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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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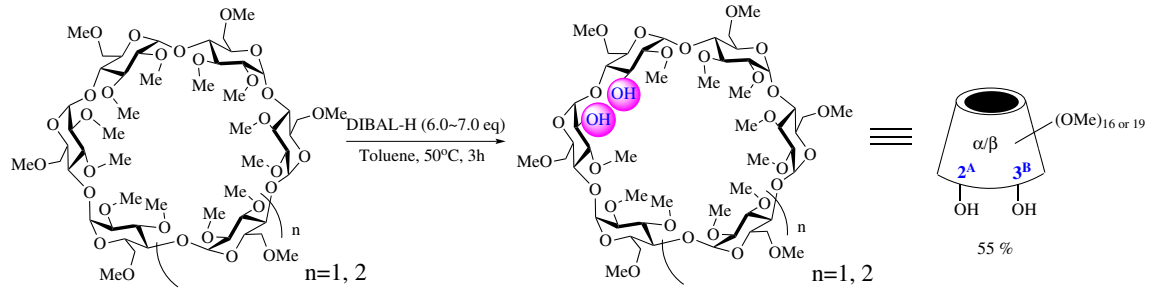
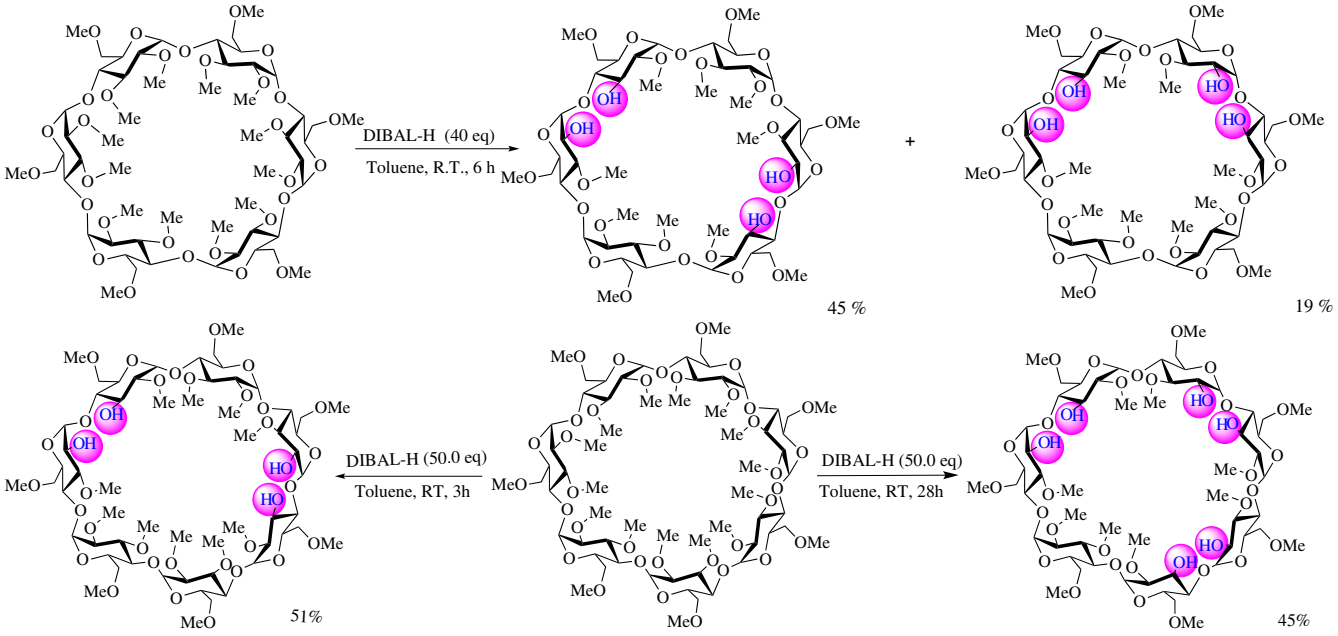
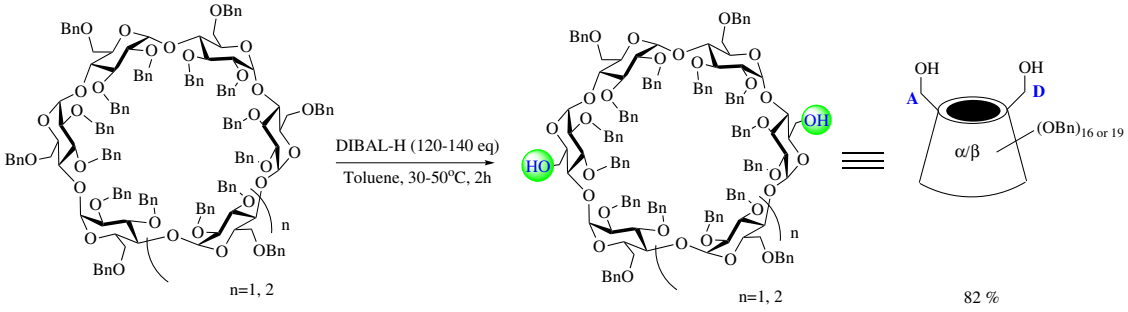


