Cyclodextrin-based enzyme models. Part 1. Synthesis of a tosylate and an epoxide derived from heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin and their characterization using 2D NMR techniques. An improved route to cyclodextrins functionalized on the secondary face

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An improved route for the synthesis of cyclodextrin (CD)-based enzyme models having catalytic groups on the secondary face is presented. An epoxide derived from heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD was prepared via intermediates that can be purified by conventional flash chromatography on a *preparative* scale. Reaction of β-cyclodextrin with *tert*-butyldimethylsilyl chloride in pyridine gave heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD (**1**). Treatment of **1** with *N*-tosylimidazole and NaOMe in chloroform gave mono(2-*O*-tosyl) heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD (**2**) in 22% yield. The latter was converted smoothly to mono(2^A, 3^A-anhydro) heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD (**3**), in which one glucose subunit has been converted to a manno-epoxide, by treatment with KOEt in refluxing ethanol (87% yield). Compounds **1**, **2**, and **3** were characterized by a variety of one- and two-dimensional NMR techniques. These results open the door to attachment of catalytic groups to the cyclodextrin in a well-defined manner. Nucleophilic attack on the epoxide, followed by removal of the silyl groups, can be used to prepare a wide variety of enzyme model systems.

Key words: functionalized cyclodextrins, silylation, 2D NMR, enzyme models.

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On présente une méthode améliorée pour la synthèse de modèles basés sur la cyclodextrine (CD) possédant des groupements catalytiques sur la face secondaire. On a préparé un époxyde, à partir de l'heptakis(6-*O*-*tert*-butyldiméthylsilyl)-β-CD, par le biais d'intermédiaires qui peuvent être purifiés, sur une base *préparative*, par la chromatographie éclair conventionnelle. La réaction de la β-cyclodextrine avec le chlorure de *tert*-butyldiméthylsilyle dans la pyridine fournit l'heptakis(6-*O*-*tert*-butyldiméthylsilyl)-β-CD (**1**). Le traitement du produit **1** par du *N*-tosylimidazole et du NaOMe dans le chloroforme conduit au mono(2-*O*-tosyl)-heptakis(6-*O*-*tert*-butyldiméthylsilyl)-β-CD (**2**), avec un rendement de 22%. Ce produit a été facilement transformé en mono(2^A, 3^A-anhydro)heptakis((6-*O*-*tert*-butyldiméthylsilyl)-β-CD (**3**) duquel une unité de glucose a été transformée en manno-époxyde par un traitement avec du KOEt dans l'éthanol au reflux (rendement de 87%). Les composées **1**, **2** et **3** ont été caractérisés par une variété de techniques RMN en une et en deux dimensions. Ces résultats ouvrent la porte à l'attachement de groupements catalytiques dans des positions bien définies de la cyclodextrine. Une attaque nucléophile sur l'époxyde, suivie de l'enlèvement des groupements silyles, peut être utilisée pour préparer une grande variété de systèmes enzymatiques modèles.

Mots clés : cyclodextrines fonctionnalisées, silylation, RMN 2D, modèles d'enzymes.

[Traduit par la revue]

Introduction

Cyclodextrins (CDs) are of interest as enzyme models because they form inclusion complexes with hydrophobic guests in solutions of polar solvents (1–3). This is directly comparable to the formation of an enzyme–substrate complex and leads to saturation (Michaelis–Menten) kinetics, competitive inhibition, and selective rate accelerations in reactions involving cyclodextrins (2). Since cyclodextrins can be modified to attach catalytic groups, they have the two important attributes of enzymes: molecular recognition and multifunctional catalysis (3).

β-Cyclodextrin is a cyclic oligosaccharide made up of seven α-D-glucose subunits. As shown in Fig. 1, the secondary hydroxyl groups make up one face of the toroidal molecule. The secondary face of the cyclodextrin is of interest in making enzyme models because it is more open and is the preferential site for the binding of large molecules, including aromatic guests (4). However, in contrast to functionalization of the primary face of cyclodextrins, which has been extensively studied, the chemistry available for functionalization of the secondary face is less well developed. Preparative methods for secondary-functionalized cyclodextrins generally involve moderate yields and purification of synthetic intermediates by reverse-phase chromatography, which is scale-limited (5–8).

The synthesis of cyclodextrin-based enzyme model systems may be improved to allow for easier purification of intermediates, and consequently for synthesis on a larger scale, if a partially silylated cyclodextrin derivative is used as the framework for further modifications. Silylation of β-cyclodextrin primary hydroxyls should lead to a number of benefits. The resulting compound is expected to be much less polar than the parent cyclodextrin, making it soluble in organic solvents and allowing purification by chromatography on silica gel. The silyl groups are stable under ordinary conditions, but are easily removed when necessary (9–11). Thus, modification of silylated CDs would provide an improvement over previous approaches because the synthetic intermediates should be more easily purified, allowing work on a large scale.

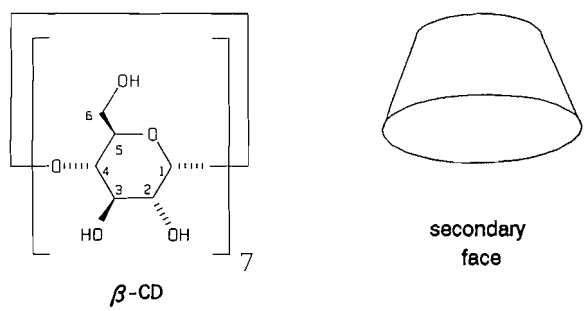


FIG. 1. β-Cyclodextrin and a representation of the shape of the molecule indicating the secondary face.

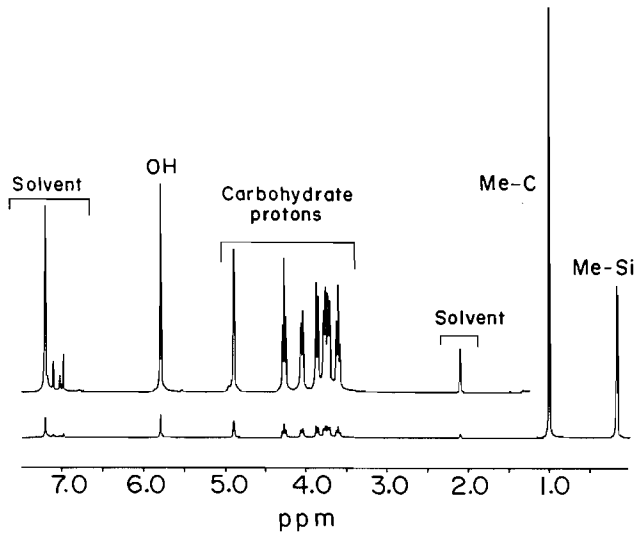


FIG. 2. ^{1}H NMR spectrum of **1** in deuterotoluene (3000–0 Hz). The carbohydrate region is expanded in Fig. 3.

