Novel Method to Prepare Dihydroxy Permethylated *β*-Cyclodextrin Isomeric Intermediates for Bifunctional Enzyme Mimics

Zhen Chen, Jerald S. Bradshaw,* Yu-Feng Shen, Yoichi Habata,† and Milton L. Lee

Department of Chemistry & Biochemistry, Brigham Young University, Provo, Utah 84602

Received August 28, 1997[⊗]

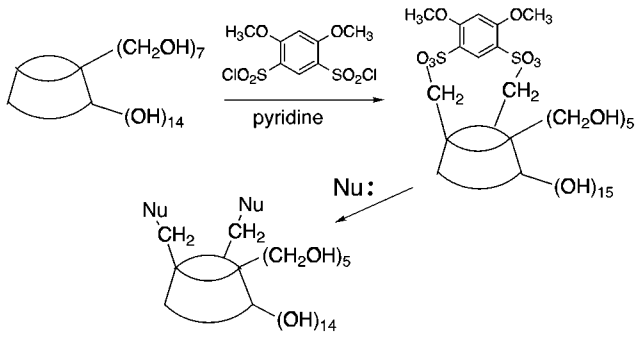
Natural *β*-cyclodextrin was treated with 3.5 equiv of *tert*-butyldimethylsilyl chloride and then with NaH and MeI in the same reaction vessel to give a mixture of oligosilyl-substituted permethylated *β*-cyclodextrins. The mixture was treated with NH_4F and the resulting $6^A,6^D$-(**1**), $6^A,6^C$-(**2**), and $6^A,6^B$-(**3**) dihydroxy permethylated *β*-cyclodextrins were isolated in 7.6−8.9% yields by two silica gel chromatographic separations. The structures of **1**−**3** were verified by comparison of spectral properties with a known diol (**2**) or preparing known derivatives (**1** and **3**). This is a superior way to prepare and isolate dihydroxy permethylated *β*-cyclodextrin intermediates for bifunctional enzyme mimics.

Introduction

Cyclodextrins are cyclic oligosaccharides obtained from starch.[1] The three best characterized forms are α-, *β*-, and *γ*-cyclodextrins consisting of six, seven, and eight D-(+)-glucopyranose units, respectively. Each of the units are linked together by α-1,4 bonds. This geometry gives cyclodextrin the shape of a hollow truncated cone with the wider side formed by the secondary 2- and 3-hydroxy groups and the narrower side by the primary 6-hydroxy groups. The intramolecular hydrogen bonds between C(2)-OH and C(3)-OH of adjacent glucose units helps to keep cyclodextrin in a symmetrical shape.[2]

The most significant property of the cyclodextrins is their ability to form inclusion complexes with a wide variety of substrates.[3] Cyclodextrins are very popular building blocks for supramolecular structures,[4,5] and their derivatives are widely used in the fields of both analytical chemistry (mainly for the purpose of chiral discrimination)[6,7] and as enzyme mimics.[8] Chemical modification of cyclodextrins has been extensively investigated.[9] However, these modifications are difficult to control because of problems arising from steric and statistical factors imposed by the torus structure and the large number of hydroxy groups. Regiospecific multifunctionalization of the cyclodextrin is especially challenging, although it is necessary for the purpose of building more refined and sophisticated enzyme models. A rigid disulfonate capping method has been developed to regiospecifically bifunctionalize the primary rim of *β*-cyclodextrin, which is the most widely studied cyclodextrin because of its good binding ability toward aromatic units and it is readily available. After one end of the disulfonyl chloride capping reagent is attached to one of the primary 6-OH groups, the other end is forced to attach to a certain 6-OH group because of the rigidity of the backbone of the capping reagent. The capped molecules are subjected to further nucleophilic substitutions leading to a series of bifunctionalized *β*-cyclodextrins (Scheme 1). Through a two-decade effort, a series of standard capping reagents has been established.[10,11] *m*-Benzenedisulfonyl chloride and 1,3-dimethoxybenzene-4,6-disulfonyl chloride are used to activate two C(6)-OH groups which belong to two adjacent glucose units designated by A and B. *p,p′*-Methylenebis(benzenesulfonyl chloride) and *m,m′*-benzophenonedisulfonyl chloride are used to activate the A and C glucose units, and 4,4′-biphenyldisulfonyl chloride and 4,4′-*trans*-stilbenedisulfonyl chloride the A and D glucose units.[10,11]

Scheme 1



Since its introduction, the capping method has been widely used. However, some problems have been identified. First, purification of the capped intermediate is usually tedious, often requiring reverse-phase HPLC; second, further nucleophilic substitution is limited to strong sulfur or nitrogen nucleophiles;[12] third, in some

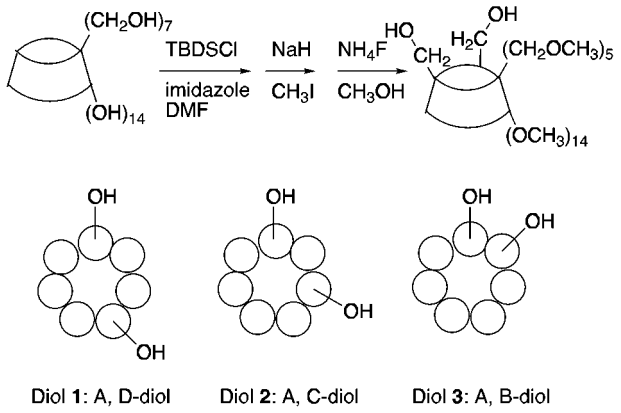
† Current address: Department of Chemsitry, Faculty of Science, Toho University, 2-2-1 Miyama Funabashi, Chiba 274 Japan

⊗ Abstract published in *Advance ACS Abstracts,* November 1, 1997.

