New Large-Scale Preparations of Versatile 6-*O*-Monotosyl and 6-Monohydroxy Permethylated α-, β-, and γ-Cyclodextrins

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(Received February 6, 2002; CL-020133)

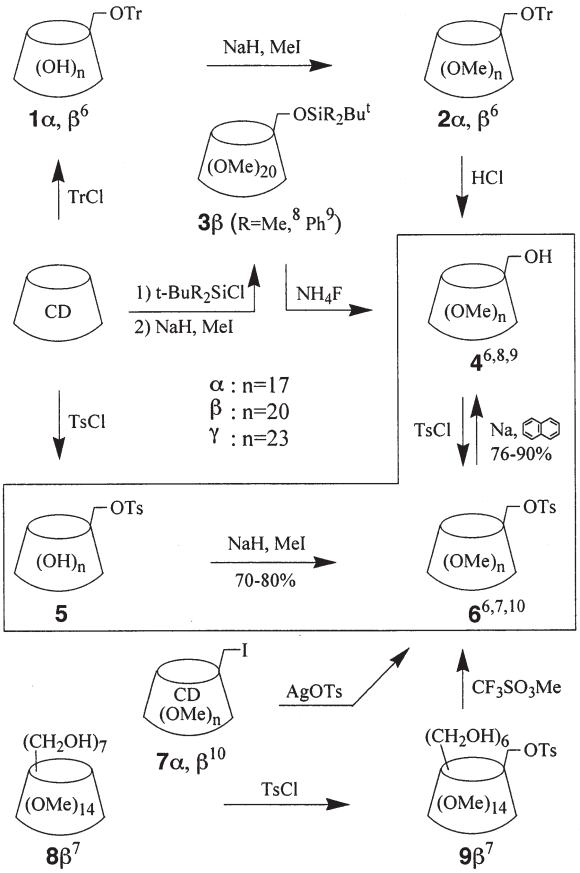
New practical methods for preparation of versatile 6-*O*-monotosyl and 6-monohydroxy permethylated α-, β-, and γ-cyclodextrins are described.

Cyclodextrins (CDs), 1,4-dehydrated cyclic hexamer (α), heptamer (β), and octamer (γ) of α-D-glucopyranose, are commercially available, hydrophilic, chiral, and native host molecules with a unique shape like a bottomless flowerpot. For their predominant characteristics, the molecules have been widely used as building blocks for assembling a variety of artificial enzymes[1] and superstructures such as molecular machines.[2]

Although the extraordinary hydrophilic properties of the host molecules are advantageous for complexation in water, they are usually disadvantageous for chemical modifications[3] because their poor solubilities in organic solvents prevent the performance of various types of organic reactions and of purification methods. If a balance between the two conflicting peculiarities can be obtained, a new trend will be added to the field of cyclodextrins. *O*-Permethylation[4] of CD skeletons provides a promising approach for this idea as represented, for examples, by super-cyclodextrins.[5]

Like the essential roles of tosylates **5** in the CD chemistry, the corresponding permethylated tosylates **6** are, undoubtedly, of great value as starting materials for making various amphiphilic and lipophilic CD derivatives, such as amines, esters, ethers, halides, and sulfides. Therefore, a facile preparative method for **6** or equivalents **4** is desired. To date, three methods have been reported (Scheme 1): the experiments were carried out on less than a 5 g-scale,[6–9] and the overall yields of **4**β and **6**β were 43[8,9] and 16%,[7] respectively, through 3 and 5 steps from the CDs. In these methods, it seemed as if a "direct" permethylation process of **5** to **6** was avoided because of the difficulties mentioned below. Here, we describe the title method based on a new 20 g-scale direct permethylation reaction.

We encountered some problems in the early stage of this work, especially with poor reproducibility on the direct permethylation of **5** to **6**. When a reaction had been started at ambient temperature, it was not easy to keep the reaction temperature constant because of the spontaneously accelerated exothermic reaction, even in a 1 g-scale experiment. The resulting products completely lost the tosyl group. When a reaction was carried out under milder conditions, the desired product was seldom obtained in a good yield or was usually accompanied by iodide **7**,[10] which could be produced by a side reaction of **6** with NaI as an expected product. Once the by-product had been formed, it was difficult to remove it from the mixture by chromatography. Although "reproduction" of **6** from **7** by



Scheme 1. Synthesis of 6-monofunctionalized permethylated α-, β-, and γ-cyclodextrins **4** and **6**.

treatment of the mixture with AgOTs[11] was successful,[10] the expensive reagent was not suited for a large-scale experiment. When much milder conditions had been employed, the incomplete permethylation produced terrible blends. After several years of patient research, we were able to establish the following reproducible procedure in which the reaction temperature was precisely regulated at 3 stages.