The silylation of β-CD to produce heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD (**1**) has been reported previously (12). Szejtli and co-workers originally reported the selective silylation of the primary hydroxyls of β-CD, using pyridine as a catalyst for the reaction of β-CD with *tert*-butyldimethylsilyl chloride; the silylated CD was isolated and characterized as the peracetate (12, 13). Treatment of the peracetate with Bu_4NF removed the silyl groups smoothly (12). Takeo *et al.* have recently prepared **1** in 70% yield by the reaction of β-CD with *t*-$BuMe_2SiCl$ in the presence of imidazole (14) and Fugedi has prepared **1** in 83% yield using pyridine as catalyst and solvent (15).

A number of compounds related to **1** have also been prepared, including heptakis(6-*O*-*tert*-butyldimethylsilyl)-α-CD (11, 16) and heptakis(6-*O*-*tert*-butyldimethylsilyl)-γ-CD (15), as well as 2,6-per(*tert*-butyldimethylsilyl)-α-CD (10, 16) and 2,6-per(*tert*-butyldimethylsilyl)-β-CD derivatives (17, 18).

The present work reports the synthesis and complete characterization of **1**, which is used as a precursor in the synthesis of two new compounds, a tosylate (**2**) and an epoxide (**3**). All three compounds are characterized with the aid of a variety of one- and two-dimensional (2D) NMR techniques. NMR studies of cyclodextrins, including the use of a variety of two-dimensional methods, have recently been reviewed (19). Two-dimensional methods are used because substituted cyclodextrins usually give complex, overlapped spectra. Spreading out overlapped signals into a second dimension often allows individual resonances to be resolved and assigned. This has been shown to be indispensable in the characterization of complex, unsymmetrically modified cyclodextrins (22). For example, Stoddart and co-workers have used COSY, *J*-resolved, and shift correlation experiments to assign the spectra of an unsymmetrical chemically modified CD, 2,6-per-*O*-methyl-3^A-*O*-methyl-β-CD (20).

Results and discussion

As part of our ongoing interest in the construction of cyclodextrin-based enzyme model systems, the use of a cyclodextrin that was soluble in nonpolar solvents as a framework for subsequent transformations appeared to offer a number of advantages. It was expected that such a CD and its derivatives could be easily purified by flash chromatography and this, in turn, would allow syntheses to be carried out on a larger scale than is presently possible. Large amounts of CD derivatives are desirable when multistep syntheses are undertaken and when the modified cyclodextrin is to undergo detailed kinetic studies.

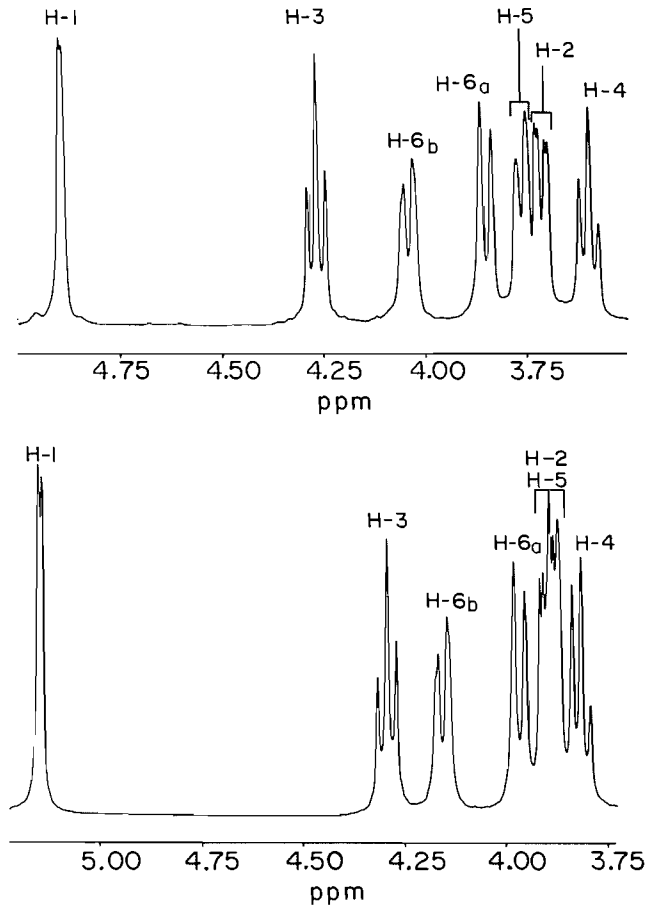


FIG. 3. ^{1}H NMR spectra of **1** in deuterotoluene (upper, 2000–1400 Hz) and deuterochloroform (lower, 2190–1590 Hz), showing resonances due to carbohydrate protons. The H-2 and H-5 resonances overlap in the spectrum recorded in $CDCl_3$.

Accordingly, a cyclodextrin silylated at its primary positions, **1**, was chosen as the starting point and was prepared as follows. Dry β-CD was allowed to react with 7.35 equivalents of *tert*-butyldimethylsilyl chloride in dry pyridine for 18 h at room temperature (eq. [1]). Heptakis(*tert*-butyldimethylsilyl)-β-CD (**1**) was isolated in 73% yield after flash chromatography. The preparative method was analogous to that reported by Fugedi (15). ^{13}C NMR data for **1** in $CDCl_3$ have been previously reported (14, 15), and the ^{13}C NMR data for the product of the present study compare well with the literature data. The ^{1}H, COSY, and ^{13}C–^{1}H shift correlation spectra for **1** have not been previously reported, and are presented below.