(1) Sanger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344.
(2) (a) Gillet, B.; Nichole, D. J.; Delpuech, J. J. *Tetrahedron Lett.* **1982**, *23*, 65. (b) Yamamoto, Y.; Inoue, Y. J. *Carbohydr. Chem.* **1989**, *8*, 29.
(3) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1978.
(4) Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803.
(5) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725.
(6) Li, S.; Purdy, W. C. *Chem. Rev.* **1992**, *92*, 1457.
(7) Easton, C. J.; Lincoln, S. F. *Chem. Soc. Rev.* **1996**, *25*, 163.
(8) Tabushi, I: Functionalized Cyclodextrins as Artificial Enzymes. In *Chemical Approaches to Understanding Enzyme Catalysis*; Green, B., Ashani, Y., Chipman, D., Eds.; Elsevier: Amsterdam, 1982.
(9) Bartsch, R. A.; Croft, A. P. *Tetrahedron* **1983**, *39*, 1417.
(10) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146.
(11) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66.
(12) It has been reported that when employing poor nucleophiles, intramolecular substitution which leads to epoxide structures may occur. For examples, see: (a) Breslow, R.; Czarnik, A. W. *J. Am. Chem. Soc.* **1983**, *105*, 1390. (b) Ashton, P. R.; Koniger, R.; Stoddart, J. F. *J. Org. Chem.* **1996**, *61*, 903.
(13) Tabushi, I.; Yamamura, K.; Nabesshima, T. *J. Am. Chem. Soc.* **1984**, *106*, 5267.
(14) Yi, G.-L.; Bradshaw, J. S.; Rossiter, B. E.; Reese, S. L.; Petersson, P.; Markides, K.; Lee, M. L. *J. Org. Chem.* **1993**, *58*, 2561.

S0022-3263(97)01604-6 CCC: $14.00

Scheme 2



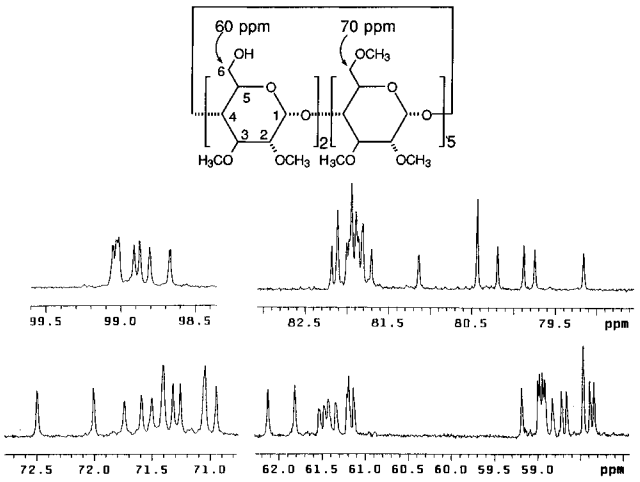
Diol **1**: A, D-diol Diol **2**: A, C-diol Diol **3**: A, B-diol

cases, the A,C/A,D bis-sulfonate ester distribution is dependent on reaction temperature and concentration;[13,14] and the capping method is most suitable for natural β-cyclodextrin. For some cyclodextrin derivatives, such as heptakis(2,3-di-*O*-methyl)-β-cyclodextrin, the yields of the capping step are very low. Reactions of 1,3-dimethoxybenzene-4,6-disulfonyl chloride and 4,4′-biphenyldisulfonyl chloride with heptakis(2,3-di-*O*-methyl)-β-cyclodextrin, to prepare the A,B- and A,D-disulfonate esters, respectively, gave low yields of 3.5%[15] and 4.9%,[16] respectively, while yields of the similar reactions with natural β-cyclodextrin were 13.0%[17] and 17.5%,[13] respectively.

We herein report a novel strategy (Scheme 2) to regiospecifically bifunctionalize the primary rim of β-cyclodextrin. $6^A,6^D$- (**1**), $6^A,6^C$- (**2**), and $6^A,6^B$- (**3**) dihydroxy permethylated β-cyclodextrins are prepared from natural β-cyclodextrin at the same time through a convenient three-step process. The first two steps are in one pot. By using compounds **1**−**3** as intermediates, bifunctionalized β-cyclodextrins are easy to obtain without encountering the problems of the capping method.

Results and Discussion

The *tert*-butyldimethylsilyl group (TBDS) is a valuable protecting group in cyclodextrin chemistry.[18,19] It can be selectively attached to the primary C(6)-OH groups of the cyclodextrin glucose residues, and the silyl groups are stable under ordinary conditions. To prepare the mixed dihydroxy isomers, natural β-cyclodextrin was treated with 3.5 equiv of *tert*-butyldimethylsilyl chloride and imidazole in DMF. After stirring at rt for 1 h, the reaction reached equilibrium. TLC analysis on silica gel (1-BuOH/EtOH/H_2O: 5/4/3 by volume) showed a series of spots which corresponded to unreacted cyclodextrin and the TBDS-substituted cyclodextrins. Exhaustive methylation of all the remaining hydroxy groups, including C(2)-OH, C(3)-OH and unreacted C(6)-OH groups, was achieved using a large excess of NaH and MeI in the same reaction vessel. Although migration of TBDS groups from O-2 to O-3 during the alkylation process is



