Complete Sets of Structurally Determined $6^A,6^X$-Unsymmetrically Disubstituted β-Cyclodextrins: 6^A-*S*-Phenyl-6^X-*O*-(β-naphthylsulfonyl)-6^A-thio-β-cyclodextrins and 6^A-*S*-(*tert*-Butyl)-6^X-*O*-(β-naphthylsulfonyl)-6^A-thio-β-cyclodextrins

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Regiochemical isomers, 6^A-*S*-phenyl-6^X-*O*-(β-naphthylsulfonyl)-6^A-thio-β-cyclodextrins and 6^A-*S*-(*tert*-butyl)-6^X-*O*-(β-naphthylsulfonyl)-6^A-thio-β-cyclodextrins, were prepared, and their structures were determined. These constitute complete sets of cyclodextrins having two functional groups that are different from one another.

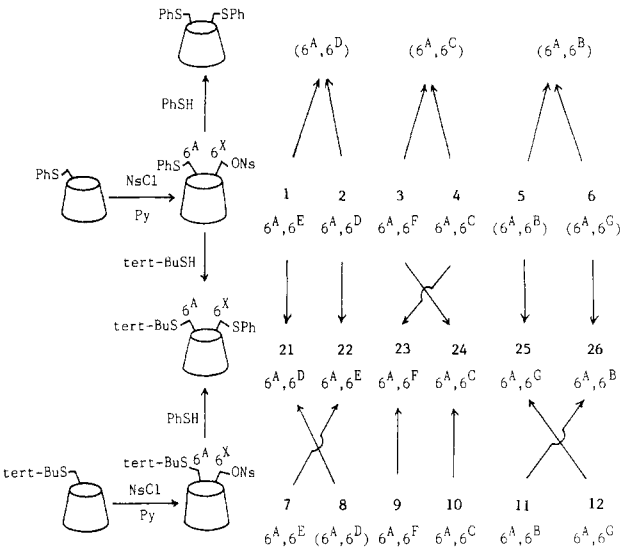
Introduction of two (or more) different kinds of functional groups onto the desired positions around a hydrophobic pocket is one challenging approach to the construction of enzyme (or receptor) mimics. Naturally occurring macrocyclic compounds, cyclodextrins, have been chemically modified as easily available hydrophobic pockets.[1] However, there are few studies on preparation of cyclodextrins unsymmetrically substituted with two different groups.[2] Moreover, there have been no authentic specimens for structure determination, even if they could be prepared selectively. We already reported the preparation and isolation of unsymmetrically disubstituted β-cyclodextrins **1**–**6**[3] and **7**–**12**[4] and assignment of $6^A,6^B$ (**5**),[3] $6^A,6^G$ (**6**),[3] and $6^A,6^D$ (**8**)[4] isomers (Scheme I). The substituent on the 6^A carbon is a phenylthio group for **5** and **6** or a *tert*-butylthio group for **8**, while the substituent on 6^B-O and 6^G-O, or 6^D-O, is a β-naphthylsulfonyl group. If the regiochemistry of either **3** or **4** is determined and the two series of compounds **1**–**6** and **7**–**12** are convertible to a series of common compounds, we will be able to obtain complete sets of unsymmetrically disubstituted β-cyclodextrins by correlation of **1**–**6** with **7**–**12** through common compounds. We describe here the structure determination of **3** and **4** and a correlation between two series of unsymmetrically disubstituted β-cyclodextrins, **1**–**6** and **7**–**12**.

