(17 mL) was stirred at 0 °C while NaHMDS (13.0 mmol) was added. The resulting solution was stirred for 15 min and then cooled to -78 °C. A solution of the aldehyde **21** (0.83 g, 2.2 mmol) in THF (8 mL) was added dropwise and stirring continued cold for 1 h and then at rt for 17 h. The mixture was diluted with ether (100 mL) and washed with NH_4Cl(aq) (40 mL) and brine (40 mL), and the organic layer was dried and evaporated to leave a semisolid (5.3 g). Chromatography eluting with 50:1 hexane–EtOAc gave the alkene **22** as a pale yellow oil (0.84 g, 99%): ^{1}H NMR δ 5.99 (1 H, m), 5.56 (1 H, ddd, J = 10, 5, and 3), 5.37 (1 H, br d, J = 10), 5.28 (1 H, dqd, J = 11, 7, and 1.1), 4.36 (1 H, m), 4.10 (2 H, m), 2.88 (2 H, m), 2.80 (2 H, dd, J = 12 and 6), 2.57 (2 H, m), 1.78 (1 H, m), 1.70 (1 H, ddd, J = 14, 5, and 3), 1.60 (1 H, m), 1.58 (3 H, dd, J = 7 and 1.8), 1.51 (1 H, td, J = 12 and 2), 1.36 (1 H, td, J = 13 and 5), 1.26 (3 H, t, J = 7), 0.87 (9 H, s), 0.86 (3 H, d, J = 7), 0.00 (3 H, s), and -0.09 (3 H, s).

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1-(*tert*-Butyldimethylsiloxy)-1,2,3,4,4a,7,8,8a-octahydro-8-(hydroxymethyl)-7-methyl-3-[(*Z*)-prop-1-enyl]naphthalene (23). The ester **22** (0.19 g, 0.48 mmol) was stirred in THF (20 mL), and $LiEt_3BH$ (1.0 mmol) was added. The mixture was warmed to 80 °C and stirred for 6 h, while more $LiEt_3BH$ (1.0 mmol/h), was added. The temperature was lowered to 0 °C, and water (1 mL) was cautiously added, followed by 3 M NaOH(aq) (2 mL) and 30% H_2O_2 (2 mL). The resulting gel was stirred at rt for 2 h and then poured onto brine (15 mL) and extracted with ether (2 × 20 mL). The combined ethereal solutions were dried and evaporated. Chromatography eluting with 25:1 hexane–EtOAc gave the alcohol **23** as a colorless oil (0.12 g, 71%): ^{1}H NMR δ 5.99 (1 H, m), 5.64 (1 H, ddd, J = 10, 5, and 1.6), 5.36 (1 H, br d, J = 10), 5.30 (1 H, dqd, J = 10, 7, and 1), 4.01 (1 H, m), 3.90 (1 H, m), 3.49 (1 H, td, J = 11 and 6), 2.83 (1 H, m), 2.54 (2 H, m), 2.02 (1 H, tt, J = 11 and 5), 1.79 (1 H, ddd, J = 14, 5, and 1.9), 1.6 (2 H, m), 1.58 (3 H, dd, J = 7 and 1.9), 1.32 (1 H, td, J = 13 and 5), 1.13 (1 H, td, J = 11 and 2), 1.00 (1 H, s, removed by D_2O), 0.96 (3 H, d, J = 7), 0.91 (9 H, s), 0.08 (3 H, s), and 0.07 (3 H, s).

(1*S*,3*S*,4a*R*,6*S*,8*S*,8a*S*)-1,2,3,4,4a,7,8,8a-Octahydro-1-hydroxy-8-(hydroxymethyl)-7-methyl-3-[(*Z*)-prop-1-enyl]-naphthalene (24). The alcohol **23** (0.54 g, 1.54 mmol) was stirred at rt in 19:1 CH_3CN/40% aqueous HF (15 mL) for 15 h. Ether (150 mL) was added followed by Na_2CO_3(aq) (50 mL). The ethereal solution was separated and dried and the solvent removed to give the diol as an off-white solid (0.35 g, 97%). A small sample was recrystallized from hexane–CH_2Cl_2 for analysis: mp 131–133 °C; IR ν_{max} (CH_2Cl_2 soln) 3620 and 3495 cm^{-1}; ^{1}H NMR δ 6.00 (1 H, m), 5.56 (1 H, ddd, J = 10, 5, and 2.6), 5.43 (1 H, dqd, J = 11, 7, and 1.4), 5.37 (1 H, br d, J = 10), 4.24 (1 H, m), 3.76 (1 H, t, J = 10), 3.65 (1 H, dd, J = 10 and 1.4), 2.88 (1 H, m), 2.76 (1 H, br s, removed by D_2O), 2.53 (1 H, m), 2.41 (1 H, br s, removed by D_2O), 2.40 (1 H, m), 2.03 (1 H, m), 1.95 (1 H, m), 1.80 (1 H, ddd, J = 14, 6, and 3), 1.63 (3 H, dd, J = 7 and 1.8), 1.6 (1 H, m), 1.33 (1 H, td, J = 13 and 5), 1.30 (1 H, td, J = 11 and 2), and 0.82 (3 H, d, J = 7). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 75.93; H, 10.06.

Methyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*,3′*R*,2″*S*)-3′-(*tert*-Butyldimethylsiloxy)-7′-[2-methyl-8-[(2″-methylbutyryl)oxy]-1,2,4a,5,6,7,8,8a-octahydro-6-[(*Z*)-prop-1-enyl]-1-naphthalenyl]-5′-oxohept-6′-enoate (40d). The aldehyde **39d** was obtained from the diol **24** by protection of the primary alcohol, acylation of the secondary alcohol, deprotection of the primary alcohol, and oxidation to give the product as an oil: ^{1}H NMR δ 9.74 (1 H, d, J = 2), 5.79 (1 H, br t, J = 10), 5.62 (1 H, m), 5.42 (1 H, br d, J = 10), 5.36 (2 H, m), 2.91 (1 H, m), 2.70 (2 H, m), 2.52 (1 H, br t, J = 12), 2.30 (1 H, sextet, J = 7), 1.59 (3 H, dd, J = 7 and 1.5), 2.05–1.35 (7 H, m), 1.13 (3 H, d, J = 7), 0.97 (3 H, d, J = 7), and 0.88 (3 H, t, J = 7).

The aldehyde **39d** (91 mg, 0.29 mmol), the keto phosphonate[13a,22] **36** (160 mg, 0.42 mmol), and LiCl (18 mg, 0.42 mmol) were stirred at rt in CH_3CN (0.22 mL), and DBU (0.055 mL, 0.37 mmol) was added. The mixture was stirred at rt for 80 h, diluted with EtOAc (25 mL), and washed with 0.5 M H_3PO_4(aq) (10 mL) and brine (10 mL). The combined aqueous layers were extracted with EtOAc (25 mL), and the combined organic layers were dried and evaporated. Chromatography eluting with 19:1 hexane–EtOAc gave the enone **40d** as a colorless oil (32 mg, 20%); ^{1}H NMR δ 6.78 (1 H, dd, J = 16 and 10), 5.98 (1 H, d, J = 16), 5.74 (1 H, m), 5.61 (1 H, ddd, J = 10, 5, and 3), 5.42 (1 H, br d, J = 10), 5.30 (1 H, dq, J = 11 and 7), 4.88 (1 H, m), 4.58 (1 H, m), 3.63 (3 H, s), 2.89 (1 H, br s), 2.75 (2 H, m), 2.7–2.4 (4 H, m), 2.31 (1 H, m), 2.26 (1 H, sextet, J = 7), 1.55 (3 H, dd, J = 7 and 1.5), 2.1–1.3 (7 H, m), 1.11 (3 H, d, J = 7), 0.95 (3 H, d, J = 7), 0.85 (3 H, t, J = 7), 0.83 (9 H, s), 0.06 (3 H, s), and 0.02 (3 H, s).

(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*,4′*R*,6′*R*,2″*S*)-6′-{2-[1,2,4a,5,6,7,8,8a-Octahydro-2-methyl-8-[(2″-methylbutyryl)oxy]-6-[(*Z*)-prop-1-enyl]-1-naphthalenyl]ethyl}-tetrahydro-4′-hydroxy-2′*H*-pyran-2′-one (5). Using methods similar to those described above the enone **40d** was converted to **5**, obtained as an oil: ^{1}H NMR δ 5.78 (1 H, m), 5.63 (1 H, m), 5.38 (1 H, br d), 5.33 (1 H, m), 5.20 (1 H, m), 4.60 (1 H, m), 4.38 (1 H, m), 2.87 (1 H, m), 2.74 (1 H, dd, J = 18 and 5), 2.60 (1 H, dd, J = 18 and 4), 2.51 (1 H, br t, J = 11), 1.57 (3 H, dd, J = 7 and 1.7), 2.4–1.2 (17 H, m), 1.11 (3 H, d, J = 7), 0.88 (3 H, t, J = 7), and 0.86 (3 H, d, J = 7).

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Supplementary Material Available: ^{1}H NMR spectra of the analogues **3**, **4**, and **5** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Preparation and Enzymatic Structure Determination of a Complete Set of 2^A,6^X-Bis-*O*-(sulfonyl)-β-cyclodextrins

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2^A,6^X-Bis-*O*-(mesitylsulfonyl)-β-cyclodextrins (X = A–G) were prepared by the reaction of 2-*O*-(mesitylsulfonyl)-β-cyclodextrin with mesitylenesulfonyl chloride in pyridine. All regioisomers were isolated and their structures determined.