C-1	98.5 - 99.1 ppm	7 peaks
C-2, 3, 4	79.0 - 82.3 ppm	21 peaks
C-5, C-6 (containing OCH_3)	70.8 - 72.6 ppm	12 peaks
2-OCH_3, C-6 (containing OH)	61.0 - 62.3 ppm	9 peaks
3-OCH_3, 6-OCH_3	58.8 - 59.2 ppm	12 peaks

Figure 1. ^{13}C NMR spectrum of diol **3** and collective assignment of peaks.

usual, the same groups at the 6 positions are stable.[20] After methylation was completed, desilylation was accomplished by refluxing the resulting mixture of oligosilyl-substituted permethylated β-cyclodextrins with NH_4F in CH_3OH overnight.[21] TLC (silica gel, $CHCl_3/CH_3OH$: 10/1) gave three very close spots (R_f = 0.40, 0.36, and 0.30) below the spots corresponding to permethylated β-cyclodextrin (R_f = 0.68) and mono-6-hydroxy permethylated β-cyclodextrin (R_f = 0.54).[22] The three close spots are caused by three regioisomeric 6,6-dihydroxy permethylated β-cyclodextrins **1**−**3,** respectively. Pure diols **1**−**3** were obtained after two careful column chromatography steps ($CHCl_3/CH_3OH$: 50/1) on silica gel.

Diols **1**−**3** were fully characterized as 6,6-dihydroxy permethylated β-cyclodextrins by ^1H and ^{13}C NMR spectroscopy, HRFABMS, and elemental analyses. ^{13}C NMR spectroscopy is an important tool to determine the structures of cyclodextrin compounds. Most of the ^1H NMR signals of cyclodextrin compounds will overlap in a small range of 3−4 ppm, while the ^{13}C NMR signals spread in a wide range and thus provide more information about the structure. Figure 1 shows the ^{13}C NMR spectrum of diol **3** and the collective assignment of peaks. The signal for the C-6 atom containing an OH group appears at about 60 ppm.[23] In the range of 61.0−62.5 ppm, there are two peaks from C(6) which are connected to hydroxy groups, the other seven peaks in that range are from methoxy groups at the C(2) positions. The DEPT NMR technique indicates which two peaks are from C(6). The DEPT spectrum is unique in that peaks corresponding to methyl and methine carbon atoms point up and those for methylene carbon atoms point down. Figure 2 shows the partial DEPT spectrum of **3**. The two down-pointing peaks are from C(6) atoms which contain

(15) Chen, Z.; Bradshaw, J. S.; Yi, G.-L.; Pyo, D.; Black, D. R.; Zimmerman, S. S.; Lee, M. L.; Tong, W.; D'Souza, V. T. *J. Org. Chem.* **1996**, *61*, 8949.
(16) Yi, G.-L.; Bradshaw, J. S.; Rossiter, B. E.; Malik, A.; Yun, H.; Lee, M. L. *J. Heterocycl. Chem.* **1995**, *32*, 621.
(17) Tabushi, I.; Nabeshima, T.; Fujita, K.; Matsunaga, A.; Imoto, T. *J. Org. Chem.* **1985**, *50*, 2638.
(18) Pregel, M. J.; Buncel, E. *Can. J. Chem.* **1991**, *69*, 130.
(19) Takeo, K.; Mitoh, H.; Uemura, K. *Carbohydr. Res.* **1989**, *187*, 203.
(20) Icheln, D.; Gehrcke, B.; Piprek, Y.; Mischnick, P.; Konig, W.; Dessoy, M. A.; Morel, A. F. *Carbohydr. Res.* **1996**, *280*, 237.
(21) Zhang, W.-J.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177.
(22) Chen, Z.; Bradshaw, J. S.; Lee, M. L. *Tetrahedron Lett.* **1996**, *37*, 6831.
(23) Boger, J.; Corcoran, R. J.; Lehn, J.-M. *Helv. Chim. Acta* **1978**, *61*, 2190.

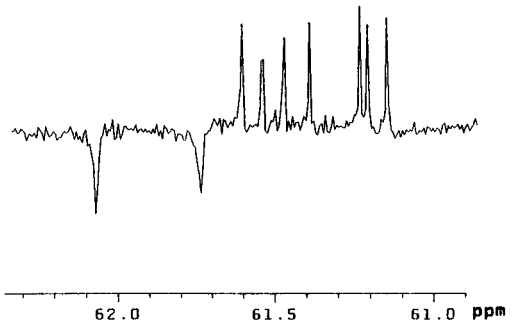
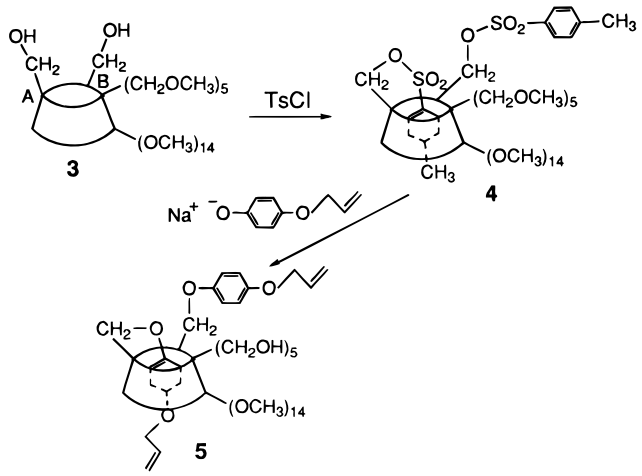


Figure 2. Partial DEPT spectrum of diol **3**.

