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Synthesis of two mono-deoxy β-cyclodextrin derivatives as useful tools for confirming DIBAL-H promoted bis-de-*O*-methylation mechanism

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Abstract

Diisobutylaluminium hydride (DIBAL-H) promotes secondary rim regioselective bis-de-*O*-methylation of permethylated β-cyclodextrin (β-CD) to give diol **2**. To gain an insight into the mechanism of this remarkable regioselective behavior, two corresponding permethylated β-CDs with an alcohol function at either 2- or 3-position were synthesized in our previous study. As a step further to this work, the two compounds were subjected to deoxygenation reaction with tributyltin hydride in the present of 2,2′-azobisisobutyronitrile affording the corresponding 2- and 3-deoxy permethylated β-CD derivatives (**19** and **16**). The structures of these two compounds were characterized by 1D and 2D NMR and HRMS. Compounds **16** and **19** were unable to react with DIBAL-H which suggests that *O*-2^A and *O*-3^B are necessary for DIBAL-H promoted bis-de-*O*-methylation reaction of permethylated β-CD.

Keywords: Cyclodextrin (CD); DIBAL-H; Deoxy; Synthesis; Mechanism

Cyclodextrins (CDs) have gained popularity among scientists due to their widespread use in many areas of science and technology and a variety of CD derivatives aimed at a specific purpose were synthesized [1]. Per-*O*-methylated CDs have attracted considerable attention due to their solubility both in water and in organic solvents [2]. On the other hand, inclusion complexes of methylated CDs are usually more stable than the corresponding complexes of unmodified CDs. For these reasons, the controlled chemical synthesis of modified methylated CDs having a few specifically located hydroxyl groups available for the preparation of more elaborate molecular systems represents a true challenge for synthetic chemists [1,3]. The traditional methods [3] for selectively modified per-*O*-methylated CD were usually performed by a temporary regioselective protection of peculiar hydroxyl groups of the native CD, followed by *O*-methylation and final removal of the protective groups to unmask the required hydroxyl functions. This

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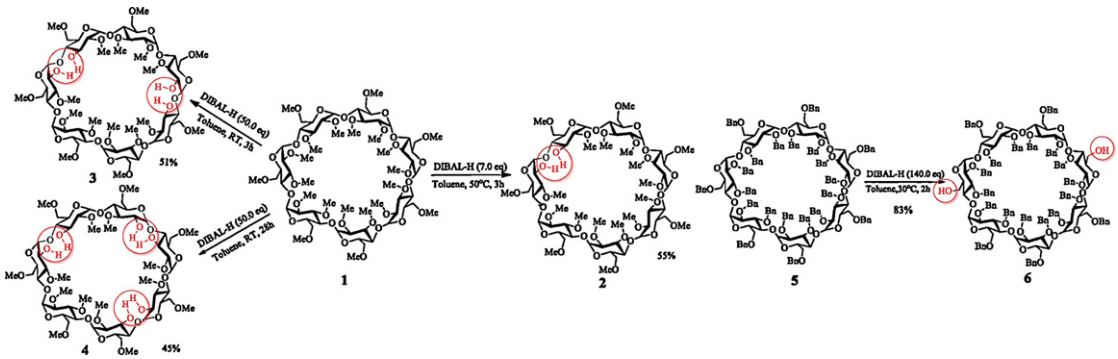


Scheme 1. De-*O*-methylation (left) and de-*O*-benzylation (right) reactions of per-*O*-alkylated *β*-CD by DIBAL-H.

process was considered as the ''long'' method [1c], where a series of lengthy protection and deprotection steps have taken place in order to selectively reach the positions which would otherwise not be selectively accessible.

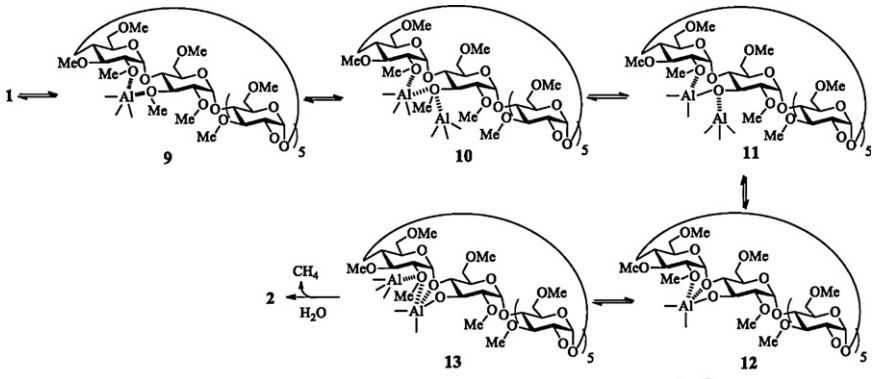
In our ongoing program for selective bis-de-*O*-alkylation reactions of α- and *β*-per-*O*-alkylated CD mediated by DIBAL-H [4], we have developed a simple and efficient method to get directly 2^A,3^B-dihydroxyl-per-*O*-methylated *β*-CD **2** from per-*O*-methylated *β*-CD **1** by DIBAL-H promoted regioselective removal of two methyl groups [5], which is well suited for further transformations [6]. This process was considered as the ''clever'' method, where the chemistry of cyclodextrin is exploited to get the desired product by the shortest route [1c]. Extension of this method led to a practical and unprecedented regioselective tetra-*O*-demethylation [7] and hexa-*O*-demethylation [8] of per-*O*-methylated *β*-CD, using an excess of commercially available DIBAL-H as a chemical ''scalpel'' (Scheme 1).