Bifunctionalization of cyclodextrins has attracted much attention with respect to the construction of artificial enzymes or receptors.[2] In this regard, it is usually necessary for the hydroxy groups of the cyclodextrins to be activated

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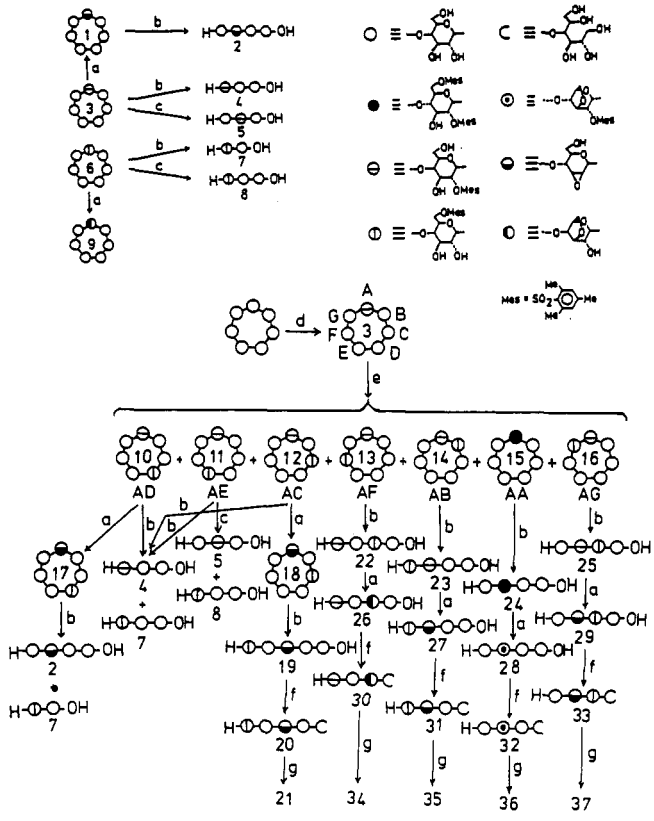
Scheme I[a]



[a] Key: (a) NaOH (pH 12); (b) Taka amylase A (TAA); (c) α-amylase (succharifying type) of *Bacillus subtillus* var. *amylosaccharitiicus* (BSA); (d) (1) $(C_4H_9)_2SnO$ in dry DMF, (2) Et_3N, (3) MesCl; (e) MesCl in pyridine; (f) $NaBH_4$; (g) Ac_2O/pyridine.

prior to their functionalization. Because of this requirement, the regiospecific disulfonylation of cyclodextrins has become important. Previously, regiospecific transannular disulfonylation was successfully accomplished by Tabushi et al.[3a-d] resulting in the activation of two primary hydroxyl groups (6-OH) of β-cyclodextrin. Furthermore, $6^A,6^X$-Di-*O*-sulfonylation followed by the effective isolation of each regioisomer was reported with α-,[4] β-,[5] and γ-cyclodextrins[6] by Fujita et al. With respect to disulfonylation of the secondary hydroxyl group (2-OH or 3-OH), there are a few reports in the literature; $2^A,2^X$-di-*O*-sulfonylation of cyclodextrins[7] and $3^A,3^X$-di-*O*-sulfonylation of β-cyclodextrin[8] were reported by Fujita et al. Since the two

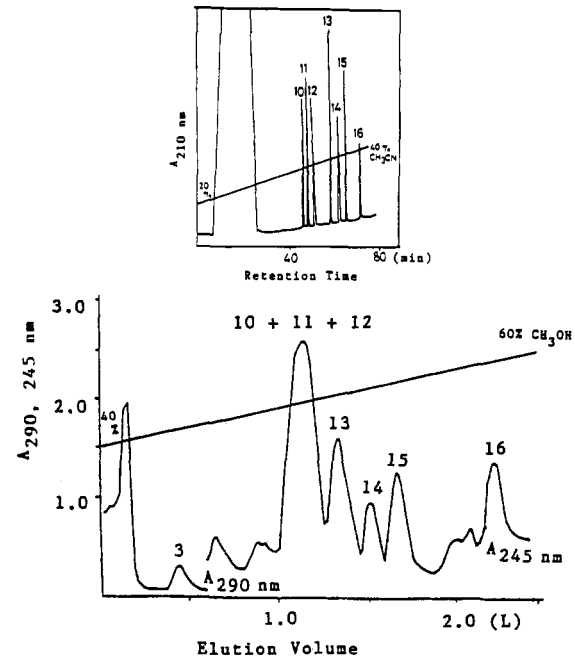


Figure 1. Reversed-phase column chromatography of the mixture of disulfonates **10–16**. A linear gradient elution of CH_3OH was applied. Inset: Reversed-phase HPLC of the same mixture. A linear gradient elution of CH_3CN was applied.

sulfonylated hydroxyls in these systems are located on the same side of the cyclodextrin torus, the artificial enzymes or receptors derived from these disulfonylcyclodextrins possess two functional groups on the same side of the substrate-binding pockets (the cavities of cyclodextrins). In order to broaden the scope of studies on the construction of artificial enzymes and receptors, a method must be developed which enables two functional groups to be located on opposite sides of the pocket with respect to each other. This goal can be attained by the regiospecific preparation of 2^A(or 3^A),6^X-di-*O*-sulfonylated cyclodextrins.