Scheme 3



the OH groups. At the same time, *O*-methylation of the hydroxy group is expected to shift the C-6 signal to about 70 ppm.[23] In fact, there are twelve peaks in the range of 70.8−72.5 ppm, seven of them are from C(5) and five from C(6) atoms which are connected to methoxy groups. As shown in Figure 1, there are seven signals each for the 2- and 3-OCH_3 groups but only five signals for the 6-OCH_3 groups. These spectral data clearly show that compound **3** is indeed a 6,6-dihydroxy permethylated compound. The ^{13}C NMR spectra of compounds **1** and **2** show similar characteristics.

Structural assignments for diols **1**−**3** were carried out by comparing them (or their derivatives) with known β-cyclodextrin compounds prepared by the capping method. Diol **2** has the same spectral and physical properties as those for $6^A,6^C$-diol prepared in our laboratory,[16] proving that diol **2** is $6^A,6^C$-dihydroxy permethylated β-cyclodextrin. $6^A,6^B$- and $6^A,6^D$-*O*-bis(*p*-(allyloxy)phenyl)-substituted permethylated β-cyclodextrins have also been prepared in our laboratory.[14,15] These dialkene-substituted cyclodextrins were hydrosilylated with a hexasiloxane containing an Si−H unit on each end. The resulting copolymers were excellent chiral stationary phases for gas chromatography.[24,25] Diol **3** was treated with tosyl chloride and (dimethylamino)pyridine (DMAP) to produce ditosylate **4** (Scheme 3). Compound **4** was treated with *p*-(allyloxy)phenoxide in DMF to produce the bifunctionalized cyclodextrin which has the same spectral and physical properties as those of $6^A,6^B$-bis-*O*-(*p*-(allyloxy)phenyl)-substituted permethylated β-cyclodextrin (**5**)[15]

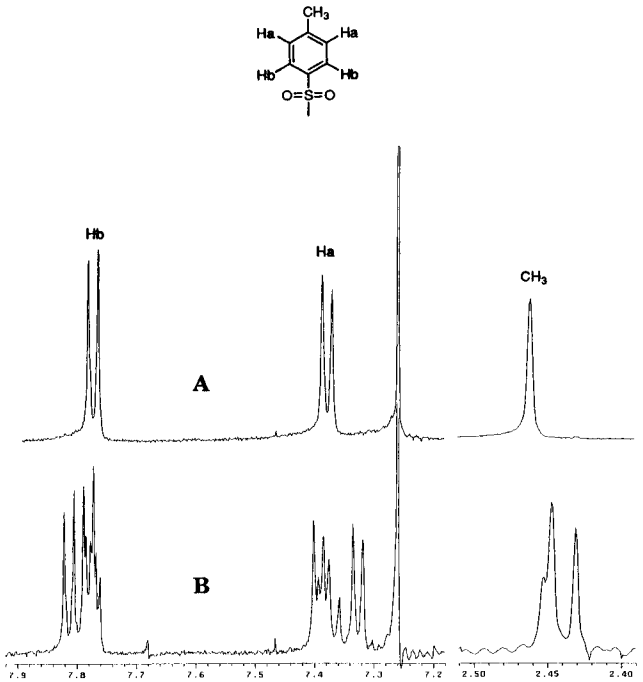


Figure 3. Partial ^1H NMR spectra of monotosyl-substituted permethylated β-cyclodextrin (A) and compound **4** (B).

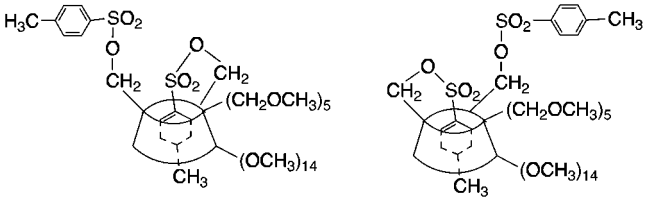


Figure 4. Proposed isomers of compound **4**.

where one of the *p*-(allyloxy)phenyl substituents is in the cyclodextrin cavity and the other out,[15] as shown. This set of reactions proves that diol **3** is $6^A,6^B$-dihydroxy permethylated β-cyclodextrin.

The conformations of the two tosyl groups in compound **4** are of interest. Figure 3 shows the ^1H NMR signals generated by the tosyl groups of **4** along with those for monotosylated permethylated β-cyclodextrin.[26] Proton Ha of the ditosylate generates four pairs of doublets as does proton Hb. This indicates that the two tosyl groups of **4** are in four different NMR environments. We propose that one of the tosyl groups is included or partially included in the cyclodextrin cavity to relieve steric strain caused by the substituents in the 6-*O* positions. Because of the chiral nature of cyclodextrin, two diastereomers may exist (Figure 4). Thus, there are four different tosyl groups. This proposal is reasonable. First, after permethylation, the molecule becomes more flexible due to a loss of the chain of circumferal intramolecular hydrogen bonds between the secondary hydroxy groups of adjacent D-glucose units. Second, in a recent paper concerning the conformational behavior of perfunctionalized β-cyclodextrins,[27] Lehn and co-workers demonstrated that for sterically hindered cyclodextrins bearing aromatic units, one of the C6-substituents could enter the cavity. This

(24) Petersson, P.; Reese, S. E.; Yi, G.-L.; Yun, H.; Malik, A.; Bradshaw, J. S.; Rossiter, B. E.; Lee, M. L. Markides, K. E. *J. Chromatogr. A* **1994**, *684*, 297.

(25) Malik, A.; Yun, H.; Yi, G.-L.; Bradshaw, J. S.; Rossiter, B. E.; Markides, K. E.; Lee, M. L. *J. Microcolumn Sep.* **1995**, *7*, 91.