The complete ^{1}H NMR spectrum of **1** in deuterotoluene is shown in Fig. 2. The spectrum is remarkably simple because of the sevenfold symmetry of the compound. An expansion of the carbohydrate portion of the spectrum (Fig. 3) reveals distinct resonances for protons on carbons 1, 2, 3, 4, 5, and 6. The two protons on carbon 6, labelled H-6_a nd H-6_b, are nonequivalent (diastereotopic). In $CDCl_3$ solution, resonances assigned to protons on carbons 2 and 5 are overlapped (Fig. 3). Aromatic guests are known to deshield the H-3 and H-5 resonances of cyclodextrins (19), so the difference in spectra in the two

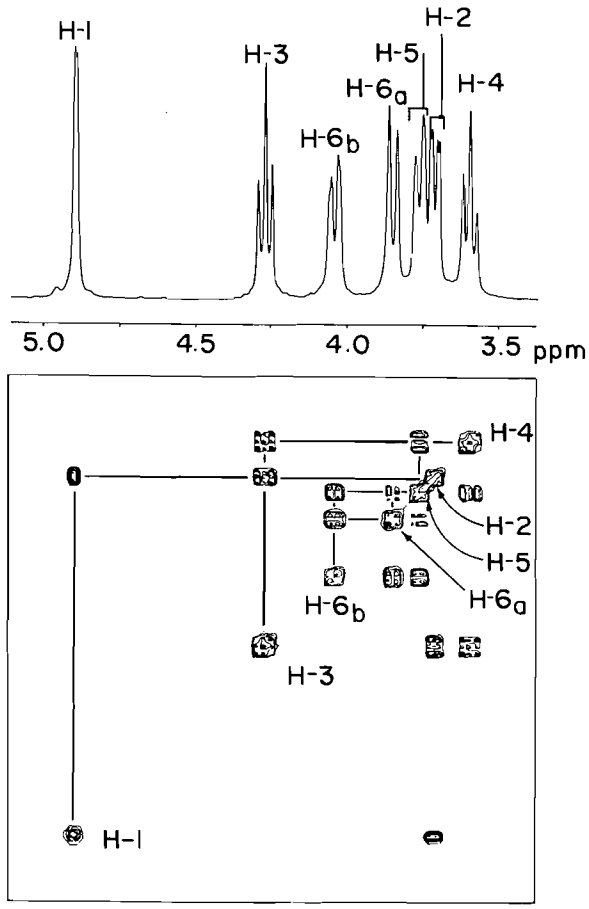


FIG. 4. Contour plot of the carbohydrate region of the COSY spectrum of **1** in deuterotoluene (2044–1349 Hz).

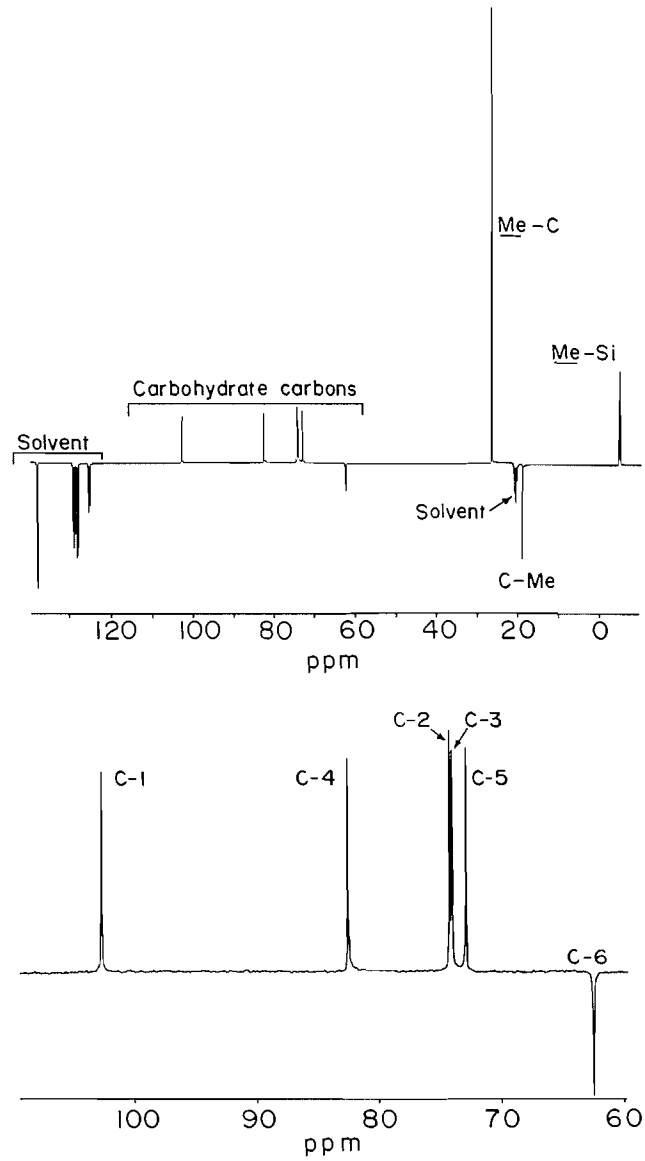


FIG. 5. *J*-Modulated ^{13}C NMR spectra of **1** in deuterotoluene (14 000 to −1000 Hz). The lower spectrum is an expansion showing resonances due to carbohydrate carbons (11 000–6000 Hz).

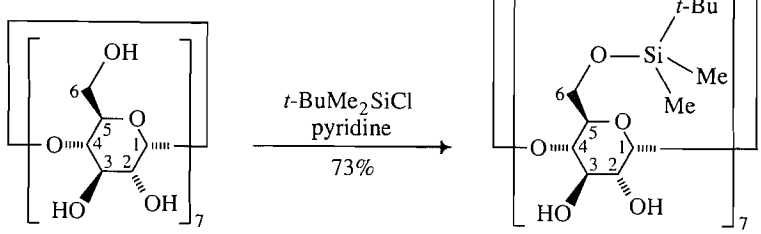
solvents can probably be ascribed to formation of an inclusion complex of deuterotoluene with the silylated CD.

The ^1H spectrum of **1** was assigned unambiguously by means of a COSY experiment, presented in Fig. 4. In this diagram, off-diagonal peaks connect coupled spins. Thus, as shown in Fig. 4, starting from the furthest downfield peak (H-1), all of the remaining resonances can be assigned.

The ^{13}C NMR spectrum of **1** was also recorded (Fig. 5). This is a *J*-modulated spectrum in which the carbon peaks are sorted according to the number of attached protons. Methyl and methine carbons point upwards; methylene and quaternary carbons point downwards. The peaks corresponding to the carbohydrate carbons were assigned by reference to the proton spectrum using a 2D ^{13}C–^1H shift correlation spectrum, presented in Fig. 6. This experiment yields responses that connect carbon peaks in one dimension to proton peaks in the other.

The title compound has two types of sites that can be modified further, the hydroxyl groups at C-2 and C-3 of each glucose unit. Ideally, tosylation of **1**, to produce **2**, would modify a single glucose subunit and would be specific for one type of hydroxyl on that subunit. In practice, one needs to check whether reaction has occurred at a C-2 hydroxyl, a C-3 hydroxyl, or both.

