Pergamon

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Tetrahedron 59 (2003) 2519–2538

TETRAHEDRON

Practical and convenient modifications of the A,C-secondary hydroxyl face of cyclodextrins

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Received 5 December 2002; accepted 13 February 2003

Abstract—A practical and convenient method for the preparation of α-, β-, and γ-cyclodextrin derivatives, in which the secondary hydroxyl faces of A- and C-glucose units are regioselectively modified, has been developed. Reactions of α-, β-, and γ-cyclodextrins with 1,4-dibenzoylbenzene-3′,3″-disulfonyl imidazole in *N*,*N*-dimethylformamide in the presence of molecular sieves regioselectively afforded the corresponding cyclic 2^{A},2^{C}-(1,4-dibenzoylbenzene-3′,3″-disulfonyl)-cyclodextrins. Subsequent treatment of the sulfonylated cyclodextrins with sodium hydroxide or aqueous ammonia afforded the corresponding 2^{A},3^{A}:2^{C},3^{C}-di-manno-epoxy-cyclodextrins or 3^{A},3^{C}-diamino-3^{A},3^{C}-dideoxy-(2^{A}S,2^{C}S,3^{A}S,3^{C}S)-cyclodextrins, respectively, which can serve as important intermediates for further functionalizations of the cyclodextrins.

1. Introduction

Cyclodextrins are cyclic oligosaccharides consisting of six or more α-1,4-linked D-(+)-glucopyranose units, which possess primary hydroxyl groups at the C-6 positions and secondary hydroxyl groups at the C-2 and C-3 positions.[1] Since cyclodextrins contain cavities that are hydrophobic and optically active, they are often utilized in the formation of inclusion complexes with a wide range of guest molecules, as transporters of hydrophobic molecules, or as miniature molecular mimics of enzymes.[2] In order to modify the inclusion behavior of cyclodextrins, a wide variety of chemically-modified cyclodextrins have been developed.[3] However, selective and efficient modification methods are still being developed for the preparation of modified cyclodextrins. Due to the large number of hydroxyl groups, modifications of these groups can result in a large number of positional isomers within the cyclodextrin framework. Correspondingly, regioselective modifications of cyclodextrins can be difficult, in which one of main obstacles is the extensive purification required.

In the last few decades, regioselective mono- and multi-functionalization techniques on the primary and/or secondary hydroxyl groups have been investigated. As a result, several significant sulfonylation techniques have been demonstrated for the mono-,[4] di-,[5] and multi-sulfonylations[6] of the primary hydroxyl groups, and mono-,[7] di-,[8] and multi-sulfonylations[9] of the secondary hydroxyl groups of cyclodextrins. These sulfonylation techniques required regioselective sulfonyl reagents and optimization of the reaction conditions. The primary hydroxyl groups of cyclodextrins are basic in nature, and are highly reactive toward normal electrophilic reagents in the presence of a weak base, such as pyridine. The secondary hydroxyl face, being larger than the primary hydroxyl face, functions as the preferential locus for the molecular inclusion of large molecules.[10] Consequently, cyclodextrin derivatives that have their secondary hydroxyl faces modified have significantly different properties than those that have their primary hydroxyl faces modified.[11] Thus, functionalization of the secondary face is as important as the primary hydroxyl groups. However, regioselective sulfonylations of the secondary hydroxyl groups have proven to be difficult, achievable only by using the following chemical controls, thus limiting the potential applications of cyclodextrins. One method for the absolute regioselective sulfonylation of the C-2 hydroxyl groups involves the protection of the primary hydroxyl groups;[7h,j,l] however this method is troublesome due to the additional protection and deprotection steps. The relatively acidic C-2 hydroxyl groups, which have pK_a values of 12,[12] can be selectively deprotonated in the presence of a limited amount of strong base, such as NaH, under anhydrous conditions, without the protection of the primary hydroxyl groups. Subsequently, the resulting alkoxides can regioselectively react with electrophilic reagents.[7f] Selective activation of the C-2 hydroxyl groups with dibutyltin oxide, followed by reaction with *p*-toluenesulfonyl chloride under anhydrous conditions,[7e] or formation of suitable inclusion complex of sulfonyl reagents and cyclodextrins[4d,7a,i,k] can also lead to C-2-monosulfonylation. Of the three hydroxyl groups, the C-3 hydroxyl groups are the least reactive, and thereby generally

Keywords: cyclodextrin; regioselectivity; sulfonylation.

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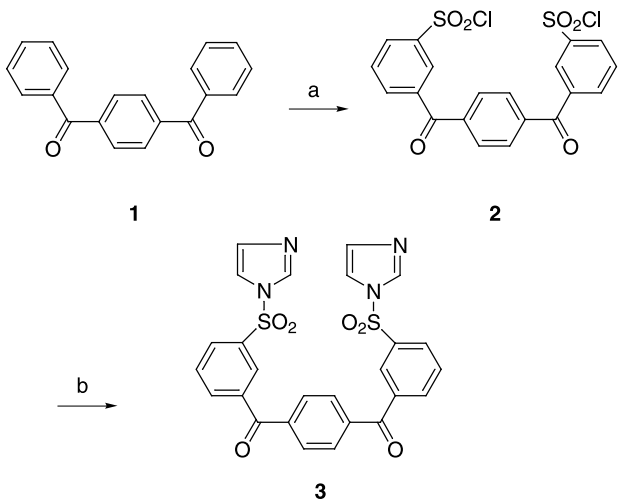
0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00259-X

react after the C-2 and C-6 sulfonylations. An exception was reported by Fujita et al., who described the successful C-3 mono-sulfonylation of α- and γ-cyclodextrins, which afforded the C-2, C-3, and C-6 mono-sulfonates as regioisomeric mixtures,[7b,c,g] and the absolute regioselective C-3 mono-sulfonylation of β-cyclodextrins.[7d] Ueno et al. have demonstrated a synthetic method for preparing mixtures of 2-*O*- and 3-*O*-monodansyl β- and γ-cyclodextrins in the construction of fluorescent sensors.[7i,k]

The regioselective $6^A,6^B$-, $6^A,6^C$-, $6^A,6^D$-, or $6^A,6^E$-disulfonylation of the C-6 hydroxyl groups of cyclodextrins (the glucose units are assigned as A through F, G, or H, clockwise, as viewed from the C-6 position of α-, β-, or γ-cyclodextrins, respectively) were accomplished by transannular disulfonylation using well-designed disulfonyl chlorides, in which the distance between the two sulfonyl groups corresponded to the distance between the two C-6 hydroxyl groups of the cyclodextrin molecules.[5a–e,g,i–l,n,o,q–t] In the case of regioselective 2-*O*-disulfonylation, Fujita et al. have obtained mixtures of regioisomeric $2^A,2^B$-, $2^A,2^C$-, and $2^A,2^D$-disulfonylated α- and β-cyclodextrins, in low yields.[7c,8a,b] Since the alkaline conditions that were employed in the 2-*O*-sulfonylations caused the conversion of the resulting 2-*O*-sulfonylated cyclodextrins to the epoxides, efficient regioselective 2-*O*-di- or 2-*O*-multi-sulfonylations could not be achieved. As a part of our studies on the chemical modification of cyclodextrins, we have developed an interesting regioselective monosulfonation of the C-2 hydroxyl groups of α-, β-, γ-, and δ-cyclodextrins using a combination of sulfonyl imidazole and molecular sieves in DMF.[7m,n,p] This monosulfonylation technique have proven to be exceptionally valuable for the following reasons: (i) the mild non-alkaline reaction conditions do not induce decomposition of the afforded sulfonylated cyclodextrins, (ii) the reaction occurs independently of the nature of the sulfonyl groups and cyclodextrins, and (iii) the reactions do not require strict anhydrous conditions. Furthermore, we have recently reported that $2^A,2^B$-disulfonylated α-, β-, and γ-cyclodextrins can be regioselectively prepared by transannular disulfonylation using benzophenone-3,3′-disulfonyl imidazole and molecular sieves in DMF.[8c,d] Herein, effective modifications of the secondary hydroxyl face of the A- and C-glucose units of α-, β-, and γ-cyclodextrins through a highly regioselective $2^A,2^C$-disulfonylation followed by further functionalization are described.[13]

2. Results and discussion

Based on the investigations of regioselective $2^A,2^C$-disulfonylations of α-, β-, and γ-cyclodextrins using several sulfonyl imidazoles in DMF in the presence of molecular sieves, it was determined that the employment of 1,4-dibenzoylbenzene-3′,3″-disulfonyl imidazole (**3**) (Scheme 1) afforded the highest $2^A,2^C$-regioselectivity. Compound **3** can be readily prepared by the reaction of 1,4-dibenzoylbenzene (**1**) with chlorosulfonic acid, followed by treatment with imidazole using the procedure of Berlin et al.[14] A mixture of β-cyclodextrin (dried under vacuum at 120°C for 12 h), disulfonyl imidazole **3** (1.0 equiv.), and freshly activated powdered 4 Å molecular sieves in DMF was



Scheme 1. Synthesis of **3**. *Reagents and conditions*: (a) $HOSO_2Cl$, 24 h, 120°C; (b) imidazole, Et_3N, $CHCl_3$, 30 min, rt.

stirred at 30°C for 48 h. The reaction was monitored using reversed-phase HPLC. Upon completion of the disulfonylation reaction, HPLC analysis (Fig. 1-[I]) of the final reaction mixture revealed that $2^A,2^C$-disulfonylated β-cyclodextrin (**5b**) (Scheme 2) was afforded, with a relatively high yield of 24%, and that $2^A,2^B$- and $2^A,2^D$-disulfonylated β-cyclodextrins (**4b** and **6b**, respectively) (Scheme 2) and cyclodextrin dimer **8** (Fig. 2) were afforded as minor sulfonylated cyclodextrins with 3.1, 1.0, and 1.5% yields, respectively (Table 1, entry 2). Moreover, 6-sulfonate(s) and 3-sulfonate(s) were not detected by HPLC analysis or by ^1H NMR measurements. Tabushi et al. reported temperature dependence of the regioisomer distribution in $6^A,6^C$-, and $6^A,6^D$-disulfonate capping of β-cyclodextrin.[5g] In this study, although a significant relationship between the $2^A,2^C$-regioselectivity and reaction temperature was not observed (Table 1, entries 1–3), the regioselectivity was found to be dependent on the nature of the solvent (Table 1, entries 4–6), which was limited due to the low solubility of cyclodextrin. In a mixture of DMF and MeCN (1:1) and in DMSO, the relative regioselectivity and yield of $2^A,2^B$-disulfonlylated β-cyclodextrin increased while those for $2^A,2^C$-disulfonlylated β-cyclodextrin decreased. In comparison, with DMA as the solvent, the relative $2^A,2^C$-regioselectivity decreased while the relative $2^A,2^D$-regioselectivity increased. These results suggested that the reaction solvents can influence the distance between the two sulfonyl groups of **3** and/or between the two C-2 hydroxyl groups of β-cyclodextrin. It is noteworthy that these sulfonylations, as well as the published sulfonylations using *p*-tolenesulfonyl imidazole[7m,n,p] or benzophenone-3,3′-disulfonyl imidazole,[8c,d] do not occur in the absence of molecular sieves. Detailed reaction mechanisms of the sulfonylations described herein, such as the roles of the molecular sieves and the imidazole moieties of the sulfonyl imidazoles, are currently under investigation. To summarize the present experiments, reaction conditions employing DMF as the solvent at 30°C exhibited the highest $2^A,2^C$-regioselectivity and yield.

Although the sulfonylation in DMF at 30°C afforded **5b** with high regioselectivity, the result was not satisfactory because of the low yield, and therefore, it was necessary to find a

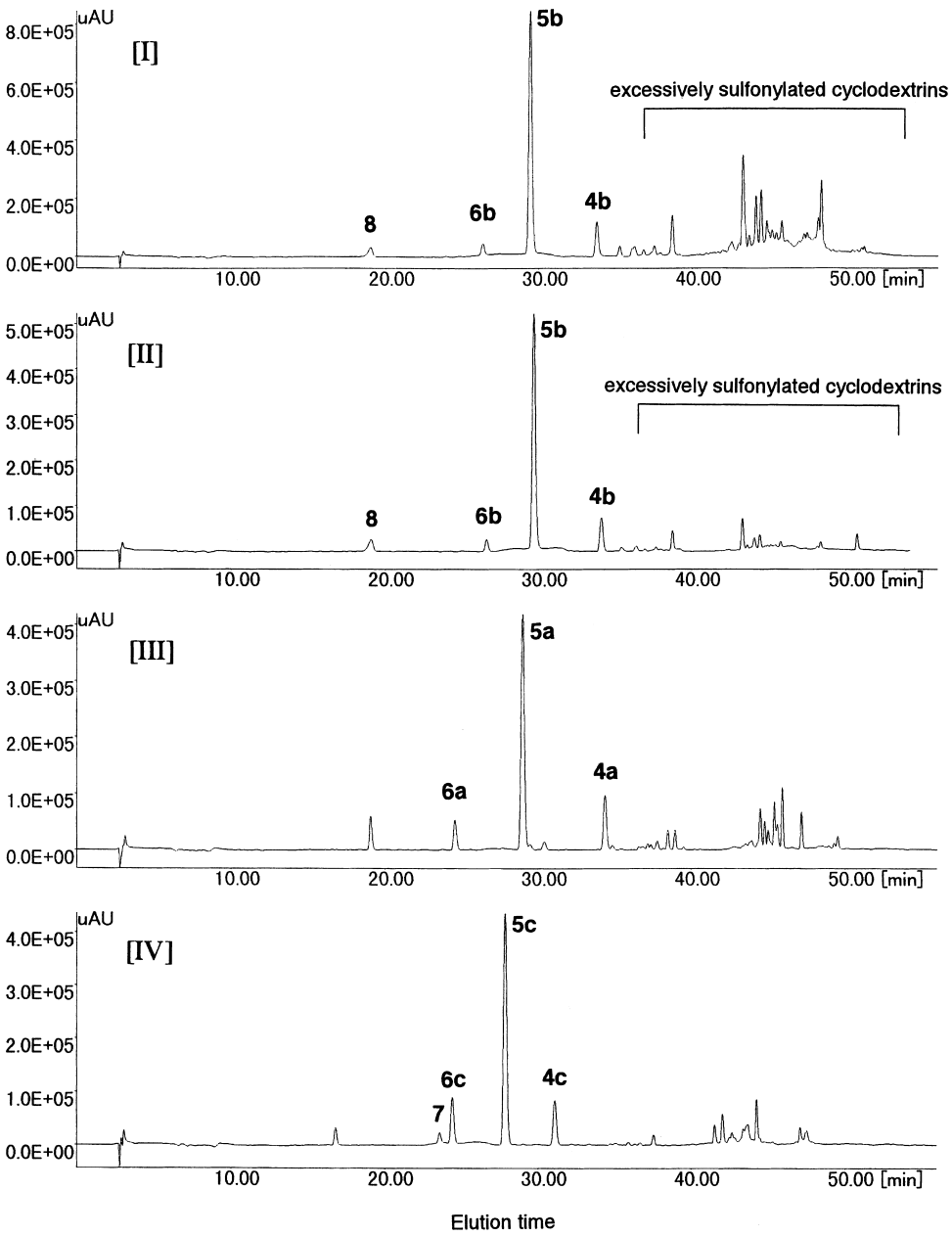
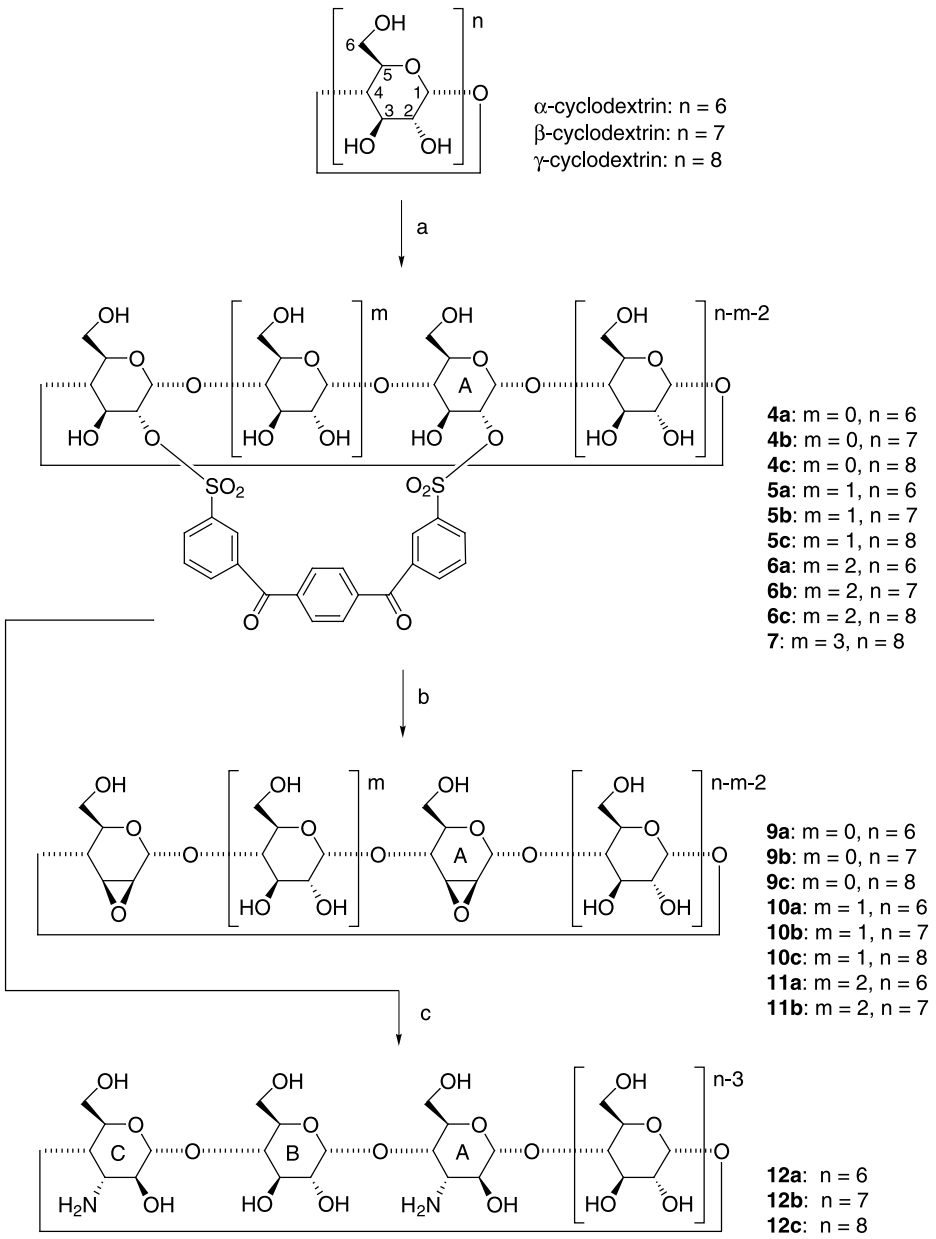