However, the mechanism of the regioselective bis-de-*O*-methylation processes of **1** has been unknown. As a characteristic, the DIBAL-H promoted regioselective bis-de-*O*-methylation of **1** occurs selectively on two closely located methoxyl groups at C-2 and C-3 of two contiguous sugar residues, we proposed that one of the methoxy group may affect the other one in DIBAL-H promoted bis-de-*O*-methylation [9]. In order to further confirm this proposition, we hereby report the synthesis of the two deoxy *β*-CD derivatives and their behavior in the de-*O*-methylation reactions promoted by DIBAL-H.

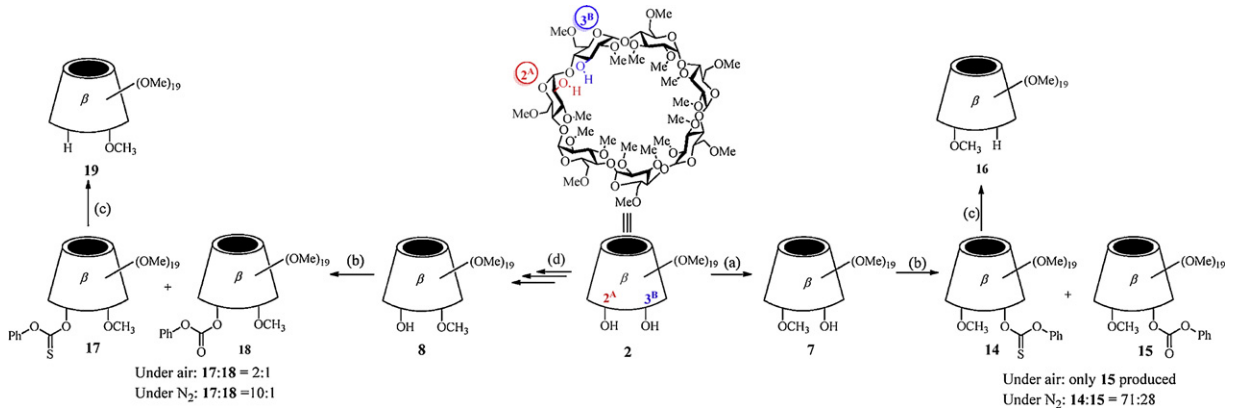
1. Results and discussion

We submitted per-*O*-methylated *β*-CD **1** to the action of DIBAL-H and observed demethylation reactions leading to a mixture of compounds and we have been able to delineate three sets of conditions to access three different CDs, **2**, **3** and **4**, as major products (Scheme 1) [5,7,8].

These remarkable results appear to be in sharp contrast to the case of benzylated CDs in which debenzylation occurs on the primary rim of the CD (Scheme 1) and such a bis-debenzylation reaction was a stepwise process [4b]. In the case of permethylated CDs, and in spite of our efforts, we were unable to isolate a mono-alcohol on the secondary rim, which suggests a subtly different mechanism. Therefore compounds **7** and **8** were logically designed and



Scheme 2. Proposed mechanism for the formation of 2^A,3^B-diol **2**.



Scheme 3. Synthesis of the mono-deoxy permethylated β-CDs **16** and **19**. Reagents and conditions: (a) CH_3I, NaH, DMF; (b) *O*-phenyl chlorothioformate, DMAP, pyridine, dichloromethane; (c) AIBN, tributylstannane, toluene; (d) (i) BnBr, NaH, DMF; (ii) CH_3I, NaH, DMF; (iii) Pd/C, H_2, CH_3OH.

synthesized for studying the mechanism of de-*O*-methylation reactions and a mechanism of DIBAL-H promoted de-*O*-methylation was proposed [9] in our previously study (Scheme 2). In this mechanism, it was thought that two oxygen atoms at *O*-2^A and *O*-3^B were necessary to form the chelating intermediates **9**–**13**.