Scheme 1. Bis-de-*O*-methylation of per-*O*-methylated α- and β-CDs by DIBAL-H.



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.

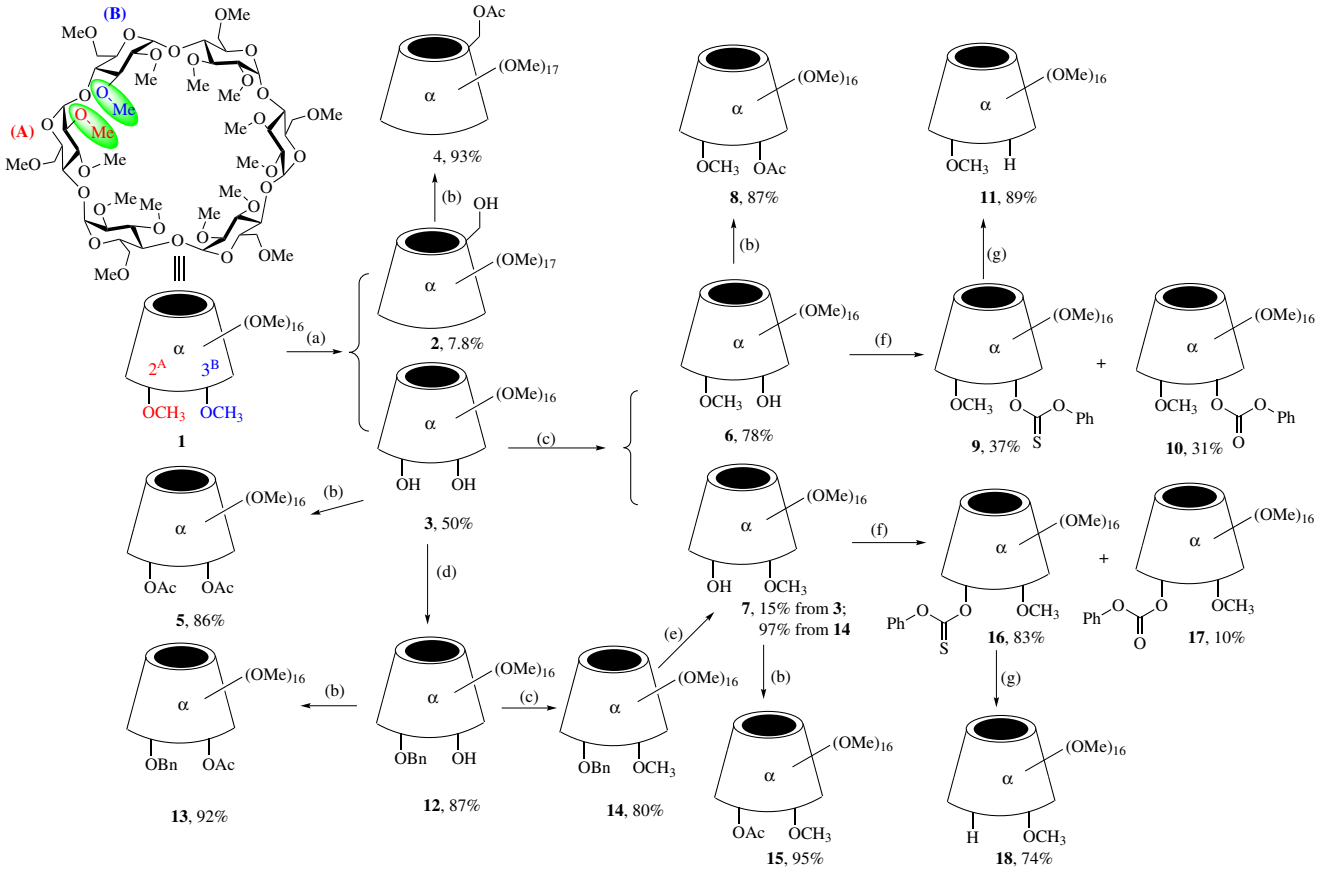


Scheme 3. Bis-de-O-benzylation of per-*O*-benzylated β-CD by DIBAL-H.

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.



Scheme 4. Synthesis of the mono-functionalized per-*O*-methylated α-CD derivatives. Reagents and condition: (a) DIBAL-H (9.0 equiv), toluene, 0.2 M, 18 h, 0 °C; (b) Ac_2O, pyridine, DMAP, rt, 18 h; (c) CH_3I, NaH, DMF; (d) BnBr, NaH, DMF; (e) Pd/C, H_2, CH_3OH; (f) *O*-phenyl chlorothioformate, DMAP, pyridine, CH_2Cl_2; (g) AIBN, tributylstannane, toluene, 80 °C.

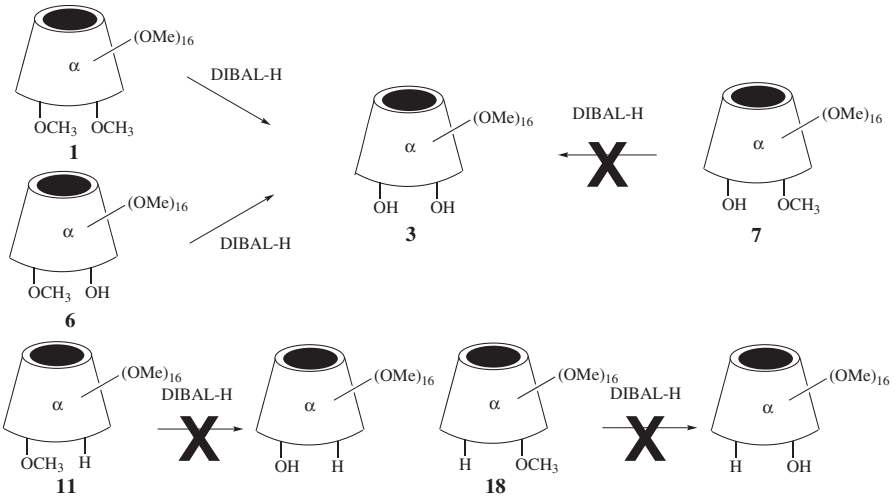
As the hydroxyl group at $C_2{}^A$ is more acidic[10b] than that at $C_3{}^B$, consequently the reaction with an electrophilic reagent was expected to happen at $C_2{}^A$ predominantly. In our experiments, selective O-methylation of **3** at $C_2{}^A$ with methyl iodide and sodium hydride in DMF at room temperature afforded **6** in 80% yield, and its regioisomer **7** was a minor component (15%). Like compound **3**, the structures of **6** and **7** were also confirmed by their acetylation derivatives. ^1H NMR spectrum of **8** displayed a deshielded methine signal at δ 5.45 (dd, $J_{2,3}$=9.3 and $J_{3,4}$=9.2 Hz), should be assigned to $H_3{}^B$, and ^{13}C NMR spectrum displayed one carbon at 71.67 ppm, should be assigned to $C_3{}^B$, due to the acetylation of $C_3{}^B$, indicating that methylation of **3** took place at position $C_2{}^A$ predominantly. On the other hand, the ^1H NMR spectrum of acetylated compound **15** showed a deshielded signal for $H_2{}^A$ at δ 4.65 (dd, $J_{1,2}$=3.1 and $J_{2,3}$=10.3 Hz) and ^{13}C NMR spectrum displayed one carbon at 74.25 ppm, should be assigned to $C_2{}^A$, indicating that methylation took place at position $C_3{}^B$.