Figure 1. Reversed-phase analytical HPLC chromatogram (Comosil 5C18-MS column) of the final reaction mixture of sulfonylations of α-, β-, and γ-cyclodextrins. Detection was done at 300 nm wavelength. Gradient elution was done from 0:100 to 20:80 MeCN–H_2O for 10 min, to 30:70 MeCN–H_2O for 20 min, to 45:55 MeCN–H_2O for 10 min, and to 100:0 MeCN–H_2O for 10 min; flow rate of 0.8 mL/min. [I] sulfonylation of β-cyclodextrin under the condition of entry 2 in Table 1; [II] sulfonylation of β-cyclodextrin under the condition of entry 9 in Table 2; [III] sulfonylation of α-cyclodextrin under the condition of entry 1 in Table 3; [IV] sulfonylation of γ-cyclodextrin under the condition of entry 5 in Table 3. Compound numbers are presented corresponding peaks.

more efficient and practical sulfonylation condition. This low yield was attributable to excessive sulfonylation (see Fig. 1-[I]), which results in the squandering of **3**. Furthermore, the resulting excessively sulfonylated cyclodextrins complicated the purification procedures due to their low solubility in water or aqueous methanol, which are used for the reversed-phase column chromatography. The distribution of the sulfonylated cyclodextrins can be controlled by reaction conditions, such as the concentrations of the cyclodextrins and/or the sulfonyl reagents, and the techniques during the addition of compounds.[15] In the case of the sulfonylation described herein, the control of the concentrations of β-cyclodextrin and **3** was found to be extremely effective in inhibiting excessive sulfonylation; however, the slow addition of **3** did not show any improved efficiency. As expected, as equivalent value of **3** used for β-cyclodextrin was lower and the overall concentrations of β-cyclodextrin and **3** were lower, as shown in Figure 1-[II], the generation of excessively sulfonylated cyclodextrins decreased, which in turn resulted in the increased yields of **5b**, on the basis of **3** (Table 2, entries 1–9). Although Tabushi et al. reported that regioselectivity was sensitive to concentration of cyclodextrin and sulfonyl reagent in the $6^A,6^C$-, and $6^A,6^D$-disulfonate capping of β-cyclodextrin,[5g] in this study the relative regioselectivities of the $2^A,2^B$-, $2^A,2^C$-, and $2^A,2^D$-disulfonylations were similar among the



Scheme 2. Modifications of α-, β-, and γ-cyclodextrins. *Reagents and conditions*: (a) **3**, 4 Å molecular sieves, DMF, 48 h, 30°C; (b) NaOH, H_2O, 0–40°C; (c) 28% aqueous NH_3, 7 days, 40°C.

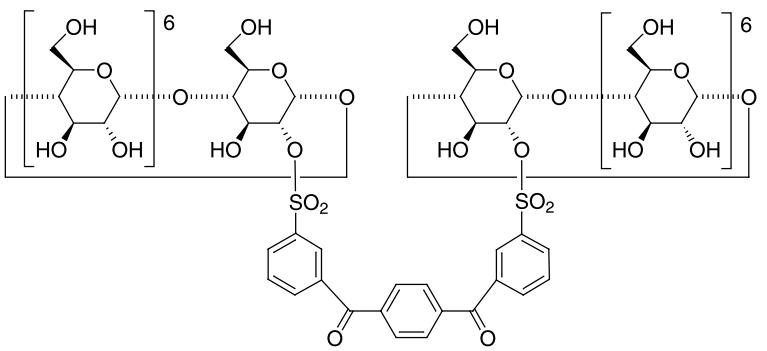


Figure 2. Structure of β-cyclodextrin dimer **8**.

Table 1. Sulfonylation of β-cyclodextrin with **3** in the presence of 4 Å molecular sieves

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]			
				8	**4b**	**5b**	**6b**
1	DMF	15	240	0.1	3.5	24	1.4
2	DMF	30	48	1.5	3.1	24	1.0
3	DMF	60	6	1.4	2.9	20	0.82
4	DMF/MeCN (1/1)	30	24	2.1	5.7	18	1.2
5	DMSO	30	48	1.6	11	16	0.93
6	DMA	30	48	0.9	3.0	19	2.0

β-Cyclodextrin (15 mM), **3** (15 mM), 4 Å molecular sieves (200 wt%, based on β-cyclodextrin).
[a] HPLC yields.

reactions; however, lower equivalent values of **3** resulted in greater amounts of cyclodextrin dimer **8**. Among the reaction conditions, concentrations of β-cyclodextrin and **3** at 11 mM and 3.7 mM, respectively, afforded the highest yield of **5b** (58%), on the basis of **3**, using HPLC analysis (Table 2, entry 9). Furthermore, these sulfonylation conditions allowed the recovery of β-cyclodextrin (55% isolation yield), which could then be reused in the subsequent sulfonylation, thus demonstrating that β-cyclodextrin and **3** can be efficiently utilized. If even lower concentrations of cyclodextrin, along with lower equivalent values of **3** are used, higher yields of **5b**, based on **3**, can be obtained; however, the use of large amounts of DMF limits the practical use of these conditions. Among the sulfonylations, conditions listed under entries 6, 8, and 9 in Table 2 were feasible.

The sulfonylations of α- and γ-cyclodextrins employing the same conditions as entry 9 in Table 2 afforded $2^A,2^C$-disulfonylated α- and γ-cyclodextrins (**5a** and **5c**, respectively) (Scheme 2) with high regioselectivities and yields of 51% and 39% (HPLC analyses), based on **3** (Table 3, entries 1 and 5, respectively). Additionally, the products were accompanied by small amounts of $2^A,2^B$-, $2^A,2^D$-, and $2^A,2^E$-disulfonylated α- and γ-cyclodextrins (for α-cyclodextrins, **4a** and **6a**; for γ-cyclodextrins, **4c**, **6c**, and **7**, respectively) (Scheme 2), as shown in Table 3, Figure 1-[III], and Figure 1-[IV]. Although the yield of **7** was extremely low, the transannular disulfonylation between the two C-2 hydroxyl groups of glucose units A and E was not anticipated, since the distance between the two C-2 hydroxyl groups of glucose units A and E is significantly greater than that between glucose units A and C. The formation of **7** suggested that the cyclic structure of γ-cyclodextrin is somewhat flexible. In comparision to these sulfonylations in DMF (Table 3, entries 1, 3, and 5), sulfonylations of α-, β-, and γ-cyclodextrins in DMSO (Table 3, entries 2, 4, and 6) showed a decrease in $2^A,2^C$-disulfonylation, and an increase in $2^A,2^B$-disulfonylation (Table 3, entries 1, 3, and 5).

Isolation of $2^A,2^B$-, $2^A,2^C$-, $2^A,2^D$-, and $2^A,2^E$-disulfonylated cyclodextrins, along with the cyclodextrin dimer and unreacted cyclodextrins, resulting from the sulfonylations (Table 3, entries 1, 3, and 5), was readily achieved using the following procedures: after removing the molecular sieves from the reaction mixture by filtration, the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in water, then purified by open reversed-phase column chromatography using Fuji Silisia Chromatorex-ODS DM1020T gel; use of reversed-phase column chromatography for separation of cyclodextrin derivatives was first demonstrated by Fujita et al.[5i] Using a stepwise gradient elution from 100% water to 50% aqueous MeOH, the compounds were eluted in the following order: unreacted cyclodextrin (α-cyclodextrin, 61% recovery yield; β-cyclodextrin, 55% recovery yield; γ-cyclodextrin, 65% recovery yield), cyclodextrin dimer, and a mixture of disulfonylated cyclodextrin isomers. Subsequent separation of the regioisomers from the mixture of disulfonylated α-cyclodextrins or disulfonylated β-cyclodextrins were readily achieved by open reversed-phase column chromatography using Fuji Silisia Chromatorex-ODS DM2035MT gel with a stepwise gradient elution from 10 to 25% aqueous MeCN. The isolation yields of the disulfonylated regioisomers are listed in Table 3. For the disulfonylated γ-cyclodextrins, similar chromatographic conditions afforded the pure $2^A,2^B$- and $2^A,2^C$-isomers (**4c** and **5c**, respectively); however, complete separation of the $2^A,2^D$- and $2^A,2^E$-isomers (**6c** and **7**, respectively) was not achieved. The isolation of **6c** and **7** was achieved using preparative HPLC column chromatography with yields of 3.8 and 0.76%, respectively. Overall, the desired $2^A,2^C$-disulfonylated α-, β-, and γ-cyclodextrins (**5a–c**, respectively) were isolated with yields of 40, 49, and 31%, respectively, based on **3**. It is important to note the following benefits: 1) the desired products ($2^A,2^C$-disulfonylated α-, β-, or γ-cyclodextrins) can be readily purified using simple open reversed-phase column

Table 2. Sulfonylation of β-cyclodextrin (β-CD) with **3** in the presence of 4 Å molecular sieves (4 Å MS)

Entry	Time (h)	Conc. of β-CD (mM)	Conc. of **3** (mM)	4 Å MS (g/DMF 100 mL)	Yield (%)[a]			
					8	**4b**	**5b**	**6b**
1	12	60	60	20	3.5	2.2	13	0.75
2	24	30	30	10	3.3	2.6	18	0.86
3	48	15	15	5	1.5	3.1	24	1.0
4	48	30	15	10	5.4	5.0	36	1.7
5	48	15	7.5	5	3.2	5.8	44	1.5
6	48	7.5	3.7	2.5	2.0	6.8	52	1.9
7	48	45	15	10	11	6.8	40	2.3
8	48	23	7.5	5	6.6	7.2	50	2.7
9	48	11	3.7	2.5	3.6	7.6	58	2.9

In DMF, at 30°C.
[a] HPLC yields on the basis of **3**.

Table 3. Sulfonylation of α-, β-, and γ-cyclodextrins with **3** in the presence of 4 Å molecular sieves

Entry	Cyclodextrin	Solvent	Time (h)	Yield (%)[a]			
				4a–c	**5a–c**	**6a–c**	**7**
1	α	DMF	48	7.6 (7.0)	51 (40)	3.3 (3.0)	–
2	α	DMSO	24	22	39	3.5	–
3	β	DMF	48	7.6 (6.1)	58 (49)	2.9 (1.5)	–
4	β	DMSO	24	27	40	1.7	–
5	γ	DMF	48	6.9 (4.5)	39 (31)	4.2 (3.8)	0.80 (0.76)
6	γ	DMSO	24	20	31	2.9	0.29

Cyclodextrins (11 mM), **3** (3.7 mM), 4 Å molecular sieves (200 wt% based on cyclodextrins), at 30°C.
[a] HPLC yields on the basis of **3**, isolation yields on the basis of **3** in paranthesis.

chromatography packed with inexpensive ODS gel, and without the use of expensive techniques, such as preparative HPLC, and 2) unreacted α-, β-, and γ-cyclodextrins and DMF could be recovered and reused in subsequent sulfonylations.