(26) Yi, G.-L.; Bradshaw, J. S.; Rossiter, B. E.; Malik, A.; Li, W.-B.; Petersson, P.; Makides, K. E.; Lee, M. L. *J. Org. Chem.* **1993**, *58*, 4844.

(27) Jullien, L.; Canceill, J.; Lacombe, L.; Lehn, J.-M. *J. Chem. Soc., Perkin Trans. 2* **1994**, 989.

self-satisfaction process is more entropically favorable than an intermolecular association.

Why the interaction of **4**, containing one included tosyl unit, with *p*-(allyloxy)phenoxide gave only **5** with one included *p*-(allyloxy)phenyl group as the exclusive product is not known. Molecular modeling has shown that a free *p*-(allyloxy)phenoxide group would preferentially attack a 6^A-*O*-(*p*-(allyloxy)phenyl)-6^B-*O*-(4,6-dimethoxy-3-sulfinato)sulfonyl-substituted permethylated cyclodextrin from inside the cavity.[28] In the case of **4**, the first attack by the *p*-(allyloxy)phenoxide could be on the carbon of the less sterically hindering included tosylate and the second on the carbon of the exterior tosylate from inside the cavity. Why some of the second nucleophilic attack does not take place from the outside to give some product **5** with both *p*-allyloxyphenyl substituents located outside the cavity is not understood.

The tosylation step is slow. Ditosylation of diol **3** took 3 days even using 20 equiv of tosyl chloride and 6 equiv of DMAP. Diols **1**−**3** were readily converted to the dimesylates in 90% yields in 30 min using 8 equiv of mesyl chloride and 6 equiv of DMAP. The dimesylate prepared from diol **1** was treated with *p*-(allyloxy)phenoxide to produce a 6,6-*O*-bis(*p*-(allyloxy)phenyl) permethylated *β*-cyclodextrin that had the same physical and spectral properties as 6^A,6^D-*O*-bis(*p*-(allyloxy)phenyl)-substituted *β*-cyclodextrin.[16] Thus, diol **1** must be the 6^A,6^D-diol derivative.

To make this method of preparing difunctionalized *β*-cyclodextrins practical, the yields of the dihydroxy compounds must be optimized. Using different amounts of *tert*-butyldimethylsilyl chloride in the first step gave varying amounts of the mono- and dihydroxy products. The product distribution was determined by peak area measurements from supercritical fluid chromatography (Figure 5). HPLC cannot easily be used in this case since the products have no UV absorption. Figure 6 shows the variation of yields of the various permethylated-cyclodextrin products versus varying amounts of the silyl chloride. When 3.5 equiv of the silyl reagent was used, the yield of the combined dihydroxy products was 38%. After purification on two silica gel columns, diols **1**−**3** were obtained in yields of 8.9%, 8.3%, and 7.6%, respectively.

Conclusion

Starting from the 6^A,6^B-, 6^A,6^C-, and 6^A,6^D-dihydroxy compounds we described here, bifunctionalized *β*-cyclodextrins are now easily available. There are some advantages of this method when compared with the classic capping method. First, three isomers are prepared easily in a reasonable yield at the same time. Second, all the hydroxy groups are methylated except the two primary 6-OH groups. Permethylation makes the compounds easy to purify, increases their solubility in organic solvents, and removes possible interference by the other hydroxy groups.[12] These diols cannot only act as nucleophiles, but they can also be transformed easily to dimesylates, which make further functionalizations more feasible.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 MHz. TLC was performed on aluminum backed silica gel 60, 0.2 mm plates ($CHCl_3$/MeOH: 10/1). Supercritical fluid chromatography was performed using a Lee Scientific Model 601 supercritical fluid chromatograph (Dionex, Salt Lake Division, Salt Lake City, UT) equipped with a 50 cm × 250 μm i.d. fused silica column packed with 10 μm silica particles (80 Å pores). Supercritical CO_2 was used as the mobile phase. Other conditions are described in the figure legend for Figure 5.

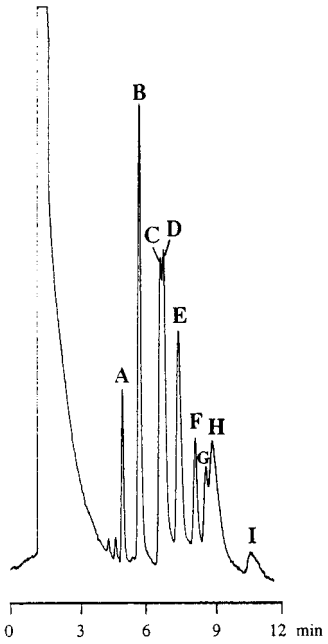


Figure 5. SFC analysis of products. A: permethylated *β*-cyclodextrins; B: mono-6-hydroxy permethylated *β*-cyclodextrin; C,D: 6,6-dihydroxy permethylated *β*-cyclodextrins; E−I: tri- and other oligohydroxy permethylated *β*-cyclodextrins. Conditions: 50 cm × 250 μm i.d. capillary column packed with 10 μm silica (80 Å pores) particles; CO_2, 70 °C, FID; pressure program from 250 atm at 5 atm min^{-1}.

