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Short Synthesis of Skeleton-Modified Cyclodextrin Derivatives with Unique Inclusion Ability

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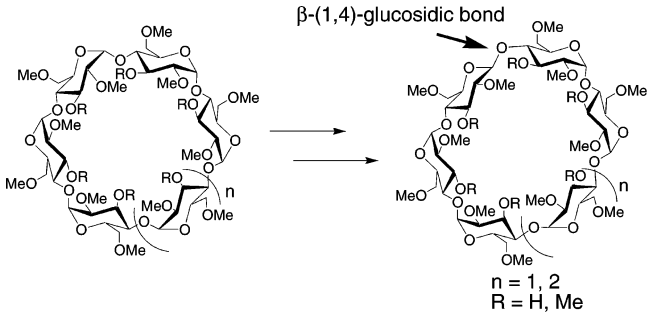
Received August 3, 2004



Skeleton-modified cyclodextrin (CD) derivatives, in which an α-(1,4)-glucosidic bond is converted into a *β*-(1,4)-glucosidic bond, were conveniently synthesized by cleavage of a single glucosidic bond in permethylated and 2,6-di-*O*-methylated α- and *β*-CDs and subsequent recyclization via the trichloroacetoimidate intermediates. The selective cleavage of an α-(1,4)-glucosidic bond of permethylated α- and *β*-CDs was accomplished by stirring in 30% aq $HClO_4$ at 25 °C to give the corresponding maltohexaose and maltoheptaose derivatives, respectively. The cleavage of a glucosidic bond of hexakis(3-*O*-benzyl-2,6-di-*O*-methyl)-α-CD was successfully carried out in a mixed 60% aq $HClO_4$ and 1,4-dioxane solution (1:20). In the case of heptakis(3-*O*-benzyl-2,6-di-*O*-methyl)-*β*-CD, the solvent-free reaction with *p*-toluenesulfonic acid was found to be effective for selective cleavage of one glucosidic bond. The permethylated *β*-CD derivative with a *β*-(1,4)-glucosidic bond (**4b**) exhibited higher inclusion ability toward sodium *m*-nitrobenzoate than the parent permethylated *β*-CD, while these hosts showed the same inclusion ability toward sodium *p*-nitrobenzoate. On the other hand, the *β*-(1,4)-type permethylated α-CD derivative **4a** exhibited lower inclusion ability toward sodium *p*- and *m*-nitrobenzoates than the parent permethylated α-CD. Interestingly, host molecules **4a** and **4b** showed inclusion selectivity for sodium *m*-nitrobenzoate as compared with the corresponding *para*-isomer, in contrast to permethylated CDs which possessed *para*-isomer selectivity. On the other hand, host molecules **4a** and **4b** showed *para*-isomer selectivity toward sodium nitrophenoxide guests, indicating that the inclusion selectivity was remarkably influenced by the guest hydrophilic groups. ^{1}H NMR studies on complexes of those *β*-(1,4)-type CD derivatives with *p*- and *m*-nitrobenzoates and *p*- and *m*-nitrophenolates were carried out to estimate their structures.

Introduction

Cyclodextrins (CDs) are a class of cyclic oligosaccharides consisting of several α-(1,4)-linked D-glucopyranose units. Each CD molecule possesses a hydrophobic cavity into which organic molecules of an appropriate size and shape can be incorporated in aqueous media. The inclusion ability of CDs has been extensively studied and applied in widespread fields including the food, cosmetic, and pharmaceutical industries.[1−6]

Much effort has been devoted to the chemical modification of CDs, such as capping, introduction of ionic groups,

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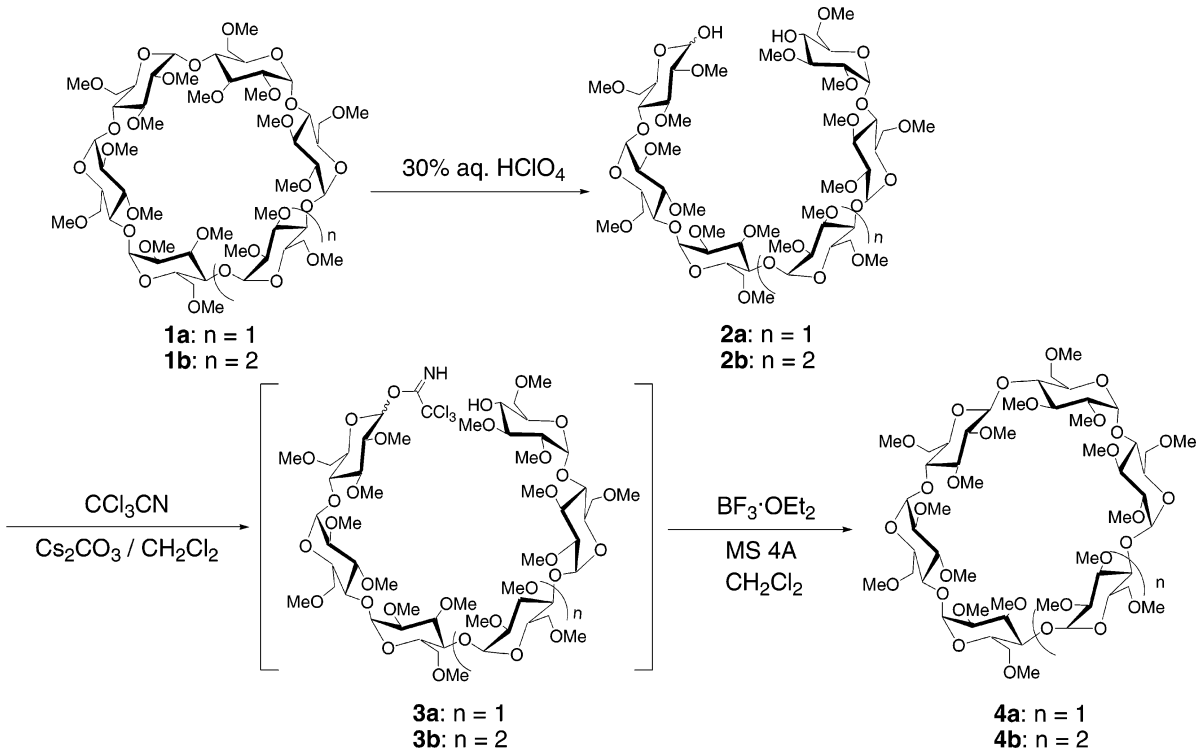
10.1021/jo048657g CCC: $30.25
Published on Web 01/22/2005

SCHEME 1. Synthetic Route to Permethylated CD Derivatives Bearing a *β*-(1,4)-Glucosidic Bond



and dimerization, to improve and control the inclusion ability.[7–9] Most of such work, however, has been limited to the modification of hydroxyl groups on the upper and/or lower rims of CDs. Recently, modification of the CD ring skeleton as an alternate chemical modification methodology has attracted increasing attention,[10–18] because such modification is believed to cause a more significant change in the cavity size and/or shape of CDs, thus more remarkably altering the original inclusion ability and selectivity, compared to the modification of hydroxyl groups. We reported the facile synthesis of a "spacer-inserted" CD by inserting an aromatic dicarbonyl spacer into the skeleton of a permethylated α-CD.[12] The inclusion ability of the host was controlled by the type of spacer inserted into the skeleton. The replacement of an α-(1,4)-glucosidic bond of CD into other types of interglucosidic linkages, such as *β*-(1,3)-glucosidic bonds[13] and *β*-(1,6)-glucosidic bonds,[14] has been previously proposed for modification of the CD skeleton.[15–18] These synthetic processes, however, have required more reaction steps, in comparison with those required for the modification of CD hydroxyl groups. For example, Ogawa et al. reported the synthesis of an interesting cyclodextrin analogue consisting of an α-(1,6)-glucosidic bond and five α-(1,4)-glucosidic bonds, but their synthetic approach required more than 15 reaction steps starting from maltose.[19] Although CD derivatives with different interglucosidic linkages are expected to show unique complexation behaviors, the binding ability of these host molecules has not yet been described except for *β*-(1,6)-linked cycloglucotetraose peracetates, which exhibit metal cation-binding properties.[20] Therefore, the development of a new method for the convenient synthesis of CD derivatives incorporating interglucosidic bonds different from α-(1,4)-glucosidic bonds and elucidation of their binding properties are strongly desired.

