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Efficient and Regioselective Preparation of an Eight-membered Interglycosidic Benzylidene Derivative of β-Cyclodextrin

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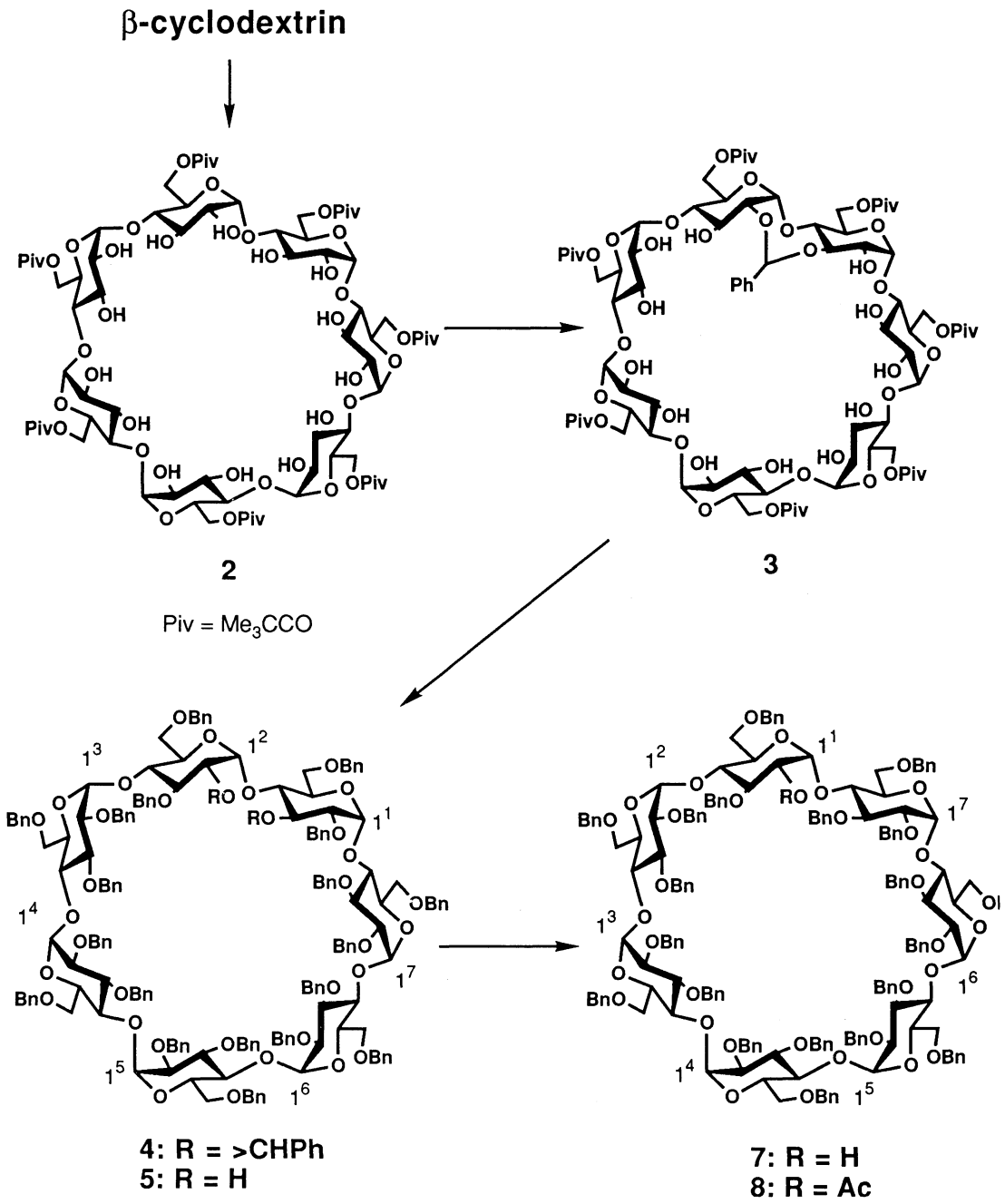
Heptakis(6-*O*-pivaloyl)-β-cyclodextrin, prepared in high yield by pivaloylation of β-cyclodextrin (β-CD), was treated with α,α-dimethoxytoluene in the presence of (+)-10-camphorsulfonic acid to give a 46% yield of eight-membered interglycosidic benzylidene acetal, $3^1,2^2$-*O*-benzylidene-$6^1,6^2,6^3,6^4,6^5,6^6,6^7$-hepta-*O*-pivaloylcyclomaltoheptaose. Further reductive ring-opening reaction or acid hydrolysis of the benzylidene group gave versatile intermediates for regioselective modification of β-CD.