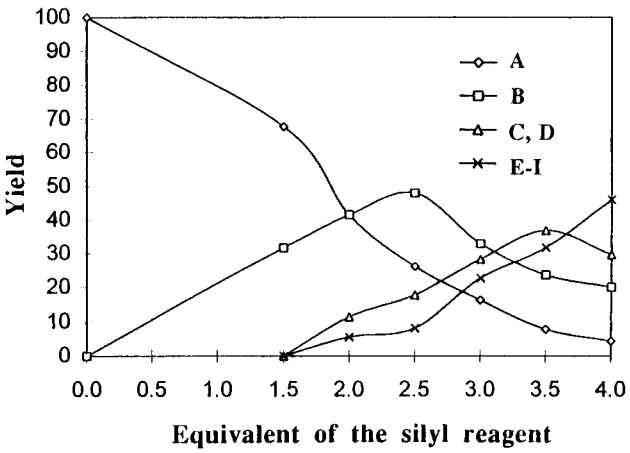


Figure 6. Optimized yields of products using differing amounts of *tert*-butyldimethylsilyl chloride. See Figure 5 for names of A−I.

6^A,6^D-, 6^A,6^C-, and 6^A,6^B-Dihydroxy Permethylated *β*-Cyclodextrins (diols 1−3). To a stirred mixture of *β*-cyclodextrin (4.54 g, 4.0 mmol) and imidazole (0.95 g, 14.0 mmol) in 200 mL of dry DMF was added *tert*-butyldimethylsilyl chloride (2.17 g, 14.0 mmol) in one portion. After stirring at rt for 1.5 h, the mixture was cooled to 0 °C and NaH (6.4 g, 260 mmol) was added. The mixture was stirred at 0 °C for 30 min and then at rt for 1 h. After cooling to 0 °C, 34 mL of CH_3I (545 mmol) was added dropwise. The mixture was kept for 1 h at 0 °C and then overnight at rt. The reaction was quenched by careful addition of 20 mL of ice−water. The resulting mixture was poured into 500 mL of ice−water with stirring and extracted with $CHCl_3$ (200 mL × 3). The combined organic

(28) Chen, Z.; Bradshaw, J. S.; Habata, Y.; Lee, M. L. *J. Heterocycl. Chem.* **1997**, *34*, 983.

layers were washed successively with 100 mL of a 6% aqueous solution of $Na_2S_2O_3$ and water (100 mL × 2) and then dried ($MgSO_4$). After concentration, the obtained solid residue (6.26 g) was refluxed with ammonium fluoride (5.16 g) in 250 mL of CH_3OH overnight. The mixture was evaporated and the residue dissolved in 200 mL of $CHCl_3$ and then filtered and concentrated. After column chromatography on silica gel (200−400 mesh; $CHCl_3$/MeOH: 50/1), pure $6^A,6^D$- and $6^A,6^B$- and a mixture of mostly $6^A,6^C$-dihydroxy permethylated β-cyclodextrins were isolated. The mixture was chromatographed a second time to give the pure $6^A,6^B$-, $6^A,6^C$-, and $6^A,6^D$-dihydroxy permethylated β-cyclodextrins. The total yields and physical and spectral properties are as follows:

$6^A,6^D$-Dihydroxy permethylated β-cyclodextrin (diol **1**, 499 mg, 8.9%): $R_f = 0.40$; mp 96−98 °C; $[\alpha]^{25}_D = +153.7°$ (*c* 1.01, $CHCl_3$); ^{1}H NMR: δ 5.20−4.95 (m, 7 H), 4.96−3.20 (m, 92 H), 3.20−3.10 (m, 7H), 2.84−3.08 (b, 2 H). ^{13}C NMR: δ 99.102, 98.858, 98.813, 98.751, 98.725, 98.520, 82.342, 82.241, 81.987, 81.935, 81.828, 81.685, 81.646, 81.627, 81.601, 81.552, 81.415, 81.392, 81.171, 81.022, 80.960, 80.784, 80.667, 80.105, 78.114, 77.875, 77.257, 77.202, 77.000, 76.746, 71.668, 71.609, 71.385, 71.333, 71.213, 71.122, 71.004, 70.985, 70.969, 61.547, 61.456, 61.404, 61.378, 61.362, 61.316, 60.835, 60.773, 59.134, 59.141, 59.008, 58.978, 58.959, 58.926, 58.900, 58.822, 58.409, 58.253, 58.195, 58.075, 57.961. HRFABMS: Calcd. for $C_{61}H_{108}O_{35}Na$: 1423.6569. Found: 1423.6583. Anal. Calcd for $C_{61}H_{108}O_{35}$: C, 52.27; H, 7.76. Found: C, 52.30; H, 7.78.

$6^A,6^C$-Dihydroxy permethylated β-cyclodextrin (diol **2**, 456 mg, 8.3%): $R_f = 0.36$; mp 104−106 °C; $[\alpha]^{25}_D = +154.1°$ (*c* 0.996, $CHCl_3$); ^{1}H NMR: δ 5.20−4.90 (m, 7 H), 4.00−3.31 (m, 92 H), 3.23−3.15 (m, 7 H), 2.80 (t, $J = 6.23$ Hz, 1 H), 2.68 (t, $J = 6.23$ Hz, 1 H). ^{13}C NMR: δ 99.062, 99.026, 99.002, 98.898, 98.813, 98.783, 98.486, 82.317, 82.123, 82.050, 82.013, 81.989, 81.928, 81.898, 81.819, 81.752, 81.667, 81.358, 81.121, 80.629, 80.496, 80.441, 80.271, 80.120, 79.470, 79.149, 71.999, 71.962, 71.714, 71.629, 71.568, 71.392, 71.331, 71.216, 71.088, 71.028, 70.973, 61.808, 61.748, 61.383, 61.365, 61.286, 61.268, 61.171, 61.098, 59.101, 58.968, 58.913, 58.865, 58.707, 58.531, 58.422, 58.409, 58.391, 58.270. HRFABMS: Calcd for $C_{61}H_{108}O_{35}Na$: 1423.6569. Found: 1423.6584. Anal. Calcd for $C_{61}H_{108}O_{35}$: C, 52.27; H, 7.76. Found: C, 52.19; H, 8.00.