The structures of **4a–c**, **5a–c**, **6a–c**, and **7** were assigned using 2D NMR spectroscopy and a matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry; which has been reported as effective techniques for the analysis of cyclic oligosaccharides,[16] and subsequent epoxidations. Peak integrations of the ^{1}H NMR spectra (Figs. 3–5) of **4a–c**, **5a–c**, **6a–c**, and **7**, along with their MALDI-TOF mass spectra, indicated that the disulfonylations onto one cyclodextrin molecule were accomplished by single molecule of **3**. The ^{1}H NMR spectra of **4a–c**, **5a–c**, **6a–c**, and **7**, which were assigned using H–H COSY NMR experiments, exhibited appreciable downfield-shifts of the H-1, H-2, and H-3 protons of the two glucose units of the cyclodextrin molecules (Figs. 3–5). In particular, the chemical shifts of the H-2 protons exhibited a larger downfield-shift than those for the H-3 protons. The ^{13}C NMR spectra (Figs. 6–8) of **4a–c**, **5a–c**, **6a–c**, and **7**, which were assigned using C–H COSY and DEPT experiments, demonstrated significant downfield-shift of the ^{13}C NMR peaks of the C-2 carbons of the substituted glucose units in comparison to the other C-2 peaks. Furthermore, upfield-shifts were observed for the ^{13}C NMR peaks of the C-1 and C-3 carbons of the substituted glucose units, in relation to the other C-1 and C-3 peaks. It has been shown that mesylation or *p*-toluenesulfonylation of the hydroxyl groups causes a downfield-shift of α-carbon of the hydroxyl group, and an upfield-shift of the β-carbon.[17] Accordingly, my NMR data indicated that the two sulfonyl groups of **3** are located at the C-2 oxygens of the two glucose units of the cyclodextrin molecules, which was

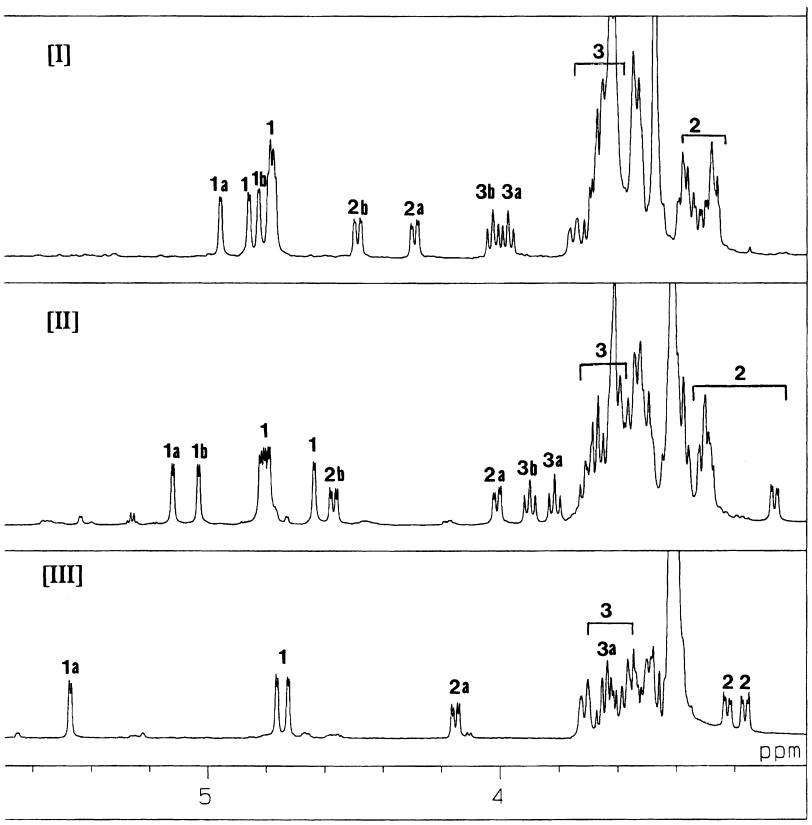


Figure 3. Partial ^{1}H NMR spectra of **4a**, **5a**, and **6a** (DMSO-d_6–5% D_2O, ref, DMSO: δ 2.49 ppm). The assigned signals are numbered according to the usual convention shown in Scheme 2, and the letters 'a' and 'b' refer to the sulfonylated glucose units. [I] ^{1}H NMR of **4a** at 50°C; [II] ^{1}H NMR of **5a** at 50°C; [III] ^{1}H NMR of **6a** at 40°C.

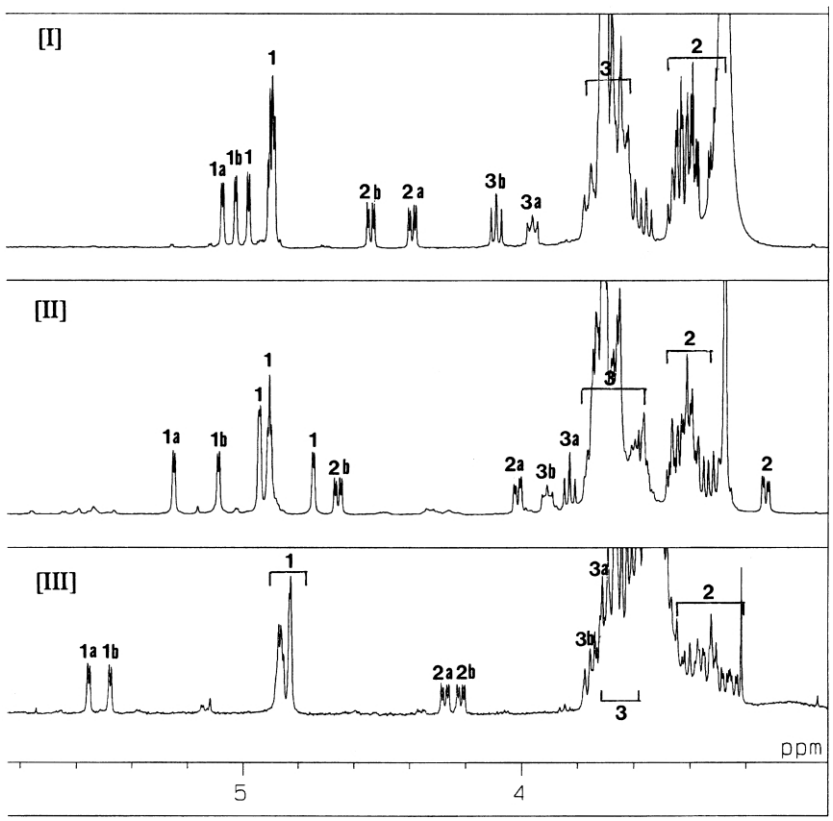


Figure 4. Partial ^{1}H NMR spectra of **4b**, **5b**, and **6b** (DMSO-d_6–5% D_2O, ref, DMSO: δ 2.49 ppm). The assigned signals are numbered according to the usual convention shown in Scheme 2, and the letters 'a' and 'b' refer to the sulfonylated glucose units. [I] ^{1}H NMR of **4b** at 80°C; [II] ^{1}H NMR of **5b** at 80°C; [III] ^{1}H NMR of **6b** at 40°C.

supported by the ^{13}C NMR properties of 2-*O*-*p*-toluenesulfonyl β-cyclodextrin, as shown by Breslow,[7a] and those of $2^{A},2^{B}$-disulfonylated α-, β-, and γ-cyclodextrins.[8c,d] However, the regiochemistries of **4a**–**c**, **5a**–**c**, **6a**–**c**, and **7** could not be determined by their NMR data. Typically, the sequence analysis of the glucose units of the substituted cyclodextrins can be determined by 2D ROESY NMR experiments,[18,19] which would show an NOE between the H-1 proton of a glucose unit and the nearby H-4 proton of the adjacent glucose unit. However, for **4a**–**c**, **5a**, **5b**, **6a**–**c**, and **7**, this technique was not available because the H-4 protons of the sulfonylated glucose units and those of adjoining glucose units could not be unambiguously assigned.

It has been reported that treatment of $2^{A},2^{B}$-, $2^{A},2^{C}$-, and $2^{A},2^{D}$-disulfonylated α-cyclodextrins,[7c,8c] $2^{A},2^{B}$-, $2^{A},2^{C}$-, and $2^{A},2^{D}$-disulfonylated β-cyclodextrins,[8a–c] and $2^{A},2^{B}$-disulfonylated γ-cyclodextrin[8d] in alkaline aqueous solvents can readily afford the corresponding di-2,3-manno-epoxides. Thus, disulfonylated cyclodextrins **4a**, **5a**, **6a**, **4b**, **5b**, **6b**, and **4c** were treated with NaOH in water, with or without MeOH, to generate the corresponding di-2,3-manno-epoxides, **9a**, **10a**, **11a**, **9b**, **10b**, **11b**, and **9c** (Scheme 2), respectively. Since their ^{1}H NMR spectra were comparable with those of authentic A,B-, A,C-, and A,D-di-2,3-manno-epoxy α-cyclodextrins,[7c,8c] A,B-, A,C-, and A,D-di-2,3-manno-epoxy β-cyclodextrins,[8a–c] and A,B-di-2,3-manno-epoxy γ-cyclodextrin,[8d] disulfonylated cyclodextrins **4a**, **5a**, **6a**, **4b**, **5b**, **6b**, and **4c** were assigned as $2^{A},2^{B}$-, $2^{A},2^{C}$-, and $2^{A},2^{D}$-isomers, as presented in Scheme 2. For the sulfonyl groups of **5c**, the regiochemistry was determined by 2D ROESY NMR experiments (Fig. 9), which showed cross-peaks between the H-4 proton of sulfonylated glucose unit A and the H-1 proton of unsulfonylated glucose unit B, and between the H-4 proton of glucose unit B and the H-1 proton of sulfonylated glucose unit C. These results indicated that the sequence of glucose units A, B, and C is as A–B–C, and therefore, the structure of **5c** was assigned as $2^{A},2^{C}$-disulfonylated γ-cyclodextrin. Although the regiochemistries of **6c** and **7** could not be definitely determined using 2D NMR techniques, the ^{1}H and ^{13}C NMR spectra of **7** (Figs. 5 and 8) were indicative of a symmetrically substituted cyclodextrin, thus suggesting that **7** should be $2^{A},2^{E}$-disulfonylated γ-cyclodextrin; consequently **6c** was assigned as the $2^{A},2^{D}$-isomer.

The structural assignment of **8** was performed using 2D NMR spectroscopy and MALDI-TOF mass spectrometry. The ^{1}H NMR spectrum of **8** (in DMSO-d_6–5% D_2O, 60°C, ref. DMSO: δ 2.49 ppm), assigned using a H–H COSY NMR experiment, exhibited a downfield-shift of the H-1 (δ 4.92 ppm), H-2 (δ 4.23 ppm), and H-3 (δ 3.92 ppm) protons of one glucose unit. In particular, the chemical shift of the H-2 proton showed a larger downfield-shift than that of the H-3 proton. The ^{13}C NMR spectrum (in DMSO-d_6–5% D_2O, 60°C, ref. DMSO: δ 39.50 ppm), assigned using C–H COSY and DEPT experiments, exhibited a significant downfield-shift of the C-2 carbon (δ 80.33 ppm) of the substituted glucose unit, relative to the other C-2 peaks (δ 71.70–72.30 ppm). The ^{13}C NMR signals for the C-1 (δ 98.28 ppm) and C-3 (δ 69.36 ppm) carbons of the

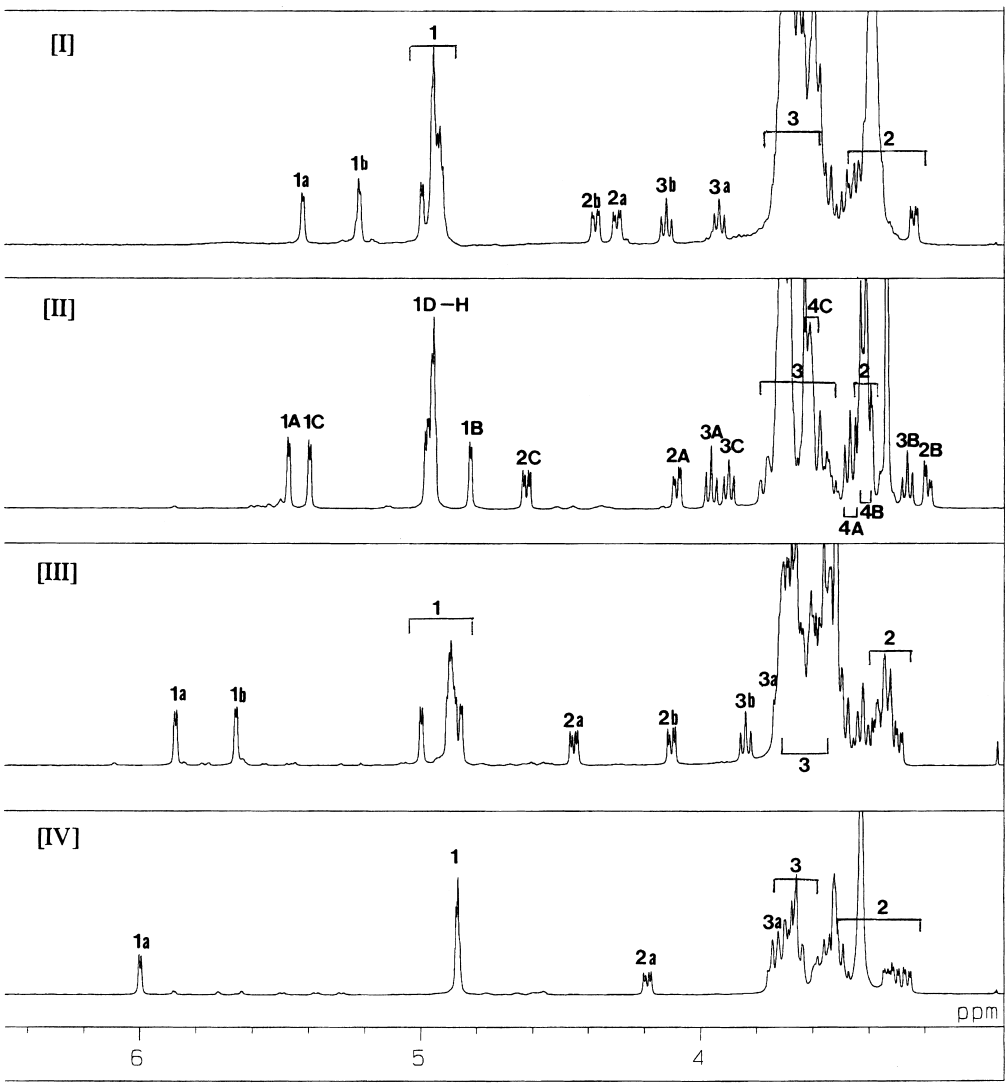


Figure 5. Partial ^{1}H NMR spectra of **4c**, **5c**, **6c**, and **7** (DMSO-d_6–5% D_2O, ref, DMSO: δ 2.49 ppm). The assigned signals are numbered according to the usual convention shown in Scheme 2, and the letters 'a' and 'b' refer to the sulfonylated glucose units. The letters A, B, C, and D–H in [II] refer to the glucose units lettered A to H clockwise, as viewed from the C-6 position of **5c** (see Scheme 2). The signals with no letters could not be clearly assigned. [I] ^{1}H NMR of **4c** at 50°C; [II] ^{1}H NMR of **5c** at 80°C; [III] ^{1}H NMR of **6c** at 40°C; [IV] ^{1}H NMR of **7** at 40°C.

substituted glucose unit showed a small upfield-shift from the other C-1 (δ 101.69–101.92 ppm) and C-3 (δ 71.70–72.98 ppm) peaks. Peak integration of the ^{1}H NMR spectrum indicated that the sulfonylation of two cyclodextrin molecules was executed by a single molecule of **3**. These NMR data indicated that the structure of **8** can be assigned as the cyclodextrin dimer, as shown in Figure 2. Furthermore, evidence supporting the structural assignment of **8** was observed in the MALDI-TOF mass spectrum of **8**.

The introduction of epoxy group(s) onto the secondary hydroxyl face of cyclodextrin molecules has proved to be an important and key technique in numerous previous studies.[20] Ring opening of the epoxy groups with various nucleophiles can afford useful modified cyclodextrins. In this study, synthesized $2^{A},2^{C}$-disulfonylated α- and β-cyclodextrins (**5a** and **5b**, respectively) could be efficiently converted to the corresponding A,C-di-2,3-manno-epoxy- α- and β-cyclodextrins (**10a** and **10b**, respectively), using alkaline conditions, as presented in the above sections. Similarly, A,C-di-2,3-manno-epoxy-γ-cyclodextrin (**10c**) (Scheme 2) could be afforded from **5c** by treatment with alkaline water. The ^{1}H NMR spectrum (in D_2O, 40°C, ref. acetone: δ 2.26 ppm) of product **10c** exhibited two doublet proton signals (δ 3.52 and 3.53 ppm), which was assigned to the H-2 protons coupled to the H-3 protons (J=4.3, 4.9 Hz, respectively). The ^{13}C NMR spectrum (in D_2O, 40°C, ref. acetone: δ 31.22 ppm) of **10c** showed signals at δ 50.39 and 50.52 ppm, which were assigned to the C-2 carbons, and signals at δ 55.17 and 55.19 ppm, assigned to the C-3 carbons. These characteristic NMR data indicated the presence of epoxy groups for **10c**. It has been reported that, for 2,3-manno-epoxide, $J_{1,2}$ is generally about 0 Hz.[11a,21] Furthermore, two singlet proton-signals (δ 5.33 and 5.34 ppm) for the H-1 protons of **10c** provided definite evidence that **10c** is A,C-di-2,3-manno-epoxy γ-cyclodextrin.