As the yield for **7** is too low (only in 15%) by this method, a method for selective O-methylation of the $C_3{}^B$ hydroxyl group was achieved from **3** in a convenient three-step procedure in an excellent overall yield (in 64% yield over three steps). Firstly, a selective protection of the hydroxyl group at $C_2{}^A$ by benzyl group to give **12**, whose structure was confirmed again from ^1H and ^{13}C NMR spectrum of acetylated derivative **13**. The remaining hydroxyl group at $C_3{}^B$ of **12** was then methylated to give **14**, which was finally hydrogenolyzed with 10% Pd/C to give **7**.

Surprisingly, when transformation of **6** into **9** was performed with *O*-phenyl chlorothioformate at 100 °C under nitrogen, an unexpected compound **10** was formed with **9** as judged by the results of ^1H NMR and ^{13}C NMR spectra of the mixture. Trying to separate the two components at this stage by usual column chromatography was very difficult because their polarities are very similar (R_f=0.24, petroleum ether/acetone=1:1). According to HPLC analysis, the ratio of **9**:**10** is 55:45 (CH_3OH/H_2O: 60/40 by volume). As far as we are aware the only example of this result in the literature was reported by Remy et al.,[16] as they 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. The mixture was subjected to deoxygenation reaction before separation was achieved. According to the classical Barton–McCombie conditions (Bu_3SnH, AIBN, 100 °C),[17] desired compound **11** was obtained in 49% yield and compound **10** was recovered in 40% yield. ^1H NMR spectrum of compound **11** showed two sets of peaks at δ 1.96–2.05 and 2.31–2.39 ppm, corresponding to two protons at $C_3{}^B$, while ^{13}C NMR spectrum displayed a signal at 29.24 ppm, corresponding to $C_3{}^B$.

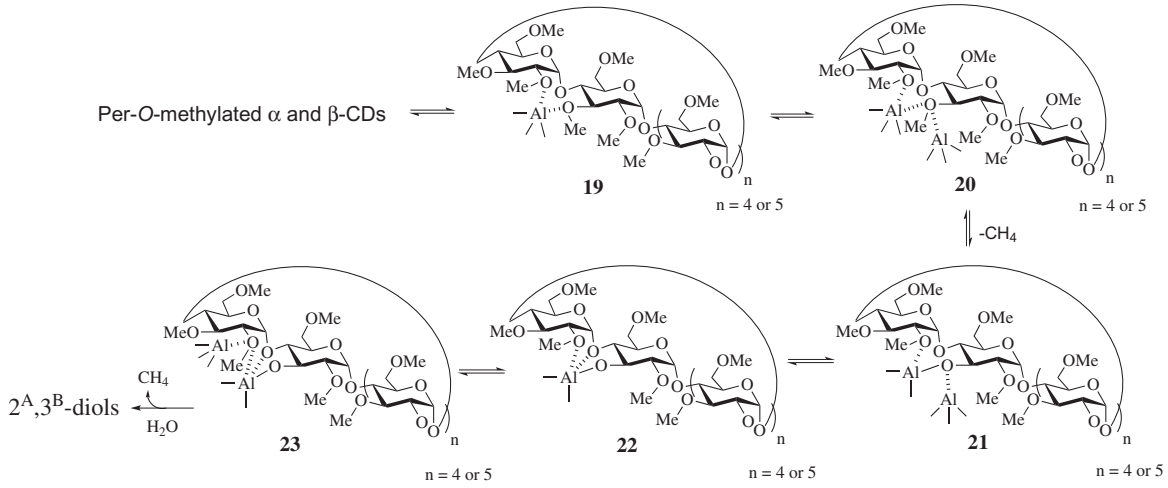
The same reaction was also carried out for compound **7**. As for compound **6**, two compounds (**16** and **17**) were formed from compound **7** under an inert atmosphere. Interestingly, unlike the mixture of compound **9** and **10**, these two compounds could be separated out by chromatography and thus characterized, respectively, by ^1H NMR, ^{13}C NMR, ^1H–^1H COSY, ^1H–^{13}C COSY, and HRMS. Compound **16** were obtained as the main product in 83% yield. Deoxygenation of compound **16** proceeded smoothly in the presence of Bu_3SnH and AIBN to give compound **18** in 74% yield. ^1H NMR spectrum of **18** showed two sets of peaks at δ 1.65–1.71 and 2.27–2.32 ppm, corresponding to two protons at $C_2{}^A$, while ^{13}C NMR spectrum displayed a signal at 35.49 ppm, corresponding to $C_2{}^A$.