$6^A,6^B$-Dihydroxy permethylated β-cyclodextrin (diol **3**, 425 mg, 7.6%): $R_f = 0.30$; mp 105−107 °C; $[\alpha]^{25}_D = +151.3°$ (*c* 0.97, $CHCl_3$); ^{1}H NMR: δ 5.20−5.00 (m, 7 H), 4.00−3.28 (m, 92 H), 3.25−3.16 (m, 7 H), 2.84 (b, 1 H), 2.50 (b, 1 H). ^{13}C NMR: δ 99.056, 99.032, 99.014, 98.911, 98.874, 98.807, 98.668, 82.183, 82.117, 82.007, 81.953, 81.898, 81.868, 81.813, 81.710, 81.139, 80.435, 80.193, 79.883, 79.749, 79.161, 72.503, 72.011, 71.738, 71.592, 71.501, 71.410, 71.319, 71.258, 71.046, 70.949, 62.130, 61.820, 61.541, 61.481, 61.432, 61.347, 59.192, 59.004, 58.986, 58.950, 58.925, 58.834, 58.725, 58.670, 58.470, 58.391, 58.343. HRFABMS: Calcd for $C_{61}H_{108}O_{35}Na$: 1423.6569. Found: 1423.6600. Anal. Calcd for $C_{61}H_{108}O_{35}$: C, 52.27; H, 7.76. Found: C, 52.20; H, 7.66.

$6^A,6^B$-Ditosyl-Substituted Permethylated β-Cyclodextrin (4). Diol **3** (0.80 g, 0.58 mmol) and DMAP (0.42 g, 3.45 mmol) were dissolved in 20 mL of dry pyridine. The solution was cooled in an ice bath. A solution of TsCl (2.19 g, 11.5 mmol) in dry pyridine (10 mL) was then added dropwise to the cooled reaction vessel. Cooling was continued for a 3 h before the solution was allowed to warm to rt. After standing for 3 days at rt, the solvent was removed under reduced pressure. The residue was dissolved in 100 mL of $CHCl_3$ and washed by H_2O (20 mL × 2). The $CHCl_3$ layer was separated, dried, and concentrated. The crude product was subjected to column chromatography (silica gel, $CHCl_3/CH_3OH$: 50/1) to give 0.61 g (62%) of a white solid; mp 119−121 °C; $[\alpha]^{25}_D = +143.8°$ (*c* 0.01, $CHCl_3$); ^{1}H NMR: δ 7.74−7.84 (m, 4 H), 7.40−7.30 (m, 4 H), 5.20−4.80 (m, 7 H), 4.20−3.0 (m, 99 H), 2.46−2.42 (m, 6 H); ^{13}C NMR: δ 144.84, 144.72, 133.16, 129.97, 129.93, 129.78, 128.04, 127.99, 127.93, 99.15, 99.00, 98.88, 98.74, 98.66, 98.42, 98.27, 98.16, 82.06, 81.86, 81.58, 81.44, 80.34, 80.13, 79.77, 79.34, 71.35, 71.30, 71.15, 71.04, 70.86, 70.80, 70.60, 69.84, 69.65, 69.52, 61.60, 61.39, 58.99, 58.46, 21.67. HRFABMS: Calcd for $C_{75}H_{120}O_{39}S_2Na$: 1731.6746. Found: 1731.6715. Anal. Calcd for $C_{75}H_{120}O_{39}S_2$: C, 52.68; H, 7.07. Found: C, 52.45; H, 6.96.

$6^A,6^B$-*O*-Bis(*p*-allyloxyphenyl)-Substituted Permethylated β-Cyclodextrin (5). Under an atmosphere of Ar, *p*-(allyloxy)phenol (600 mg, 4 mmol) was stirred with NaH (100 mg, 4 mmol) at rt in 10 mL of dry DMF for 1 h. Compound **4** (171 mg, 0.1 mmol) was added to the solution in one portion. After stirring at rt for 24 h, DMF was removed under reduced pressure. The residue was partitioned between $CHCl_3$ and H_2O. The organic layer was separated, dried, and concentrated. The crude product was subjected to column chromatography on silica gel ($CHCl_3/CH_3OH$: 50/1) to give 103 mg (62%) of **5**. The physical and spectral properties of **5** are the same as those reported.[15]