Results and Discussion

Preparation of Isomeric Mixtures of Unsymmetrically Disubstituted Cyclodextrins 1–6 and 7–12. The unsymmetrically disubstituted β-cyclodextrins **1**–**6** or **7**–**12** were prepared from the reaction of 6-*S*-phenyl-6-thio-β-cyclodextrin or 6-*S*-(*tert*-butyl)-6-thio-β-cyclodextrin with β-naphthylsulfonyl chloride, respectively, and were isolated by reverse-phase column chromatography.[3,4] The numbers of the compounds in the three horizontal series shown in Scheme I are given in order of increasing retention time in reverse-phase HPLC. As shown previously,[3] **1** and **2**, or **3** and **4**, were converted to $6^A,6^D$-di-*S*-phenyl-$6^A,6^D$-dithio-β-cyclodextrin or $6^A,6^C$-di-*S*-phenyl-$6^A,6^C$-dithio-β-cyclodextrin, respectively. Therefore, **1**, **2**, **3**, and **4** must be $6^A,6^E$ (or $6^A,6^D$), $6^A,6^D$ ($6^A,6^E$), $6^A,6^F$ ($6^A,6^C$), and $6^A,6^C$ ($6^A,6^F$) isomers, respectively.

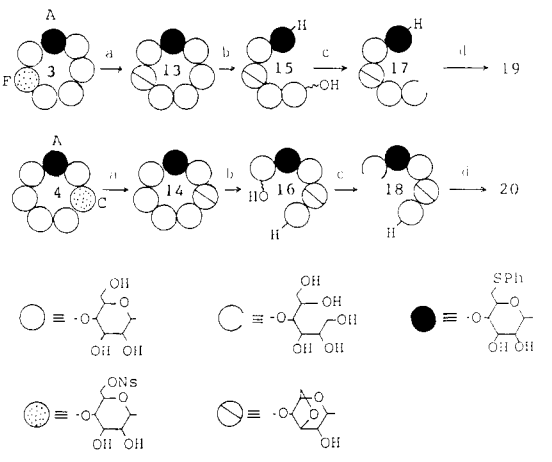
Structure Determination of Unsymmetrically Disubstituted Cyclodextrins 3 and 4. This is summarized in Scheme II. Compounds **3** and **4** were converted to 3,6-anhydrocyclodextrins **13** and **14**, respectively, by treatment with 1 N NaOH at 60 °C.[5] It is known that enzymatic hydrolysis of 3,6-anhydro-α(or β or γ)-cyclodextrin by Taka amylase[5] produces 3″,6″-anhydromaltotetraose and that 6-*S*-phenyl-6-thio-β-cyclodextrin gives 6′-*S*-phenyl-6′-thiomaltose.[6] These facts suggest that

Scheme I[a]



[a] The structures determined in our previous studies are designated in parentheses. NsCl and Py represent β-naphthylsulfonyl chloride and pyridine, respectively.

Scheme II[a]



[a] (a) Aqueous NaOH, 1 N. (b) Taka amylase. (c) $NaBH_4$. (d) Ac_2O/Py. Ns: β-naphthylsulfonyl.

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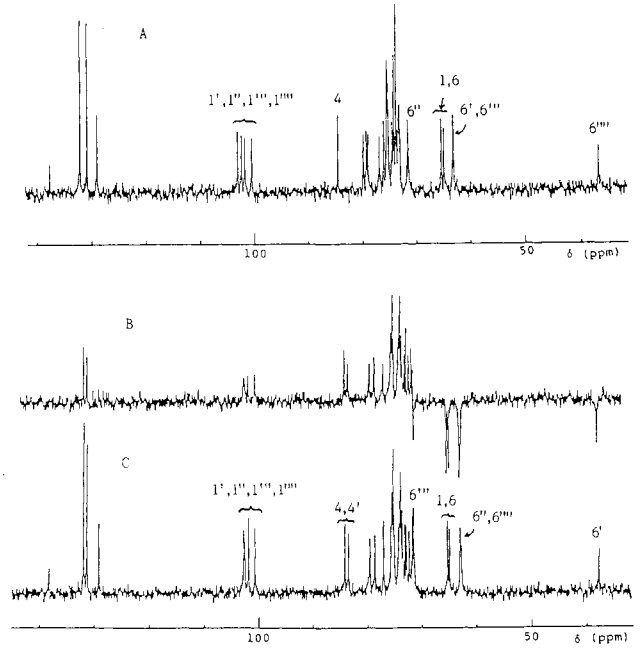


Figure 1. ^{13}C NMR spectra of **17** (A) and **18** (C) and INEPT ^{13}C NMR spectrum of **18** (B) in D_2O.

