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Synthesis of four mono-functionalized α-cyclodextrin derivatives for further confirming DIBAL-H-promoted bis-de-O-methylation mechanism

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ABSTRACT

In our previous studies, a mechanism for DIBAL-H promoted regioselective bis-de-O-methylation of per-*O*-methylated cyclodextrin (CD) was proposed based on per-*O*-methylated β-CDs. As a further step to this work, four per-*O*-methylated α-CD derivatives (**6**, **7**, **11**, and **18**) with mono functional group at the secondary rim have been designed and synthesized. Using DIBAL-H as a chemical 'scalpel', we found that (1) only the *O*-methyl at C-2^A of **6** could be easily removed and (2) the *O*-methyl at $C_3{}^B$ could be firstly regioselectively removed slowly, followed by a rapid removal of the second *O*-methyl at $C_2{}^A$ to provide **3**. Combined with our previous studies, we think that not only *O*-3^B-methyl but also *O*-2^A and *O*-3^B are necessary for the formation of 'tweezers' during DIBAL-H promoted bis-de-O-methylation reaction of per-*O*-methylated CD.

1. Introduction

α-, β- and γ-cyclodextrins (CDs) are macrocyclic oligomers of D-glucose with the secondary C_2 and C_3 hydroxyl groups on the secondary rim and the primary C_6 hydroxyl group on the primary rim.[1] Due to their different hydrophobic cavity volume (for α-CD: 0.174, β-CD: 0.262, and γ-CD: 0.427 nm^3),[2] CDs have the ability to form host–guest or inclusion complexes with a large range of hydrophobic molecules, which made them potentially useful in the fields of pharmacology,[3] analytical chemistry,[4] enzyme mimics,[5] etc. However, the relatively low solubility of native CDs in water (e.g., 14.5 g and 1.85 g in 100 mL for α-CD and β-CD, respectively)[6] and organic solvents (e.g., methanol, ethanol, acetonitrile, and tetrahydrofuran)[7] significantly limits their utility. Per-*O*-methylated CDs and their derivatives have attracted considerable attention due to their improved solubility both in water and in organic solvents.[8] Much effort has been directed toward the synthesis of novel per-*O*-methylated CDs with various functional groups.[9] It is well known that highly selective modification of only one hydroxyl group of native CDs to obtain mono-functionalized per-*O*-methylated CDs remains a significant challenge for synthetic chemists.[10]

In our ongoing program to selective de-O-alkylation of α- and β-per-*O*-alkylated CDs by diisobutylaluminium hydride (DIBAL-H),[11] a general simple way to access 2^A,3^B-dihydroxyl-per-*O*-methylated α- and β-CD from per-*O*-methylated α- and β-CD was developed in our laboratory (Scheme 1).[12] As an extension to this study, unprecedented regioselective synthesis of two tetra-de-*O*-methylated α-CDs[13] and tetra- or hexa-de-*O*-methylated β-CDs[14] were discovered when a large excess of DIBAL-H was used as a chemical 'scalpel' (Scheme 2).

These reactions are remarkable in two ways: firstly, de-O-methylation takes place selectively on the secondary rim of α- or β-CD, which is strikingly different from the one of per-*O*-benzylated α- or β-CD, where only the primary rim is selected for de-O-benzylation (Scheme 3);[11a] secondly, only the pair of hydroxyl groups is obtained, which occurs on two adjacent sugars to give diol, tetrol or hexol, respectively.

Recently, a mechanism for DIBAL-H promoted regioselective bis-de-O-methylation of per-*O*-methylated cyclodextrin (CD) was proposed based on per-*O*-methylated β-CDs by our group.[15] As a further step to this work, we extend our studies on per-*O*-methylated α-CD to further confirm the mechanism. We report herein the preparation