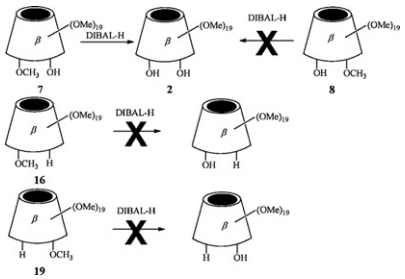
In order to further confirm this mechanism, two mono-deoxy-permethylated β-CD derivatives (**16** and **19**) were logically designed and synthesized regioselectively from the major intermediate **2** (Scheme 3) [9].

When transformation of **7** into **14** was performed with *O*-phenyl chlorothioformate in the presence of DMAP at 80 °C, an unexpected carbonyl compound **15** was obtained in 82% yield. This compound was characterized by ^{13}C NMR spectrum, which showed a signal at δ 151.48 ppm (C=O), instead of a signal at δ 195.76 ppm for C=S group. The replacement of C=S group by C=O group was probably due to the presence of oxygen in the reaction medium. In order to get the desired compound, a similar reaction was performed under an inert atmosphere condition which gave a mixture of **14** and **15** in a ratio of 71:28, according to HPLC analysis (CH_3OH/H_2O:60/40 by volume). Having the same Rf (0.43, eluent:cyclohexane/acetone = 1:1) on TLC, the separation by chromatography was not feasible at this stage. This phenomenon was first reported by Remy et al. [10], who observed in a similar reaction the formation of a side product with replacement of C=S group by C=O group in 8.3% yield. Since these two compounds could not be separated, further deoxygenation of **14** was performed directly from the mixture of **14** and **15** according to the classical Barton–McCombie conditions (Bu_3SnH, AIBN, 100 °C) [11] to give the compound **16** in 54% yield, compound **15** being recovered in 35% yield. ^1H NMR spectrum of **16** showed two sets of peaks at δ 1.88 and 2.32 ppm, corresponding to two protons at $C_3{}^B$, while ^{13}C NMR spectrum displayed a signal at δ 30.84 ppm, corresponding to $C_3{}^B$.

The same reaction was also carried out for compound **8**. In contrast with reaction of **7**, the two compounds (**17** and **18**) could be separated out by chromatography and thus characterized respectively by ^1H, ^{13}C, ^1H–^1H COSY, ^1H–^{13}C COSY NMR and HRMS. When the reaction was carried under the air, the ratio of **17**:**18** = 2:1; if the reaction was performed under nitrogen, the ratio of **17**:**18** = 10:1. Similarly, deoxygenation of **17** provided compound **19** in good yield. ^1H NMR spectrum of **19** showed two sets of peaks at δ 1.73 and 2.27 ppm, corresponding to two protons at $C_2{}^A$, while ^{13}C NMR spectrum displayed a signal at δ 34.65 ppm, corresponding to $C_2{}^A$. The detailed data for NMR and HRMS can be found as supporting information in this journal.

With the two mono functionalized per-*O*-methylated β-CDs (**16** and **19**) in hand, we turned our attention to investigation of their behaviors upon action of DIBAL-H. The reaction conditions were that used for preparing the 2^A,3^B-dihydroxy-per-*O*-methylated β-CD **3** [6] as well as de-*O*-methylation reaction of compound **7** and **8** [9]. Unlike compound **7**, no new product was formed on TLC analysis when the two deoxy-derivatives were treated for 18 h at 0 °C in toluene with a commercially available DIBAL-H (0.2 M, 9 equiv.) and the recovered product was characterized by NMR as the starting material (Scheme 4). This result indicates that *O*-2^A and *O*-3^B of per-*O*-methylated β-CD were necessary for DIBAL-H promoted double 2^A,3^B-de-*O*-methylation reaction, which agreed well with our previously proposed mechanism [9].

Combined with our previous studies, the DIBAL-H promoted regioselective bis-de-*O*-methylation of **1** may include two steps: the first step would consist in the formation of the complex of **1** with DIBAL-H slowly between two



Scheme 4. DIBAL-H promoted de-*O*-methylation reactions of compounds **16** and **19**, as well as compounds **7** and **8** [9].

methoxy groups at C-2^A and C-3^B located on two adjacent sugar units, followed by de-*O*-methylation at $C_3{}^B$; the second step would be the formation of the complex of **13** with an excess of DIBAL-H quickly between the methoxy group at C-2^A and the hydroxyl group at C-3^B, followed by de-*O*-methylation at $C_2{}^A$ to afford almost quantitatively the 2^A,3^B-diol **3**. In both cases, the presence of a C-2 methoxy group and a C-3 methoxy or hydroxyl group are necessary for complex formation. Being in absence of C-3 methoxy group, compound **16** could not form an appropriate complex, thus failed to give rise to further de-*O*-methylation. The same explanation could be applied to compound **19**, in which the methoxy group at C-2 was replaced by a hydrogen atom, the complex of transition state could not be formed, therefore no de-*O*-methylation occurred.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2012.10.023.

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