Since the preparation of mono-functionalized per-*O*-methylated-α-CDs (**6**, **7**, **11**, and **18**) had been accomplished, we turned our attention to investigation of their behaviors upon action of DIBAL-H (Scheme 5). The reaction conditions were the same as that used for



Scheme 5. DIBAL-H promoted de-O-methylation reactions of compounds **6**, **7**, **11**, and **18**. Reagents and condition: DIBAL-H (9.0 equiv), toluene, 0.2 M, 18 h, 0 °C.

preparing the compound **3**. As expected, when 2^A-hydroxyl-per-*O*-methylated-α-CD **7** was treated with a commercially available DIBAL-H (0.2 M, 9 equiv) for 18 h at 0 °C in toluene, no new product was formed on TLC analysis, and the recovered product was characterized by NMR as the starting material. Interestingly, when 3^B-hydroxyl-per-*O*-methylated-α-CD **6** was treated under the same condition, the starting material disappeared rapidly (within 0.5 h), and a new spot with the same R_f as **3** on TLC appeared solely which, after purification, showed the identical ^{1}H NMR and ^{13}C NMR spectra as **3** obtained from **1** under the same condition. This with DIBAL-H slowly between two methoxy groups at $C_2{}^A$ and $C_3{}^B$ located on two adjacent sugar units, followed by de-O-methylation at $C_3{}^B$ to provide the intermediate **21**; the second step would be the formation of the complex of **22** with an excess of DIBAL-H quickly between the methoxy group at $C_2{}^A$ and the hydroxyl group at $C_3{}^B$, with participation of the interglycosidic oxygen atom, demethylation at $C_2{}^A$ then proceeds via complex **23** to afford almost quantitatively the 2^A,3^B-diols. In both cases, the presence of a C_2 methoxy group and a C_3 methoxy or hydroxyl group are necessary for complex formation.



Scheme 6. Proposed mechanism for the formation of 2^A,3^B-diols from per-*O*-methylated α and β-cyclodextrins.

particular behavior met during this reaction is not so surprising, since several authors already reported 'reactivity discriminations'.[6,8b,12,18] This work complements de-O-methylation performed with phenylthiotrimethylsilane reported by Chaise et al.,[9a] which allow access to only 3^B-hydroxyl-per-*O*-methyl-α-CD **6** by removing the methyl group at $C_3{}^B$. However, no reaction was observed of the other two deoxy-derivatives at C_2 and C_3 (**11** and **18**) under these reaction conditions.

Combined with our previous studies,[15] we think that the DIBAL-H promoted regioselective bis-de-O-methylation of per-*O*-methylated CDs may include two steps (Scheme 6): the first step would consist in the formation of the complex of per-*O*-methylated CDs

3. Conclusion

Starting from per-*O*-methylated α-CD, four mono-functionalized per-*O*-methylated α-CD derivatives were prepared in a regioselective manner. All the products were unambiguous characterized by ^{1}H and ^{13}C NMR, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HMQC or HSQC, and HRMS. This study further confirmed that 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 2^A,3^B-diol. Moreover, not only *O*-3^B-methyl but also *O*-2^A and *O*-3^B methyls are necessary for the formation of 'tweezers' during DIBAL-H promoted bis-de-O-methylation reaction of per-*O*-methylated CD.