By means of the conventional diaxial opening[22] of the epoxy group by treating 2,3-manno-epoxy cyclodextrins with aqueous NH_3,[20a,23] the resulting 3-amino group(s) (on the cyclodextrin molecules) can be utilized as functional

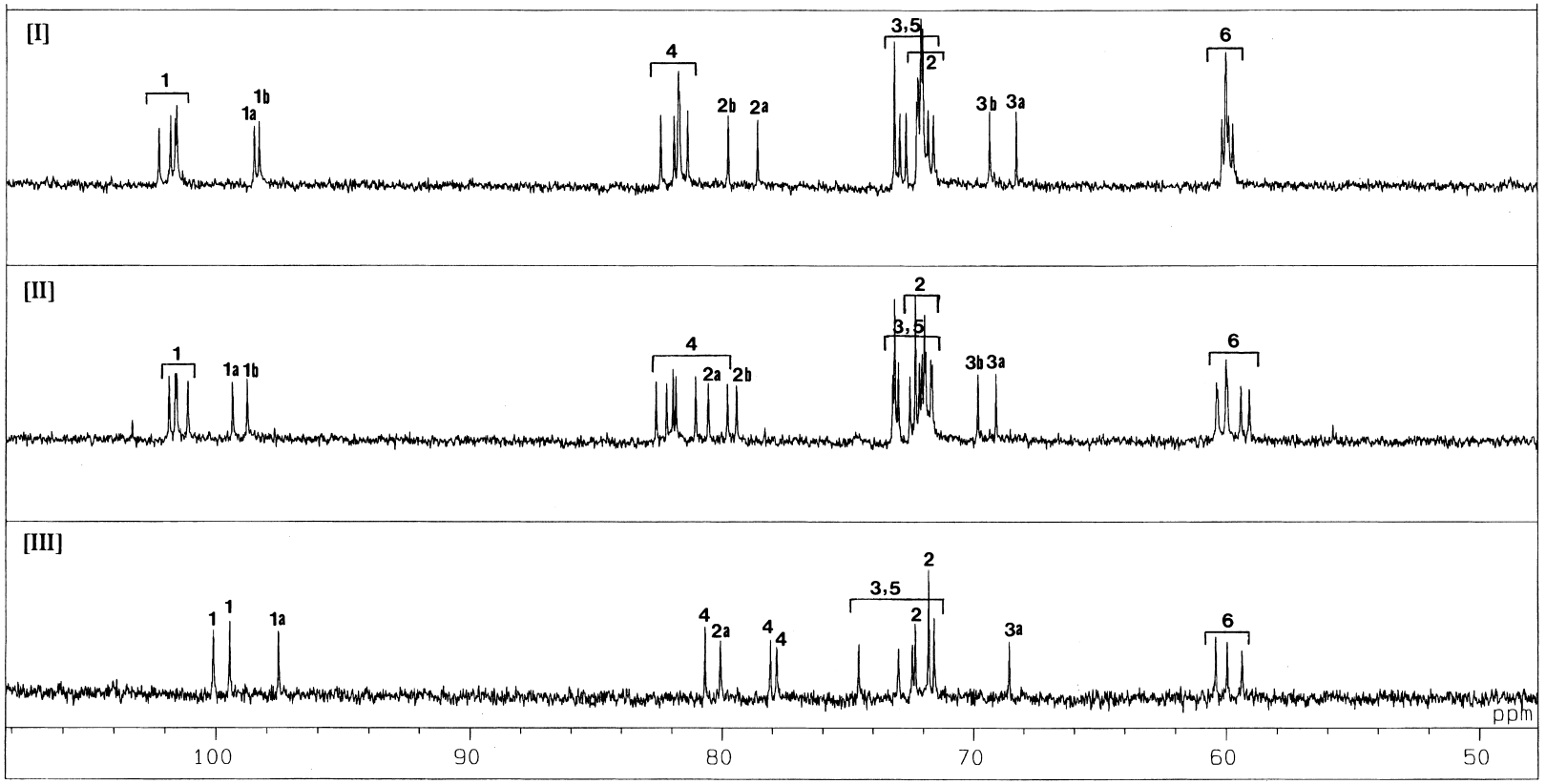


Figure 6. Partial ^{13}C NMR spectra of **4a**, **5a**, and **6a** (DMSO-d_6–5% D_2O, ref, DMSO: δ 39.50 ppm). The assigned signals are numbered according to the usual convention shown in Scheme 2, and the letters a and b refer to the sulfonylated glucose units. [I] ^{13}C NMR of **4a** at 50°C; [II] ^{13}C NMR of **5a** at 50°C; [III] ^{13}C NMR of **6a** at 40°C.

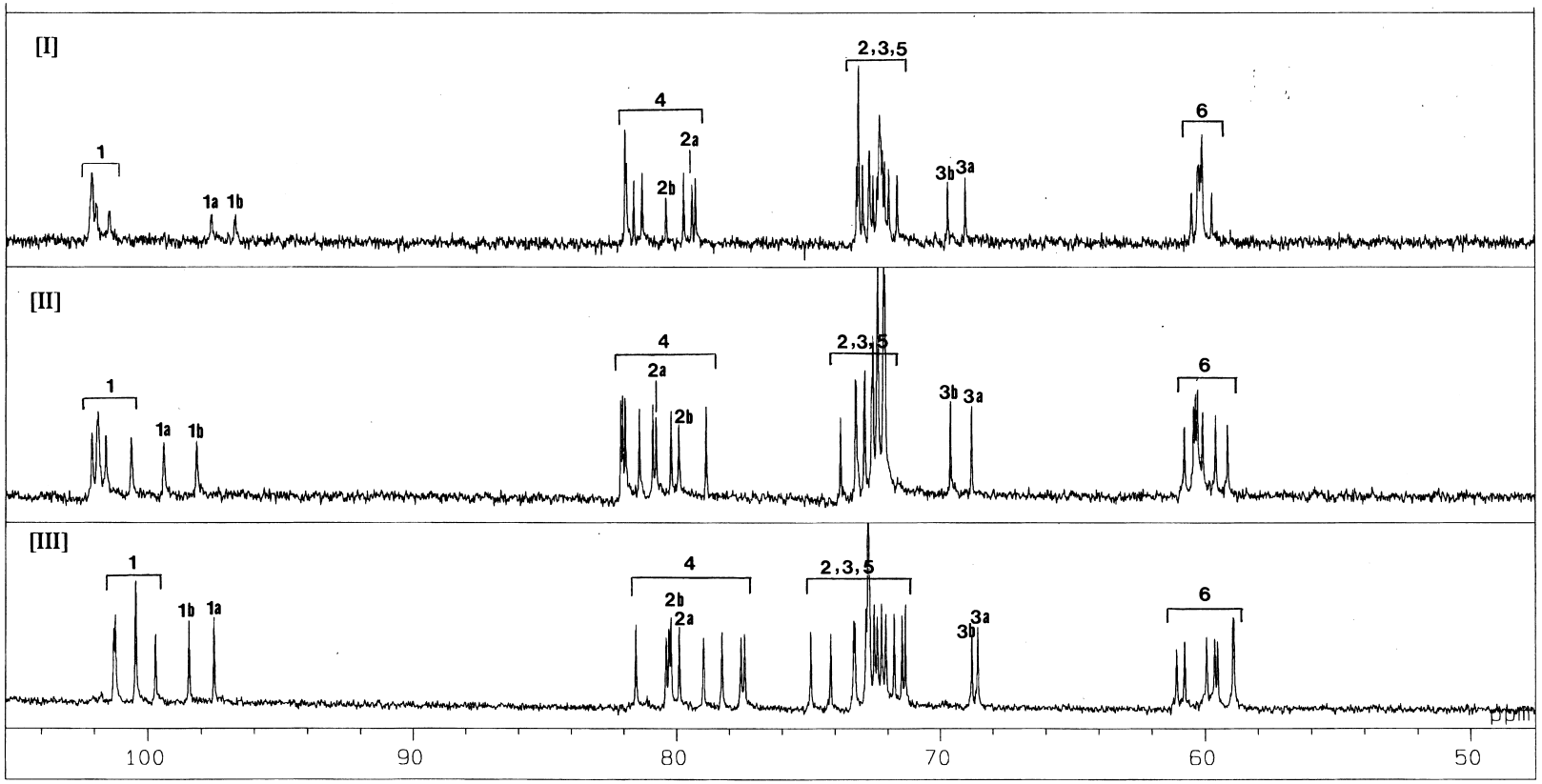


Figure 7. Partial ^{13}C NMR spectra of **4b**, **5b**, and **6b** (DMSO-d_6–5% D_2O, ref, DMSO: δ 39.50 ppm). The assigned signals are numbered according to the usual convention shown in Scheme 2, and the letters a and b refer to the sulfonylated glucose units. [I] ^{13}C NMR of **4b** at 80°C; [II] ^{13}C NMR of **5b** at 80°C; [III] ^{13}C NMR of **6b** at 40°C.

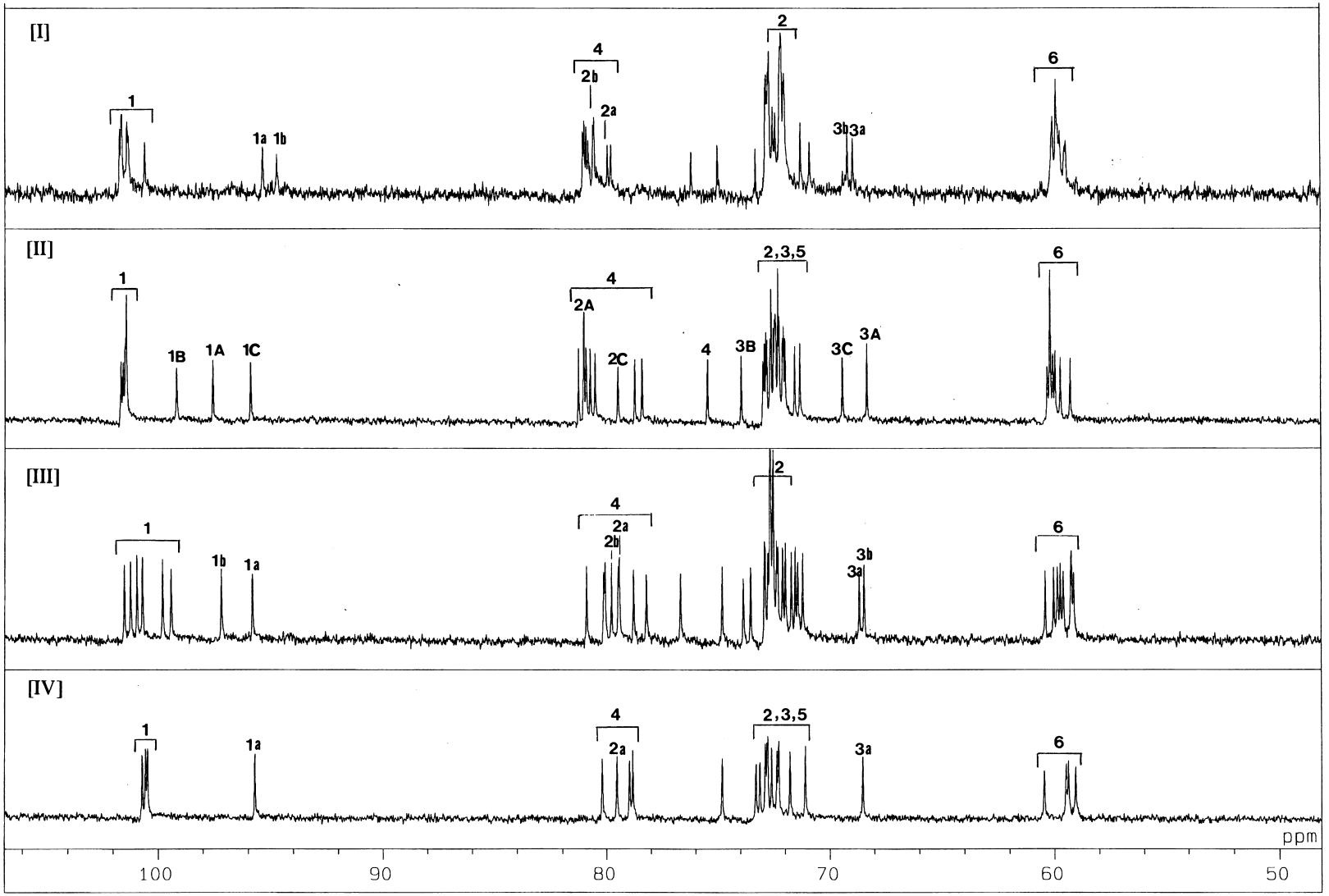


Figure 8. Partial ^{13}C NMR spectra of **4c**, **5c**, **6c**, and **7** (DMSO-d_6–5% D_2O, ref, DMSO: δ 39.50 ppm). The assigned signals are numbered according to the usual convention shown in Scheme 2, and the letters a and b refer to the sulfonylated glucose units. The letters A, B, C, and D–H in [II] refer to the glucose units lettered A to H clockwise, viewed from the C-6 position of **5c** (see Scheme 2). The signals with no letters could not be clearly assigned. [I] ^{13}C NMR of **4c** at 50°C; [II] ^{13}C NMR of **5c** at 80°C; [III] ^{13}C NMR of **6c** at 40°C; [IV] ^{13}C NMR of **7** at 40°C.