Recently, we issued a preliminary report on the preparation and isolation of $3^A,6^X$-bis-*O*-(arylsulfonyl)-α-cyclodextrins (X = A–F) and the partial determination of their regiochemical structures.[9]

However, since the 3-*O*-sulfonate does not easily react with nucleophiles and since the $2^A,3^A$-alloepoxide derived from the 3-*O*-sulfonate does not give a sole product in the reaction with a nucleophile,[10] the $3^A,6^X$-di-*O*-sulfonates may not necessarily be appropriate starting materials for the preparation of bifunctional cyclodextrins.

We describe herein the preparation and structure determination of $2^A,6^X$-bis-*O*-(mesitylsulfonyl)-β-cyclodextrins (X = A–G), whose sulfonylated hydroxyl groups are located on opposite sides of the cyclodextrin cavity with respect to each other. Also, since the $2^A,3^A$-mannoepoxide derived from the 2-*O*-sulfonate produces mainly one product in the reaction with a nucleophile,[11] the present $2^A,6^X$-di-*O*-sulfonates have proven to be more desirable for the stated goal.

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Results and Discussion

Preparation and Isolation of $2^A,6^X$-Bis-*O*-(mesitylsulfonyl)-β-cyclodextrins (10–16). The starting material, 2-*O*-(mesitylsulfonyl)-β-cyclodextrin (3) was prepared by the reaction of β-cyclodextrin with dibutyltin oxide and mesitylenesulfonyl chloride according to the reported procedure.[12]

A mixture of $2^A,6^X$-bis-*O*-(mesitylsulfonyl)-β-cyclodextrins (10–16, X = A–G) was prepared by the reaction of 2-*O*-(mesitylsulfonyl)-β-cyclodextrin (3) with mesitylenesulfonyl chloride in pyridine (Scheme I). The two arylsulfonyl groups in 10–16 were selected from among phenylsulfonyl, *p*-tosyl, mesitylsulfonyl, 1-naphthylsulfonyl, and 2-naphthylsulfonyl groups to give the best resolution in reversed-phase column chromatography as described below. Each regioisomer was effectively separated from the other by reversed-phase HPLC. The numbers of the compounds (10–16) were assigned in order of increasing retention time in reversed-phase HPLC (Figure 1). Reversed-phase column chromatography gave 13 (3.1%), 14 (2.0%), 15 (2.7%), 16 (2.2%), and a mixture (10–12) (10.4%) (Figure 1). The compounds 10 (2.1%), 11 (1.6%), and 12 (1.3%) were each isolated by preparative HPLC of the mixture.

Structure Determination of $2^A,6^X$-Bis-*O*-(mesitylsulfonyl)-β-cyclodextrins (10–16). The compounds were shown to be $2^A,6^X$-di-*O*-sulfonates by the fast-atom-bombardment mass (FABMS) spectra. The positions of the two sulfonylations were determined on the basis of the following results (i–iii) (Scheme I). (i) Enzymatic hydrolysis of 2-*O*-(arylsulfonyl)-β-cyclodextrin 3 by Taka amylase A (TAA) or α-amylase (succharifying type) of *Bacillus subtilis* var. *amylosaccharitiicus* (BSA)[13] gives 2″-*O*-(arylsulfonyl)maltotriose 4[14] or 2′-*O*-(arylsulfonyl)-maltotriose 5,[15] respectively, as main products. (ii) Enzymatic hydrolysis of 6-*O*-(arylsulfonyl)-β-cyclodextrin 6 by TAA or BSA gives, respectively, 6′-*O*-(arylsulfonyl)-maltose 7[14] or 6″-*O*-(arylsulfonyl)maltotriose 8,[15] respectively, as main products. (iii) On treatment with aqueous alkali, 2-*O*-(arylsulfonyl)-β-cyclodextrin 3 and 6-*O*-(arylsulfonyl)-β-cyclodextrin 6 are converted to (2*S*)-2,3-anhydro-β-cyclodextrin (1)[11a,16] and 3,6-anhydro-β-cyclodextrin (9),[17b] respectively. Compound 1 is hydrolyzed by TAA to give (2″*S*)-2″,3″-anhydromaltotetraose (2).[14]

Structures of 10–12. The disulfonates 10–12 were hydrolyzed by TAA to afford 4 and 7. Furthermore, only 11 gave 5 and 8 in the enzymatic hydrolysis by BSA. Therefore, 11 is the $2^A,6^E$-di-*O*-sulfonate,[18] and 10 or 12 is either the $2^A,6^C$-di-*O*-sulfonate or the $2^A,6^D$-di-*O*-sulfonate.