Cyclodextrins (CDs) are cyclic oligosaccharides composed of six or more α(1→4) linked glucopyranosyl residues. Numerous investigations have been carried out on chemical modification of CDs in order to improve their properties of substrate complexation and/or to attach novel reactive functional groups.[1] The available methods, however, have been limited by the rigid cyclic structures of CDs and the extreme congestion of hydroxyl groups.

Recently, we have developed an efficient procedure for preparation of eight-membered interglycosidic benzylidene derivatives of phenyl α-maltoside[2] and 1,6-anhydro-β-maltotriose[3] employing modified Evans acetal-exchange reaction[4] with an excess reagent and subsequent selective hydrolysis of the over-acetalation products. The usefulness of those interglycosidic acetals for synthetic intermediates was shown by the finding that the benzylidene group can be cleaved in highly regioselective manner[2]. Since CDs can be regarded as cyclic analogues of malto-oligosaccharides, we have now directed our attention toward applicability of such acetalation reaction to the CD derivatives. This communication deals with preparation of a novel interglycosidic benzylidene derivative of β-CD and examination of its chemical behaviors toward some acetal-cleavage reactions.

Formation of the interglycosidic benzylidene acetal of CDs was examined by use of β-CD and its derivatives. The first attempt for direct benzylidenation of unprotected β-CD with α,α-dimethoxytoluene (2 mol. equiv.) under Evans conditions[4] failed because it gave an intractable mixture. Similar treatment of heptakis(6-*O*-*tert*-butyldimethylsilyl)-β-CD[5] (**1**) was also unsatisfactory because of substantial removal of the *O*-silyl groups. For the next examination, heptakis(6-*O*-pivaloyl)-β-CD[6] (**2**) {mp 272-274 °C (from aq. MeOH); $[\alpha]_D^{25}$ +124° (*c* 0.24, $CHCl_3$)} was prepared in 89% yield by treatment of dried β-CD with pivaloyl chloride (9.1 mol. equiv.) in pyridine at room temperature → 60 °C overnight and subsequent selective removal of the pivaloyl groups on the secondary hydroxyl groups with hydrazine hydrate[7] (15 mol. equiv.) in pyridine at room temperature for 16 h. In contrast to above two experiments, benzylidenation of **2** proceeded with high regioselectivity. Thus, a solution of dried **2** and α,α-dimethoxytoluene (2 mol. equiv.) in DMF, which



was adjusted to pH ca. 3 by addition of (+)-10-camphorsulfonic acid (CSA), was stirred at 60-70 °C under reduced pressure (ca. 2 kPa) for 3-5 h. After quenching with $NaHCO_3$ followed by concentration, the resulting mixture was chromatographed on silica gel with $CHCl_3$-MeOH-pyridine (90:10:1, v/v/v), giving pure monobenzylidene derivative[8] {46%; $[\alpha]_D^{25}$ +93° (*c* 0.19, $CHCl_3$)} as a hygroscopic amorphous solid. Examination of its 500 MHz ^{1}H-NMR spectrum in DMSO-d_6-D_2O at 80 °C suggested the structure of a cyclic benzylidene acetal, which was later identified with $3^1,2^2$-*O*-benzylidene-$6^1,6^2,6^3,6^4,6^5,6^6,6^7$-hepta-*O*-pivaloylcyclomaltoheptaose (**3**) by converting into the $3^1,2^2$-diacetyl derivative (**6**).

The interglycosidic benzylidene group of **3** was stable enough to undergo several modifications under basic conditions. Thus, **3** was successively treated with BnBr-NaH in DMF, aq. NaOH in DMF, and BnBr-

NaH in DMF to give the nonadeca-*O*-benzyl derivative[9] (**4**) {$[\alpha]_D^{25}$ +36° (*c* 0.18, $CHCl_3$)} in 82% overall yield. Hydrolysis of the *O*-benzylidene group of **4** smoothly proceeded in aqueous MeOH-THF in the presence of catalytic amount of CSA at room temperature, giving the $3^1,2^2$-unprotected derivative[9] (**5**) {73%; $[\alpha]_D^{25}$ +60° (*c* 0.26, $CHCl_3$)}, which was acetylated with Ac_2O-pyridine to give the $3^1,2^2$-diacetate[9] (**6**) {82%; $[\alpha]_D^{25}$ +38° (*c* 0.41, $CHCl_3$)}.