4. Experimental

4.1. General

Optical rotations were measured at 20±2 °C with a Perkin Elmer Model 343 digital polarimeter, using a 10 cm, 1 mL cell. High Resolution Mass Spectrometry (HRMS) were obtained with a LTQ—Orbitrap spectrometer (ThermoFischer Company) or APEX IV FT-MS (7.0 T) spectrometer (Bruker). NMR spectra were recorded on a Bruker DRX 400 spectrometer or Varian INONVA-500 spectrometer at ambient temperature. ^{1}H NMR chemical shifts are referenced to residual protic solvent ($CDCl_3$, δ_H=7.28). ^{13}C NMR chemical shifts are referenced to the solvent signal (δ_C=77.00 for the central line of $CDCl_3$). Reactions were monitored by thin-layer chromatography (TLC) on a pre-coated silica gel 60 F_{254} plate (layer thickness 0.2 mm; E. Merck, Darmstadt, Germany) and detected by charring with a 10% solution of sulfuric acid in ethanol. Flash column chromatography was performed on silica gel 60 (230–400 mesh, E. Merck or 200–300 mesh, Qingdao Haiyang Chemical Co. Ltd.). HPLC was carried on a Varian Star instrument using a 330 UV–vis, PDA detector and the chromatographic data was acquired by LC workstation version 6.20.

4.2. 6^A-Hydroxyl-per-*O*-methyl-α-cyclodextrin (2) and 2^A,3^B-dihydroxyl-per-*O*-methyl-α-cyclodextrin (3)

To a solution of dried per-*O*-methyl-α-cyclodextrin (670.5 mg, 0.55 mmol) in anhydrous toluene (21.4 mL) was added 3.29 mL (4.93 mmol, 9.0 equiv), DIBAL-H (1.5 M in toluene) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 18 h under nitrogen. Aqueous HCl (1 M) was carefully added dropwise to quench the reaction and the mixture was stirred vigorously at room temperature for 30 min. The toluene phase was separated and the water phase was extracted by ethyl acetate (3×20 mL). The combined organic phase was washed with brine, dried with $MgSO_4$, filtrated, and the solvent was removed in vacuo. The residue was subjected to flash chromatography (eluent: CH_2Cl_2/CH_3OH=50:1–25:1) to give compound **2** and **3** in 7.8% and 50% yield, respectively.[12]

The NMR data of **2** are in agreement with those reported previously.[19]

Compound **3**: R_f=0.20 (CH_2Cl_2/CH_3OH=15:1); $[\alpha]_D$ +144 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.16–3.21 (m, 6H, 6× H_2), 3.39 (s, 9H, 3× OCH_3 (C_6)), 3.40 (3× s, 9H, 3× OCH_3 (C_6)), 3.41 (s, 3H, OCH_3 (C_6)), 3.50 (2× s, 12H, 4× OCH_3 (C_2)), 3.52 (2× s, 6H, 2× OCH_3 (C_2)), 3.56 (s, 3H, OCH_3 (C_2)), 3.59 (m, 1H, $H_2{}^A$), 3.62 (2× s, 6H, 2× OCH_3 (C_3)), 3.63 (s, 3H, OCH_3 (C_3)), 3.64 (s, 3H, OCH_3 (C_3)), 3.65 (s, 3H, OCH_3 (C_3)), 3.73 (s, 3H, OCH_3 (C_3)), 3.44–3.93 (m, 35H, 6× H_3, 7× H_4, 7× H_5, 7× H_{6a}, 7× H_{6b}, OH), 3.99 (t, 1H, $J_{2,3}$=$J_{3,4}$=9.5 Hz, $H_3{}^B$), 4.09 (br s, 1H, D_2O exchangeable, OH), 5.01 (d, 1H, $J_{1,2}$=3.7 Hz, $H_1{}^A$), 5.09–5.10 (m, 2H, 2× H_1), 5.11–5.14 (m, 4H, 4× H_1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 58.24, 58.29, 58.36, 58.44, 58.63, 58.85, 58.88, 58.91, 58.97 (13C, 6× OCH_3 (C_2), 7× OCH_3 (C_6)), 61.23, 61.30, 61.33, 61.35, 61.49, 62.11 (6C, 6× OCH_3 (C_3)), 70.35, 70.75, 70.85, 70.93, 71.64 (7C, 7× C_5), 70.78, 71.16, 71.25, 71.33, 71.48 (7C, 7× C_6), 71.72 ($C_3{}^B$), 73.40 ($C_2{}^A$), 80.02, 80.33, 80.95, 80.99, 81.29, 81.38, 81.58, 81.62, 81.75, 81.98, 82.01, 82.19, 82.37, 82.91 (19C, 6× C_2, 6× C_3, 7× C_4), 98.68, 98.93, 99.30, 99.46 (6C, 6× C_1), 102.01 ($C_1{}^A$); HRMS calcd for $C_{52}H_{96}NO_{30}$ $[M+NH_4]^+$: 1214.6012. Found 1214.5599; $C_{52}H_{92}NaO_{30}$ $[M+Na]^+$: 1219.5566. Found 1219.5550.