In this paper, we describe a short synthesis of novel CD derivatives incorporating a *β*-(1,4)-glucosidic bond from permethylated α- and *β*-CDs and 2,6-di-*O*-methylated α- and *β*-CDs and their unique inclusion ability.[21]

Results and Discussion

Synthesis of Host Molecules. Skeleton-modified CD derivatives bearing a *β*-(1,4)-glucosidic bond were synthesized in three and five steps from permethylated α- and *β*-CDs and 2,6-di-*O*-methylated α- and *β*-CDs, respectively. Scheme 1 shows the synthetic route to per-

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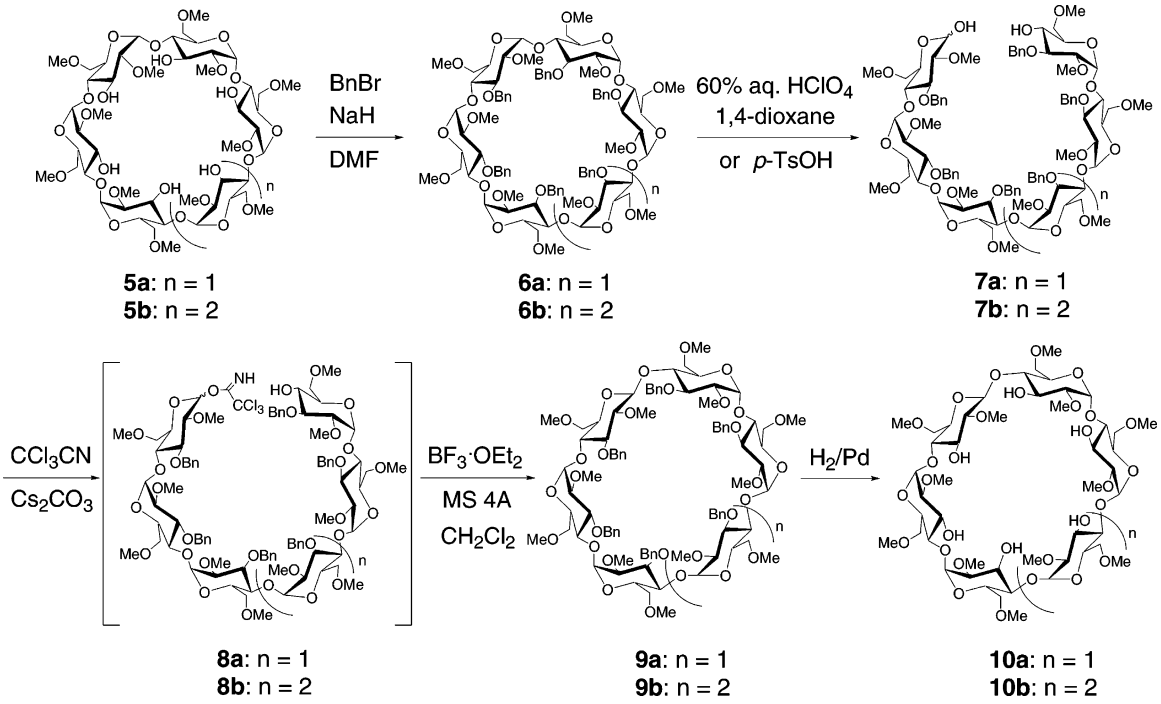
SCHEME 2. Synthetic Route to 2,6-Di-*O*-methylated CD Derivatives Bearing a *β*-(1,4)-Glucosidic Bond



methylated CD derivatives **4a** and **4b**. α- and *β*-CDs were converted into permethylated α-CD **1a** and *β*-CD **1b** by a previously reported method, respectively.[22] Conversion of the α-(1,4)-glucosidic bond into a *β*-(1,4)-glucosidic bond was carried out in three reaction steps: ring-opening of permethylated CDs by cleavage of a single α-(1,4)-glucosidic bond, the reaction of a C-1 hydroxyl group on acyclic maltooligosaccharide derivatives with trichloroacetonitrile,[23] and intramolecular cyclization of the resulting trichloroacetimidates.[24] Recently, we found an efficient method for the selective cleavage of a glucosidic bond of permethylated α-CD **1a** by the use of 30% aq $HClO_4$ at room temperature.[12] This method was also successfully applied to the cleavage of one glucosidic bond of permethylated *β*-CD **1b** to give the desired maltoheptaose derivative in 75% yield. **2a** and **2b** were allowed to react with trichloroacetonitrile in the presence of Cs_2CO_3 in CH_2Cl_2 at room temperature to afford the corresponding trichloroacetimidates **3a** and **3b**, respectively. Under such reaction conditions, the C-4 hydroxyl groups of the terminal glucose unit in **2a** and **2b** did not react with trichloroacetonitrile because of the larger steric hindrance. Intramolecular glucosidation was carried out by the use of $BF_3{\cdot}OEt_2$ as an activator in the presence of powdered molecular sieves 4A in CH_2Cl_2 at room temperature to give the cyclic compounds **4a** and **4b** having a *β*-(1,4)-glucosidic bond in 14% and 18% yields, respectively. In these reactions, permethylated CDs **1a** and **1b** were also formed as byproducts in 4% and 5% isolated yields, respectively. The separation of **4a** and **4b** from the corresponding reaction mixtures was easily carried out by reversed-phase column chromatography with acetonitrile as an eluent.

Scheme 2 shows the synthetic route to 2,6-di-*O*-methylated α- and *β*-CD derivatives **10a** and **10b**. First, according to a previously reported method, α- and *β*-CDs were converted into 2,6-di-*O*-methylated 3-*O*-benzyl-α- and -*β*-CDs **6a** and **6b** via 2,6-di-*O*-methylated α- and *β*-CDs **5a** and **5b**, respectively.[25] Selective cleavage of a glucosidic bond of **6a** and **6b** could not be carried out under the same reaction conditions used for **2a** and **2b**, because of the poor solubility of **6a** and **6b** in $HClO_4$ aqueous solution. This solubility problem was resolved by using 60% aq $HClO_4$−1,4-dioxane (1:20) solution. The selective cleavage of a glucosidic bond of **6a** was accomplished by stirring in the mixed solution for 3 days at room temperature. On the other hand, treatment of **6b** with the same reagent gave rise to an inseparable mixture of **7b** and byproducts, which were formed by elimination of a benzyl group from **7b**. Selective cleavage of a glucosidic bond of **6b** was attained by the solvent-free reaction of **6b** and *p*-toluenesulfonic acid. Under such conditions, compound **7b** was isolated in 34% yield. The solvent-free reaction was also applied to the selective cleavage of a glucosidic bond of **1b** to give **2b** in 42% isolated yield with recovered **1b** (43% yield). In sharp contrast, solvent-free reactions with *p*-toluenesulfonic acid did not proceed in α-CD derivatives **1a** and **6a**. This result can be explained by assuming that *p*-toluenesulfonic acid is not incorporated into the cavity of α-CD derivatives deeply enough to cause protonation of the glucoside oxygen atom inside the cavity because of the smaller cavity size of α-CD derivatives in comparison to *β*-CD derivatives. The synthesis of **9a** from **7a** (or **9b** from **7b**) was carried out similarly to that of **4a** and **4b**. Hydrogenolysis of **9a** and **9b** gave the desired products **10a** and **10b** in 55% and 66% yields, respectively. Compounds **4a**, **4b**, **10a**, and **10b** were moderately soluble in water (the water solubilities of **4a**, **4b**, **10a**,