$6^A,6^D$-Dimesyl-Substituted Permethylated β-Cyclodextrin. Diol **1** (420 mg, 0.3 mmol) was disolved in 10 mL of dry pyridine containing DMAP (220 mg, 1.8 mmol). The solution was cooled in an ice bath. A solution of MsCl (275 mg, 2.4 mmol) in 5 mL of dry pyridine was added dropwise into the cooled solution. A white precipitate appeared immediately and a gellike mixture was formed. The mixture was then stirred at rt for another 20 min. The solvent was removed under reduced pressure. The residue was dissolved in 100 mL of $CHCl_3$ and washed by H_2O (20 mL × 2). The $CHCl_3$ layer was separated, dried, and concentrated. The crude product was purified by coloumn chromatography (silica gel, $CHCl_3/CH_3OH$: 50/1) to give 388 mg (83.4%) of a white solid; mp 108−110 °C; $[\alpha]^{25}_D = +142.6°$ (*c* 0.02, $CHCl_3$); ^{1}H NMR: δ 5.20−5.0 (m, 7H), 4.60−4.40 (m, 4H), 4.15−3.25 (m, 91H), 3.24−3.15 (m, 7H), 3.06 (s, 3H). ^{13} C NMR: δ 99.43, 99.30, 99.14, 99.09, 98.75, 98.56, 98.41, 82.18, 82.06, 81.84, 81.80, 81.75, 81.67, 81.63, 81.56, 80.75, 80.54, 80.35, 80.22, 80.00, 79.45, 71.46, 71.19, 71.11, 71.02, 70.96, 70.88, 69.83, 69.72, 69.46, 69.43, 61.65, 61.63, 61.60, 61.57, 61.54, 61.52, 61.48, 61.47, 61.46, 61.31, 61.29, 59.09, 59.07, 59.04, 59.00, 58.75, 58.73, 58.63, 58.60, 58.45, 58.42, 58.32, 58.31, 58.28, 37.29, 37.26. HRFABMS: Calcd for $C_{63}H_{112}O_{39}S_2Na$: 1579.6120. Found: 1579.6136. Anal. Calcd for $C_{63}H_{112}O_{39}S_2$: C, 48.58; H, 7.25. Found: C, 48.70; H, 7.16.

$6^A,6^C$-Dimesyl-Substituted Permethylated β-Cyclodextrin. This compound was prepared from diol **2** in a 97% yield using the same method as for the $6^A,6^D$-dimesylate; mp 115−117 °C; $[\alpha]^{25}_D = +151.44°$ (*c* 0.03, $CHCl_3$); ^{1}H NMR δ: 5.18−4.96 (m, 7H), 4.60−4.30 (m, 4H), 4.0−3.2 (m, 91H), 3.2−3.05 (m, 7H), 3.0 (s, 3H); ^{13}C NMR δ: 99.24, 99.00, 98.70, 98.39, 98.31, 81.93, 81.78, 81.70, 81.61, 81.49, 81.39, 81.32, 80.50, 80.16, 79.82, 79.72, 77.26, 77.19, 77.00, 76.75, 71.36, 71.17, 70.98, 70.85, 70.76, 69.61, 69.47, 69.40, 69.35, 61.45, 61.42, 61.40, 61.37, 61.33, 61.28, 61.23, 61.21, 61.17, 58.96, 58.93, 58.90, 58.87, 58.85, 58.81, 58.77, 58.74, 58.49, 58.46, 58.42, 58.38, 58.35, 58.32, 58.25, 58.22, 37.24, 37.22, 37.15, 37.13. HRFABMS: Calcd for $C_{63}H_{112}O_{39}S_2Na$: 1579.6120. Found: 1579.6121. Anal. Calcd for $C_{63}H_{112}O_{39}S_2$: C, 48.58; H, 7.25. Found: C, 48.60; H, 7.22.

$6^A,6^B$-Dimesyl-Substituted Permethylated β-Cyclodextrin. This compound was prepared from diol **3** in an 81% yield using the same method as for the $6^A,6^D$-dimesylate; mp 102−104 °C; $[\alpha]^{25}_D = +131.5°$ (0.01, $CHCl_3$); ^{1}H NMR δ: 5.20−5.0 (m, 7 H), 4.70−4.40 (m, 4 H), 4.0−3.2 (m, 91 H), 3.3−3.05 (m, 7 H), 3.10 (s, 3 H); ^{13}C NMR δ: 99.52, 99.06, 98.98, 98.74, 98.72, 98.69, 98.40, 81.95, 81.89, 81.77, 81.68, 81.63, 81.52, 81.32, 81.29, 80.58, 80.40, 80.34, 80.29, 80.12, 79.73, 79.69, 71.26, 71.19, 71.06, 70.91, 70.76, 70.73, 70.66, 69.72, 69.40, 69.28, 61.52, 61.49, 61.42, 61.39, 61.36, 61.17, 61.15, 61.14, 59.05, 59.01, 58.99, 58.96, 58.88, 58.87, 58.85, 58.82, 58.77, 58.74, 58.67, 58.64, 58.59, 58.56, 58.43, 58.40, 58.39, 58.36, 58.23, 58.20, 37.38, 37.35, 37.04, 37.02. HRFABMS: Calcd for $C_{63}H_{112}O_{39}S_2Na$: 1579.6120. Found: 1579.6116. Anal. Calcd for $C_{63}H_{112}O_{39}S_2$: C, 48.58; H, 7.25. Found: C, 48.34; H, 7.17.

$6^A,6^D$-*O*-Bis(*p*-(allyloxy)phenyl)-Substituted Permethylated β-Cyclodextrin. Under an atmosphere of Ar, *p*-(allyloxy)phenol (180 mg, 1.2 mmol) was stirred with NaH (36 mg, 1.5 mmol) in 10 mL of dry DMF for 1 h at rt. Compound **1** (60 mg, 0.04 mmol) was added into the system in one portion. After stirring at rt overnight, DMF was removed under

reduced pressure. The residue was dissolved in 50 mL of $CHCl_3$ and washed by H_2O (20 mL). The $CHCl_3$ layer was separated, dried, and concentrated. The crude product was purified by a silica gel column ($CHCl_3/CH_3OH$: 50/1) and a sephadex column to give the product (38 mg, 59%). The physical and spectral properties of the $6^A,6^D$-*O*-bis(*p*-(allyloxy)-phenyl) derivative are as the same as those reported.[14]

Acknowledgment. The authors thank Dr. Guo-Liang Yi of IBC Advanced Technologies, Inc. (American Fork, Utah) for his many helpful discussions and Dr. Du Li of BYU for his help with the high-resolution NMR spectoscopy.

JO971604X