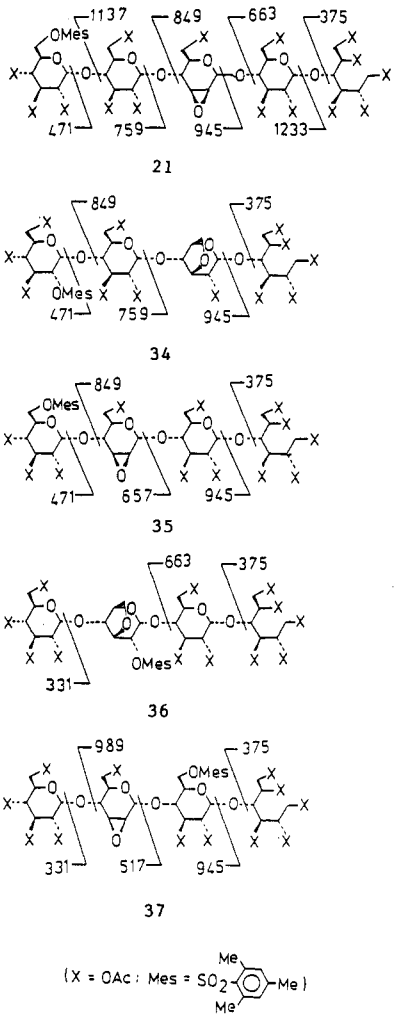

Figure 2. FABMS spectral fragmentation patterns of 21 and 34–37.

The disulfonates (10 and 12) were treated with aqueous alkali (pH 12) to give the 2,3-anhydro derivatives 17 and 18, respectively. The 2,3-anhydrations were confirmed by the FABMS and ^{13}C NMR spectra where the characteristic absorptions of epoxy ring carbons were observed at 55.1 and 50.3 ppm for 17 and at 55.2 and 50.3 ppm for 18. The TAA-catalyzed hydrolysis of 17 gave 2 and 7, demonstrating that 10 is the $2^A,6^D$-di-*O*-sulfonate. On the other hand, the TAA-catalyzed hydrolysis of 18 gave 19, which was reduced with aqueous $NaBH_4$ to afford 20. Complete acetylation of 20 with acetic anhydride/pyridine followed by FABMS spectral fragmentation analysis demonstrated that the 2,3-anhydration was located on the third glucose unit from the nonreducing end in 21 (Figure 2). Therefore, 12 is the $2^A,6^C$-di-*O*-sulfonate.

Structures of 13–16. Maltotetraose derivatives 22–25 were obtained by TAA-catalyzed hydrolysis of 13–16, respectively. These results are in accord with the expectation based on the TAA action patterns described in i and ii, except for the case of the disulfonates 15 and 16 which are expected to give a bis(mesitylsulfonyl)moltotriose. Reaction of the maltotetraose derivatives with aqueous NaOH (pH 12) gave (mesitylsulfonyl)anhydromaltotetraose (26–29), the structures of which were confirmed by the FABMS and ^{13}C NMR spectra. Since characteristic absorptions of the epoxy ring carbons in the ^{13}C NMR spectra were observed at 55.5 and 52.3 ppm for 27 and at 56.0 and 52.3 ppm for 29, the compounds 27 and 29 are (mesityl-

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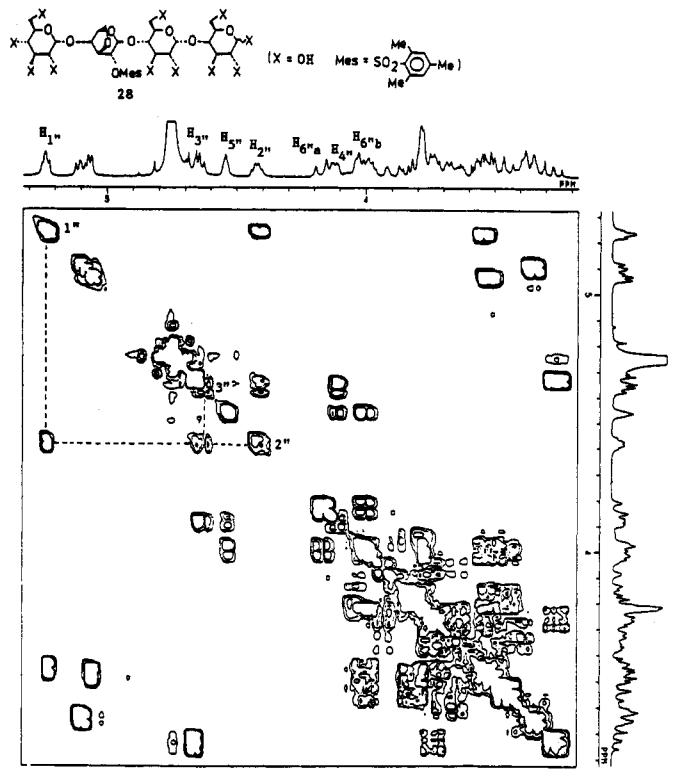

Figure 3. ^{1}H COSY NMR spectrum of **28**.

sulfonyl)-2,3-anhydromaltotetraoses. On the other hand, **26** and **28** are (mesitylsulfonyl)-3,6-anhydromaltotetraoses since such characteristic absorptions were not observed for these compounds.[9,17]

The (mesitylsulfonyl)anhydromaltotetraoses were reduced with aqueous $NaBH_4$ to **30–33**, which were completely acetylated and then analyzed by FABMS spectra. The results of these analyses are summarized in Figure 2, demonstrating that the anhydrations are located on the third, second, second, and second glucose units from the nonreducing end in **34–37**, respectively. It is therefore concluded that **13–16** are the $2^A,6^F$-, $2^A,6^B$-, $2^A,6^A$-, and $2^A,6^G$-disulfonates, respectively.