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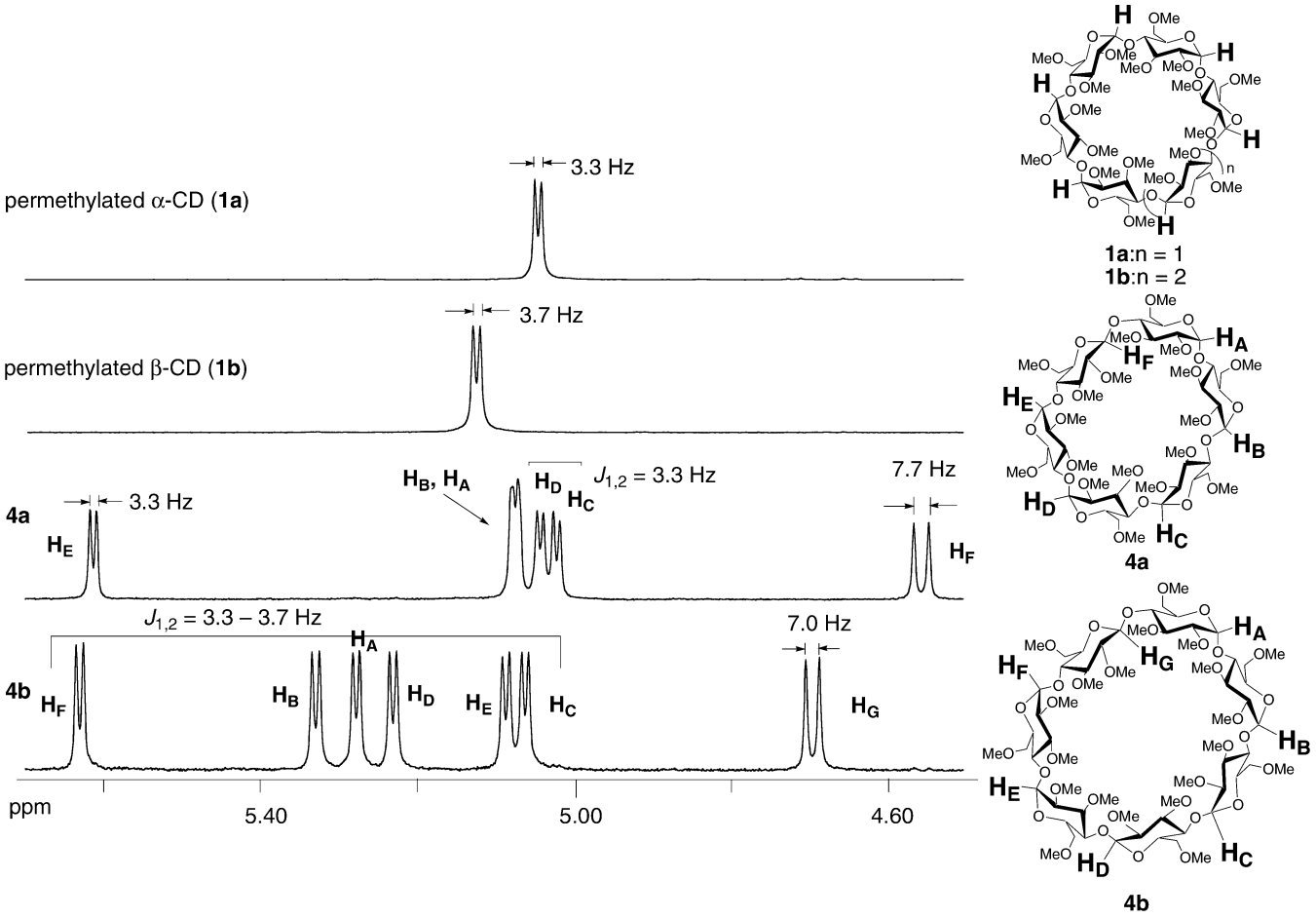

FIGURE 1. Comparison of anomeric proton signals for **1a**, **1b**, **4a**, and **4b**.

and **10b** at 25 °C are 1.4×10^{-1}, 7.3×10^{-2}, 3.4×10^{-2}, and 2.9×10^{-2} mol/L, respectively). The structures of the new CD derivatives were confirmed by NMR and MALDI-TOF mass spectra.

Figure 1 shows the ^{1}H NMR signals corresponding to anomeric protons in **1a**, **1b**, **4a**, and **4b**. While anomeric proton signals of permethylated CDs **1a** and **1b** were present as a single doublet in ^{1}H NMR spectra, those of **4a** were observed as five signals, one of them accounting for two protons, ranging from 4.5 to 5.7 ppm. Among them, a doublet at 4.56 ppm can be identified as a proton with a β-D-configuration by its larger coupling constant ($J_{1,2}$ = 7.7 Hz). Anomeric proton signals for **4b** were clearly separated into seven signals, and a doublet ($J_{1,2}$ = 7.0 Hz) at 4.70 ppm was identified as a proton with a β-D-configuration. NMR spectra confirm that both **4a** and **4b** are asymmetrical in structure. In the cases of **10a** and **10b**, the anomeric proton signals were not so clearly separated. A doublet at 4.49 ppm for **10a** (a doublet signal at 4.45 ppm for **10b**) was identified as a proton with a β-D-configuration by the larger coupling constant $J_{1,2}$ = 8.1 Hz (7.3 Hz).

Inclusion Ability. We determined stability constants of complexes of hosts **4a**, **4b**, **10a**, and **10b** with aromatic guest molecules by NMR titration in D_2O including 132 mM NaOD and 50 mM KCl.[26] Sodium *m*- and *p*-nitrophenoxides (MNP and PNP), sodium *m*- and *p*-nitrobenzoates (MNB and PNB), sodium 3,5-dinitrobenzoate (3,5-DNB), and sodium 2,4-dinitrobenzoate (2,4-DNB) were chosen as guest molecules. Almost all the anomeric proton signals of the host molecules were shifted upfield upon addition of the guest molecules, indicating that guest molecules were incorporated into host molecule cavities. Figure 2 illustrates the upfield shifts of the anomeric proton signals of **4b** induced by complex formation with PNP.

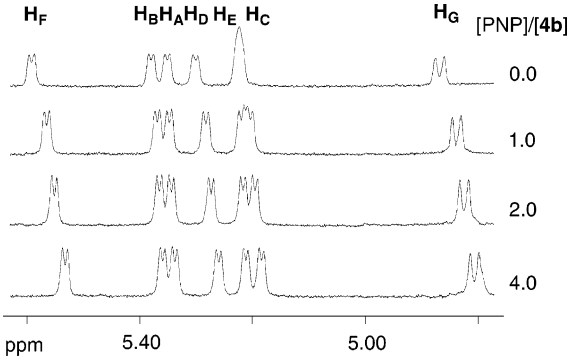

FIGURE 2. ^{1}H NMR spectral changes observed for host **4b** (5.0×10^{-3} M) in D_2O including NaOD (132 mM) and KCl (50 mM) upon addition of PNP at 25 °C.

Table 1 shows the stability constants of complexes of host molecules **4a**, **4b**, **10a**, and **10b** with MNP and PNP, together with the results obtained using **1a**, **1b**, **5a**, and

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TABLE 1. Stability Constants (M^{-1}) of Complexes of Hosts with MNP and PNP in D_2O[a] at 25 °C

	guest		
host	MNP	PNP	K_{MNP}/K_{PNP} (K_{PNP}/K_{MNP})
4a	17 ± 3	44 ± 2	0.4 ± 0.1 (2.7 ± 0.6)
4b	15 ± 2	75 ± 8	0.2 ± 0.05 (5.2 ± 1.2)
10a	11 ± 3	16 ± 4	0.8 ± 0.4 (1.7 ± 0.8)
10b	25 ± 3	170 ± 6	0.15 ± 0.02 (7.0 ± 1.0)
1a	300 ± 20	6000 ± 400	0.05 ± 0.01 (20 ± 2.0)
1b	30 ± 3	200 ± 10	0.15 ± 0.02 (6.7 ± 1.0)
5a	135 ± 5	750 ± 50	0.18 ± 0.02 (5.6 ± 0.6)
5b	42 ± 3	250 ± 20	0.17 ± 0.03 (6.0 ± 0.9)

[a] Including NaOD (132 mM) and KCl (50 mM).