[1]



β-CD **1**

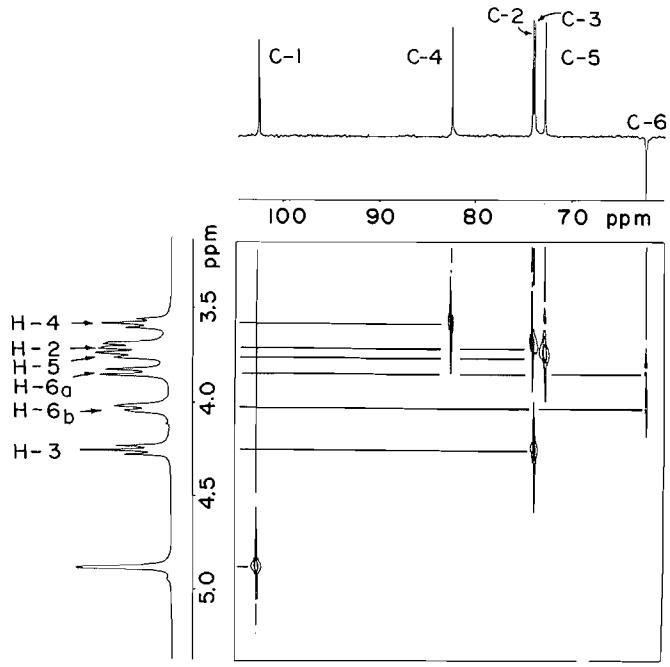


FIG. 6. Contour plot of the carbohydrate region of the ^{13}C–^{1}H shift correlation spectrum of **1** in deuterotoluene (^{1}H: 2151–1250 Hz, ^{13}C: 104.6–60.2 ppm).

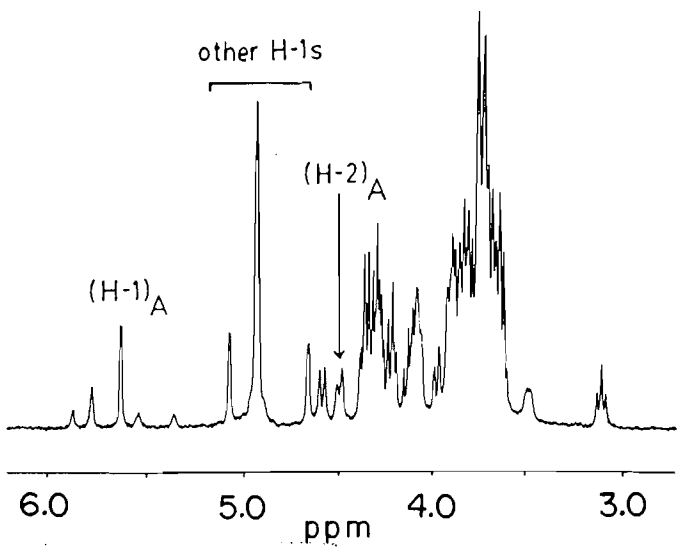


FIG. 7. The carbohydrate region of the ^{1}H NMR spectrum of **2** in deuterotoluene (2483–1092 Hz).

Reaction of **1** with *N*-tosylimidazole and sodium methoxide in chloroform gives **2** in 22% yield after flash chromatography (eq. [2]). This procedure has been shown to yield the C-2 tosylate in the reaction of 4,6-*O*-benzylidene-α-D-glucose (21).

The carbohydrate regions of the ^{1}H and ^{13}C NMR spectra are presented in Figs. 7 and 8, respectively. These spectra are complex and highly overlapped because modification of one of the seven subunits of the cyclodextrin destroys the symmetry of the molecule and all resonances are now nonequivalent.

In practice, resonances for the H-1's of the glucose units are easiest to analyze because they are well separated from other resonances. Three individual H-1 resonances are seen at 5.65, 5.07, and 4.63 ppm, as well as a larger (overlapped) group at

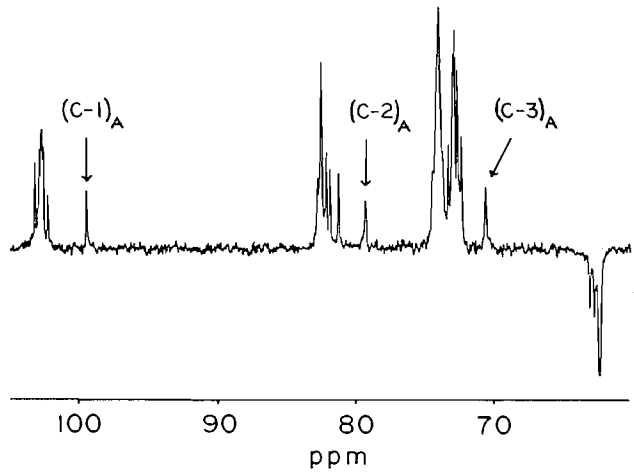


FIG. 8. The ^{13}C NMR spectrum of **2** in deuterotoluene (105.0–60.0 ppm).

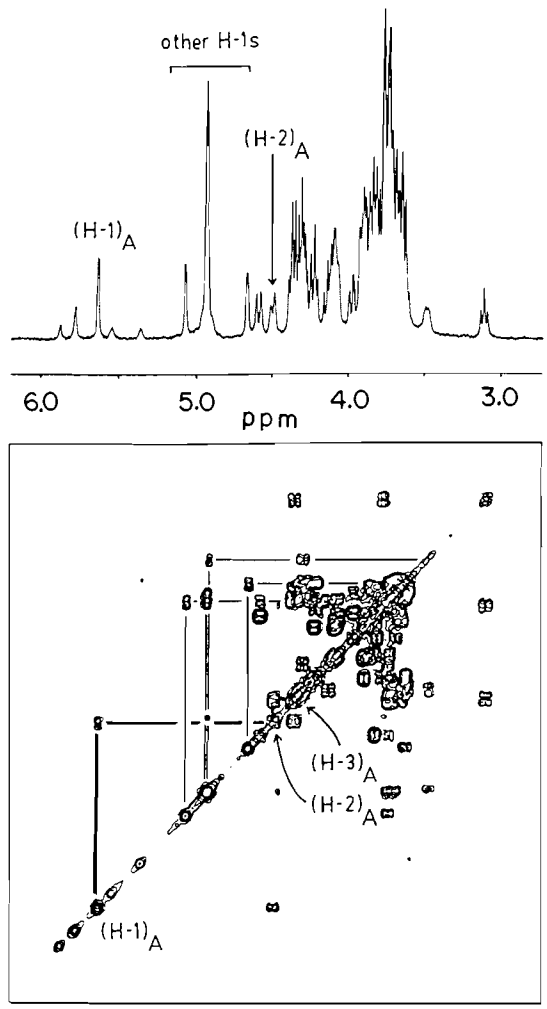


FIG. 9. Contour plot of the carbohydrate region of the COSY spectrum of **2** in deuterotoluene (2483–1092 Hz).