The ^{1}H NMR and ^{1}H COSY NMR spectra confirmed the structure of **28** (Figure 3). Each one of the absorptions due to $H_{1''}$, $H_{2''}$, $H_{3''}$, $H_{4''}$, $H_{5''}$, $H_{6''a}$, and $H_{6''b}$ in the ^{1}H NMR spectrum was assigned by the ^{1}H COSY NMR spectrum and by comparing their chemical shifts and coupling patterns with those of methyl 3,6-anhydro-α-D-glucoside.[17b] The chemical shift of $H_{2''}$ (4.43 ppm) was lower by 0.49 ppm than that of methyl 3,6-anhydro-α-D-glucoside,[17b] demonstrating that the sulfonyl group is located at the 2″-OH. This fact implies that **24** was converted to 2″-*O*-(mesitylsulfonyl)-3″,6″-anhydromaltotetraose (**28**), and not to 6″-*O*-(mesitylsulfonyl)-2″,3″-anhydromaltotetraose.

Thus, we were able to obtain all (seven) regioisomers of $2^A,6^X$-bis-*O*-(sulfonyl)-β-cyclodextrin with two activating groups situated on opposite sides of their cavities, thus introducing a new aspect in the studies on construction of artificial enzymes and receptors with novel properties of molecular recognition and catalysis. Furthermore, the present study suggests the possibility of wide application of BSA to the structure determinations of variously substituted cyclodextrins.

Experimental Section

General. ^{13}C and ^{1}H NMR spectra were determined with a JEOL FX 100 (25 MHz) and a JEOL FX 270 (270 MHz) spectrometer, respectively. Fast-atom-bombardment and field-desorption mass (FABMS and FDMS) spectra were recorded with a JEOL, JMS DX-300, DX-303 data system. Merck Lobar prepacked columns of Rp18 (A, 10 × 240 mm and B, 25 × 310 mm) and Rp8 (C, 37 × 440 mm) were used for reversed-phase column chromatography. HPLC was performed on a Hitachi L-3000 instrument with a column (4.6 × 250 mm) of TSKgel ODS-80TM (5 μm, TOSOH) for analysis or with a column (20 × 150 mm) of Cosmosil $10C_{18}$ (10 μm, Nacalai) for preparative separation. Thin-layer chromatography (TLC) was run with precoated silica gel plates (Merck, Art. No. 5554). Spot detection was carried out by UV light and/or staining with 0.1% 1,3-naphthalenediol in $EtOH/H_2O/H_2SO_4$ (200/157/43 (v/v/v)). The elution solvent for TLC was n-C_3H_7OH/AcOEt/H_2O (7/7/5 (v/v/v)). TAA was purchased from Sigma (α-amylase Type X-A). BSA was obtained from Ueda Chemical Industries Co., Ltd.

2-*O*-(Mesitylsulfonyl)-β-cyclodextrin (3). The title compound was prepared from β-cyclodextrin according to the reported procedure.[12]

$2^A,6^X$-Bis-*O*-(mesitylsulfonyl)-β-cyclodextrins (10–16). A mixture of 2-*O*-(mesitylsulfonyl)-β-cyclodextrin (**3**) (550 mg) and mesitylenesulfonyl chloride (1.37 g) in pyridine (20 mL) was stirred at room temperature for 15 min. Since the amount of the sulfonyl chloride and the reaction time were dependent on the dryness of the pyridine and β-cyclodextrin, the reaction should be monitored with silica gel TLC. After water (1 mL) was added, the mixture was concentrated in vacuo, dissolved in aqueous 30% methanol (500 mL), filtered, and chromatographed on column B with gradient elution from aqueous 40% methanol (1 L) to aqueous 60% methanol (1 L) to give a mixture of **10–12** (65 mg, 10.4%), **13** (19.1 mg, 3.1%), **14** (12.6 mg, 2.0%), **15** (17 mg, 2.7%), and **16** (13.5 mg, 2.2%) (see Figure 2). Each component of the mixture (**10**, 13.0 mg, 2.1%; **11**, 9.8 mg, 1.6%; **12**, 8.2 mg, 1.3%) was isolated by preparative HPLC with elution of aqueous 30% CH_3CN at flow rate 1.0 mL/min; the retention times; **10**, 71 min; **11**, 80 min; **12**, 94 min.