Powdered tosylate **5**α[12] (19.4 g, 17.2 mmol), which had been dried at 60 °C for 2 d in vacuo, was placed in a 1-L, four-necked, jacketed flask equipped with a mechanical stirrer and a thermometer. During stirring at 300 rpm, dry DMF (500 ml) was added. The resulting clear solution was cooled to 0 °C by circulating the medium from a thermostat to the jacket, and then NaH (40 g, 1.0 mol, 60% dispersion in oil) was added. After maintaining the temperature for 2 h, MeI (100 ml, 228 g, 1.61 mol) was added. The temperature was raised to 15 °C after

3 h and then to 20 °C after 2 h, and the stirring was continued for 24 h. After the addition of EtOH (50 ml) and sat. aq NaCl solution (1.2 L) containing $Na_2S_2O_3$, the mixture was extracted with toluene (3 × 800 ml). The organic layer was dried over Na_2SO_4 and concentrated to about 100 ml under reduced pressure. The residue was subjected to flash column chromatography on silica gel (230 g) using EtOAc–toluene and EtOH–EtOAc as eluents. The desired product **6**α was obtained as white foam (18.6 g, 79%) from 5% (v/v) EtOH–EtOAc eluates.

Compared with the tosylate, alcohol **4**α may be a less versatile intermediate but has an advantage in the S_N2 reaction site; that is, the alkoxyl oxygen atom of **4**α locates at an outer or less-hindered site from the CD framework than the carbon atom bearing the tosyl group of **6**α. The tosylate was converted to **4**α according to reductive detosylation with sodium naphthalenide[13] as follows.

To a solution of naphthalene (7.32 g, 57.1 mmol) in dry THF (100 ml), sodium (1.22 g, 53.0 mmol) was added and the mixture was stirred at rt for 3 h. The resulting deep blue solution of sodium naphthalenide was cooled in a dry ice-acetone bath, and a solution of **6**α (12.2 g, 8.94 mmol) in dry THF (73 ml) was then added at such a rate that the temperature was maintained below −65 °C. After the addition, the reaction mixture was allowed to stir for 80 min, neutralized with 3N HCl in the bath, and concentrated to dryness under reduced pressure. The residue was subjected to flash column chromatography on silica gel (120 g) using EtOAc–toluene and EtOH–EtOAc as eluents. The desired product **4**α was obtained as white powder (9.10 g, 84.0%) from 10% (v/v) EtOH–EtOAc eluates.

Similarly, **4**β (4.28 g, 76.0%), **4**γ[14] (4.45 g, 89.5%), **6**β (15.2 g, 79.6%), and **6**γ[14] (6.79 g, 69.6%) were obtained from **6**β (5.00 g), **6**γ (5.44 g), **5**β[15] (16.7 g), and **5**γ[16] (8.00 g), respectively.

In conclusion, we have demonstrated new practical preparations of versatile starting materials **4** and **6** for non-hydrophilic CD derivatives. The present permethylation technique with a NaH-MeI combination is applicable to other polyhydroxy compounds with NaI-susceptible substituents.

We are indebted to Nihon Shokuhin Kako Co. Ltd., Mercian Corporation, and Wacker Chemicals East Asia Ltd. for generous gifts of α-, β-, and γ-CDs, respectively. T.K. also thanks the Ministry of Education, Science, Sports, and Culture of Japan for its Grant-in-Aid for Scientific Research (C) (No. 11640582) which provided financial support of this work.

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14 **4**γ: white foam, mp 114–117 °C. Anal. Found: C, 51.84; H, 7.94%. Calcd for $C_{71}H_{126}O_{40}\cdot H_2O$: C, 52.07; H, 7.88%. TOFMS (m/z) 1641 $[M+Na]^+$. ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.32 (t, J = 3.4 Hz, 2H, H_1), 5.25 (d, J = 3.2 Hz, 1H, H_1), 5.22–5.18 (m, 4H, H_1), 5.12 (d, J = 3.2 Hz, 1H, H_1), 4.0–3.2 (m, 117H), 2.80 (bt, J = 6.1 Hz, 1H, *OH*). **6**γ: white foam, mp 102–105 °C. Anal. Found: C, 52.55; H, 7.49; S, 1.79%. Calcd for $C_{78}H_{132}O_{42}S\cdot H_2O$: C, 52.28; H, 7.54; S, 1.79%. TOFMS (m/z) 1795 $[M+Na]^+$. ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.77 (d, J = 8.2 Hz, 2H, *OTs*), 7.34 (d, J = 8.2 Hz, 2H, *OTs*), 5.3–5.2 (m, 6H, CD-H_1), 5.10 (d, J = 3.5 Hz, 1H, H_1), 5.07 (d, J = 3.2 Hz, 1H, H_1), 4.52 (d, J = 9.5 Hz, 1H, CH_2OTs), 4.16 (dd, J = 9.5, 6.5 Hz, 1H, CH_2OTs), 3.9–3.1 (m, 114H), 3.04 (dd, J = 9.6, 3.1 Hz, 1H), 2.45 (s, 3H, *OTs*).
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