4.91 ppm. The lowest field H-1 signal is assigned to the subunit bearing the tosyl group (this subunit will be called subunit A and $(H\text{-}1)_A$ is labelled in Fig. 7). Examination of the COSY spectrum of **2**, presented in Fig. 9, shows that $(H\text{-}1)_A$ is coupled to an H-2 resonance at 4.50 ppm that is pulled downfield by ca. 0.8 ppm relative to H-2 resonances in parent silylated CD (**1**),

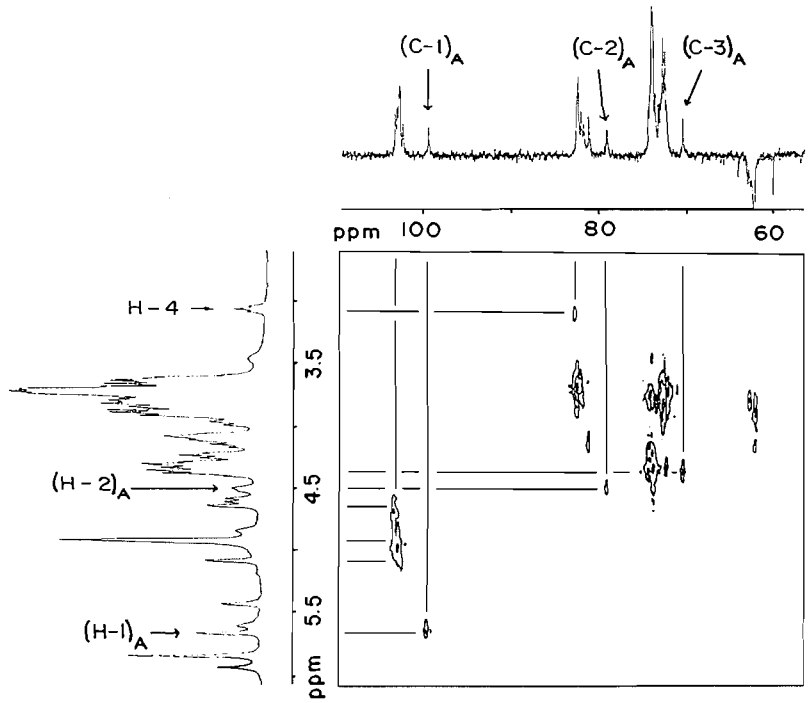


FIG. 10. Contour of the carbohydrate region of the $^{13}C-^{1}H$ shift correlation spectrum of **2** in deuterotoluene (^{1}H: 1047–2418 Hz, ^{13}C: 56.5–110.0 ppm).

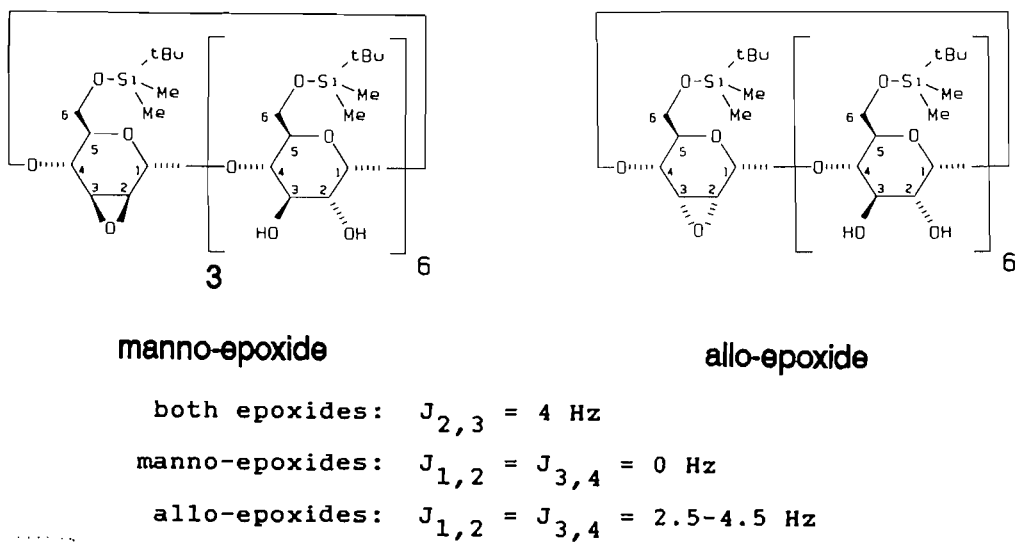
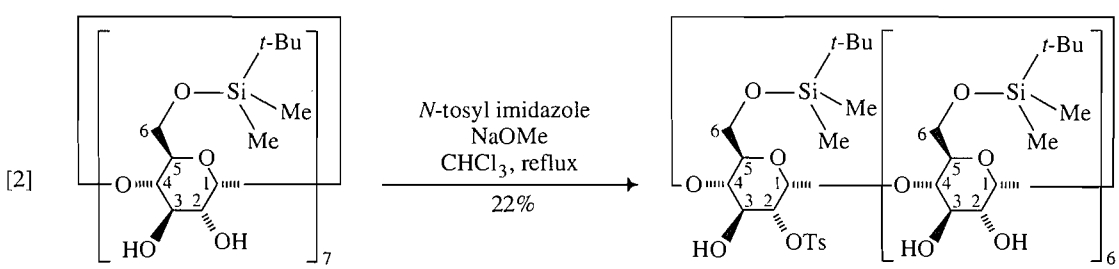


FIG. 11. Structural formulae and ^{1}H coupling constants for the allo- and manno-epoxides derived from **1**.



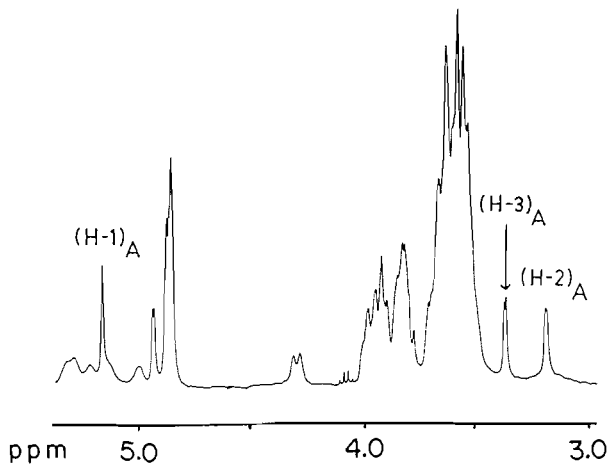


FIG. 12. The carbohydrate region of the ^{1}H NMR spectrum of **3** in deuterochloroform (2151–1185 Hz).