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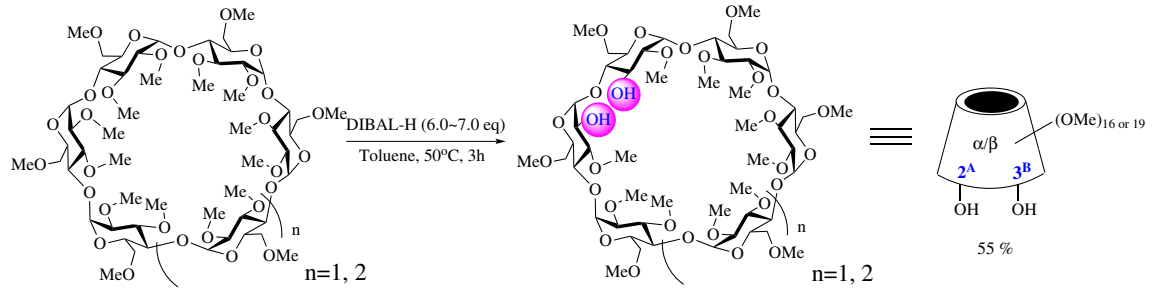
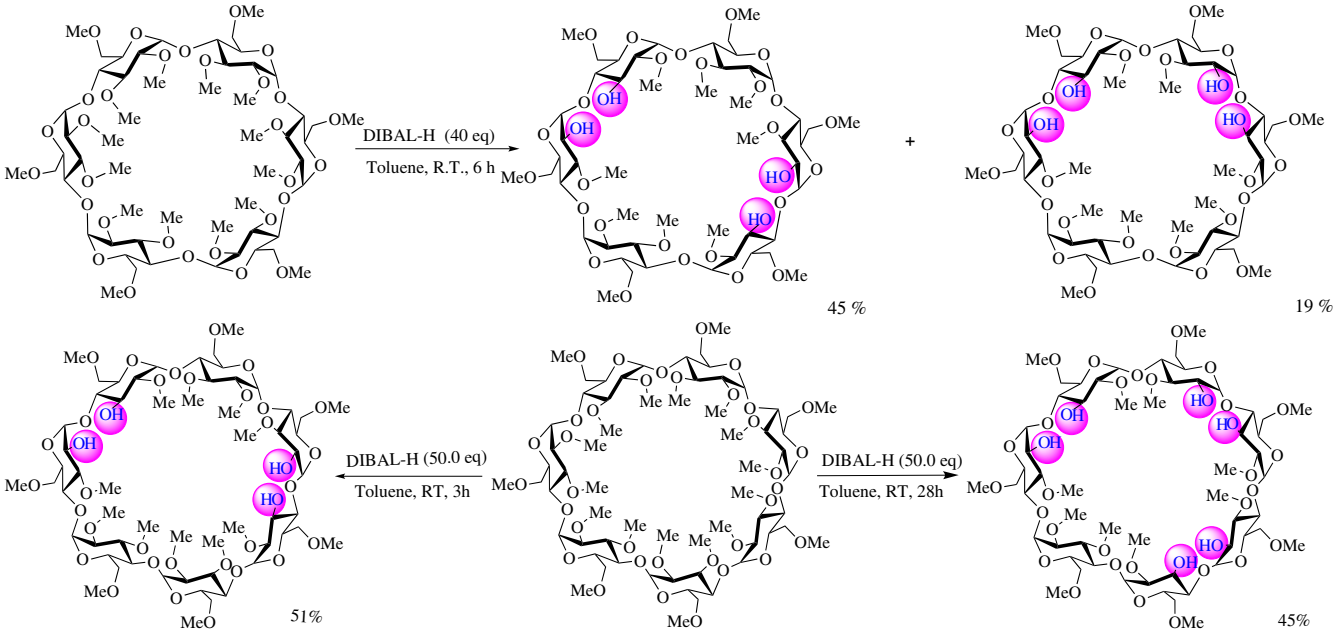
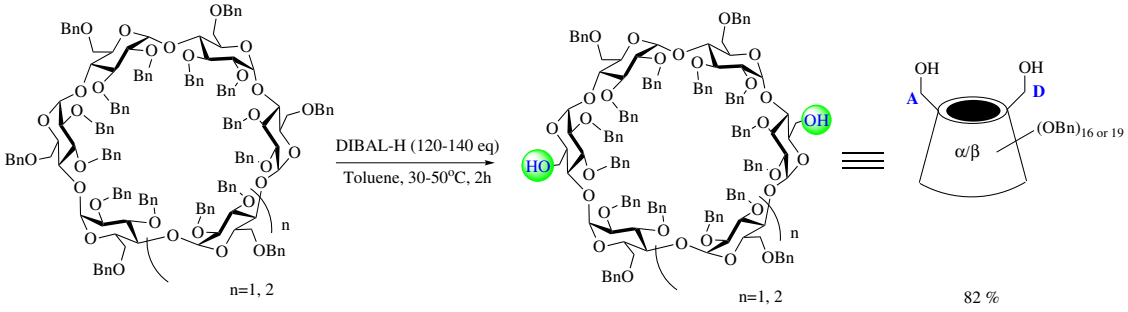


Scheme 1. Bis-de-*O*-methylation of per-*O*-methylated α- and β-CDs by DIBAL-H.



Scheme 2. The di-bis-de-O-methylation or tri-bis-de-*O*-methylation of per-*O*-methylated α- and β-CDs by a large excess of DIBAL-H.



Scheme 3. Bis-de-O-benzylation of per-*O*-benzylated β-CD by DIBAL-H.

of four mono-functionalized per-*O*-methylated α-CDs (**6**, **7**, **11**, and **18**) from per-*O*-methylated α-CD **1**, and their behaviors upon actions of DIBAL-H.

2. Results and discussion

Synthesis of the four mono-functionalized per-*O*-methylated α-CDs (**6**, **7**, **11**, and **18**) is summarized in Scheme 4. $2^A,3^B$-diol **3**, obtained after careful silica gel column chromatography (CH_2Cl_2/CH_3OH: 50/1–25/1) according to our previously reported method,[12,15] which is the key intermediate to synthesize novel per-*O*-methylated α-CD derivatives. The structure of **3** was confirmed by 1D NMR, 2D NMR, and HRMS and was further confirmed by its acetylated derivative **5**. ^1H NMR spectrum of **5** showed two acetyl groups at δ 2.20, 2.22 ppm, while ^{13}C NMR spectrum displayed two methyl and carbonyl groups of the acetate at 21.45, 21.68, and 170.39 (2C, 2× C=O) ppm, respectively. The low-field doublets of doublet at 4.70 ppm ($J_{1,2}$=2.6 and $J_{2,3}$=10.3 Hz) and 5.47 ($J_{2,3}$=10.1 and $J_{2,3}$=9.0 Hz), each referring to 1H, were assigned to $H_2{}^A$ and $H_3{}^B$, respectively, and two carbons appearing at 71.66 and 74.38 ppm, should be assigned to $C_3{}^B$ and $C_2{}^A$, respectively, due to the acetylation of the hydroxyl groups.