26H), 3.40−3.21 (m, 14H), 2.78 (t, ^3J = ∼9.8 Hz, 2H). FAB-MS *m*/*z* 1133 (M + H).

$3^A,3^D$-Diamino-$3^A,3^D$-dideoxy-β-cyclodextrin (36). General procedure B was used starting with **33** to give diamine **36** (92%) as a colorless solid. R_f 0.15 (solvent D). ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 102.4, 102.2, 101.6, 81.8, 81.7, 81.5, 81.4, 80.6, 73.6, 73.5, 73.4, 73.3, 73.0, 72.9, 72.7, 72.6, 72.4, 72.3, 72.2, 60.5, 60.1. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 4.90−4.86 (m, 7H), 3.75−3.59 (m, 26H), 3.43−3.26 (m, 14H), 2.82 (t, ^3J = 9.8 Hz, 2H). FAB-MS *m*/*z* 1133 (M + H).

$3^A,3^C,3^E$-Triamino-$3^A,3^C,3^E$-trideoxy-β-cyclodextrin (37). General procedure B was used starting with **34** to give triamine **37** (93%) as a colorless solid. R_f 0 (solvent D). ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 102.1, 101.8, 101.3, 101.2, 81.4, 81.1, 81.0, 80.3, 73.4, 73.3, 73.0, 72.9, 72.8, 72.6, 72.5, 72.0, 71.9, 60.1, 59.8, 55.6, 55.5. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 4.85−4.80 (m, 7H), 3.71−3.56 (m, 25H), 3.37−3.12 (m, 14H), 2.75 (t, ^3J = ∼9.8 Hz, 2H), 2.74 (t, ^3J = 9.8 Hz, 1H). FAB-MS *m*/*z* 1132 (M + H), 1154 (M + Na).

$2^A,3^A$-Didehydro-$2^A,3^A$-dideoxy-β-cyclodextrin (42). General procedure C was used starting with β-CD alloepoxide **5** to give olefin **42** (70%) as a colorless solid. R_f 0.47 (solvent C). ^{13}C NMR (125 MHz, DMSO-d_6, TMS int.) δ 130.3, 126.7, 102.0, 101.7, 101.2, 101.1, 95.6, 81.9, 81.8, 81.7, 81.3, 80.5, 78.5, 72.5, 74.0, 72.8, 72.1, 71.9, 71.8, 71.3, 60.6, 60.4, 60.1, 60.0, 59.8, 59.7, 59.5. ^{1}H NMR (500 MHz, DMSO-d_6, TMS int., deuterated) δ 6.04 (br d, ^3J = ∼11 Hz, 1H), 5.90 (dt, ^3J = ∼10.2, ∼2.3 Hz, 1H), 5.21 (d, ^3J = 2.3 Hz, 1H), 4.91−4.81 (m, 6H), 4.12 (br d, ^3J = 8.9 Hz, 1H), 3.84−3.55 (m, 27H), 3.49−3.27 (m, 12H). FAB-MS *m*/*z* 1101 (M + H).

$2^A,2^B,3^A,3^B$-Tetradehydro-$2^A,2^B,3^A,3^B$-tetradeoxy-β-cyclodextrin (43). General procedure C was used starting with diepoxide **2** to give diene **43** (45%) as a colorless solid. The reaction time was prolonged to 5 d to ensure a complete conversion, otherwise it was difficult to separate diene **43** from the reaction intermediates. R_f 0.48 (solvent C). ^{13}C NMR (125 MHz, D_2O, CH_3CN int.) δ 131.4, 130.7, 127.6, 127.4, 102.7, 102.6, 102.4, 101.8, 101.0, 97.5, 95.9, 81.9, 81.8, 81.7, 81.3, 80.3, 74.0, 73.9, 73.8, 73.6, 73.2, 73.1, 72.9, 72.8, 72.7, 72.6, 72.3, 72.1, 71.7, 63.4, 62.1, 61.9, 60.5, 61.2. ^{1}H NMR (500 MHz, D_2O, CH_3CN int.) δ 6.00 (dd, ^3J = 11.7, 1.5 Hz, 1H), 5.94 and 5.91 (m, 2H), 5.85 (ddd, ^3J = 10.2, 3.1, 1.7 Hz, 1H), 5.21 (d, ^3J = 3.1 Hz, 1H), 5.19 (d, ^3J = 2.4 Hz, 1H), 5.03−4.95 (m, 5H), 4.28 (br d, ^3J = 7.5 Hz, 1H), 4.16 (br d, ^3J = 9.8 Hz, 1H), 3.92−3.65 (m, 26H), 3.59−3.45 (m, 10H). FAB-MS *m*/*z* 1067 (M + H), 1089 (M + Na).