Enzymatic Hydrolysis of 10–16 by Taka Amylase A. A solution of each disulfonate **10–12** (5.5 mg) and TAA (16.5 mg) in 1 mL of 0.2 M acetate buffer (pH 5.5) containing 0.01 M $CaCl_2$ was kept at 40 °C for 2 d. After being immersed in boiling water for 10 min, the mixture was filtered and analyzed by HPLC with gradient elution from aqueous 20% CH_3CN (30 mL) to aqueous 50% CH_3CN (30 mL); the retention times (flow rate; 0.5 mL/min): **4**, 18 min; **7**, 41 min. The sulfonates **4** and **7** were isolated by HPLC on the analytical column and analyzed by FABMS: m/z **4** 687 ($M + H^+$), 709 ($M + Na^+$), 725 ($M + K^+$), **7** 547 ($M + H^+$).

A solution obtained from **13** (50 mg) according to the enzymatic reaction described above was chromatographed on column A with elution of aqueous 10% methanol (100 mL) and then gradient elution from aqueous 30% methanol (500 mL) to aqueous 70% methanol (500 mL) to give **22** (19.3 mg, 56.0%). Similarly, **14** (78.0 mg), **15** (100.0 mg), and **16** (26.5 mg) gave **23** (34.2 mg, 63.7%), **24** (54.3 mg, 78.9%), and **25** (5.8 mg, 31.8%), respectively.

The similar enzymatic reaction of **17** (19.4 mg) for 1 d afforded a solution which was chromatographed on column A with gradient elution from aqueous 10% methanol (500 mL) to aqueous 50% methanol (500 mL) to give **2** (2.37 mg, 30.3%) and **7** (3.45 mg, 35.8%). A similar procedure to that described above afforded **19** (5.0 mg, 54.5%) from **18** (12.0 mg). FABMS: m/z **2** 649 ($M + H^+$), 671 ($M + Na^+$), **7** 547 ($M + Na^+$), **19** 993 ($M + H^+$), 1015 ($M + Na^+$).

Enzymatic Hydrolysis of 11 by α-Amylase (Succharifying Type) of *Bacillus subtilis* var. *amylosaccharitieus*. BSA (0.1 mg) was added to an ice-cooled solution of **11** (5.0 mg) in water (1 mL). The mixture was kept at room temperature for 4 d and then in boiling water for 10 min. After being filtered, the solution was analyzed by HPLC with gradient elution from aqueous 20% CH_3CN (30 mL) to aqueous 50% CH_3CN (30 mL); the retention times (flow rate 0.5 mL/min): **5**, 17 min; **8**, 39 min. The sulfonates **5** and **8** were isolated by chromatography on the analytical column and analyzed by FABMS: m/z **5** 687 ($M + H^+$), **8** 687 ($M + H^+$), 709 ($M + Na^+$), 725 ($M + K^+$).

Reduction of 19 with $NaBH_4$. A solution of **19** (5.0 mg) in aqueous 1% $NaBH_4$ (3 mL) was stirred at room temperature for 1 d, neutralized with 5% HCl, and chromatographed on column A with gradient elution from aqueous 20% methanol (500 mL) to aqueous 50% methanol (500 mL) to give **20** (3.0 mg, 59.9%). FABMS: m/z 1017 ($M + Na^+$).

Anhydrations of 10, 12, and 22-25. A solution of **10** (24.5 mg) in 5 mL of aqueous NaOH (Ph 12) was stirred at room temperature for 50 min, neutralized with aqueous 5% HCl, filtered, and chromatographed on column A. After elution with water (100 mL), gradient elution from aqueous 10% methanol (500 mL) to aqueous 40% methanol (500 mL) gave **17** (16.5 mg, 77.5%). A procedure similar to that described above afforded **18** (13.1 mg, 73.7%) from **12** (18 mg). FABMS: *m/z* **17** 1299 (M + H^+), 1321 (M + Na^+), **18** 1299 (M + H^+). ^{13}C NMR (CD_3OD, characteristic absorptions): δ **17** 22.90, 50.29, 55.11, 61.64, 72.80, 73.68, 74.46, 74.66, 83.04, 103.45, 103.70, 132.74; **18** 22.90, 50.29, 55.16, 61.55, 71.15, 73.00, 73.58, 74.60, 82.69, 103.94, 104.23, 132.69.