Taka amylolyses of **13** and **14** gave dimodified maltopentaoses, **15** and **16**, respectively. the Taka-amylolysis products (**15** and **16**) and their derivatives (**17** and **18**) obtained by $NaBH_4$ reduction of **15** and **16** showed the expected molecular ions of the dimodified maltopentaoses in the FABMS spectra. Two absorptions around δ 65 (C1 and C6) in the ^{13}C NMR spectra of **17** and **18** (Figure 1) demonstrate that **15** and **16** were reduced and that neither a 3,6-anhydroglucose unit nor a 6-*S*-phenyl-6-thioglucose unit is located at the reducing end.[7] Moreover, two absorptions around δ 85 (C4 and C4′) for **18** demonstrate that the phenylthioglucose unit is not located at the nonreducing end, because only one absorption should be observed around δ 85 (C4) if the phenylthioglucose unit were located at the nonreducing end. On the other hand, one absorption around δ 85 (C4) for **17** shows that the phenylthioglucose unit is located that the nonreducing end. Therefore, **15** must be 6′′′′-*S*-phenyl-3′′,6′′-anhydro-6′′′′-thiomaltopentaose.

The structure assignments for **17** and **18** were confirmed by the following independent results. The completely acetylated compounds **19** and **20** whose FDMS spectra show the correct molecular ions were analyzed by EIMS spectrometry. The fragmentations in the EIMS spectra shown in Figure 2 demonstrate that the phenylthio and 3,6-anhydro modifications are located at the first and the third glucose units from the nonreducing end, respectively, for **19** and at the fourth and the second glucose units for **20**. Therefore, the structures of **3** and **4** can be assigned

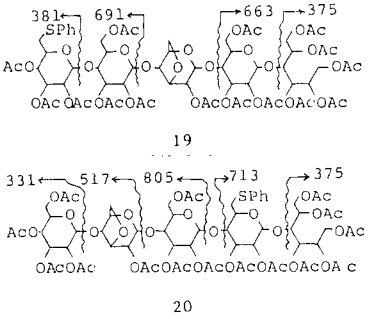


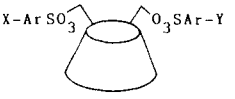
Figure 2. EIMS spectral fragmentations (m/z). The acetates **19** and **20** showed the correct molecular ions in their FDMS spectra.

as 6^A-*S*-phenyl-6^F-*O*-(β-naphthylsulfonyl)-6^A-thio-β-cyclodextrin and its $6^A,6^C$ isomer, respectively.

Correlation between Two Series of Unsymmetrically Disubstituted Cyclodextrins, 1–6 and 7–12. The unsymmetrically disubstituted cyclodextrins **1–6** were converted to **21–26** by the reaction with *tert*-butyl mercaptan as shown in Scheme I. Reverse-phase HPLC could separate the mixture of **21** (**22**)/**26**, although it did not differentiate **21** from **22**. The compounds **21** and **22** are differentiated on the basis of ^1H NMR chemical shifts of the *tert*-butyl group (1.18 for **21** and 1.19 for **22**) and ^1H NMR spectral patterns of the phenyl groups. Moreover, they could be easily and unequivocally differentiated on the basis of characteristic HPLC patterns of the mixtures of trisubstituted cyclodextrins obtained by 6-O-sulfonylations of the disulfonylated cyclodextrins **21** and **22** with β-naphthylsulfonyl chloride in pyridine. Compounds **7–12** were converted to the common bis-derivatives **21–26** by treatment with thiophenol. The products were identified by comparing their retention times in reverse-phase HPLC, their ^1H NMR spectra, and for **21** and **22** only, their characteristic patterns of HPLC of the additionally sulfonylated products with those derived from **1–6**. The results of the correlations are shown in Scheme I, from which we can completely assign the structures of unsymmetrically disubstituted β-cyclodextrins **1–6**, **7–12**, and **21–26**.