The ^{1}H-NMR spectrum of the diacetate **6** in $CDCl_3$ at 40 °C revealed seven 1-proton doublets having small coupling constants (J = 3.4-3.7 Hz) assignable to anomeric protons and two 3-proton singlets for methyl groups of the two acetoxy groups. Although the heavy signals overlap of the spectrum prevented identification of all proton resonances, the 2D HOHAHA (homonuclear Hartmann-Hahm) experiment revealed that the heptasaccharide **6** possessed a 3-*O*-acetyl-2,6-di-*O*-benzyl-α-D-glucopyranosyl residue [δ 5.30 (H-1^1), 3.33 (H-2^1), 5.57 (H-3^1), 3.78 (H-4^1), and ca. 3.9 (H-5^1)] and a 2-*O*-acetyl-3,6-di-*O*-benzyl-α-D-glucopyranosyl residue [δ 5.15 (H-1^2), 4.84 (H-2^2), and 3.90-3.95 (H-3^2)] as two of the constituent monosaccharides. Furthermore, the sequence of the monosaccharide residues of **6** was established by 2D ^{1}H-^{13}C chemical shift correlation experiments. Unambiguous assignment of the signals due to C-1^1 (δ 97.8), C-1^2 (δ 97.0), and C-1^4 (δ 76.0) could be made using PFG-HMQC (pulsed field gradient-heteronuclear multiple quantum coherence) method.[10] In addition, cross-peaks due to the long-range coupling between C-1^2 and H-4^1 and between C-4^1 and H-1^2 were observed in the PFG-HMBC (pulsed field gradient-heteronuclear multiple bond correlation) spectrum,[10] indicating that the 2-*O*-acetyl-α-D-glucopyranosyl residue linked to the 3-*O*-acetyl-α-D-glucopyranosyl residue through an α(1→4) glycosidic bond. These results of NMR analyses were compatible with the proposed structure of **6**, confirming the exact position of the benzylidenation.

The reductive cleavage of the interglycosidic benzylidene acetal was also quite interesting. On treatment with $LiAlH_4$-$AlCl_3$[11] in dichloromethane-Et_2O at room temperature for 5 h, **4** underwent regioselective cleavage of the benzylidene group to give the 2^1-unprotected derivative[9] (**7**) {70%; $[\alpha]_D^{25}$ +60° (*c* 0.27, $CHCl_3$)} as the sole product. For structural elucidation, **7** was subsequently treated with Ac_2O-pyridine to give the 2^1-*O*-acetyl derivative[9] (**8**) {87%; $[\alpha]_D^{25}$ +50° (*c* 0.23, $CHCl_3$)}. In the ^{1}H-NMR spectrum of **8**, 1-proton doublet of doublets ($J_{1,2}$ = 3.7 and $J_{2,3}$ = 9.8 Hz) assignable to H-2^1 was observed at low magnetic field (δ 5.13), suggesting the acetylated position. Similarly to our pervious experiments of linear maltooligosaccharides,[2] the observed high regioselectivity of the reductive cleavage of the interglycosidic benzylidene acetal in **4** might also be explainable by considering electron-withdrawing effect of an anomeric center.

In conclusion, our procedure for formation of interglycosidic benzylidene acetals was also applicable to β-CD and provided regioselectively protected derivatives, some of which would be versatile intermediates for syntheses of elaborately designed novel host compounds. Further studies on modification of CDs along this line are in progress.

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6) Satisfactory data of elemental analysis were obtained as trihydrate; ^{1}H-NMR data; δ (400 MHz, DMSO-d_6, 55 °C)=1.22 (63H, s, CH_3), 3.17 (14H, br.s, OH), 3.36 (7H, dd, *J*=3.9, 9.5 Hz, H-2), 3.41 (7H, t, *J*=9.3 Hz, H-4), 3.66 (7H, t, *J*=9.0 Hz, H-3), 3.84 (7H, br.d, *J*=10.2 Hz, H-5), 4.04 (7H, dd, *J*=3.7, 12.2 Hz, H-6), 4.23 (7H, d, *J*=12.2 Hz, H-6), 4.80 (7H, d, *J*=3.4 Hz, H-1). Direct acylation of β-CD with pivaloyl chloride (10 mol. equiv.) in pyridine at 60 °C overnight gave **2** only in 18% yield.