TABLE 2. Stability Constants (M^{-1}) of Complexes of Hosts with MNB and PNB in D_2O[a] at 25 °C

	guest		
host	MNB	PNB	K_{MNB}/K_{PNB} (K_{PNB}/K_{MNB})
4a	50 ± 10	28 ± 2	1.8 ± 0.5 (0.6 ± 0.2)
4b	40 ± 10	23 ± 2	1.8 ± 0.6 (0.6 ± 0.2)
10a	11 ± 3	16 ± 1	0.7 ± 0.2 (1.6 ± 0.5)
10b	8 ± 1	19 ± 3	0.4 ± 0.1 (2.5 ± 0.6)
1a	200 ± 30	410 ± 20	0.5 ± 0.1 (2.1 ± 0.4)
1b	9 ± 2	21 ± 4	0.5 ± 0.2 (2.6 ± 1.0)
5a	42 ± 3	76 ± 8	0.6 ± 0.1 (1.8 ± 0.3)
5b	23 ± 3	60 ± 5	0.4 ± 0.1 (2.7 ± 0.5)

[a] Including NaOD (132 mM) and KCl (50 mM).

5b as hosts for comparison. The inclusion ability of host molecules **4a**, **4b**, **10a**, and **10b** toward MNP and PNP is lower than that of the corresponding permethylated and 2,6-di-*O*-methylated CDs. The inclusion ability of β-CD-derived **4b** toward these guests is equal to or higher than that of α-CD-derived **4a**, in sharp contrast to the parent permethylated CDs in which the inclusion ability of the α-CD derivative **1a** is much higher than that of the β-CD derivative **1b**. A similar trend was observed in the cases of 2,6-di-*O*-methylated CDs.

TABLE 3. Stability Constants (M^{-1}) of Complexes of Hosts with 3,5-DNB and 2,4-DNB in D_2O[a] at 25 °C

	guest		
host	3,5-DNB	2,4-DNB	$K_{3,5-DNB}/K_{2,4-DNB}$
4a	30 ± 2	11 ± 3	3.0 ± 1.0
4b	21 ± 3	14 ± 1	1.5 ± 0.3
10a	25 ± 2	7 ± 1	4.2 ± 0.3
10b	7 ± 1	13 ± 2	0.6 ± 0.15
1a	20 ± 3	32 ± 3	0.6 ± 0.15
1b	14 ± 2	7 ± 1	2.1 ± 0.6
5a	25 ± 5	28 ± 3	0.9 ± 0.3
5b	5 ± 1	26 ± 5	0.21 ± 0.08

[a] Including NaOD (132 mM) and KCl (50 mM).

Stability constants of complexes of hosts with MNB and PNB are summarized in Table 2. The inclusion ability of host **4a** toward these guests is lower than that of permethylated α-CD **1a**. In contrast, host **4b** exhibited higher inclusion ability toward MNB than permethylated β-CD **1b**. Interestingly, hosts **4a** and **4b** showed inclusion selectivity toward the *meta*-isomer (K_{MNB}/K_{PNB} = 1.8 ± 0.5 for **4a**, K_{MNB}/K_{PNB} = 1.8 ± 0.6 for **4b**), while hosts **1a** and **1b** showed inclusion selectivity toward the *para*-isomer (K_{PNB}/K_{MNB} = 2.1 ± 0.4 for **1a**, K_{PNB}/K_{MNB} = 2.6 ± 1.0 for **1b**). These results clearly show that hosts **4a** and **4b** have cavity shapes different from those of permethylated CDs, and conversion of an α-(1,4)-glucosidic bond into a β-(1,4)-glucosidic bond causes a reversal of the original inclusion selectivity. It is also noteworthy that guest selectivity of β-(1,4)-type CD derivatives **4a** and **4b** changes from *para*-isomer selectivity to *meta*-isomer selectivity by changing the hydrophilic moiety of the guest molecule from phenoxide (−O^-) to benzoate (−COO^-). The β-(1,4)-types **10a** and **10b** bearing free hydroxyl groups at C-3 positions showed *para*-isomer selectivity in complexation not only with nitrophenolates but also with nitrobenzoates, unlike permethylated CD derivatives **4a** and **4b**. These results may show that the distortion of the CD ring caused by replacement of an

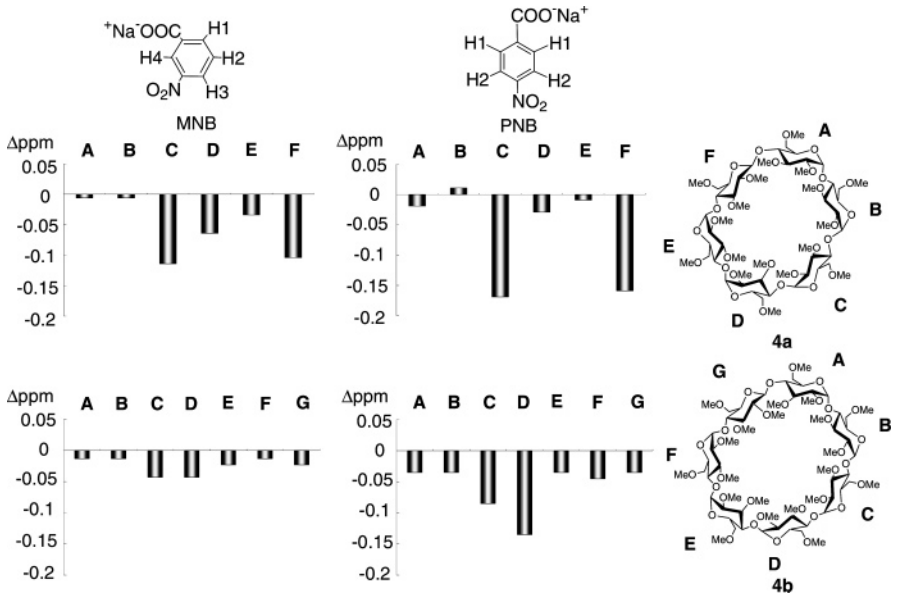

FIGURE 3. Chemical shift changes (Δδ) of C-3 proton signals for **4a** (top) and **4b** (bottom) upon addition of MNB (left) and PNB (right), in D_2O including NaOD (132 mM) and KCl (50 mM). [**4a**] = [**4b**] = 5.0 × 10^{-3} M. [MNB] = [PNB] = 1.5 × 10^{-2} M.