Conclusion

Complete sets of unsymmetrically bifunctional β-cyclodextrin are now available. If cyclodextrins, such as **27**, having two sulfonyl groups whose reactivities toward nu-



27

X: electron-withdrawing group
Y: electron-donating group
Ar: aromatic group

cleophiles are very different from one another are prepared as precursors of bifunctional cyclodextrins (artificial enzymes or receptors), their structure determination will be easily carried out through their chemical conversion to **1–6**, **7–12**, or **21–26**. Moreover, unique artificial enzymes having a hydrophobic group on a 6^B–6^E carbon will be easily obtained by appropriate nucleophilic substitution of the sulfonyl group.

Experimental Section

^1H NMR and ^{13}C NMR spectra were determined at 100 and 25 MHz respectively. Fast-atom-bombardment mass (FABMS), field-desorption mass (FDMS), and electron-impact mass (EIMS) spectra were obtained with a JEOL JMS DX-300/JMA 3500 data

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(7) Assignments of the ^{13}C NMR spectra of maltooligosaccharides having the 6-*S*-phenyl-6-thioglucose unit were already reported. See ref 3.

system. 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-dihydroxynaphthalene 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)). Prepacked columns (Merck, Lobar column LiChroprep Rp18 and Rp8) were used for reverse-phase column chromatography. High-performance liquid chromatography (HPLC) was performed on a TSKgel-410 ODS SIL column (4 × 300 mm, 5 μm, Toyo Soda, Japan).

Preparation and Isolation of Unsymmetrically Disubstituted Cyclodextrins 1–6 and 7–12. These have been reported by us.[3,4]

Conversion of Disubstituted β-Cyclodextrins 3 and 4 to Oligosaccharides 15 and 16. A solution of **3** (50 mg) in 0.1 N aqueous NaOH (3 mL) was kept at 60 °C for 4.5 h. After neutralization by addition of diluted HCl, the mixture was concentrated in vacuo to dryness. The residue was dissolved in 5 mL of 0.2 M acetate buffer (pH 5.5) containing 0.01 M $CaCl_2$. After 50 mg of Taka amylase (Sigma, α-amylase type X-A) was added to the solution, the mixture was kept at 40 °C for 20 days. The enzyme was denatured by addition of 3 N ammonium hydroxide (2 mL), and the precipitated protein was separated by centrifugation. The supernatant was concentrated in vacuo to dryness, dissolved in water (50 mL), and applied on a reverse-phase column (Rp18). After elution with water (300 mL), a gradient elution from water (300 mL) to 30% aqueous ethanol (300 mL) was applied to give **15**, which was purified by reverse-phase HPLC. **13**: R_f 0.30. **15**: 14 mg (43.3%); R_f 0.42.

Similarly, **4** (50 mg) was converted to **16** via **14**. In the isolation of **16** by reverse-phase column chromatography, a gradient elution from water (300 mL) to 20% aqueous ethanol (300 mL) followed by an elution of 20% aqueous ethanol (500 mL) was used after an elution of water (250 mL). **14**: R_f 0.30. **16**: 20 mg (63.0%); R_f 0.43.

$NaBH_4$ Reduction of Modified Oligosaccharides 15 and 16. A solution of **15** (10 mg) in 1% aqueous $NaBH_4$ (2.7 mL) was kept at room temperature for 24 h. After neutralization, the mixture was adsorbed on a reverse-phase column (Rp18) and chromatographed with an elution of water (200 mL) and then a gradient elution from 10% aqueous ethanol (300 mL) to 30% aqueous ethanol (300 mL) to give **17**. **17**: 8.5 mg (85.1%); R_f 0.43; FABMS, m/z 905 ($M + H^+$), 927 ($M + Na^+$), 943 ($M + K^+$); ^{13}C NMR, Figure 1.

Similarly, **16** (10 mg) gave **18**. **18**: 8.3 mg (83.2%); R_f 0.37; FABMS, m/z 905 ($M + H^+$), 927 ($M + Na^+$), 943 ($M + K^+$); ^{13}C NMR, Figure 1.