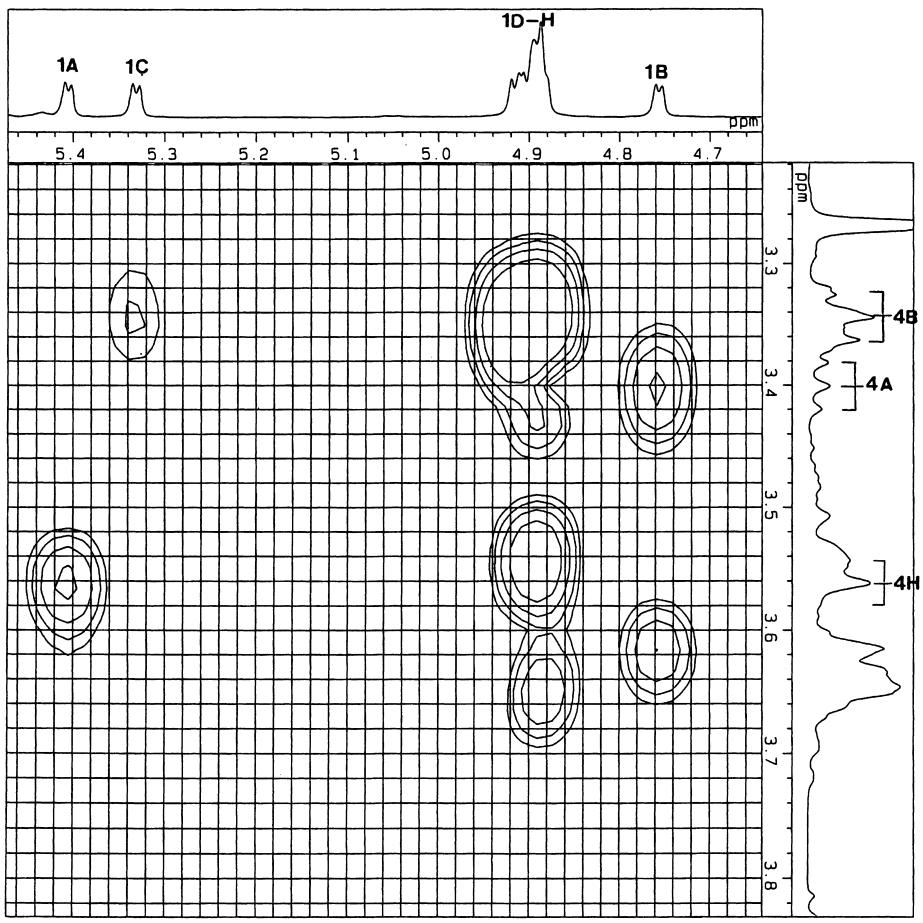


Figure 9. Partial 2D ROESY NMR spectrum of **5c** (500 MHz, DMSO-d_6–5% D_2O, 80°C, ref. DMSO:δ 2.49 ppm) with mixing time of 250 ms.

groups for binding the cyclodextrin molecule to guest molecules[24] or linkers.[25] In this study, in order to reduce the reaction steps, $2^A,2^C$-disulfonylated α-, β-, and γ-cyclodextrins **5a–c** were directly treated with aqueous NH_3, resulting in the efficient generation of $3^A,3^C$-diamino-3^A, 3^C-dideoxy-($2^AS,2^CS,3^AS,3^CS$)-cyclodextrins **12a–c** (Scheme 2) with yields of 79–95%, without regioisomers and stereoisomers. The ^1H and ^{13}C NMR (in DMSO-d_6–5% D_2O, 40°C) of **12a** were identical with the published spectrum[23a] of an authentic sample of $3^A,3^C$-diamino-$3^A,3^C$-dideoxy-($2^AS,2^CS,3^AS,3^CS$)-α-cyclodextrin, in which characteristic ^1H-signals at δ 2.64 ($J_{2,3}$=10.6 Hz and $J_{3,4}$=3.1 Hz) and 2.70 ppm ($J_{2,3}$=10.1 Hz and $J_{3,4}$=3.4 Hz), as the two H-3 protons of two amino glucose units, and ^1H-signals at δ 4.52 ($J_{1,2}$=7.3 Hz) and 4.58 ppm ($J_{1,2}$=6.1 Hz), as the two H-1 protons of two amino glucose units. The selective conversion of **5a** to **12a** suggested that the amination must occur via diaxial opening of the manno-epoxide intermediate that was generated during this reaction. The ^1H NMR spectrum of **12b** (in DMSO-d_6–5% D_2O, 50°C) showed characteristic signals at δ 2.70 ($J_{2,3}$=10.1 Hz and $J_{3,4}$=3.7 Hz) and 2.76 ppm ($J_{2,3}$=9.8 Hz and $J_{3,4}$=3.7 Hz), which were assigned using H–H COSY experiment as the two H-3 protons of two amino glucose units. The ^{13}C NMR spectrum of **12b** showed two signals at δ 52.55 and 53.15 ppm for the two C-3 carbons of the two glucose units, corresponding to the above two H-3 protons. These NMR data and MALDI-TOF mass spectrum indicated that, similar to the conversion of **5a** to **12a**, **5b** was selectively converted to $3^A,3^C$-diamino compound **12b**. The observed coupling constants of the two H-3 protons ($J_{2,3}$=10.1 and 9.8 Hz) suggested that the H-3 protons prefer the axial conformation in DMSO-d_6–5% D_2O.

Conformation of the altropyranose unit is in equilibrium between the $^1C_4$, $^0S_2$, and $^4C_1$conformations (Fig. 10). Methyl α-D-altroside[8b] and 3-azido-3-deoxy-α-D-altropyranosyl β-D-fructofuranoside[26,27] have been shown to prefer the $^4C_1$ conformation. Altropyranose units of 3-amino-3-deoxy-α-D-altropyranosyl β-D-fructofuranoside,[27] α-cycloaltrin,[20g] and β-cycloaltrin[9g] prefer $^0S_2$ conformation. For 3-amino-3-deoxy-(2*S*,3*S*)-α-cyclodextrin,[23] 3-amino-3-deoxy-(2*S*,3*S*)-β-cyclodextrins,[20a] and mono-altro-β-cyclodextrin,[8b] their altropyranose units prefer the $^1C_4$ conformation. The observed coupling constants ($J_{1,2}$=7.3 and 6.1 Hz for **12a**, $J_{1,2}$=6.7 and 6.9 Hz for **12b**) of the H-1 protons of the four amino glucose units of **12a** and **12b**, in comparison to the coupling constant values for the $^1C_4$, $^0S_2$, and $^4C_1$ conformations ($J_{1,2}$=8.0 Hz for $^1C_4$, 4.0 Hz for $^0S_2$, and 2.2 Hz for $^4C_1$), as calculated by Fujita et al.,[28] suggested that all amino glucose units in DMSO-d_6–5% D_2O prefer the $^1C_4$ conformation, which is in accord to the preference of the axial conformation by the H-3 protons. The conformations of the unmodified glucose units of **12a** and **12b**, as well as native β-cyclodextrins, were $^4C_1$ according to the coupling constants ($J_{1,2}$=3.1–3.7 Hz for **12a**, $J_{1,2}$=3.7–4.3 Hz for **12b**) of the corresponding H-1 protons. The ^1H NMR spectrum of **12c** (in DMSO-d_6–5%

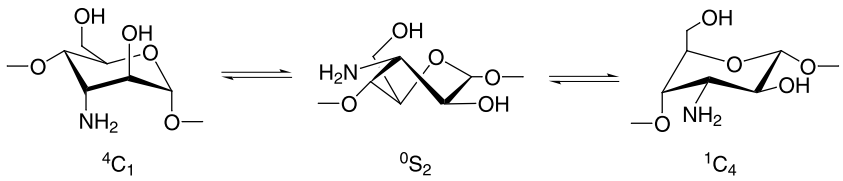


Figure 10. Conformational equilibrium of 3-amino-3-deoxy-altropyranose ring.

D_2O, 40°C) exhibited signals at δ 2.74 ($J_{2,3}$=9.2 Hz and $J_{3,4}$=3.1 Hz) and 2.95 ppm ($J_{2,3}$=4.3 Hz and $J_{3,4}$=4.3 Hz), which were assigned as the two H-3 protons of the two amino glucose units. The ^{13}C NMR spectrum showed two signals (δ 51.53 and 52.78 ppm), which were assigned as the C-3 carbons of the two amino glucose units. These NMR data and MALDI-TOF mass spectrum strongly indicated that the structure of **12c** can be assigned as $3^A,3^C$-diamino-$3^A,3^C$-dideoxy-($2^AS,2^CS,3^AS,3^CS$)-γ-cyclodextrin. Moreover, this structural assignment was in accord with the conversions of **5a** and **5b** to the corresponding $3^A,3^C$-diamino-$3^A,3^C$-dideoxy-($2^AS,2^CS,3^AS,3^CS$)-cyclodextrins. The coupling constant of the H-1 proton ($J_{1,2}$=6.7 Hz) of the amino glucose unit, whose H-3 proton signal appeared at δ 2.74 ppm, suggested that the amino glucose unit, as well as the amino glucose units of **12a** and **12b**, prefers the $^1C_4$ conformation. The coupling constant of the H-3 proton ($J_{2,3}$=9.2 Hz) supported the preference of $^1C_4$ conformation. However, the coupling constants of the H-1 proton of another amino glucose unit and its H-3 protons were 3.7 and 4.3 Hz, respectively, suggesting that the conformational equilibrium of the amino glucose unit could shifted from $^4C_1$ toward the $^0S_2$ conformation. It is interesting to note that, as presented above, the amino glucose units can change their conformation depending on the cyclodextrin type, and on the substitution position. Regarding A,B-, A,C-, and A,D-dialtro-β-cyclodextrins, the conformations of the altropyranose units in D_2O were systematically studied by Fujita et al.,[8b] who reported that the altropyranose ring can change their conformations depending on their positions in the cyclodextrin molecule. The present study showed the conformation of the amino glucose units of only $3^A,3^C$-diamino-$3^A,3^C$-dideoxy-($2^AS,2^CS,3^AS,3^CS$)-α,β and γ-cyclodextrins in DMSO-d_6–5% D_2O. Consequently, a systematic study on the conformation of the amino glucose units of $3^A,3^B$-, $3^A,3^C$-, $3^A,3^D$-, and $3^A,3^E$-diamino-α,β and γ-cyclodextrins, and on the reactivity of their amino groups, in particular, the differences in the reactivity of the two amino groups on these modified cyclodextrins, are in progress.

3. Summary

Discovery of the 2-*O*-regioselective sulfonylation with *p*-tolenesulfonyl imidazole and molecular sieves has led to a novel synthetic strategy for the efficient preparation of $2^A,2^C$-disulfonylated cyclodextrins. This strategy involves the use of 1,4-dibenzoylbenzene-$3',3''$-disulfonyl imidazole (readily prepared from 1,4-benzoylbenzene) in the presence of molecular sieves, and has proven to be highly practical and convenient. Furthermore, this methodology successfully overcame the typical main obstacles, such as lack of regioselectivity, low efficiencies, and poor isolation techniques, to provide for the practical preparation of $2^A,2^C$-disulfonylated cyclodextrins. Moreover, usefulness of this method was broadened by the syntheses of A,C-di-2,3-manno-epoxy-cyclodextrins and $3^A,3^C$-diamino-$3^A,3^C$-dideoxy-($2^AS,2^CS,3^AS,3^CS$)-cyclodextrins in excellent yields.

4. Experimental

4.1. General

Analytical and preparative HPLC column chromatography were done using a JASCO Gulliver HPLC system with a MD-910 detector. A Cosmosil 5C18-MS column (4.6 mm×150 mm) was used for the analytical HPLC. Gradient elution for the analytical HPLC was done from 0:100 to 20:80 MeCN–H_2O for 10 min, to 30:70 MeCN–H_2O for 20 min, to 45:55 MeCN–H_2O for 10 min, and to 100:0 MeCN–H_2O for 10 min; flow rate of 0.8 mL/min. HPLC preparative chromatography was carried out with a Cosmosil 5C18-MS column (20 mm×250 mm). Preparative open column chromatography was conducted with a Fuji Silysia Chromatorex DM1020T ODS gel, a Fuji Silysia Chromatorex DM 2035MT ODS gel, a Fuji Silysia silica gel AW-200, or Sephadex-CM C-25. Analytical TLC was performed on Merck Kieselgel 60 F254 precoated, glass-packed plates of 0.25 mm layer thickness. Spots of compounds on the TLC were visualized under a UV lamp or with a *p*-anisaldehyde–H_2SO_4–EtOH solution, and R_f values for the compounds were measured. Melting point (mp) values were measured using a Yanagimoto Seisakusho apparatus and are uncorrected. Elemental analyses were measured with a Yanaco CHNCORDER MT-3 instrument. IR spectra were taken with a JASCO FTIR-410 spectrometer, and UV–Vis spectra were obtained with a JASCO V-530DS spectrometer. ^1H NMR spectra were measured with a JEOL JNM-A500 spectrometer operating at 500 MHz. ^{13}C NMR spectra were measured with a JEOL JNM-A500 spectrometer operating at 125.65 MHz. Since some carbon peaks in the ^{13}C spectra were piled up, the number of carbon peaks presented in below data sections is not always coincident with the number of carbon atoms of compounds. Chemical shift values are reported in δ (ppm) and coupling constants (J) are in Hz. FAB mass spectra (positive) were measured using a JEOL DX-303 instrument with glycerol as a matrix. MALDI-TOF mass spectra (positive) were recorded on a Kratos Analytical Ltd. Kompact Discovery instrument using 2,5-dihydroxybenzoic acid as a matrix and an average of 50 laser shots per sample. 1,4-Dibenzoylbenzene (**1**) was purchased from Aldrich Chemical Co. (Milwaukee, WI). All chemicals not otherwise mentioned were purchased from Nacalai Tesque, INC. (Kyoto, Japan) in chemically pure grade and were used as

such. Cyclodextrins were dried under vacuum at 120°C for 12 h.

4.2. Synthesis

4.2.1. 1,4-Dibenzoylbenzene-3′,3″-disulfonyl chloride (2). A mixture of 1,4-dibenzoylbenzene (10.0 g, 35.0 mmol) and chlorosulfonic acid (50 mL) was heated at 120°C for 24 h, and then the cooled reaction mixture was poured dropwise into crashed ice (200 g). The resulting precipitate was filtered and washed with water followed by crystallization from ethyl acetate and recrystallization from chloroform to give pure 1,4-dibenzoylbenzene-3′,3″-disulfonyl chloride (7.30 g, 43% yield) as colorless needles. Mp 188–190°C. UV (MeCN) λ_{max} (ε) 267 nm (33,500). IR (KBr) ν 3075 and 1676 cm^{-1}. ^1H NMR (20°C, $CDCl_3$, ref. TMS: δ 0.0 ppm) δ 7.84 (2H, t, J=7.9 Hz), 7.96 (4H, s), 8.22 (2H, d, J=7.9 Hz), 8.31 (2H, d, J=7.9 Hz), and 8.49 (2H, b.s). FABMS m/z 483 for $[M+1]^+$; Anal. Found: C, 49.69; H, 2.53%, Calcd for $C_{20}H_{12}Cl_2O_6S_2$: C, 49.70; H, 2.50%.

4.2.2. 1,4-Dibenzoylbenzene-3′,3″-disulfonyl imidazole (3). To a solution of 1,4-dibenzoylbenzene-3′,3″-disulfonyl chloride (6.20 g, 12.8 mmol) in chloroform (240 mL) was added imidazole (2.04 g, 30.0 mmol) and triethylamine (4.20 mL, 30.2 mmol) at room temperature. After the reaction mixture was stirred for 30 min, the mixture was washed with water (200 mL×2). The chloroform solution was dried over anhydrous Na_2SO_4 and evaporated to dryness followed by crystallization from a mixture of chloroform and dichloromethane to give title compound **3** (6.96 g, 99% yield) as colorless needles. Mp 175–177°C. UV (MeCN) λ_{max} (ε) 267 nm (30,900). IR (KBr) ν 3147, 3132, 3072, and 1676 cm^{-1}. ^1H NMR (20°C, $CDCl_3$, ref. TMS: δ 0.0 ppm) δ 7.14 (2H, s), 7.35 (2H, s), 7.78 (2H, t, J=7.9 Hz), 7.86 (4H, s), 8.05 (2H, s), 8.13 (2H, d, J=7.9 Hz), 8.20 (2H, d, J=7.9 Hz), 8.40 (2H, s). FABMS m/z 547 for $[M+1]^+$. Anal. Found: C, 57.31; H, 3.53; N, 10.20%, Calcd for $C_{26}H_{18}N_4O_6S_2$: C, 57.13; H, 3.32; N, 10.25%.

