Regioselective Synthesis of Methylated β-Cyclodextrins Leaving Hydroxy Groups

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Abstract

A series of methylated β-cyclodextrins (CDs) regioselectively leaving one or two hydroxy groups were prepared, and fluorescence spectroscopic measurements showed that they have unique binding characteristics against 2-*p*-toluidinylnaphthalene-6-sulfonate as a guest molecule in aqueous solution.

Keywords: cyclodextrins; methylations; regiospecificity; inclusion; host compounds

In developing an enzyme mimic, attractive molecules as starting materials are cyclodextrins (CDs), which are cyclic oligosaccharides composed of α(1→4) glucosyl residues.[1] CDs are known to function as host molecules making inclusion complexes with hydrophobic guest compounds in aqueous solution.[2] Although CDs have a number of hydrophilic functional groups such as primary and secondary hydroxy groups, CDs, particularly β-CD, have low solubility in water.[3] Furthermore, the β-CD inclusion complexes have much lower solubility in water. In order to enhance the solubility of β-CD in an aqueous medium, totally and partially methylated β-CD derivatives have been synthesized.[4] Hitherto, regioselective modifications of the specific hydroxy groups in β-CD by methylation leaving one or two hydroxy groups for future manipulating functions have not been accomplished. Successful protection of two hydroxy groups of a primary face by an interglycosidic bridge of sulfonamide was first reported by Tabushi *et al.*.[5] We recently reported the successful

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protection of two hydroxy groups of a secondary face with benzylidene acetal after protection of primary hydroxy groups by pivaloyl esters.[6] This communication describes a novel method for the synthesis of partially methylated β-CDs in a regiospecific manner and their binding properties with 2-*p*-toluidinylnaphthalene-6-sulfonate (TNS) as determined by examination of fluorescence spectra of the inclusion complexes in aqueous solution.

Heptakis 6-pivaloate **1** and the inter glycosidic benzylidene derivative **2** were prepared according to the method previously reported.[6a] Since direct benzylation of **2** has been successfully demonstrated using a combination of NaH and BnBr in DMF,[6b] direct methylation for **2** was firstly examined in similar conditions. Unfortunately, **3** was obtained in only 18% yield. Therefore, we focused our attention on a two-step procedure (i. e., de-*O*-pivaloylation in a Zemplén manner and then usual methylation). Thus, de-*O*-pivaloylation of **2** in methanol in the presence of excess sodium methoxide at 50 °C gave 3^1, 2^2-benzylidene derivative, which was further transformed by methyl iodide in the presence of NaH in DMSO to give per-methylated benzylidene derivative **3** in 89.0% yield, ^{1}H NMR ($CDCl_3$) δ: 5.93 (s, 1 H, C*H*Ph).

When transformation of **1** into **2** was performed with an excess amount of α, α-dimethoxy toluene (12 equiv. mol.) followed by treatment of malti-benzylidenated products using 0.1 molar amount of CSA in 1:1 $CHCl_3$—MeOH at 0 °C, an unexpected compound **4** was formed with **2** having the same R_f (0.55, 4:1 $CHCl_3$—MeOH) on TLC as judged by the results of ^{1}H NMR spectra of the mixture. Since these compounds could not be separated, further manipulation of the mixture was performed. Thus, de-*O*-pivaloylation followed by methylation of the mixture were carried out in the same manner as that described above to afford a still-unseparable mixture of **3** and **5**, R_f (0.57, 10:1 $CHCl_3$—MeOH), ^{1}H NMR ($CDCl_3$) δ: 5.93 (s, 2/3 H, C*H*Ph), 5.86 (s, 1/3 H, C*H*Ph).

Scheme 1

For the preparation of mono alcohol at the C-3 position, a reductive ring opening reaction of benzylidene derivative of **3** proceeded smoothly and regioselectively in the presence of LAH and $AlCl_3$ to give **6** having a mono hydroxy group at the C-2^2 position and a benzyl group at the C-3^1 position, $[\alpha]_D^{20}$ +141.7° (*c* 1.07, $CHCl_3$). When BH_3•NMe_3 was used for the reducing reagent, the reaction did not proceeded. In order to