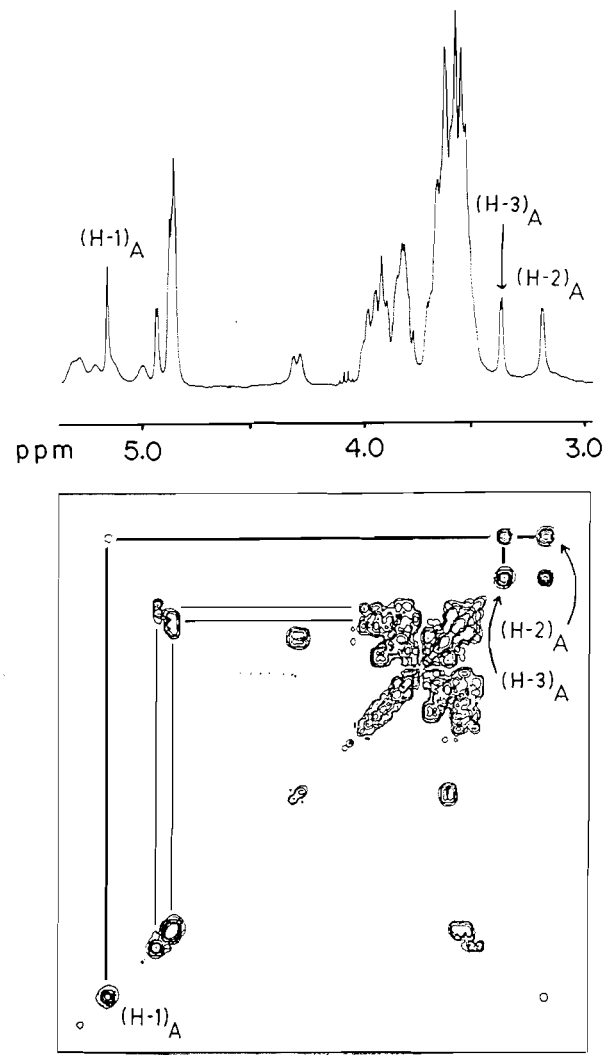


FIG. 13. Contour plot of the carbohydrate region of the COSY spectrum of **3** in deuterochloroform (2149–1192 Hz).

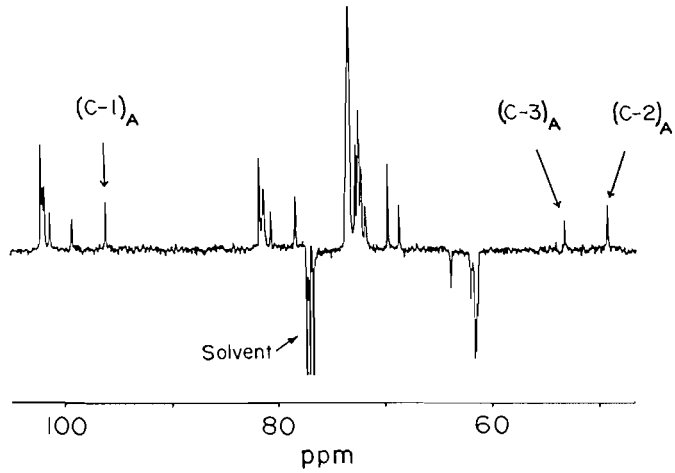


FIG. 14. The carbohydrate region of the *J*-modulated ^{13}C NMR spectrum of **3** in deuterochloroform (105.0–46.5 ppm).

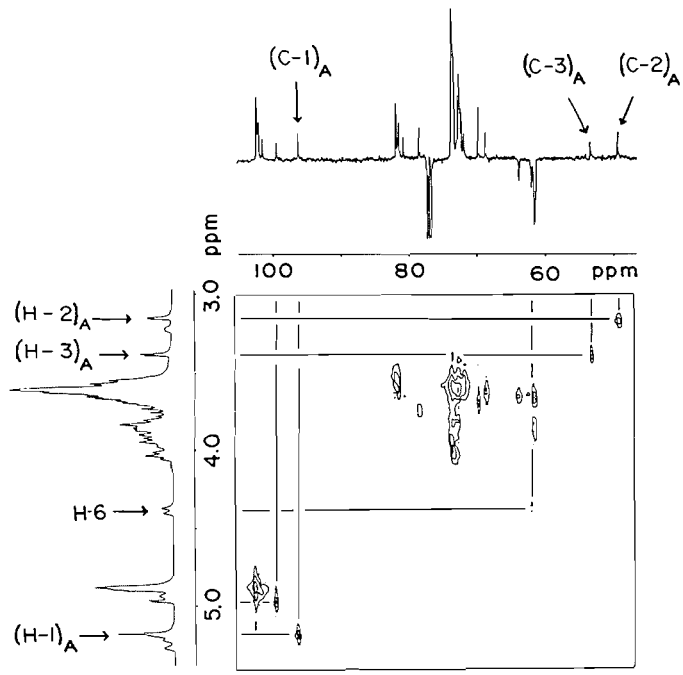
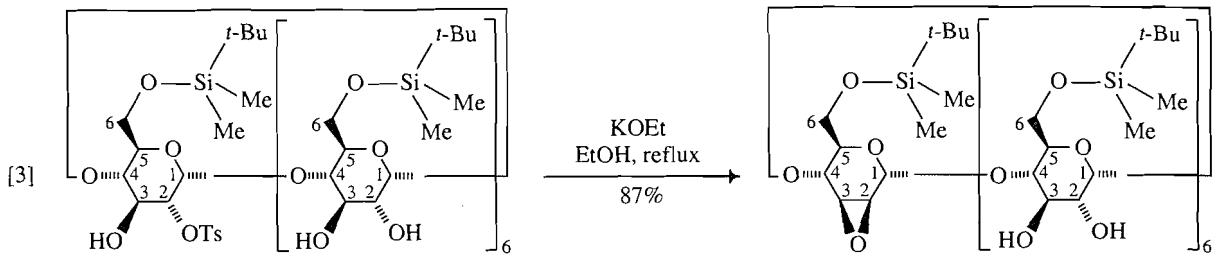


FIG. 15. Contour plot of the carbohydrate region of the ^{13}C–^{1}H shift correlation spectrum of **3** in deuterochloroform (^{1}H: 2151–1183 Hz, ^{13}C: 105.0–46.5 ppm).

which appear at 3.72 ppm. This is consistent with the electron-withdrawing effect of tosylation at C-2 of subunit A. All other H-1 resonances are coupled to H-2 resonances with chemical shifts similar to the H-2 resonances in **1**. The aromatic region shows only one set of ring protons and only one tosyl methyl group is observed. Examination of the ^{13}C spectrum of **2** also shows only one set of aromatic and methyl resonances for the tosyl group. Consequently, it appears that the reaction has produced the C-2 tosylate exclusively.