4.2.3. 2^A,2^B-(1,4-dibenzoylbenzene-3′,3″-disulfonyl)-α-cyclodextrin (4a), 2^A,2^C-(1,4-dibenzoylbenzene-3′,3″-disulfonyl)-α-cyclodextrin (5a), 2^A,2^D-(1,4-dibenzoylbenzene-3′,3″-disulfonyl)-α-cyclodextrin (6a). Method of entry 1 in Table 3—To a solution of α-cyclodextrin (6.00 g, 6.17 mmol) in DMF (560 mL) were added freshly activated powder 4 Å molecular sieves (12.0 g) and **3** (1.12 g, 2.05 mmol) at room temperature and the mixture was stirred at 30°C for 48 h. The completion of the disulfonyl reaction was confirmed by HPLC analysis. Then, molecular sieves were removed by filtration and the filtrate was concentrated under reduced pressure. DMF (10 mL) and H_2O (200 mL) were added to dissolve the residue. The solution was subjected on a simple open reversed-phase column (ϕ 25×150 mm, Fuji Silisia Chromatorex-ODS DM1020T gel). Elution with H_2O and subsequent 10% aqueous MeOH gave fractions of unreacted α-cyclodextrin. Subsequent stepwise gradient elution to 50% aqueous MeOH could satisfactorily gave the fractions of a mixture of **4a**, **5a**, and **6a**. The fractions of α-cyclodextrin were concentrated, and the residue was dissolved with water, then the aqueous solution was poured into acetone to give a powder of α-cyclodextrin followed by filtration and drying (3.66 g, 61% recovery yield). The fractions of a mixture of **4a**, **5a**, and **6a** were concentrated, and then the residue was dissolved with 10% aqueous MeOH (200 mL). The solution was subjected on an open reversed-phase column (ϕ 25×150 mm, Fuji Silisia Chromatorex-ODS DM2035MT gel). Stepwise gradient elution from 10 to 25% aqueous MeCN gave pure fractions in the following order: **6a**, **5a**, and **4a**. The fractions were combined and then concentrated in vacuuo to give pure **4a** (0.198 g, 7.0%, based on **3**), **5a** (1.13 g, 40%, based on **3**), and **6a** (0.085 g, 3.0%, based on **3**) as colorless solids.

Data for **4a**: R_f 0.56 (TLC on silica gel, MeCN–H_2O 3:1). Mp 155°C (decomp). UV (H_2O) λ_{max} (ε) 271 nm (23,180). IR (KBr) ν 3408, 2931, and 1664 cm^{-1}. ^1H NMR (50°C, DMSO-d_6–5% D_2O, ref. DMSO: δ 2.49 ppm) δ 3.15–3.76 (m), 3.98 (1H, t, J=9.8 Hz), 4.03 (1H, t, J=9.8 Hz), 4.29 (1H, dd, J=3.1, 9.8 Hz), 4.49 (1H, dd, J=3.1, 9.8 Hz), 4.7–4.8 (3H, m), 4.83 (1H, d, J=3.1 Hz), 4.86 (1H, d, J=3.1 Hz), 4.96 (1H, d, J=3.1 Hz), 7.90–7.95 (3H, m), 7.98 (2H, d, J=7.3 Hz), 8.03 (2H, d, J=7.3 Hz), 8.17–8.22 (3H, m), 8.26 (1H, s), and 8.28 (1H, s). ^{13}C NMR (50°C, DMSO-d_6–5% D_2O, ref. DMSO: δ 39.50 ppm) δ 59.83, 60.05, 60.11, 60.26, 68.39, 69.46, 71.70, 71.91, 72.12, 72.19, 72.32, 72.78, 73.03, 73.24, 78.69, 79.86, 81.47, 81.83, 82.01, 82.54, 98.43, 98.63, 101.65, 101.72, 101.90, 102.34, 129.04, 129.57, 130.43, 130.80, 130.97, 132.35, 132.45, 134.75, 134.92, 136.22, 137.48, 137.53, 139.36, 139.46, 193.34, and 193.48. MALDI-TOF-MS m/z 1405.3 for $[M+Na]^+$. Anal. Found: C, 48.48; H, 5.49%, Calcd for $C_{56}H_{70}O_{36}S_2$: C, 48.63; H, 5.10%.

Data for **5a**: R_f 0.56 (TLC on silica gel, MeCN–H_2O, 3:1). Mp 170°C (decomp). UV (H_2O) λ_{max} (ε) 268 nm (25,900). IR (KBr) ν 3398, 2931, and 1664 cm^{-1}. ^1H NMR (50°C, DMSO-d_6–5% D_2O, ref. DMSO: δ 2.49 ppm) δ 3.06 (1H, dd, J=3.1, 9.8 Hz), 3.2–3.7 (m), 3.82 (1H, t, J=9.8 Hz), 3.90 (1H, t, J=9.2 Hz), 4.01 (1H, dd, J=3.1, 9.8 Hz), 4.57 (1H, dd, J=3.1, 9.8 Hz), 4.64 (1H, d, J=3.1 Hz), 4.79 (1H, d, J=3.1 Hz), 4.81 (1H, d, J=3.1 Hz), 4.82 (1H, d, J=3.1 Hz), 5.03 (1H, d, J=3.1 Hz), 5.12 (1H, d, J=3.1 Hz), 7.76 (1H, t, J=7.3 Hz), 7.82 (1H, t, J=7.9 Hz), 7.84 (2H, d, J=7.9 Hz), 7.93 (1H, d, J=7.9 Hz), 7.99 (2H, d, J=7.9 Hz), 8.06–8.11 (3H, m), 8.14 (1H, d, J=7.3 Hz), 8.18 (1H, d, J=7.9 Hz). ^{13}C NMR (50°C, DMSO-d_6–5% D_2O, ref. DMSO: δ 39.50 ppm) δ 59.11, 59.44, 60.00, 60.03, 60.38, 60.41, 69.13, 69.85, 71.60, 71.73, 71.98, 72.00, 72.07, 72.17, 72.34, 72.55, 73.01, 73.16, 73.20, 79.44, 79.81, 80.56, 81.07, 81.85, 81.96, 82.22, 82.64, 98.81, 99.38, 101.13, 101.57, 101.60, 101.87, 128.09, 128.75, 129.36, 129.92, 129.98, 130.18, 131.08, 131.56, 133.95, 134.05, 136.43, 137.20, 138.19, 138.73, 140.25, 195.01, and 195.51. MALDI-TOF-MS m/z 1405.7 for $[M+Na]^+$. Anal. Found: C, 48.41; H, 5.47%, Calcd for $C_{56}H_{70}O_{36}S_2$: C, 48.63; H, 5.10%.

Data for **6a**: R_f 0.56 (TLC on silica gel, MeCN–H_2O, 3:1). Mp 170°C (decomp). UV (H_2O) λ_{max} (ε) 272 nm (25,560). IR (KBr) ν 3398, 2931, and 1664 cm^{-1}. ^1H NMR (40°C, DMSO-d_6–5% D_2O, ref. DMSO: δ 2.49 ppm) δ 3.16 (2H, dd, J=3.1, 9.8 Hz), 3.22 (2H, dd, J=3.1, 9.2 Hz), 3.4–3.8 (m), 4.15 (2H, dd, J=3.7, 9.8 Hz), 4.72 (2H, d, J=3.1 Hz),

4.76 (2H, d, J=3.1 Hz), 5.47 (2H, d, J=3.7 Hz), 7.84 (2H, t, J=8.5 Hz), 8.06 (4H, s), and 8.25 (6H, m). ^{13}C NMR (40°C, DMSO-d_6–5% D_2O, ref. DMSO: δ 39.50 ppm) δ 59.39, 59.98, 60.43, 60.48, 68.59, 71.58, 71.79, 72.32, 72.44, 72.98, 74.56, 77.83, 78.08, 80.07, 80.68, 97.56, 99.47, 100.11, 129.92, 130.15, 131.97, 134.42, 136.64, 136.84, 139.44, and 193.25. MALDI-TOF-MS m/z 1405.4 for $[M+Na]^+$. Anal. Found: C, 48.28; H, 5.43%, Calcd for $C_{56}H_{70}O_{36}S_2$: C, 48.63; H, 5.10%.

4.2.4. $2^A,2^B$-(1,4-Dibenzoylbenzene-3′,3″-disulfonyl)-β-cyclodextrin (4b), $2^A,2^C$-(1,4-dibenzoylbenzene-3′,3″-disulfonyl)-β-cyclodextrin (5b), $2^A,2^D$-(1,4-dibenzoylbenzene-3′,3″-disulfonyl)-β-cyclodextrin (6b). Method of entry 3 in Table 3—Essentially the same procedure was used as for α-cyclodextrin starting with β-cyclodextrin (6.00 g, 5.29 mmol), freshly activated powder 4 Å molecular sieves (12.0 g), **3** (0.960 g, 1.76 mmol), and DMF (472 mL) to give after 48 h at 30°C a mixture of unreacted β-cyclodextrin, **4b**, **5b**, **6b**, and **8**. An open reversed-phase column chromatography (ϕ 25× 150 mm, Fuji Silisia Chromatorex-ODS DM1020T gel) using stepwise gradient elution from H_2O to 50% aqueous MeOH gave unreacted β-cyclodextrin (3.32 g, 55%, based on β-cyclodextrin), **8** (0.218 g, 4.6%, based on **3**), and a mixture of **4b**, **5b**, and **6b**. Subsequent open reversed-phase column chromatography (ϕ 25× 150 mm, Fuji Silisia Chromatorex-ODS DM2035MT gel) of the mixture of **4b**, **5b**, and **6b** using stepwise gradient elution from 10 to 25% aqueous MeCN gave pure fractions in the following order: **6b**, **5b**, and **4b**. The fractions were combined, and then concentrated in vacuuo to give pure **4b** (0.166 g, 6.1%, based on **3**), **5b** (1.33 g, 49%, based on **3**), and **6b** (0.041 g, 1.5%, based on **3**) as colorless solids.

Data for **4b**: R_f 0.47 (TLC on silica gel, MeCN–H_2O, 3:1). Mp 161°C (decomp). UV (H_2O) λ_{max} (ε) 270 nm (29,050). IR (KBr) ν 3398, 2930, and 1669 cm^{-1}. ^{1}H NMR (80°C, DMSO-d_6–5% D_2O, DMSO: δ 2.49 ppm) δ 3.1–3.8 (m), 3.90 (1H, t, J=9.8 Hz), 4.03 (1H, t, J=9.8 Hz), 4.33 (1H, dd, J=3.7, 9.8 Hz), 4.47 (1H, dd, J=3.7, 9.8 Hz), 4.82–4.84 (4H, m), 4.92 (1H, d, J=3.7 Hz), 4.96 (1H, d, J=3.7 Hz), 5.01 (1H, d, J=3.7 Hz), 7.91 (1H, t, J=7.9 Hz), 7.93 (1H, t, J=7.9 Hz), 7.94 (2H, d, J=8.5 Hz), 8.04 (2H, d, J=8.5 Hz), 8.19 (1H, s), 8.21 (1H, s), 8.24 (1H, d, J=7.9 Hz), 8.26 (1H, d, J=7.9 Hz), 8.27 (1H, d, J=7.9 Hz), and 8.30 (1H, d, J=7.9 Hz). ^{13}C NMR (80°C, DMSO-d_6–5% D_2O, DMSO: δ 39.50 ppm) δ 59.41, 59.77, 59.80, 59.93, 59.98, 60.16, 68.73, 69.39, 71.30, 71.63, 71.78, 71.96, 72.22, 72.35, 72.62, 72.76, 72.80, 78.97, 79.10, 79.41, 80.09, 80.99, 81.30, 81.63, 96.40, 97.31, 101.17, 101.62, 101.78, 128.76, 129.11, 129.90, 129.97, 130.41, 130.54, 131.97, 134.11, 134.34, 135.08, 136.09, 137.30, 137.47, 139.29, 193.15, and 193.37. MALDI-TOF-MS m/z 1567.2 for $[M+Na]^+$. Anal. Found: C, 47.93; H, 5.59%, Calcd for $C_{62}H_{80}O_{41}S_2$: C, 48.19; H, 5.22%.

Data for **5b**: R_f 0.47 (TLC on silica gel, MeCN–H_2O, 3:1). Mp 165°C (decomp). UV (H_2O) λ_{max} (ε) 269 nm (24,400). IR (KBr) ν 3398, 2929, and 1665 cm^{-1}. ^{1}H NMR (80°C, DMSO-d_6–5% D_2O, DMSO: δ 2.49 ppm) δ 3.06 (1H, dd, J=3.1, 9.2 Hz), 3.2–3.7 (m), 3.76 (1H, t, J=9.8 Hz), 3.84 (1H, m), 3.95 (1H, dd, J=3.7, 9.8 Hz), 4.59 (1H, dd, J=3.7, 9.8 Hz), 4.68 (1H, d, J=3.1 Hz), 4.83 (1H, d, J=3.7 Hz), 4.84 (1H, d, J=3.1 Hz), 4.87 (2H, d, J=3.1 Hz), 5.02 (1H, d, J=3.7 Hz), 5.18 (1H, d, J=3.7 Hz), 7.76 (1H, t, J=7.9 Hz), 7.82 (2H, d, J=8.6 Hz), 7.82 (1H, t, J=7.9 Hz), 7.89 (1H, d, J=7.9 Hz), 7.97 (1H, s), 7.98 (2H, d, J=8.6 Hz), 8.07 (1H, s), 8.13 (2H, m), and 8.18 (1H, d, J=7.9 Hz). ^{13}C NMR (80°C, DMSO-d_6–5% D_2O, DMSO: δ 39.50 ppm) δ 58.85, 59.29, 59.77, 59.97, 60.05, 60.11, 60.46, 68.50, 69.31, 71.78, 71.83, 72.06, 72.25, 72.55, 72.91, 73.47, 78.57, 79.61, 79.90, 80.48, 80.60, 81.11, 81.65, 81.75, 81.81, 97.97, 99.10, 100.32, 101.26, 101.55, 101.60, 101.78,128.16, 128.58, 128.99, 129.52, 129.67, 130.05, 130.79, 131.03, 133.45, 133.54, 135.72, 137.40, 137.80, 139.36, 139.72, 140.44, 194.82, and 195.42. MALDI-TOF-MS m/z 1567.4 for $[M+Na]^+$. Anal. Found: C, 47.86; H, 5.53%, Calcd for $C_{62}H_{80}O_{41}S_2$: C, 48.19; H, 5.22%.

Data for **6b**: R_f 0.47 (TLC on silica gel, MeCN–H_2O, 3:1). Mp 188°C (decomp). UV (H_2O) λ_{max} (ε) 269 nm (26,500). IR (KBr) ν 3402, 2928, and 1663 cm^{-1}. ^{1}H NMR (40°C, DMSO-d_6–5% D_2O, DMSO: δ 2.56 ppm) δ 3.2–3.8 (m), 4.22 (1H, dd, J=3.7, 9.8 Hz), 4.27 (1H, dd, J=3.7, 10.4 Hz), 4.83 (3H, m), 4.86 (1H, d, J=4.9 Hz), 4.87 (1H, d, J=4.3 Hz), 5.48 (1H, d, J=3.7 Hz), 5.56 (1H, d, J=3.7 Hz), 7.91 (1H, t, J=7.9 Hz), 7.93 (1H, t, J=7.9 Hz), 8.09 (2H, d, J=7.9 Hz), 8.20 (2H, d, J=7.9 Hz), 8.22 (1H, s), 8.30 (1H, d, J=7.9 Hz), 8.31 (1H, d, J=7.9 Hz), 8.35 (1H, d, J=7.9 Hz), 8.38 (1H, d, J=7.9 Hz), and 8.40 (1H, s). ^{13}C NMR (40°C, DMSO-d_6–5% D_2O, DMSO: δ 39.50 ppm) δ 58.95, 59.65, 59.95, 60.77, 61.08, 68.59, 68.82, 71.33, 71.47, 71.76, 72.07, 72.24, 72.40, 72.52, 72.75, 73.20, 73.29, 74.16, 74.92, 77.44, 78.29, 78.98, 79.90, 80.22, 80.30, 80.40, 81.55, 97.52, 98.46, 99.71, 100.45, 101.23, 101.30, 129.72, 130.00, 130.08, 130.20, 130.29, 132.04, 132.58, 134.57, 134.82, 136.45, 136.55, 136.73, 137.09, 139.13, 139.74, 193.09, and 193.32. MALDI-TOF-MS m/z 1567.4 for $[M+Na]^+$. Anal. Found: C, 47.89; H, 5.59%, Calcd for $C_{62}H_{80}O_{41}S_2$: C, 48.19; H, 5.22%.