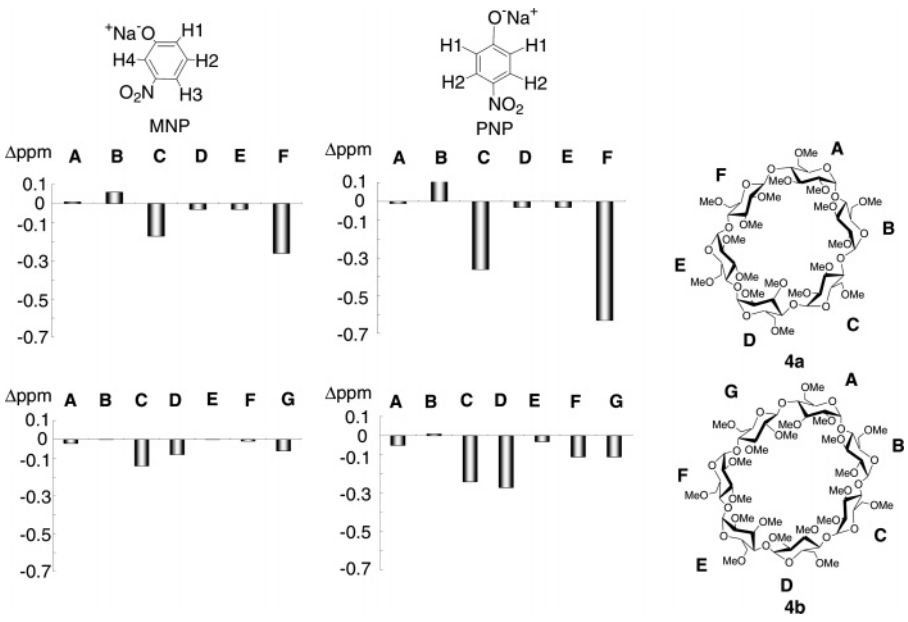

FIGURE 4. Chemical shift changes (Δδ) of C-3 proton signals of **4a** (top) and **4b** (bottom) upon addition of MNP (left) and PNP (right), in D_2O including NaOD (132 mM) and KCl (50 mM). [**4a**] = [**4b**] = 5.0×10^{-3} M. [MNP] = [PNP] = 2.5×10^{-2} M.

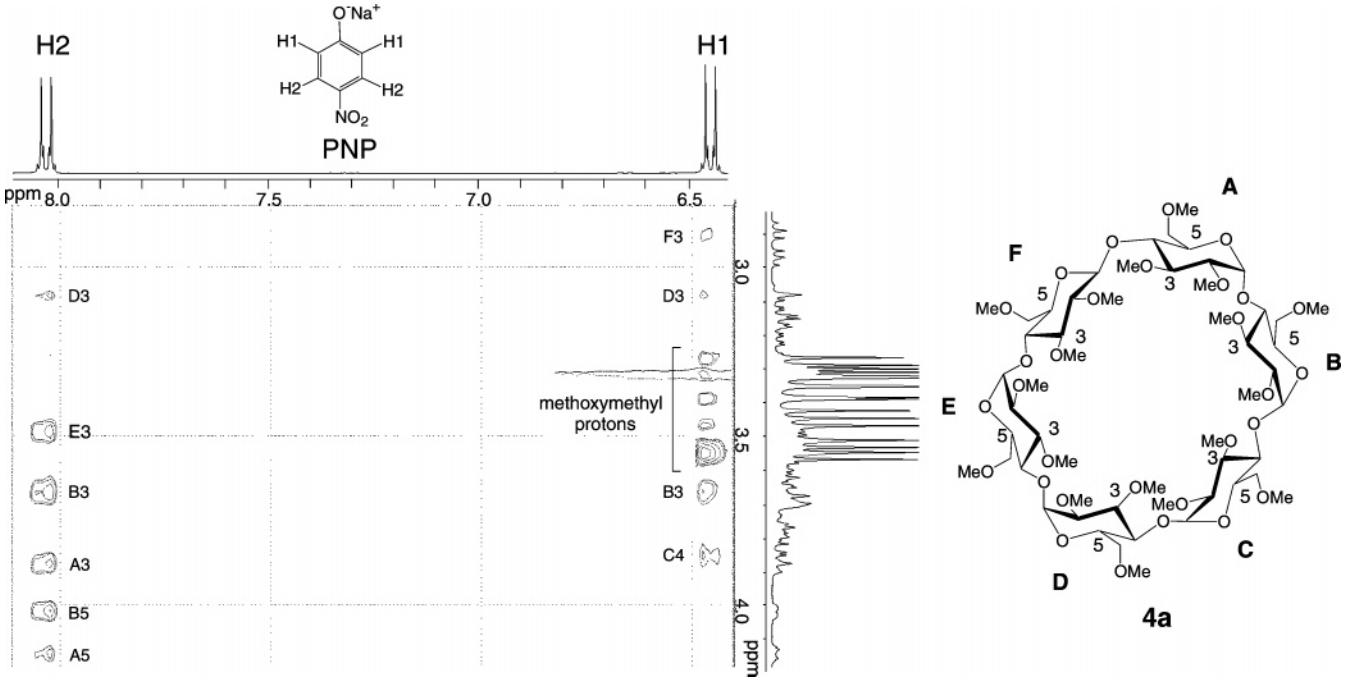

FIGURE 5. Partial 400 MHz ROESY spectrum of the **4a**−PNP complex in D_2O including NaOD (132 mM) and KCl (50 mM). [**4a**] = 5.0×10^{-3} M. [PNP] = 2.5×10^{-2} M.

α-(1,4)-glucosidic bond with a β-(1,4)-glucosidic bond is depressed by intramolecular hydrogen bonding between C-3 hydroxyl groups and C-2 methoxy groups of neighboring glucose units.

Use of disubstituted benzoates 3,5-DNB and 2,4-DNB as guests, which largely differ from one another in the shape of the hydrophobic group, is expected to cause a larger difference in inclusion selectivity between α-(1,4)-type and β-(1,4)-type CD hosts, compared to cases in which monosubstituted benzoates are used as guests (Table 3). In fact, β-(1,4)-type hosts **4a** and **10a** possessed remarkable inclusion selectivity toward 3,5-DNB over 2,4-DNB, while the parent hosts **1a** and **5a** showed inclusion selectivity toward 2,4-DNB over 3,5-DNB. These results support the hypothesis that β-(1,4)-type CD hosts have cavity shapes different from those of the parent α-(1,4)-type CDs.

Structure of the Complexes. It is well-known that C-5 and/or C-3 proton signals of α- and β-CDs are shifted upfield upon addition of an appropriate aromatic guest compound, such as *p*-nitrophenol, due to an aromatic ring current effect.[27] In β-(1,4)-type CD derivatives bearing asymmetrical cavities, there should be a difference in chemical shift changes induced by complexation with an

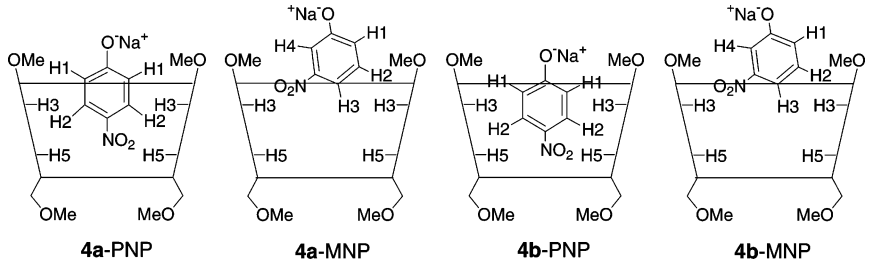

FIGURE 6. Proposed structures of **4a**−PNP, **4a**−MNP, **4b**−PNP, and **4b**−MNP complexes.

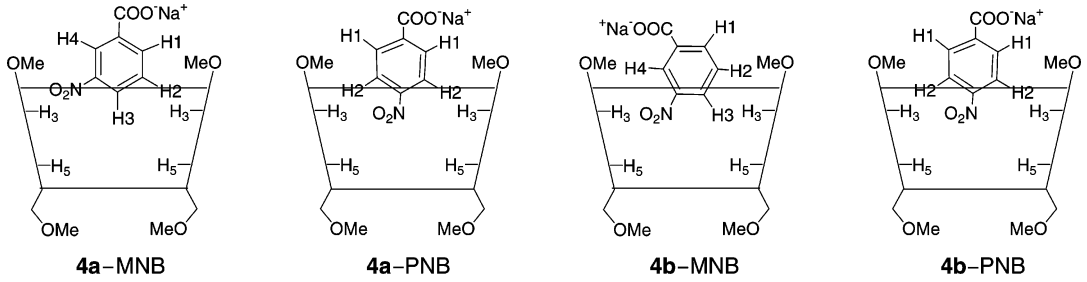

FIGURE 7. Proposed structures of **4a**−MNB, **4a**−PNB, **4b**−MNB, and **4b**−PNB complexes.

aromatic guest among C-3/C-5 proton signals, depending on the guest immersion mode within the cavity: for example, signals of C-3 protons which are situated above the guest aromatic ring should be more largely upfield shifted compared to other C-3 proton signals. On the basis of chemical shift changes and ROESY spectra of host−guest complexes, the orientation and position of guest molecules in β-(1,4)-type CD host cavities can be determined.