The ^{13}C–^{1}H shift correlation spectrum of **2** is presented in Fig. 10. It allows the assignment of $(C\text{-}1)_A$, $(C\text{-}2)_A$, and $(C\text{-}3)_A$ resonances from the known $(H\text{-}1)_A$, $(H\text{-}2)_A$, and $(H\text{-}3)_A$ resonances. $(C\text{-}1)_A$ and $(C\text{-}3)_A$ are shifted upfield from the C-1 and C-3 resonances of **1**, respectively, while $(C\text{-}2)_A$ is shifted



2 3

downfield from the C-2 resonances of **1**. This behavior is expected when a tosylate group is introduced at the C-2 position of **1**, and has been observed in comparisons of the spectra of β-CD and its C-2 tosylate (8).

The silylated CD epoxide **3** is prepared from the tosylate in good yield (87%) by treatment with 1 equivalent of KOEt in refluxing ethanol (eq. [3]).

Confirmation that a C-2 tosylate was produced above is possible from an examination of the spectra of the epoxide. A C-2 tosylate yields a manno-epoxide, while a C-3 tosylate yields an allo-epoxide, and ^{1}H coupling patterns are different in the two epoxides.

In both epoxides, one expects $J_{2,3}$ = 4 Hz. For manno-epoxides, weak coupling between hydrogens that are mutually *trans* results in $J_{1,2} = J_{3,4} = 0$ Hz. In contrast, $J_{1,2} = J_{3,4}$ = 2.5–4.5 Hz for allo-epoxides (22). Consequently, allo- and manno-epoxides are readily distinguished on the basis of the coupling patterns of their epoxide protons, as summarized in Fig. 11.

The H-2 and H-3 resonances of 2,3-anhydroaldopyranoses appear between 3.1 and 3.6 ppm in deuterochloroform solution (22). The carbohydrate region of the ^{1}H spectrum of epoxide **3** (Fig. 12) contains two *doublets* at 3.20 and 3.37 ppm, with coupling constants of 3.4 Hz. There is also one H-1 resonance at 5.19 ppm, which appears as a sharp *singlet*, i.e., coupling to H-2 has been lost. These observations and the absence of any other resonances in the epoxide region with more complex coupling patterns are consistent with a manno-epoxide structure and are parallel to observations for the manno-epoxide derived from unmodified β-CD (5).

The COSY spectrum of the epoxide (Fig. 13) confirms that the resonances assigned to $(H\text{-}2)_A$ and $(H\text{-}3)_A$ are mutually coupled and that $(H\text{-}2)_A$ is weakly coupled to $(H\text{-}1)_A$. Coupling of $(H\text{-}3)_A$ to $(H\text{-}4)_A$ was not detected.

The ^{13}C spectrum of the epoxide (Fig. 14) is also informative. The C-2 and C-3 resonances of 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranose appear at 50.4 and 53.0 ppm, respectively, while those of the analogous manno-epoxide appear at 50.6 and 53.9 ppm, respectively (deuterobenzene solution) (23). The ^{13}C spectrum of **3** contains only two peaks in this region, at 49.1 and 53.1 ppm (deuterotoluene solution, spectrum not shown), confirming that the sample contains only one type of epoxide.

The ^{13}C–^{1}H shift correlation spectrum of **3** in $CDCl_3$ is shown in Fig. 15. The sharp downfield singlet at 5.19 ppm ($(H\text{-}1)_A$) correlates with a peak at 96.2 ppm in the ^{13}C spectrum, which is assigned to $(C\text{-}1)_A$. The upfield doublets assigned to $(H\text{-}2)_A$ and $(H\text{-}3)_A$ correlate with peaks at 49.1 and 53.1 ppm (the epoxide carbons, $(C\text{-}2)_A$ and $(C\text{-}3)_A$), as expected. The doublet at 4.30 ppm can now be assigned to an H-6 resonance because it correlates with a peak in the C-6 region of the ^{13}C spectrum.

Conclusions

The manno-epoxide derived from heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD was prepared in three steps and 15% overall yield from β-cyclodextrin via intermediates that are easily purified. This allows reactions to be carried out on a larger scale than was previously possible. Synthetic intermediates were characterized by two-dimensional NMR methods and the stereochemistry of the final product was assigned. Attachment of catalytic groups to the cyclodextrin in a well-defined manner is now possible. Nucleophilic attack on the epoxide, followed by removal of the silyl groups, can be used in future work to prepare a wide variety of enzyme model systems.

Experimental

Methods and materials

NMR spectra were recorded on a Bruker AM 400 spectrometer (^{1}H: 400 MHz; ^{13}C: 100 MHz) in deuterotoluene or deuterochloroform solution. Chemical shifts are reported in parts per million downfield from TMS.

Representative parameters used to obtain the two-dimensional spectra were as follows: COSY: spectral width of 2500 Hz, centered at 6150 Hz, 256 experiments, each consiting of 8 scans stored in 1K of data, a recycle delay of 3 s. The transformed spectrum was symmetrized about the diagonal. Heteronuclear shift correlation: ^{1}H: spectral width of 2500 Hz, centered at 6150 Hz, ^{13}C: spectral width of 10 kHz, centered at 52 000 Hz, 256 experiments, each consisting of 48 scans stored in 1K of data, τ_1 = 3.5 ms, τ_2 = 2 ms.

Thin-layer chromatography (TLC) was performed using HP-TLC plates (Merck) coated with silica gel 60 in the following solvent system (A): ethyl acetate – ethanol–water 50:7:4 (v/v). Compounds were visualized by spraying the plates with a solution of 10% sulfuric acid containing 1% cerium sulfate and 1.5% molybdic acid, followed by heating.

Flash chromatography was performed using Kieselgel 60 (Merck, 230–400 mesh), following the procedure of Still *et al.* (24), using the following solvent systems: ethyl acetate – ethanol–water (B) 25:2:1, (C) 16:2:1, (D) 12:2:1, and (E) 50:2:1 (v/v).

Optical rotations were measured with a Perkin–Elmer 241 polarimeter using the sodium D line.

β-CD was dried overnight at 100°C under vacuum (<2 Torr; 1 Torr = 133.3 Pa). Pyridine was distilled from CaH_2 and stored over 3 Å molecular sieves.