Data for **8**: R_f 0.56 (TLC on silica gel, MeCN–H_2O–28% aqueous NH_3, 3:2:1). Mp 185°C (decomp). UV (H_2O) λ_{max} (ε) 269 nm (23,440). IR (KBr) ν 3397, 2930, and 1655 cm^{-1}. ^{1}H NMR (60°C, DMSO-d_6–5% D_2O, ref, DMSO: δ 2.49 ppm) δ 3.25–3.75 (m), 3.92 (2H, t, J=9.8 Hz), 4.23 (2H, dd, J=3.1, 9.8 Hz), 4.82 (12H, b.s), 4.92 (2H, d, J=3.7 Hz), 7.85 (2H, t, J=7.3 Hz), 7.93 (4H, s), 8.09 (2H, d, J=7.3 Hz), 8.26 (2H, d, J=7.3 Hz), and 8.27 (2H, s). ^{13}C NMR (60°C, DMSO-d_6–5% D_2O, DMSO: δ 39.50 ppm) δ 59.75, 60.00, 69.36, 71.70, 72.09, 72.30, 72.80, 72.98, 80.33, 81.15, 81.63, 98.28, 101.69, 101.92, 128.53, 129.87, 130.13, 132.01, 135.10, 136.78, 137.42, 139.72, and 193.94. MALDI-TOF-MS m/z 2702.9 for $[M+Na]^+$. Anal. Found: C, 46.27; H, 5.82%, Calcd for $C_{104}H_{150}O_{76}S_2$: C, 46.60; H, 5.64%.

4.2.5. $2^A,2^B$-(1,4-Dibenzoylbenzene-3′,3″-disulfonyl)-γ-cyclodextrin (4c), $2^A,2^C$-(1,4-dibenzoylbenzene-3′,3″-disulfonyl)-γ-cyclodextrin (5c), $2^A,2^D$-(1,4-dibenzoylbenzene-3′,3″-disulfonyl)-γ-cyclodextrin (6c), $2^A,2^E$-(1,4-dibenzoylbenzene-3′,3″-disulfonyl)-γ-cyclodextrin (7). Method of entry 5 in Table 3—Essentially the same procedure was used as for α-cyclodextrin starting with

γ-cyclodextrin. (6.00 g, 4.63 mmol), freshly activated powder 4 Å molecular sieves (12.0 g), **3** (0.840 g, 1.54 mmol), and DMF (420 mL) to give after 48 h at 30°C a mixture of unreacted γ-cyclodextrin, **4c**, **5c**, **6c**, and **7**. An open reversed-phase column chromatography (ϕ 25× 150 mm, Fuji Silisia Chromatorex-ODS DM1020T gel) using stepwise gradient elution from H_2O to 50% aqueous MeOH gave unreacted γ-cyclodextrin (3.90 g, 65%, based on γ-cyclodextrin) and a mixture of **4c**, **5c**, **6c**, and **7**. Subsequent simple open reversed-phase column chromatography (ϕ 25× 150 mm, Fuji Silisia Chromatorex-ODS DM2035MT gel) of the mixture of **4c**, **5c**, **6c**, and **7** using stepwise gradient elution from 10% to 25% aqueous MeCN gave a mixture of **7** and **6c**, pure **5c**, and pure **4c**. The fractions of **4c** or **5c** were combined, and then concentrated in vacuuo to give pure **4c** (0.118 g, 4.5%, based on **3**) and **5c** (0.815 g, 31%, based on **3**) as colorless solids. The mixture of **6c** and **7** was applied to a preparative HPLC column eluting with 20% aqueous MeCN with flow rate of 6.0 mL/min, gave pure **6c** (0.100 g, 3.8%, based on **3**) and pure **7** (0.020 g, 0.76%, based on **3**) as colorless solids.

Data for **4c**: R_f 0.38 (TLC on silica gel, MeCN–H_2O, 3:1). Mp 190°C (decomp). UV (H_2O) λ_{max} (ε) 270 nm (21,820). IR (KBr) ν 3398, 2929, and 1665 cm^{-1}. ^1H NMR (50°C, DMSO-d_6–5% D_2O, ref, DMSO: δ 2.49 ppm) δ 3.19 (1H, dd, J=3.7, 9.2 Hz), 3.3–3.8 (m), 3.89 (1H, t, J=9.2 Hz), 4.08 (1H, t, J=9.2 Hz), 4.25 (1H, dd, J=3.7, 9.2 Hz), 4.33 (1H, dd, J=3.7, 9.2 Hz), 4.89–4.91 (5H, m), 4.95 (1H, d, J=3.7 Hz), 5.18 (1H, d, J=3.7 Hz), 5.37 (1H, d, J=3.7 Hz), 7.92–7.98 (2H, m), 7.98 (2H, d, J=7.9 Hz), 8.05 (2H, d, J=7.9 Hz), 8.20 (1H, s), 8.24 (2H, d, J=7.9 Hz), 8.25 (1H, s), and 8.29 (2H, d, J=7.9 Hz). ^{13}C NMR (50°C, DMSO-d_6–5% D_2O, DMSO: δ 39.50 ppm) δ 59.41, 59.44, 59.68, 59.88, 60.00, 68.92, 69.16, 70.86, 71.25, 71.99, 72.14, 72.42, 72.50, 72.67, 73.27, 74.97, 79.75, 79.90, 80.51, 80.60, 80.79, 80.90, 80.96, 81.02, 94.75, 95.34, 100.55, 101.36, 101.60, 126.61, 128.37, 129.01, 129.21, 129.41, 129.80, 130.20, 130.74, 131.82, 134.30, 134.55, 135.31, 135.84, 137.48, 137.75, 139.31, 139.44, 193.20, and 193.88. MALDI-TOF-MS m/z 1729.8 for $[M+Na]^+$. Anal. Found: C, 47.46; H, 5.64%, Calcd for $C_{68}H_{90}O_{46}S_2$: C, 47.83; H, 5.31%.

Data for **5c**: R_f 0.38 (TLC on silica gel, MeCN–H_2O, 3:1). Mp 162°C (decomp). UV (H_2O) λ_{max} (ε) 268 nm (25,400). IR (KBr) ν 3398, 2930, and 1664 cm^{-1}. ^1H NMR (80°C, DMSO-d_6–5% D_2O, ref, DMSO: δ 2.49 ppm) δ 3.12 (1H, dd, J=3.1, 9.2 Hz), 3.20 (1H, t, J=9.2 Hz), 3.3–3.8 (m), 3.83 (1H, t, J=9.8 Hz), 3.90 (1H, t, J=9.8 Hz), 4.02 (1H, dd, J=3.7, 9.8 Hz), 4.55 (1H, dd, J=3.7, 9.8 Hz), 4.76 (1H, d, J=3.1 Hz), 4.89–4.92 (5H, m), 5.33 (1H, d, J=3.7 Hz), 5.41 (1H, d, J=3.7 Hz), 7.81 (1H, t, J=7.9 Hz), 7.84 (1H, t, J=7.9 Hz), 7.89 (2H, d, J=7.9 Hz), 7.95 (2H, d, J=7.9 Hz), 8.01 (1H, d, J=7.9 Hz), 8.06 (1H, s), 8.08 (1H, s), 8.13 (1H, d, J=7.9 Hz), 8.15 (1H, d, J=7.9 Hz), and 8.20 (1H, d, J=7.9 Hz). ^{13}C NMR (80°C, DMSO-d_6–5% D_2O, DMSO: δ 39.50 ppm) δ.59.19, 59.64, 59.87, 59.97, 60.10, 60.23, 68.24, 69.34, 71.23, 71.47, 71.91, 71.98, 72.17, 72.22, 72.34, 72.42, 72.53, 72.72, 72.76, 72.83, 72.90, 73.87, 75.36, 78.31, 78.64, 79.38, 80.41, 80.64, 80.83, 80.92, 81.17, 95.81, 97.47, 99.09, 101.32, 101.46, 101.55, 128.27, 128.55, 129.50, 129.67, 129.83, 130.15, 131.08, 131.13, 133.63, 134.08, 136.00, 137.35, 137.68, 138.67, 139.57, 140.12, 194.42, and 194.80. MALDI-TOF-MS m/z 1730.1 for $[M+Na]^+$. Anal. Found: C, 47.52; H, 5.61%, Calcd for $C_{68}H_{90}O_{46}S_2$: C, 47.83; H, 5.31%.

Data for **6c**: R_f 0.38 (TLC on silica gel, MeCN–H_2O, 3:1). Mp 165°C (decomp). UV (H_2O) λ_{max} (ε) 270 nm (25,350). IR (KBr) ν 3389, 2930, and 1663 cm^{-1}. ^1H NMR (40°C, DMSO-d_6–5% D_2O, ref, DMSO: δ 2.49 ppm) δ 3.2–3.7 (m), 3.77 (1H, t, J=9.2 Hz), 4.03 (1H, dd, J=3.7, 9.2 Hz), 4.38 (1H, dd, J=3.7, 9.8 Hz), 4.79 (d, J=3.1 Hz), 4.80–4.83 (4H, m), 4.93 (1H, d, J=3.7 Hz), 5.59 (1H, d, J=3.7 Hz), 5.81 (1H, d, J=3.7 Hz), 7.83 (1H, t, J=7.9 Hz), 7.87 (1H, t, J=7.9 Hz), 8.01 (2H, d, J=8.5 Hz), 8.03 (2H, d, J=8.5 Hz), 8.19–8.23 (5H, m), and 8.43 (1H, d, J=7.9 Hz). ^{13}C NMR (80°C, DMSO-d_6–5% D_2O, DMSO: δ 39.50 ppm) δ 59.30, 59.36, 59.72, 59.85, 59.98, 60.15, 60.53, 68.57, 68.80, 71.32, 71.53, 71.65, 71.83, 72.09, 72.22, 72.40, 72.49, 72.63, 72.78, 72.90, 73.03, 73.65, 73.98, 74.92, 76.78, 78.33, 78.90, 79.53, 79.55, 79.98, 80.17, 80.25, 81.01, 95.94, 97.31, 99.53, 99.91, 100.80, 101.04, 101.32, 101.60, 129.19, 129.55, 130.00, 130.11, 130.18, 130.41, 132.19, 132.40, 134.65, 135.11, 135.81, 136.81, 137.25, 137.55, 139.16, 140.02, 193.65, and 193.71. MALDI-TOF-MS m/z 1729.4 for $[M+Na]^+$. Anal. Found: C, 47.73; H, 5.64%, Calcd for $C_{68}H_{90}O_{46}S_2$: C, 47.83; H, 5.31%.

Data for **7**: R_f 0.38 (TLC on silica gel, MeCN–H_2O, 3:1). Mp 167°C (decomp). UV (H_2O) λ_{max} (ε) 271 nm (24,830). IR (KBr) ν 3398, 2931, and 1655 cm^{-1}. ^1H NMR (40°C, DMSO-d_6–5% D_2O, ref, DMSO: δ 2.56 ppm) δ 3.26 (1H, dd, J=3.7, 9.8 Hz), 3.30 (1H, dd, J=3.7, 9.8 Hz), 3.34 (1H, dd, J=3.1, 8.5 Hz), 3.4–3.8 (m), 4.19 (1H, dd, J=3.7, 9.8 Hz), 4.87 (7H, m), 6.00 (1H, d, J=3.7 Hz), 7.96 (2H, t, J=7.9 Hz), 8.10 (4H, s), 8.24 (2H, s), 8.34 (2H, d, J=7.9 Hz), and 8.38 (2H, d, J=7.9 Hz). ^{13}C NMR (40°C, DMSO-d_6–5% D_2O, DMSO: δ 39.50 ppm) δ 59.06, 59.39, 59.49, 60.48, 68.54, 71.10, 71.79, 72.29, 72.37, 72.62, 72.78, 72.90, 73.13, 73.31, 74.82, 78.84, 78.98, 79.54, 80.22, 95.71, 100.47, 100.57, 100.72, 129.39, 130.00, 130.28, 132.45, 134.70, 135.95, 136.89, 139.33, and 193.25. MALDI-TOF-MS m/z 1729.2 for $[M+Na]^+$. Anal. Found: C, 47.79; H, 5.45%, Calcd for $C_{68}H_{90}O_{46}S_2$: C, 47.83; H, 5.31%.

4.2.6. $2^A,3^A$:$2^B,3^B$-Dianhydro-($2^AS,3^AS$:$2^BS,3^BS$)-α-cyclodextrin (9a). To a solution of **4a** (0.050 g, 0.036 mmol) in a mixture of H_2O (1.0 mL) and MeOH (1.0 mL) was added 1.0 M aqueous NaOH (0.25 mL, 0.25 mmol) at room temperature. The mixture was stirred at 40°C for 5 h, then to the reaction mixture was added MeCN (10 mL). The mixture was applied to a silica gel column (ϕ 15×80 mm), eluting with MeCN, MeCN–H_2O (6:1), and then MeCN–H_2O (6:2), gave **9a** (0.020 g, 59%) as a colorless solid. ^1H and ^{13}C NMR spectral data of **9a** were identical with published authentic sample.[7c] ^1H NMR (40°C, D_2O, ref. acetone: 2.26) δ 3.47 (1H, d, J=3.7 Hz), 3.53 (1H, d, J=3.7 Hz), 3.60–4.12 (m), 5.07 (1H, d, J=3.1 Hz), 5.08 (1H, d, J=3.7 Hz), 5.10 (1H, d, J=3.7 Hz), 5.16 (1H, d, J=4.3 Hz), 5.33 (1H, s), and 5.38 (1H, s). ^{13}C NMR (40°C, D_2O, acetone: 31.22) δ 49.75, 50.31, 54.34, 54.54, 61.23, 61.48, 62.27, 62.47, 70.58, 70.97, 71.30, 71.45, 72.63, 72.66, 72.76, 73.01, 73.14, 73.57, 74.00,

74.18, 74.20, 81.86, 81.90, 81.96, 81.99, 97.79, 98.41, 101.52, 101.96, 101.99, and 102.38.

4.2.7. $2^A,3^A:2^C,3^C$-Di-manno-epoxy-α-cyclodextrin (10a). To a solution of **5a** (0.070 g, 0.051 mmol) in H_2O (1.0 mL) was added 1.0 M aqueous NaOH (0.33 mL, 0.33 mmol) at 0°C. The mixture was stirred at 0°C for 48 h, then to the reaction mixture was added MeCN (10 mL). The mixture was applied to a silica gel column (ϕ 15×80 mm), eluting with MeCN, MeCN–H_2O (6:1), and then MeCN–H_2O (6:2), gave **10a** (0.039 g, 82%) as a colorless solid. ^1H and ^{13}C NMR spectral data of **10a** were identical with published authentic sample.[7c] ^1H NMR (40°C, D_2O, ref. acetone: 2.26) δ 3.51 (1H, d, J=3.7 Hz), 3.53, (1H, d, J=3.7 Hz), 3.60–4.02 (m), 5.09 (1H, d, J=3.7 Hz), 5.10 (1H, d, J=3.7 Hz), 5.12 (1H, d, J=3.7 Hz), 5.12 (1H, d, J=3.7 Hz), 5.32 (1H, s), and 5.34 (1H, s). ^{13}C NMR (40°C, D_2O, acetone: 31.22) δ 49.73, 49.80, 53.94, 54.09, 54.50, 61.31, 61.36, 61.54, 62.28, 62.48, 71.07, 71.15, 71.28, 71.48, 71.51, 72.10, 72.62, 72.65, 72.73, 72.86, 72.95, 73.11, 73.36, 73.59, 73.88, 74.10, 81.52, 81.91, 98.28, 98.49, 102.06, 102.21, 102.36, and 102.51.