Figure 3 shows chemical shift changes ($\Delta\delta$) of C-3 proton signals for **4a** and **4b** upon addition of MNB and PNB. Some C-5 proton signals of these hosts were also shifted when the guests were added, but the observed shift changes were much smaller than those of the C-3 proton signals. Thus, we used only the chemical shift changes of C-3 proton signals to accurately estimate the degree to which each proton signal was affected by the guest aromatic ring current. In the **4a**−MNB complex, a larger upfield shift of C-3 proton signals in glucose units C, D, and F was observed. This result indicates that these protons are located on the aromatic guest ring plane. In the **4b**−MNB complex, C-3 proton signals in glucose units C and D were more largely upfield shifted, showing that these protons are situated on the aromatic plane of MNB. In **4a** and **4b** complexes with PNB, C-3 protons in glucose units C and F of **4a** and C-3 protons in glucose units C and D of **4b** appear to be located on the aromatic ring plane of the guest.

Figure 4 shows chemical shift changes of C-3 proton signals of **4a** and **4b** upon addition of MNP and PNP. In both **4a**−MNP and **4a**−PNP complexes, C-3 protons in glucose units C and F of the hosts appear to be situated on the aromatic ring plane. On the other hand, in complexes of **4b** with MNP and PNP, C-3 protons in glucose units C, D, and G and C-3 protons in glucose units C, D, F, and G should be located on MNP and PNP aromatic ring planes, respectively. These results show that there is little difference in the orientation of the guest in the host cavity among the complexes of **4a** (or **4b**) with MNB, PNB, MNP, and PNP.

ROESY spectra of host−guest complexes can provide information about host−guest proximity. A partial ROESY spectrum of the **4a**−PNP complex, as a typical example, is shown in Figure 5. NOE cross-peaks between guest H2 protons and the C-5 protons of host glucose units A and B as well as the C-3 protons of glucose units A, B, D, and E indicate that those host protons lie close to the guest H2 protons in the **4a**−PNP complex. Additionally, in this complex, NOEs between guest H1 protons and the C-3 protons of host glucose units B and D as well as host C-2 methoxymethyl protons were detected. In a **4b**−PNP complex, NOE cross-peaks between the guest H2 proton and the C-5 protons of host glucose units B and D as well as the C-3 protons in the glucose units F and D and those between the guest H1 proton and the C-3 protons of host glucose units D and F as well as host C-2 methoxymethyl protons were observed. On the other hand, in a **4a**−MNP complex, an NOE cross-peak was detected between the C-3 proton in glucose unit B and the guest H3 proton and between C-2 methoxymethyl protons of the host and guest H1, H2, and H4 protons. In a **4b**−MNP complex, an NOE cross-peak was found between the C-3 proton in glucose unit A and the guest H3 proton and between C-2 methoxymethyl protons of the host and guest H1, H2, and H4 protons. No NOE cross-peak, however, was observed between the C-5 protons of hosts **4a** and **4b** and any proton of the guest MNP. These results indicate that PNP is more deeply incorporated into the cavity of hosts **4a** and **4b** than MNP. Figure 6 shows proposed structures of **4a**−PNP, **4a**−MNP, **4b**−PNP, and **4b**−MNP complexes on the basis of the above-mentioned chemical shift changes and ROESY spectra. The difference in immersion depth inside the cavity of hosts **4a** and **4b** between PNP and MNP is probably responsible for higher inclusion abilities of those hosts toward PNP than toward MNP. In the **4b**−PNP complex, a stronger NOE cross-

(27) Schneider, H.-J.; Hacket, F.; Rudiger, V.; Ikeda, H. *Chem. Rev.* **1998**, *98*, 1755.

peak was observed between the host C-5 proton and guest H2 protons, compared to the NOE between corresponding protons in the **4a**−PNP complex. This result reflects higher stability of the **4b**−PNP complex compared to the **4a**−PNP complex. In **4a**−MNP and **4b**−MNP complexes, the guest is located close to both C-3 protons and C-2 methoxymethyl protons inside the host cavities. NMR data show no difference in immersion depth of the guest inside the cavity between **4a**−MNP and **4b**−MNP complexes. These findings are in accord with the fact that **4a**−MNP and **4b**−MNP complexes have almost the same stability constants.

A ROESY spectrum of a **4a**−MNB complex shows that the C-3 proton of host glucose unit D and C-2 methoxymethyl protons are proximal to the guest H2 proton and guest H1 and H4 protons, respectively. In a **4b**−MNB complex, an NOE cross-peak between the C-3 proton in glucose unit C and the guest H3 proton and that between C-2 methoxymethyl protons of the host and guest H2 and H4 protons were observed. In **4a** and **4b** complexes with PNB, only cross-peaks between host C-2 methoxymethyl protons and guest H1 and H2 protons were observed. On the other hand, no NOE cross-peak between C-5 protons of **4a** and **4b** and any proton of MNB and PNB was observed. Figure 7 shows the proposed structures of **4a**−MNB, **4a**−PNB, **4b**−MNB, and **4b**−PNB complexes. Even by using these structural data, it is difficult to explain the reason **4a** and **4b** form more stable complexes with MNB than with PNB. One possible explanation is that the shape of MNB more closely fits the shapes of the upper cavities of hosts **4a** and **4b** than that of PNB.

Conclusion

We have developed a short synthetic route to produce skeleton-modified CD derivatives incorporating a β-(1,4)-glucosidic bond from permethylated α- and β-CDs and 2,6-di-*O*-methylated α- and β-CDs. Among those skeleton-modified CD derivatives, permethylated ones showed inclusion selectivities for *m*-nitrobenzoates over the corresponding *para*-isomers contrary to the parent permethylated CDs, indicating that the conversion of an α-(1,4)-glucosidic bond into a β-(1,4)-glucosidic bond caused a reversal of the original inclusion selectivity. On the other hand, the β-(1,4)-type hosts showed *para*-isomer selectivity toward nitrophenoxide guests, indicating that the host inclusion selectivity is remarkably influenced by the guest hydrophilic groups. ^{1}H NMR studies on the complexes of β-(1,4)-type hosts with nitrobenzoates and nitrophenoxides suggest that *m*- and *p*-nitrobenzoates are incorporated into host cavities in modes different from those of the corresponding nitrophenoxides.

Experimental Section

General Procedures. All solvents except 1,4-dioxane were freshly distilled before use. Compounds **1a**, **1b**, **5a**, **5b**, **6a**, and **6b** were synthesized according to a previously reported method.[22,25] ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz spectrometers, respectively. The NMR signals of the carbohydrate protons of compounds **4a**, **4b**, **10a**, and **10b** were assigned by 2D NMR spectroscopy (^{1}H−^{1}H COSY, ^{1}H−^{13}C COSY, TOCSY, and ROESY).[26]

Synthesis of Maltohexaose Derivative 2a. Permethylated α-CD **1a** (9.20 g, 7.51 mmol) was dissolved in 30% aq $HClO_4$ (500 mL), and the solution was stirred for 4 days at room temperature. After neutralization with aq NaOH, the mixture was extracted with $CHCl_3$ (500 mL × 3) and dried over anhydrous $MgSO_4$. The combined $CHCl_3$ solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (acetone−hexane, in a gradient from 1:3 to 1:1) to give compound **2a** (4.01 g, 43% yield) as a white solid: R_f 0.36 (methanol−chloroform, 1:10); mp 75−76 °C; MALDI-TOF MS *m/z* 1266 $[M + Na]^+$, 1282 $[M + K]^+$; ^{1}H NMR ($CDCl_3$) δ 3.19−3.92 (m, 90H), 4.62 (dd, 0.45H, J = 7.3 Hz, 5.9 Hz), 5.35 (t, 0.55H, J = 3.3 Hz), 5.52−5.57 (m, 4H), 5.65 (d, 1H, J = 3.7 Hz). Anal. Calcd for $C_{54}H_{98}O_{31}\cdot H_2O$: C, 51.42; H, 7.99. Found: C, 51.39; H, 7.62.