elucidate the structure of **6**, the remaining hydroxy group was acetylated to afford mono-2-*O*- acetete **7** in quantitative yield, ^{1}H NMR ($CDCl_3$) δ: 4.68 (dd, 1 H, $J_{1,2}$ 3.5 Hz and $J_{2,3}$ 9.7 Hz, H-2^2), 1.71 (s, 3 H, OAc). Protection of the free hydroxy group of **6** was carried out in the usual way to afford per-methylated **8** in 98% yield, $[\alpha]_D^{20}$ +151.6° (*c* 1.09, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ: 5.09 (d, 1 H, J_{gem} 10.6 Hz, CH_a-Ph), 4.81 (d, 1 H, CH_b-Ph). Final deprotection of the benzyl group in **8** by hydrogenolysis gave mono-3-hydroxy derivative **9** in 91% yield, $[\alpha]_D^{20}$ +156.7° (*c* 0.96, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ: 5.19 (s, 1 H, OH-3^1), 3.97 (t, 1 H, *J* 9.4 Hz, H-3^1), which was further transformed into the acetate **10**, ^{1}H NMR ($CDCl_3$) δ: 5.39 (t, 1 H, $J_{3,4}$ 9.5 Hz, H-3^1), 5.28 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1^1), 3.73 (t, 1 H, H-4^1), 3.28 (dd, 1 H, $J_{2,3}$ 10.4 Hz, H-2^1), 2.13 (s, 3 H, OAc).

Since the acetal mixture of **3** and **5** could be regarded as the precursors of mono- and di-hydroxy derivatives, acid hydrolysis of the mixture was attempted, and two separate mixtures were obtained. These mixtures were purified by silica gel chromatography, giving 2^1-monoalcohol **11** in 71% yield, $[\alpha]_D^{17}$ +160.6° (*c* 1.57, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ: 4.36 (d, 1 H, $J_{2,OH}$ 11.2 Hz, OH-2^1) and 3^1,2^2-diol **13** in 28% yield, $[\alpha]_D^{24}$ +160.8° (*c* 1.28, $CHCl_3$). The structures of **11** and **13** were determined from the results of ^{1}H NMR after acetylation of the remaining hydroxyl groups, 2^1-acetate **12**, ^{1}H NMR ($CDCl_3$) δ: 5.17 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1^1), 4.65 (dd, 1 H, $J_{2,3}$ 10.1 Hz, H-2^1), 2.16 (s, 3 H, OAc) and 3^1,2^2-diacetate **14**, ^{1}H NMR ($CDCl_3$) δ: 5.42 (t, 1 H, $J_{3,4}$ 9.7 Hz, H-3^1), 5.31 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1^1), 5.06 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1^2), 4.68 (dd, 1 H, $J_{2,3}$ 10.1 Hz, H-2^2), 3.25 (dd, 1 H, $J_{2,3}$ 10.3 Hz, H-2^1), 2.21 (s 3 H, OAc), 2.16 (s, 3 H, OAc).

Scheme 2

Since the preparation of methylated β-CD having regioselective hydroxyl groups had been accomplished, we turned our attention to evaluation of the alcoholic products using fluorescence measurement. After dissolving the same amounts of 2-monoalcohol **11**, 3-monoalcohol **9**, benzylalcohol **6**, 2,3-diol **13**, per-methylated β-CD, and β-CD in 0.1 M phosphate-buffered water (pH 7) in the presence of 2-*p*-toluidinylnaphthalene-6-sulfonate (TNS), respectively, fluorescence measurements were carried out at 20 °C.[7] As shown in Fig. 1, fluorescence intensities of these compounds against TNS resulted in a potential binding ability for TNS. In this case, the order of the fluorescence intensities of these compounds was benzylalcohol **6** > 2-monoalcohol **11** > 3^1,2^2-diol **13** > 3-monoalcohol **9** > per-methylated β-CD > β-CD itself. This result suggested that an alcohol in the chiral

products is able to interact with hydrophilic functional groups in other chiral guest compounds through some hydrogen bond.

In conclusion, we have reported the successful synthesis of a series of partially methylated β-CD derivatives leaving regulated hydroxy groups and the inclusion properties against TNS in water. These regularly methylated β-CDs are significantly potential intermediates for constructing new types of artificial enzymes.

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Legend to Figure and Schemes

Figure 1. The fluorescence emission spectra excited at 366 nm of TNS at 20 °C.

Scheme 1. *Reagents and conditions:* i) α,α-Dimethoxytoluene (6 molar exess), CSA, DMF, 60 °C, reduced pressure, ii) α,α-Dimethoxytoluene (12 molar exess), CSA, DMF, 60 °C, reduced pressure, iii) NaOMe, MeOH, 50 °C, then NaH, MeI, DMSO, r.t..

Scheme 2. *Reagents and conditions:* i) LAH, $AlCl_3$, THF, 0 °C→r.t., ii) 80% aq. AcOH, 90 °C, iii) Ac_2O, Pyr., iv) NaH, MeI, THF, r.t., v) H_2, $Pd(OH)_2$, MeOH, r.t..