4.2.8. $2^A,3^A:2^D,3^D$-Di-manno-epoxy-α-cyclodextrin (11a). To a solution of **6a** (0.050 g, 0.036 mmol) in H_2O (1.0 mL) was added 1.0 M aqueous NaOH (0.23 mL, 0.23 mmol) at 20°C. The mixture was stirred at 20°C for 30 min, then to the reaction mixture was added MeCN (10 mL). The mixture was applied to a silica gel column (ϕ 15×80 mm), eluting with MeCN, MeCN–H_2O (6:1), and then MeCN–H_2O (6:2), gave **11a** (0.027 g, 79%) as a colorless solid. ^1H and ^{13}C NMR spectral data of **11a** were identical with published authentic sample.[7c] ^1H NMR (40°C, D_2O, ref. acetone: 2.26) δ 3.53 (2H, d, J=3.7 Hz), 3.60–4.02 (m), 5.11 (2H, d, J=3.7 Hz), 5.13 (2H, d, J=3.1 Hz), and 5.35 (2H, s). ^{13}C NMR (40°C, D_2O, acetone: 31.26) δ 49.52, 53.98, 61.26, 61.43, 62.61, 71.37, 71.51, 71.69, 72.65, 72.71, 73.17, 73.60, 73.98, 81.71, 82.03, 98.51, 102.18, and 102.39.

4.2.9. $2^A,3^A:2^B,3^B$-Di-manno-epoxy-β-cyclodextrin (9b). To a solution of **4b** (0.060 g, 0.039 mmol) in a mixture of H_2O (1.0 mL) and MeOH (1.0 mL) was added 1.0 M aqueous NaOH (0.28 mL, 0.28 mmol) at room temperature. The mixture was stirred at room temperature for 3 h, then to the reaction mixture was added MeCN (10 mL). The mixture was applied to a silica gel column (ϕ 15×80 mm), eluting with MeCN, MeCN–H_2O (6:1), and then MeCN–H_2O (6:2), gave **9b** (0.030 g, 70%) as a colorless solid. ^1H and ^{13}C NMR spectral data of **9b** were identical with published authentic sample.[8a] ^1H NMR (40°C, DMSO-d_6–5% D_2O, ref. DMSO: 2.49) δ 3.20 (1H, d, J=3.7 Hz), 3.25 (1H, d, J=3.1 Hz), 3.26–3.74 (m), 3.87 (1H, d, J=9.2 Hz), 4.80–4.84 (5H, m), 5.15 (1H, s), and 5.64 (1H, s). ^{13}C NMR (40°C, DMSO-d_6–5% D_2O, DMSO: 39.50) δ 48.43, 48.98, 53.35, 53.42, 59.69, 59.92, 60.00, 60.05, 60.71, 60.84, 69.00, 69.54, 69.72, 71.07, 72.02, 72.11, 72.27, 72.45, 72.80, 72.92, 73.01, 73.31, 79.79, 80.84, 81.62, 81.73, 81.81, 95.71, 97.03, 101.04, 101.55, 101.96, 101.99, and 102.08.

4.2.10. $2^A,3^A:2^C,3^C$-Di-manno-epoxy-β-cyclodextrin (10b). To a solution of **5b** (0.140 g, 0.0907 mmol) in H_2O (2.0 mL) was added 1.0 M aqueous NaOH (0.56 mL, 0.56 mmol) at 0°C. The mixture was stirred at 0°C for 5 h, then to the reaction mixture was added MeCN (10 mL). The mixture was applied to a silica gel column (ϕ 15× 80 mm), eluting with MeCN, MeCN–H_2O (6:1), and then MeCN–H_2O (6:2), gave **10b** (0.090 g, 90%) as a colorless solid. ^1H and ^{13}C NMR spectral data of **10b** were identical with published authentic sample.[8a] ^1H NMR (40°C, DMSO-d_6–5% D_2O, ref. DMSO: 2.49) δ 3.2–3.7 (m), 4.7–4.9 (5H, m), 5.08 (1H, s), and 5.09 (1H, s). ^{13}C NMR (40°C, DMSO-d_6–5% D_2O, DMSO: 39.50) δ 48.65, 48.81, 53.76, 53.81, 59.87, 59.95, 60.00, 60.33, 60.66, 60.72, 69.62, 70.07, 70.20, 70.51, 71.20, 71.79, 72.07, 72.19, 72.25, 72.49, 72.83, 72.90, 73.03, 73.51, 79.86, 79.99, 81.19, 81.55, 97.19, 97.28, 101.67, 101.75, 101.92, and 102.00.

4.2.11. $2^A,3^A:2^D,3^D$-Di-manno-epoxy-β-cyclodextrin (11b). To a solution of **6b** (0.070 g, 0.045 mmol) in H_2O (2.0 mL) was added 1.0 M aqueous NaOH (0.23 mL, 0.23 mmol) at 0°C. The mixture was stirred at 0°C for 5 h, then to the reaction mixture was added MeCN (10 mL). The mixture was applied to a silica gel column (ϕ 15× 80 mm), eluting with MeCN, MeCN–H_2O (6:1), and then MeCN–H_2O (6:2), gave **11b** (0.043 g, 86%) as a colorless solid. ^1H and ^{13}C NMR spectral data of **11b** were identical with published authentic sample.[8a] ^1H NMR (40°C, DMSO-d_6–5% D_2O, ref. DMSO: 2.49) δ 3.2–3.7 (m), 4.7–4.9 (5H, m), 5.10 (1H, s), and 5.10 (1H, s). ^{13}C NMR (40°C, DMSO-d_6–5% D_2O, DMSO: 39.50) δ 48.60, 48.70, 53.62, 59.83, 60.31, 60.61, 69.74, 69.89, 70.51, 70.64, 71.23, 71.38, 71.99, 72.05, 72.20, 72.24, 72.45, 72.55, 72.80, 72.85, 72.95, 73.42, 73.50, 79.76, 79.95, 80.99, 81.09, 81.29, 97.15, 101.55, 101.70, 101.75, 102.06, and 102.21.

4.2.12. $2^A,3^A:2^B,3^B$-Di-manno-epoxy-γ-cyclodextrin (9c). To a solution of **4c** (0.044 g, 0.026 mmol) in H_2O (1.0 mL) was added 1.0 M aqueous NaOH (0.10 mL, 0.10 mmol) at 0°C. The mixture was stirred at 0°C for 5 h, then to the reaction mixture was added MeCN (10 mL). The mixture was applied to a silica gel column (ϕ 15× 80 mm), eluting with MeCN, MeCN–H_2O (6:1), and then MeCN–H_2O (6:2), gave **9c** (0.023 g, 72%) as a colorless solid. ^1H and ^{13}C NMR spectral data of **9c** were identical with published authentic sample.[8d] ^1H NMR (40°C, D_2O, ref. acetone: 2.26) δ 3.49 (1H, d, J=3.7 Hz), 3.53 (1H, d, J=3.7 Hz), 3.60–4.00 (m), 4.05 (1H, d, J=8.5 Hz), 5.14–5.19 (6H, m), 5.35 (1H, s), and 5.40 (1H, s). ^{13}C NMR (40°C, D_2O, acetone: 31.22) δ 50.44, 50.77, 55.41, 55.46, 61.13, 61.28, 61.76, 69.51, 70.03, 70.15, 72.09, 72.62, 72.68, 72.78, 73.16, 73.30, 73.34, 73.41, 73.68, 73.93, 79.82, 80.58, 80.74, 80.91, 81.29, 81.32, 96.62, 98.02, 100.73, 101.92, 102.06, 102.11, 102.41, and 102.47.

4.2.13. $2^A,3^A:2^C,3^C$-Di-manno-epoxy-γ-cyclodextrin (10c). To a solution of **5c** (0.164 g, 0.0961 mmol) in H_2O (3.0 mL) was added 1.0 M aqueous NaOH (0.40 mL, 0.40 mmol) at 0°C. The mixture was stirred at 0°C for 1 h, then to the reaction mixture was added MeCN (20 mL). The mixture was applied to a silica gel column (ϕ 15× 80 mm), eluting with MeCN, MeCN–H_2O (6:1), MeCN–H_2O (6:2), and then MeCN–H_2O (6:3), gave **10c** (0.096 g, 79%) as a colorless solid.

Data for **10c**: R_f 0.50 (TLC on silica gel, MeCN–H_2O-28%

aqueous NH_3, 3:2:1). Mp 230°C (decomp). IR (KBr) ν 3397, 2931, and 1638 cm^{-1}. ^1H NMR (40°C, D_2O, ref. acetone: δ 2.26 ppm) δ 3.52 (1H, d, J=4.3 Hz), 3.53 (1H, d, J=4.9 Hz), 3.6–4.0 (m), 5.14–5.21 (6H, m), 5.33 (1H, s), and 5.34 (1H, s). ^{13}C NMR (40°C, D_2O, ref. acetone: δ 31.22 ppm) δ 50.39, 50.52, 55.17, 55.19, 61.15, 61.25, 61.33, 61.81, 61.91, 69.46, 70.07, 70.23, 71.96, 72.17, 72.50, 72.60, 72.65, 72.75, 72.99, 73.21, 73.24, 73.41, 73.75, 73.88, 73.95, 79.39, 80.04, 80.82, 80.91, 81.20, 97.64, 98.16, 100.30, 100.81, 102.01, 102.18, and 102.33. MALDI-TOF-MS m/z 1283.1 for $[M+Na]^+$. Anal. Found: C, 45.48; H, 6.42%, Calcd for $C_{48}H_{76}O_{38}$: C, 45.72; H, 6.07%.

4.2.14. $3^A,3^C$-Diamino-$3^A,3^C$-dideoxy-($2^AS,2^CS,3^AS,3^CS$)-α-cyclodextrin (12a). A solution of **5a** (0.180 g, 0.130 mmol) in 28% aqueous NH_3 (4.0 mL) was kept with stopple at 40°C for 7 days. The mixture was concentrated, and the residue was dissolved in water, then the solution was applied to a Sephadex-CM C-25 column. Eluting with water and 1.0 M aqueous NH_3 gave fractions of **12a**, and the fractions were concentrated in vacuuo to give pure **12a** (0.116 g, 92%) as a colorless solid. ^1H and ^{13}C NMR spectral data of **12a** were identical with published authentic sample.[23a] ^1H NMR (40°C, DMSO-d_6–5% D_2O, ref. DMSO: 2.49) δ 2.64 (1H, dd, J=10.6, 3.1 Hz), 2.70 (1H, dd, J=10.1, 3.4 Hz), 3.2–4.0 (m), 4.52 (1H, d, J=7.3 Hz), 4.58 (1H, d, J=6.1 Hz), 4.73 (1H, d, J=3.7 Hz), 4.76 (2H, d, J=3.1 Hz), and 4.80 (1H, d, J=3.1 Hz). ^{13}C NMR (40°C, DMSO-d_6–5% D_2O, ref. DMSO: 39.50) δ 52.07, 53.19, 59.39, 60.00, 60.11, 60.30, 60.45, 60.51, 71.58, 71.81, 71.88, 72.05, 72.11, 72.21, 72.42, 72.68, 72.90, 73.00, 73.05, 73.26, 73.32, 73.75, 75.99, 78.03, 79.59, 79.87, 80.28, 81.04, 81.39, 82.42, 101.03, 101.39, 102.25, 102.34, 104.01, and 105.14.

4.2.15. $3^A,3^C$-Diamino-$3^A,3^C$-dideoxy-($2^AS,2^CS,3^AS,3^CS$)-β-cyclodextrin (12b). A solution of **5b** (0.440 g, 0.285 mmol) in 28% aqueous NH_3 (8.0 mL) was kept with stopple at 40°C for 7 days. The same procedure as for **12a** gave **12b** (0.255 g, 79%) as a colorless solid.

Data for **12b**: R_f 0.22 (TLC on silica gel, MeCN–H_2O-28% aqueous NH_3, 3:2:1). Mp 220°C (decomp). IR (KBr) ν 3374 and 2928 cm^{-1}. ^1H NMR (50°C, DMSO-d_6–5% D_2O, ref. DMSO: δ 2.49 ppm) δ 2.70 (1H, dd, J=3.7, 10.1 Hz), 2.76 (1H, dd, J=3.7, 9.8 Hz), 3.2–4.0 (m), 4.53 (1H, d, J=6.9 Hz), 4.54 (1H, d, J=6.7 Hz), 4.74 (1H, d, J=3.7 Hz), 4.78 (1H, d, J=3.7 Hz), 4.79 (1H, d, J=4.3 Hz), 4.81 (1H, d, J=3.7 Hz), and 4.82 (1H, d, J=3.7 Hz). ^{13}C NMR (50°C, DMSO-d_6–5% D_2O, ref. DMSO: δ 39.50 ppm) δ 52.55, 53.15, 59.67, 59.90, 60.06, 71.38, 71.66, 71.95, 72.06, 72.22, 72.30, 72.40, 72.50, 72.70, 72.81, 73.01, 73.10, 73.39, 76.35, 76.53, 78.13, 79.31, 80.18, 80.28, 81.22, 81.43, 81.81, 101.13, 101.55, 101.83, 101.90, 102.08, 104.01, and 104.17. MALDI-TOF-MS m/z 1133.3 for $[M+1]^+$. Anal. Found: C, 44.22; H, 6.75; N, 2.15%, Calcd for $C_{42}H_{72}N_2O_{33}$: C, 44.52; H, 6.41; N, 2.47%.

4.2.16. $3^A,3^C$-Diamino-$3^A,3^C$-dideoxy-($2^AS,2^CS,3^AS,3^CS$)-γ-cyclodextrin (12c). A solution of **5c** (0.399 g, 0.234 mmol) in 28% aqueous NH_3 (6.0 mL) was kept with stopple at 40°C for 7 days. The same isolation procedure as for **12a** gave **12c** (0.288 g, 95%) as a colorless solid.

Data for **12c**: R_f 0.18 (TLC on silica gel, MeCN–H_2O-28% aqueous NH_3, 3:2:1). Mp 230°C (decomp). IR (KBr) ν 3376 and 2930 cm^{-1}. ^1H NMR (40°C, DMSO-d_6–5% D_2O, ref. DMSO: δ 2.49 ppm) δ 2.74 (1H, dd, J=3.1, 9.2 Hz), 2.95 (1H, t, J=4.3 Hz), 3.2–3.8 (m), 4.55 (1H, d, J=6.7 Hz), 4.60 (1H, d, J=3.7 Hz), 4.74 (1H, d, J=3.7 Hz), 4.76 (1H, d, J=3.7 Hz), and 4.83–4.87 (4H, m). ^{13}C NMR (40°C, DMSO-d_6–5% D_2O, DMSO: δ 39.50 ppm) δ 51.53, 52.78, 59.60, 59.74, 59.95, 60.08, 60.92, 69.79, 71.53, 71.86, 72.04, 72.16, 72.30, 72.44, 72.63, 72.72, 72.98, 74.00, 77.91, 78.60, 79.72, 80.89, 80.97, 81.04, 99.51, 101.49, 101.62, 101.70, 101.78, 102.23, and 103.64. MALDI-TOF-MS m/z 1317.4 for $[M+Na]^+$. Anal. Found: C, 44.45; H, 6.64; N, 1.83%, Calcd for $C_{48}H_{82}N_2O_{38}$: C, 44.51; H, 6.38; N, 2.16%.

Acknowledgements

Author thanks Grant-in-Aid for Scientific Research on Priority Areas (A) (No. 13024241) and Grant-in-Aid for Scientific Research (C) (No. 14560082) from the Japanese Ministry of Education, Science, and Culture. The NMR instrument used in this research was installed at the Cooperative Research Center of Mie University.

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