A solution of **22** (19.3 mg) in 10 mL of aqueous NaOH (pH 12) was stirred at room temperature for 7 h, neutralized with 1% HCl, filtered, and chromatographed on column A. After elution with water (75 mL), gradient elution from aqueous 10% methanol (500 mL) to aqueous 40% methanol (500 mL) gave **26** (9.3 mg, 59.9%). Similarly, **23** (30.0 mg), **24** (45.0 mg), and **25** (10.0 mg) afforded, respectively, **27** (15.7 mg, 61.2%), **28** (24.5 mg, 73.9%), and **29** (3.8 mg, 46.9%), where the reaction times were 2.1, 1, and 2.3 h for **23-25**, respectively. FABMS: *m/z* **26-29** 831 (M + H^+), 853 (M + Na^+). ^{13}C NMR (D_2O, characteristic absorptions): δ **26** 24.61, 63.12, 72.77, 73.35, 73.89, 74.96, 76.57, 76.81, 77.05, 96.99, 101.18, 134.61; **27** 24.56, 52.30, 55.51, 63.21, 71.16, 71.89, 73.16, 73.94, 76.08, 98.55, 99.18, 134.37. **28** 25.05, 63.16, 71.94, 73.84, 74.47, 75.15, 75.74, 75.98, 76.96, 79.39, 102.54, 134.22; **29** 24.52, 52.30, 55.95, 63.12, 72.03, 73.59, 75.59, 75.74, 99.62, 134.52. ^1H NMR (D_2O): δ **28** 3.97-4.02 ($H_{6''b}$), 4.12 ($H_{4''}$, dd, $J_{3'',4''}$ = 4.3 Hz, $J_{4'',5''}$ = 2.1 Hz), 4.17 ($H_{6''a}$, d, $J_{6''a,6''b}$ = 10.9 Hz), 4.43 ($H_{2''}$, dd, $J_{1'',2''}$ = 2.5 Hz, $J_{2'',3''}$ = 5.8 Hz), 4.54 ($H_{5''}$), 4.62-4.69 ($H_{3''}$), and 5.23 ($H_{1''}$, d, $J_{1'',2''}$ = 2.5 Hz) (see Figure 3).

Anhydrations of 22-25 Followed by Reduction with $NaBH_4$. A solution of **22** (5.0 mg) in 5 mL of aqueous NaOH (pH 12) was stirred at room temperature for 8 h and then neutralized with 5% HCl. Under ice-cooling, $NaBH_4$ (50 mg) was added to the solution. The solution was kept at 2 °C overnight, neutralized with 5% HCl, and chromatographed on column A with elution of water (100 mL) followed by gradient elution from aqueous 10% methanol (500 mL) to aqueous 40% methanol (500 mL) to give **30** (2.5 mg, 61.9%). Similarly, **23** (6.9 mg), **24** (11.9 mg), and **25** (3.4 mg) gave, respectively, **31** (2.1 mg, 37%), **32** (2.4 mg, 21%), and **33** (1.0 mg, 35%), where the times of alkali treatment were 2.5, 3, and 2 h, respectively. FABMS: *m/z* **30** and **31** 833 (M + H^+), 855 (M + Na^+), **32** 855 (M + Na^+), **33** 833 (M + H^+).

Complete Acetylation of 20 and 30-33. The title compound (2.0 mg) was treated conventionally with pyridine (0.5 mL) and acetic anhydride (0.5 mL) at room temperature for 2 d. The crude product was purified by HPLC on the analytical column with gradient elution from aqueous 50% CH_3CN (30 mL) to aqueous 80% CH_3CN (30 mL) to give the completely acetylated oligosaccharide. The retention times (the flow rate; 0.5 mL/min) were 84, 65, 65, 57, and 66 min for **21**, **34**, **35**, **36**, and **37**, respectively. FABMS: *m/z* **21** 1625 (M + H^+), 1647 (M + Na^+), **34** 1337 (M + H^+), 1359 (M + Na^+), **37** 1337 (M + H^+), FDMS: *m/z* **35** and **36** 1359 (M + Na^+). The FABMS fragmentation patterns were shown in Figure 2.

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Supplementary Material Available: ^{13}C NMR spectra of **17**, **18**, and **26-29** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Selenium-Directed Stereoselective [2 + 2] Cycloaddition Reactions Promoted by Lewis Acids: A Novel Zwitterionic Intermediate

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The reaction of (trimethylsilyl)vinyl selenide **1** and (trimethylsilyl)allenyl selenide **2** with vinyl ketones **3a-c** in the presence of a Lewis acid gave cyclobutane derivatives stereoselectively. The reaction of **1** and **3a-c** with $SnCl_4$ was quenched either with Et_3N to give cyclobutanes **4a-c** or with H_2O to give acylsilanes **11a-c**. The formation of both products is explained in terms of a zwitterionic intermediate. The cis relationship between the phenylseleno group and the carbonyl group of **4a-c** is rationalized by consideration of a combination of secondary-orbital interactions and steric effects in the early stage of intermediate formation.

Introduction

[2 + 2] Cycloadditions are symmetry forbidden but important reactions in organic synthesis. Cyclobutane skeletons, which are formed in these reactions, are used for many organic transformations[1] and appear in several natural products.[2] The photochemical cycloaddition of olefins,[3] the thermal cycloaddition of electrophilic and nucleophilic olefins,[4] and the cycloaddition of ketenes with olefins[5] have been extensively studied. Recently, several studies on the Lewis acid-promoted [2 + 2] cycloaddition reaction of heteroatom-substituted olefins with olefins activated by an electron-withdrawing group (for example, [2 + 2] cycloadditions of silyl enol ethers,[6] simple enol ethers,[7] and vinyl sulfides[8] with electron-deficient olefins)

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