Synthesis of 1

In a dry box, dried β-CD (3.72 g, 3.28 mmol) was weighed into a glass bulb fitted with a ground glass joint. The glass bulb was then attached to a three-neck round bottom flask equipped with a stirring bar and the flask was septum-sealed in the dry box. *tert*-Butyldimethylsilyl chloride (3.636 g, 24.1 mmol, 7.35 equiv.) was weighed into a septum-sealed vial.

Dry pyridine (35 mL) was added to the flask by syringe. The weighed CD was added to the stirred pyridine in small portions by inverting the glass bulb. Dry pyridine was also added to the vial containing the silyl chloride and the solution was then added to the CD solution dropwise by syringe. The reaction mixture was stirred overnight (18 h), then

poured into ice-cold water (350 mL) and stirred vigorously for 10 min.[1] The resulting precipitate was filtered off, washed with ice-cold water, and dissolved in ethyl acetate (70 mL). The solution was washed with 5% aqueous HCl solution (3 × 50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and saturated brine (50 mL). Finally, the solution was dried (anhydrous Na_2SO_4), filtered, concentrated, and traces of solvent were removed at 100°C under vacuum (<2 Torr) to give 5.69 g (90%) of crude product.

A portion of the crude product (0.423 g) was purified by flash chromatography using a gradient elution with solvents B, C, and D. Pure **1** (0.342 g) was obtained, resulting in an overall yield of 73%, mp 299–300°C (dec., from ethanol) (lit. (14) mp 299–302°C (dec., from ethanol); $[\alpha]_D^{22}$ +111° (*c* 1.04, $CHCl_3$) (lit. (14) $[\alpha]_D^{22}$ +113° (*c* 1.4, $CHCl_3$)); ^1H NMR (toluene-d_8) δ: 0.18 (s, Me-Si), 1.02 (s, Me-C), 3.61 (t, J = 9 Hz, H-4), 3.72 (dd, J = 3.2, 9.5 Hz, H-2), 3.78 (d, J = 9.5 Hz, H-5), 3.86 (d, J = 11 Hz, H-6_a), 4.05 (dd, J = 2.5, 11 Hz, H-6_b), 4.28 (t, J = 9 Hz, H-3), 4.91 (d, J = 3 Hz, H-1); ^{13}C NMR (toluene-d_8) δ: −1.9 (*Me*-Si), 18.4 (Me-*C*), 26.1 (*Me*-C), 62.4 (C-6), 73.0 (C-5), 74.0 (C-3), 74.3 (C-2), 82.6 (C-4), 102.7 (C-1); ($CDCl_3$) δ: −5.2, −5.1 (*Me*-Si), 18.3 (Me-*C*), 25.9 (*Me*-C), 61.6 (C-6), 72.5 (C-5), 73.4 (C-3), 73.6 (C-2), 81.8 (C-4), 102.0 (C-1). Anal. calcd. for $(C_{12}H_{24}O_5Si)_7$: C 52.15, H 8.75; found: C 51.54, H 8.52.

Synthesis of **2**

Compound **1** (0.392 g, 0.203 mmol) and *N*-tosylimidazole (prepared according to ref. 21, 0.067 g, 0.303 mmol) were dissolved in chloroform (2.5 mL), then sodium methoxide (0.162 g, 0.300 mmol) was added and the mixture refluxed for 6 h. Chloroform (6 mL) was added and the reaction mixture was washed with water (10 mL), then dried (anhydrous Na_2SO_4). The crude product was purified by flash chromatography (solvent E), giving pure **2** (0.083 g, 22% yield), mp 199–200°C (dec., from ethanol); $[\alpha]_D^{19}$ +102° (*c* 0.83, $CHCl_3$); ^1H NMR (toluene-d_8) δ: 0.10–0.27 (Me-Si), 0.88–1.12 (Me-C), 2.15 (s, tosyl Me), 3.07 (t, H-4), 3.45 (H-2), 3.61–3.47 (heavily overlapped), 4.50 (d, (H-2)$_A$), 4.59 (d), 4.63 (s, H-1), 4.91 (H-1s), 5.07 (s, H-1), 5.65 (s, (H-1)$_A$), 8.18 (d, tosyl aromatic, other aromatic doublet obscured by solvent); ^{13}C NMR (toluene-d_8) δ: −4.9, −4.6 (Me-Si), 18.3 (*C*-Me), 21.3 (tosyl Me), 26.1 (*Me*-C), 62.3, 62.7, 63.0 (C-6s), 70.5 ((C-3)$_A$), 72.3, 72.6, 72.8, 73.3 (C-2s, C-3s), 74.0 ((C-2)$_A$), 79.2, 81.2, 81.8, 82.1, 82.5, 82.7 (C-4s), 99.5 ((C-1)$_A$), 102.3, 102.6, 102.7, 102.9, 103.2 (C-1s). Anal. calcd. for $C_{91}H_{174}O_{37}Si_7S$: C 52.32, H 8.40; found: C 51.79, H 8.18.

Synthesis of **3**

Following the procedure of Hough *et al.* (25), **2** (0.104 g, 4.96 × 10^{-5} mol) and potassium ethoxide (45 μL of a 1.132 M solution of KOEt in ethanol, 5.09 × 10^{-5} mol, 1.0 equiv.) were added to ethanol (1.2 mL). The solution was refluxed for 70 min, at which point TLC showed a single band. Ice water (10 mL) was added to the reaction mixture and the resultant precipitate was filtered off, washed with cold water, and dried under high vacuum to yield pure **3** (0.083 g, 87% yield), mp 259–260°C (from ethanol); $[\alpha]_D^{19}$ +99.3° (*c* 0.88, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 0.85 (Me-Si), 1.74 (Me-C), 3.20 (d, (H-2)$_A$), 3.37 (d, (H-3)$_A$), 3.53–4.02 (heavily overlapped), 4.30 (d, H-6), 4.89–4.91 (H-1s), 4.95 (s, H-1), 5.19 (s, (H-1)$_A$); ^{13}C NMR ($CDCl_3$) δ: −5.37 (Me-Si), 18.1 (*C*-Me), 25.8 (*Me*-C), 49.1 ((C-2$_A$), 53.1 ((C-3)$_A$), 61.3, 61.4, 61.6, 61.9, 63.8 (C-6s), 68.6, 69.7, 71.8, 72.2, 72.4, 72.7, 73.3, 78.3, 80.7, 81.3, 81.7 (C-2s, C-3s, C-4s), 96.2 ((C-1$_A$), 99.3, 101.3, 101.8, 102.0, 102.2 (C-1s). Anal. calcd. for $C_{84}H_{166}O_{34}Si_{79}$: C, 52.64; H, 8.73; found: C, 51.89; H, 8.66.

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[1]The work-up is similar to that of Takeo *et al.* (14).

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