$2^A,2^C,3^A,3^C$-Tetradehydro-$2^A,2^C,3^A,3^C$-tetradeoxy-β-cyclodextrin (44). General procedure C was used starting with diepoxide **6** to give diene **44** (60%) as a colorless solid. R_f 0.48 (solvent C). ^{13}C NMR (125 MHz, D_2O, CH_3CN int.) δ 131.7, 130.9, 127.0, 126.6, 102.4, 102.3, 102.2, 101.6, 100.4, 97.5, 81.8, 81.7, 81.5, 80.1, 79.8, 74.1, 73.9, 73.8, 73.6, 73.5, 73.3, 73.0, 72.9, 72.8, 72.7, 72.5, 72.3, 72.2, 72.0, 71.6, 62.2, 61.7, 61.3, 61.1. ^{1}H NMR (500 MHz, D_2O, CH_3CN int.) δ 6.02−5.87 (m, 4H), 5.25 (d, ^3J = 2.5 Hz, 1H), 5.20 (d, ^3J = 2.5 Hz, 1H), 4.98 (m, 5H), 4.24 (br d, ^3J = 8.7 Hz, 1H), 4.16 (br d, ^3J = 8.9 Hz, 1H), 3.93−3.65 (m, 26H), 3.57−3.47 (m, 10H). FAB-MS *m*/*z* 1067 (M + H), 1089 (M + Na).

$2^A,2^D,3^A,3^D$-Tetradehydro-$2^A,2^D,3^A,3^D$-tetradeoxy-β-cyclodextrin (45). General procedure C was used starting with diepoxide **7** to give diene **45** (70%) as a colorless solid. R_f 0.48 (solvent C). ^{13}C NMR (125 MHz, D_2O, CH_3CN int.) δ 131.6, 131.2, 126.9, 126.7, 102.3, 102.2, 101.9, 101.2, 97.4, 97.3, 81.9, 81.8, 81.6, 79.6, 79.3, 74.4, 74.3, 74.2, 73.8, 73.5, 73.4, 73.3, 73.2, 72.9, 72.7, 72.6, 72.5, 72.4, 72.3, 71.8, 71.7, 62.0, 61.8, 61.3, 61.1. ^{1}H NMR (500 MHz, D_2O, CH_3CN int.) δ 6.00 (br d, ^3J = ∼10.8 Hz, 2H), 5.93 (dt, ^3J = ∼10.8, 2.5 Hz, 1H), 5.91 (dt, ^3J = ∼10.8, 2.5 Hz, 1H), 5.26 (d, ^3J = 2.5 Hz, 1H), 5.23 (d, ^3J = 2.5 Hz, 1H), 4.96 (m, 5H; H1), 4.20 (br d, ^3J = 9 Hz, 1H), 4.16 (br d, ^3J = 9 Hz, 1H), 3.90−3.63 (m, 26H), 3.56−3.47 (m, 10H). FAB-MS *m*/*z* 1067 (M + H), 1089 (M + Na).

$2^A,2^C,2^E,3^A,3^C,3^E$-Hexadehydro-$2^A,2^C,2^E,3^A,3^C,3^E$-hexadeoxy-β-cyclodextrin (46). General procedure C was used starting with triepoxide **8** to give triene **46** (47%) as a colorless solid. R_f 0.49 (solvent C). ^{13}C NMR (125 MHz, D_2O, CH_3CN int.) δ 131.4, 131.3, 131.2, 126.9, 126.8, 102.2, 101.4, 101.0, 100.7, 97.3, 97.2, 97.1, 81.7, 79.7, 79.5, 79.3, 74.2, 73.9, 73.8, 73.7, 73.4, 73.3, 73.2, 72.7, 72.5, 72.4, 72.3, 72.2, 72.1, 71.8, 62.1, 61.9, 61.8, 61.4, 61.3, 61.2, 61.1. ^{1}H NMR (500 MHz, D_2O, CH_3CN int.) δ 6.00 (m, 3H), 5.96 (m, 3H), 5.27 (d, $^3J \approx$ 2.5 Hz, 1H), 5.24 (d, $^3J \approx$ 2.5 Hz, 2H), 4.97 (m, 4H), 4.19 (m, 3H), 3.91−3.64 (m, 25H), 3.59−3.46 (m, 8H). FAB-MS *m*/*z* 1033 (M + H), 1055 (M + Na).

Per(3-deoxy)-β-cyclomannin (48). $LiAlH_4$ (60 mg, 1.58 mmol) was added to a solution of persilyl permannoepoxy-β-CD **47** (100 mg, 0.055 mmol) in THF (25 mL) cooled at 0 °C and the resultant solution was stirred at room temperature for 2 h and then at 65 °C for 7 d until no further changes were detected on TLC. After decomposition of the excess $LiAlH_4$ with ethyl acetate (1 mL), the reaction mixture was evaporated to dryness. The residue was taken in distilled water (50 mL), adjusted to neutral pH with 1 M HCl, filtered, and applied to reversed-phase chromatography on a reversed-phase Lobar column (size B). A gradient elution of the column from 5% to 30% aqueous EtOH afforded **48** (29 mg, 51%). R_f 0.25 (solvent A). ^{13}C NMR (125 MHz, D_2O, CH_3CN int.) δ 100.6(1), 73.9(4), 72.3(4), 67.5(2), 61.0(6), 32.3(3). ^{1}H NMR (500 MHz, D_2O, CH_3CN int.) δ 4.69 (overlapped with HOD, 7H; H1), 3.92 (br, 14H; H4, H5), 3.83 (ddd, $^3J_{1,2}$, $^3J_{2,3a}$, $^3J_{2,3b}$, = 3−5 Hz, 7H; H2), 3.79 (br, 14H; H6), 1.97 (br, 14H; H3a, H3b). FAB-MS *m*/*z* 1023 (M + H), 1045 (M + Na).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all the compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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