Acetylation of Reduced Oligosaccharides 17 and 18. A mixture of **17** (5 mg), acetic anhydride (1.5 mL), and pyridine (1.5 mL) was kept at room temperature overnight and concentrated by evaporation of volatile materials together with a stream of nitrogen. After dry chloroform (0.5 mL) was added to the residue, the evaporation was repeated. This procedure was carried out two more times to give **19**. **19**: R_f 0.38; FDMS, m/z 1535 ($M + H^+$).

Similarly, **20** was prepared. **20**: R_f 0.52; FDMS, m/z 1535 ($M + H^+$).

Reaction of 6^A-*S*-Phenyl-6^X-*O*-(β-naphthylsulfonyl)-6^A-thio-β-cyclodextrins 1–6 with *tert*-Butyl Mercaptan. A solution of the sulfonate (20 mg), *tert*-butyl mercaptan (80 mg), and sodium hydride (13 mg) in dimethylformamide (0.5 mL) was kept at 80 °C overnight in a sealed tube. After evaporation of dimethylformamide and *tert*-butyl mercaptan, the residue was, in the case of the reaction of **1**, **3**, or **5**, recrystallized from water to give **21** (9 mg, 49%), **24** (8 mg, 44%), or **25** (6 mg, 33%), respectively, and in the case of the reaction of **2**, **4**, or **6**, chromatographed with a reverse-phase column to give **22** (6 mg, 33%), **23** (8 mg, 44%), or **26** (12 mg, 60%), respectively. ^1H NMR absorption of *tert*-butyl group (Me_2SO-d_6, δ): **21**, 1.18; **22**, 1.19; **23**, 1.22; **24**, 1.20; **25**, 1.20; **26**, 1.28.

Reaction of 6^A-*S*-(*tert*-Butyl)-6^X-(β-naphthylsulfonyl)-6^A-thio-β-cyclodextrins 7–12 with Thiophenol. A solution of **7** (20 mg), thiophenol (13 mg), and sodium carbonate (4 mg) in dimethylformamide (0.5 mL) was stirred at 80 °C for 5 h. After evaporation of dimethylformamide, the residue was dissolved in aqueous ethanol, acidified with HCl, and extracted with ether. The aqueous layer was neutralized with NaOH, concentrated in vacuo, and chromatographed with a reverse-phase column (Rp8) to give **22** (10 mg, 54%).

Similarly, **8** (15 mg), **9** (4 mg), **10** (20 mg), **11** (20 mg), or **12** (20 mg) gave **21** (8 mg, 58%), **23** (3 mg, 81%), **24** (10 mg, 54%), **26** (10 mg, 54%), or **25** (11 mg, 59%), respectively.

The ^1H NMR spectra were the same as those of the corresponding compounds prepared from 6^A-*S*-phenyl-6^X-(β-naphthylsulfonyl)-6^A-thio-β-cyclodextrins.

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From Carbohydrates to Carbocycles. 2. A Free Radical Route to Corey Lactone and Other Prostanoid Intermediates[1]

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The hex-5-enyl radical cyclization methodology was applied for the synthesis of optically active Corey lactone (**7**) with readily available 3-deoxy-D-glucopyranose as starting material. The cyclic radical (**19**) generated from the 4,6-*O*-benzylidene-protected hexose derivative (**16**) cyclizes with high stereoselectivity, i.e., 1,5-trans ring closure, to give cyclopentane (**20**) with the correct absolute and relative configuration of Corey lactone. This unusual stereoselectivity is rationalized by invoking a boatlike transition state for the radical cyclization. Also described here are several chemical transformations of **20**, which are potentially useful for the synthesis of prostaglandin-like molecules. Degradations of a commercially available Corey lactone derivative, which were initially found useful for structural correlations with synthetic intermediates are also described.

The cyclization of hex-5-enyl radicals to cyclopentylmethyl radicals, "the radical clock reaction", has attracted considerable attention in synthetic and physical organic chemistry.[2] Kinetic parameters for the individual steps[3]

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