Synthesis of Maltoheptaose Derivative 2b. Permethylated β-CD **1b** (0.46 g, 0.32 mmol) was dissolved in 30% aq $HClO_4$ (30 mL), and the solution was stirred for 6 days at room temperature. After neutralization with aq NaOH, the mixture was extracted with CH_2Cl_2 (50 mL × 3) and dried over $MgSO_4$. The combined CH_2Cl_2 solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol−chloroform, in a gradient from 1:100 to 1:50) to give compound **2b** (0.34 g, 75% yield) as a white solid: R_f 0.47 (acetone−hexane, 4:1); mp 83−85 °C; MALDI-TOF MS *m/z* 1470 $[M + Na]^+$; ^{1}H NMR ($CDCl_3$) δ 3.23−3.92 (m, 105H), 4.63 (dd, 0.35H, J = 7.3 Hz, 5.9 Hz), 5.36 (t, 0.65H, J = 2.9 Hz), 5.57 (d, 5H, J = 4.8 Hz), 5.66 (d, 1H, J = 3.7 Hz). Anal. Calcd for $C_{63}H_{114}O_{36}$: C, 52.27; H, 7.94. Found: C, 52.02; H, 7.77.

Synthesis of Compound 3a. A maltohexaose derivative (**2a**) (136 mg, 0.11 mmol) and Cs_2CO_3 (17.9 mg, 0.055 mmol) were added into dry CH_2Cl_2 (10 mL) under an atmosphere of Ar. After the addition of CCl_3CN (55.0 μL, 0.55 mmol), the mixture was stirred overnight at room temperature. Then CH_2Cl_2 (100 mL) was added, and the mixture was washed with saturated aq NaCl (100 mL) and dried over anhydrous $MgSO_4$. The CH_2Cl_2 solution was concentrated under reduced pressure. The crude product was used in the following reaction without further purification: R_f 0.58 (acetone−hexane, 4:1).

Synthesis of Compound 3b. 3b was prepared similarly to **3a**: R_f 0.47 (acetone−hexane, 4:1).

Synthesis of Compound 4a. 3a (148 mg) was added to dry CH_2Cl_2 (10 mL) including dried molecular sieves 4A (150 mg) under an atmosphere of Ar. The mixture was stirred for 10 min at room temperature. After $BF_3\cdot OEt_2$ (15.0 μL, 0.11 mmol) was added, the mixture was stirred overnight at room temperature. The reaction was quenched with 5% aq $NaHCO_3$ (100 mL), and the reaction mixture was extracted with CH_2Cl_2 (100 mL × 2). The combined CH_2Cl_2 solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (acetone−hexane, in a gradient from 1:3 to 1:1) to give an α/β anomeric mixture (24.3 mg). The separation of the α/β anomeric mixture was carried out by reversed-phase column chromatography (acetonitrile) to give compound **4a** (18.9 mg, 14% yield) as a white solid: R_f 0.36 (methanol−chloroform, 1:10); $[\alpha]^{25}_D$ +127.01 (*c* 0.20, $CHCl_3$); mp 88−90 °C; MALDI-TOF MS *m/z* 1248 $[M + Na]^+$, 1264 $[M + K]^+$; ^{1}H NMR ($CDCl_3$) δ 3.09 (t, J = 8.43 Hz, 1H), 3.15−3.18 (m, 4H), 3.24−3.27 (m, 1H), 3.33−3.91 (m, 83H), 4.14−4.18 (m, 1H), 4.56 (d, 1H, J = 7.7 Hz), 5.02 (d, 1H, J = 3.3 Hz), 5.04 (d, 1H, J = 3.3 Hz), 5.07−5.08 (m, 2H), 5.62 (d, 1H, J = 3.3 Hz). ^{13}C NMR ($CDCl_3$) δ 57.95, 57.61, 58.32, 58.36, 58.39, 58.77, 58.78, 58.80, 58.90, 59.03, 59.11, 59.25, 59.27, 59.58, 59.64, 61.31, 61.43, 61.71, 61.73, 61.74, 70.72, 70.90, 70.94, 71.04, 71.21, 71.33, 71.34, 71.39, 71.82, 72.00, 73.44, 74.31, 75.13, 81.34, 81.42, 81.47, 81.68, 81.71, 81.76, 81.95, 82.14, 82.25, 82.28, 82.56, 83.38, 83.97, 86.61, 95.33, 98.24, 99.16, 99.56, 100.01, 100.26. Anal. Calcd for $C_{54}H_{96}O_{30}$: C, 52.93; H, 7.90. Found: C, 52.74; H, 7.64.

Synthesis of Compound 4b. 4b was prepared similarly to **4a** to give a white solid (18% yield): R_f 0.52 (acetone−hexane, 4:1); $[\alpha]^{25}_D$ +101.09 (*c* 0.20, $CHCl_3$); mp 92−94 °C; MALDI-TOF MS *m/z* 1452 $[M + Na]^+$, 1468 $[M + K]^+$; ^{1}H NMR

($CDCl_3$) δ 3.07−4.02 (m, 112H), 4.69 (d, 1H, J = 7.0 Hz), 5.06 (d, 1H, J = 3.7 Hz), 5.09 (d, 1H, J = 3.7 Hz), 5.23 (d, 1H, J = 3.7 Hz), 5.28 (d, 1H, J = 3.7 Hz), 5.33 (d, 1H, J = 3.7 Hz), 5.63 (d, 1H, J = 3.7 Hz); ^{13}C NMR ($CDCl_3$) δ 57.96, 58.25, 58.32, 58.80, 58.84, 58.90, 58.93, 58.97, 59.05, 59.20, 59.25, 59.39, 60.80, 60.84, 61.29, 61.71, 61.77, 70.37, 70.52, 70.56, 70.65, 70.67, 70.82, 71.12, 71.16, 71.20, 71.55, 73.25, 75.00, 79.08, 81.04, 81.30, 81.58, 81.62, 81.74, 81.85, 81.90, 82.04, 82.11, 82.12, 82.23, 82.44, 83.53, 83.64, 86.30, 94.97, 97.47, 98.06, 98.73, 98.78, 98.87, 99.19. Anal. Calcd for $C_{63}H_{112}O_{35}$: C, 52.93; H, 7.90. Found: C, 52.58; H, 7.56.

Synthesis of Maltohexaose Derivative 7a. Hexakis(3-*O*-benzyl-2,6-di-*O*-methyl)-α-CD **6a** (200 mg, 0.12 mmol) was dissolved in 1,4-dioxane (4.0 mL) at room temperature, 60% aq $HClO_4$ (0.2 mL) was added to the solution, and the mixed solution was stirred for 3 days. After neutralization using aq NaOH, the mixture was extracted with CH_2Cl_2 (50 mL × 3). The combined CH_2Cl_2 solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (acetone−hexane, in a gradient from 1:10 to 1:3) to give compound **7a** (47.2 mg, 23% yield) as a white solid: R_f 0.47 (methanol−chloroform, 1:19); mp 75−77 °C; MALDI-TOF MS *m/z* 1723 $[M + Na]^+$, 1739 $[M + K]^+$; ^{1}H NMR ($CDCl_3$) δ 3.07−4.12 (m, 74H), 4.70−5.00 (m, 12H), 4.70−5.00 (m, 0.36H), 5.39 (t, 0.64H, J = 2.6 Hz), 5.13 (d, 2H, J = 3.7 Hz), 5.66 (d, 1H, J = 3.7 Hz), 5.70 (d, 1H, J = 3.7 Hz), 5.72 (d, 1H, J = 3.7 Hz), 7.19−7.36 (m, 30H). Anal. Calcd for $C_{90}H_{122}O_{31}\cdot 2H_2O$: C, 62.27; H, 7.32. Found: C, 62.05; H, 6.94.