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8) Satisfactory data of elemental analysis were obtained as dihydrate; ^{1}H-NMR data; δ (500 MHz, DMSO-d_6-D_2O, 80 °C)=4.86 (1H, d, *J*=3.1 Hz, H-1), 4.89 (1H, d, *J*=3.3 Hz, H-1), 4.91 (1H, d, *J*=3.4 Hz, H-1), 4.93 (1H, br.s, H-1), 4.94 (1H, d, *J*=3.7 Hz, H-1), 4.96, (1H, d, *J*=3.4 Hz, H-1), 5.29 (1H, d, *J*=3.3 Hz, H-1), 6.07 (1H, s, CHPh).

9) All new compounds gave satisfactory data of elemental analyses. Selected NMR data: **4**; δ_H (500 MHz, $CDCl_3$)=4.55, 4.69, 4.71, 4.77, 4.79, 4.81, 4.84, 4.86, 4.98, 5.09, 5.10, 5.21, 5.27 (13H, 13 x d, *J* =9.7-12.0 Hz, CH_2Ph), 4.87 (1H, d, *J*=3.7 Hz, H-1), 4.95 (1H, d, *J*=3.3 Hz, H-1), 5.00 (1H, d, *J*=3.3 Hz, H-1), 5.04 (1H, d, *J*=3.4 Hz, H-1), 5.19 (1H, d, *J*=3.1 Hz, H-1), 5.36 (1H, d, *J*=3.4 Hz, H-1), 5.38 (1H, d, *J*=3.9 Hz, H-1), 5.84 (1H, s, CHPh); **6**; δ_C (67.9 MHz, $CDCl_3$)=20.9 (Me), 21.3 (Me), 68.4, 68.9, 69.1, 69.3, 70.9, 71.1, 71.3, 71.4, 72.0, 75.6, 76.0 (C-4^1), 78.3, 78.5, 78.6, 78.8, 78.9, 79.1, 79.3, 79.4, 79.8, 80.3, 80.5, 80.6, 80.7, 80.9, 97.0 (C-1^2), 97.8 (C-1^1), 98.1, 98.3, 98.4, 98.6, 99.3, 126.5-139.6, 169.7 (C=O), 170.5 (C=O); δ_H (400 MHz, $CDCl_3$, 40 °C)=1.89 (3H, s, OAc), 1.90 (3H, s, OAc), 3.33 (1H, dd, *J*=3.7, 10.0 Hz, H-2^1), 3.39 (1H, dd, *J*=3.4, 11.0 Hz, H-2), 3.41-3.56 (11H, m, H-2,6a), 3.78 (1H, t, *J*=9.0 Hz, H-4^1), 3.90-4.06 (27H, m, H-3,4,5,6b), 4.18-4.55 (27H, m, CH_2Ph), 4.55, 4.56, 4.68, 4.74, 4.76, 4.82, 4.89, 5.03, 5.06, 5.08, 5.23 (11H, 11 x d, *J* =10.3-12.2 Hz, CH_2Ph), 4.84 (1H, dd, *J*=3.4, 10.0 Hz, H-2^2), 5.00 (1H, d, *J*=3.4 Hz, H-1), 5.02 (1H, d, *J*=3.6 Hz, H-1), 5.10 (1H, d, *J*=3.6 Hz, H-1), 5.13 (1H, d, *J*=3.7 Hz, H-1), 5.15 (1H, d, *J*=3.4 Hz, H-1^2), 5.30 (1H, d, *J*=3.7 Hz, H-1^1), 5.32 (1H, d, *J*=3.6 Hz, H-1), 5.57 (1H, t, *J*=9.5 Hz, H-3^1); **8**; δ_H (500 MHz, C_6D_6)=1.95 (3H, s, OAc), 3.41 (1H, dd, *J*=3.7, 9.8 Hz, H-2), 3.45-3.52 (5H, m, H-2), 3.99 (1H, t, *J*=9.2 Hz, H-3), 3.78-3.81, 4.08-4.30, 4.33-4.55 (m, H-3,4,5,6,CH_2Ph), 4.71, 4.85, 4.89, 4.94, 4.95, 5.05, 5.16, 5.21, 5.25, 5.27 (10H, 10 x d, *J*=10.2-11.5 Hz, CH_2Ph), 5.13 (1H, dd, *J*=3.7, 9.8 Hz, H-2^1), 5.34 (1H, d, *J*=3.3 Hz, H-1), 5.37 (1H, d, *J*=3.6 Hz, H-1), 5.39 (1H, d, *J*=3.4 Hz, H-1), 5.40-5.43 (3H, m, H-1), 5.65 (1H, d, *J*=3.6 Hz, H-1^1).

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