Synthesis of Maltoheptaose Derivative 7b. After heptakis(3-*O*-benzyl-2,6-di-*O*-methyl)-β-CD **6b** (2.0 g, 1.0 mmol) and *p*-toluenesulfonic acid monohydrate (388 mg, 2.0 mmol) were mixed using a mortar and pestle, the mixture was kept for 2 days at room temperature. Then $CHCl_3$ (250 mL) was added, and the mixture was washed with saturated aq NaCl (250 mL × 2). The $CHCl_3$ solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate−hexane, in a gradient from 1:4 to 2:1) to give compound **7b** (681 mg, 34% yield) as a white solid: R_f 0.52 (methanol−chloroform, 1:19); mp 76−78 °C; MALDI-TOF MS *m/z* 2003 $[M + Na]^+$, 2019 $[M + K]^+$; ^{1}H NMR ($CDCl_3$) δ 3.06−4.10 (m, 86H), 4.65−4.98 (m, 14H), 4.65−4.98 (m, 0.4H), 5.37 (t, 0.6H, J = 2.9 Hz), 5.61 (d, 1H, J = 3.7 Hz), 5.63−5.65 (m, 3H), 5.68 (d, 1H, J = 3.7 Hz), 5.70 (d, 1H, J = 3.7 Hz), 7.17−7.32 (m, 35H). Anal. Calcd for $C_{105}H_{142}O_{36}\cdot 2H_2O$: C, 62.55; H, 7.30. Found: C, 62.15; H, 7.23.

Synthesis of Compounds 9a and 9b. 9a and **9b** were prepared similarly to **4a**. Data for compound **9a**: yield 20%; R_f 0.51 (ethyl acetate−hexane, 4:1); mp 51−52 °C; MALDI-TOF MS *m/z* 1705 $[M + Na]^+$, 1721 $[M + K]^+$; ^{1}H NMR ($CDCl_3$) δ 3.17−4.40 (m, 72H), 4.67−5.24 (m, 16H), 5.37 (d, 1H, J = 4.0 Hz), 5.72 (d, 1H, J = 3.3 Hz), 7.22−7.43 (m, 30H). Anal. Calcd for $C_{90}H_{120}O_{30}\cdot H_2O$: C, 63.59; H, 7.23. Found: C, 63.31; H, 6.89. Data for compound **9b**: yield 22%; R_f 0.51 (ethyl acetate−hexane, 5:1); mp 94−96 °C; MALDI-TOF MS *m/z* 1985 $[M + Na]^+$, 2001 $[M + K]^+$; ^{1}H NMR ($CDCl_3$) δ 3.18−4.09 (m, 84H), 4.67−5.28 (m, 17H), 5.36 (d, 1H, J = 3.3 Hz), 5.42 (d, 1H, J = 3.7 Hz), 5.44 (d, 1H, J = 3.7 Hz), 5.70 (d, 1H, J = 3.7 Hz), 7.11−7.44 (m, 35H). Anal. Calcd for $C_{105}H_{140}O_{35}\cdot H_2O$: C, 63.69; H, 7.23. Found: C, 63.42; H, 6.96.

Synthesis of Compound 10a. Compound **9a** (87.3 mg, 0.051 mmol) was dissolved in a mixed 1,4-dioxane (6.0 mL) −acetic acid (3.0 mL) solution. Palladium hydroxide, 20 wt % Pd on carbon (40 mg), was added to the solution. The mixture was placed in an autoclave and stirred under an atmosphere of H_2 (5 atm) for 3 days. A 5% aq Na_2CO_3 solution (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined CH_2Cl_2 solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (acetone−hexane, in a gradient from 1:3 to 1:1) to give compound **10a** (32.3 mg, 55% yield) as a white solid: R_f 0.20 (acetone−hexane, 4:1); $[\alpha]^{25}_D$ +25.89 (*c* 0.15, $CHCl_3$); mp 243−244 °C; MALDI-TOF MS *m/z* 1164 $[M + Na]^+$, 1180 $[M + K]^+$; ^{1}H NMR ($CDCl_3$) δ 3.09−4.10 (m, 72H), 4.49 (d, 1H, J = 8.1 Hz), 4.60 (s, 1H), 4.70 (m, 2H), 4.94−5.01 (m, 7H), 5.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 58.89, 58.97, 59.18, 60.01, 60.10, 60.21, 60.36, 60.69, 60.78, 69.39, 70.30, 70.41, 70.64, 70.85, 71.00, 71.10, 71.34, 71.68, 71.85, 73.23, 73.38, 73.59, 73.96, 74.90, 81.00, 81.11, 81.50, 81.93, 82.12, 82.35, 82.90, 83.32, 83.48, 83.64, 84.14, 84.83, 96.02, 100.43, 100.53, 101.13, 101.80. Anal. Calcd for $C_{48}H_{84}O_{30}$: C, 50.50; H, 7.40. Found: C, 50.14; H, 7.10.

Synthesis of Compound 10b. 10b was prepared similarly to **10a** to give a white solid (66% yield): R_f 0.30 (acetone−hexane, 5:1); $[\alpha]^{25}_D$ +49.76 (*c* 0.15, $CHCl_3$); mp 293−295 °C; MALDI-TOF MS *m/z* 1354 $[M + Na]^+$, 1370 $[M + K]^+$; ^{1}H NMR ($CDCl_3$) δ 3.09 (dd, 1H, J = 9.5, 7.7 Hz), 3.24−3.98 (m, 89H), 4.12 (t, 1H, J = 9.9 Hz), 4.33 (d, 1H, J = 1.1 Hz), 4.45 (d, 1H, J = 7.3 Hz), 4.96−5.02 (m, 8H), 5.05 (s, 1H), 5.10 (d, 1H, J = 1.1 Hz), 5.19 (s, 1H), 5.31 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 58.77, 59.01, 59.04, 59.08, 59.16, 60.28, 60.36, 60.39, 60.47, 60.50, 60.69, 60.88, 69.73, 70.26, 70.30, 70.41, 70.86, 71.15, 73.21, 73.25, 73.43, 73.59, 74.34, 81.88, 81.94, 82.17, 82.43, 82.45, 82.48, 83.24, 83.47, 83.55, 83.67, 83.75, 95.66, 101.18, 101.29, 101.32, 101.53, 102.25, 103.26. Anal. Calcd for $C_{56}H_{98}O_{35}$: C, 50.50; H, 7.40. Found: C, 50.42; H, 7.06.

^{1}H NMR Titration. ^{1}H NMR titrations were performed at 25 °C in D_2O including NaOD (132 mM) and KCl (50 mM) with DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) as an external standard. A solution of the host molecule (0.45 mL, 5.0 mM) was titrated in an NMR tube with increasing amounts of guest stock solution (0.5 mL, 75 mM) as follows: 0, 30, 60, 90, 120, 150, 240, 300, 360 and 450 μL. The resulting plot of changes in the chemical shifts of the host anomeric protons against [guest]/[host] was analyzed by a nonlinear least-squares curve fitting method with the program developed by Hirose[26] to give a stability constant of the host−guest complex.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (No. 16750120) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **4a**, **4b**, **10a**, and **10b**, determination of the stoichiometries of the host−guest complexes (Job plots), and NMR chemical shifts of the carbohydrate protons of **4a** and **4b** in the presence and absence of PNP, MNP, PNB, and MNB in D_2O (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO048657G