4.3. 6^A-*O*-Acetyl-per-*O*-methyl-α-cyclodextrin (4)

To a solution of **2** (36.5 mg, 0.030 mmol) in dry pyridine (2 mL) was added 3.7 mg of DMAP (0.030 mmol, 1.0 equiv) and 1 mL Ac_2O at room temperature. The reaction mixture was stirred for 18 h under nitrogen. The solvent was removed in vacuo. The residue was subjected to flash chromatography (eluent: CH_2Cl_2/CH_3OH=30:1) to give 35.1 mg (93%) of compound **4** as a white foam. R_f=0.39 (CH_2Cl_2/CH_3OH=10:1); $[\alpha]_D$ +128.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3CO), 3.16–3.20 (m, 6H, 6× H_2), 3.39 (s, 3H, OCH_3 (C_6)), 3.41 (br s, 12H, 4× OCH_3 (C_6)), 3.50 (2× s, 12H, 4× OCH_3 (C_2)), 3.51 (s, 6H, 2× OCH_3 (C_2)), 3.52 (s, 3H, OCH_3 (C_2)), 3.54 (m, 1H, $H_4{}^A$), 3.64 (s, 6H, 2× OCH_3 (C_3)), 3.65 (2× s, 9H, 3× OCH_3 (C_3)), 3.66 (s, 3H, OCH_3 (C_3)), 3.92 (m, 1H, $H_5{}^A$), 3.44–3.92 (m, 26H, 6× H_3, 5× H_4, 5× H_5, 5× H_{6a}, 5× H_{6b}), 4.26 (dd, 1H, $J_{5,6a}$=4.6 Hz, $J_{6a,6b}$=12.0 Hz, $H_{6a}{}^A$), 4.59 (m, 1H, $H_{6b}{}^A$), 5.04–5.07 (m, 6H, 6× H_1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.81 (*C*H_3CO), 57.79, 57.84, 58.16 (6C, 6× OCH_3 (C_2)), 58.96, 59.09 (5C, 5× OCH_3 (C_6)), 61.77, 61.80, 61.87 (6C, 6× OCH_3 (C_3)), 63.72 ($C_6{}^A$), 69.69 ($C_5{}^A$), 70.74, 71.28, 71.46 (5C, 5× C_6), 71.22, 71.42 (5C, 5× C_5), 81.18, 81.21, 81.32, 82.00, 82.06, 82.15, 82.22, 82.30, 82.40, 82.45, 82.59 (18C, 6× C_2, 6× C_3, 6× C_4), 99.65, 99.89, 100.09, 100.18, 100.55 (6C, 6× C_1), 170.49 (C=O); HRMS calcd for $C_{55}H_{96}NaO_{31}$ $[M+Na]^+$: 1275.5828. Found 1275.5829.

4.4. 2^A,3^B-*O*-Diacetyl-per-*O*-methyl-α-cyclodextrin (5)

To a solution of **3** (31.8 mg, 0.027 mmol) in dry pyridine (2 mL) was added 3.2 mg of DMAP (0.027 mmol, 1.0 equiv) and 1 mL Ac_2O at room temperature. The reaction mixture was stirred for 18 h under nitrogen. The solvent was removed in vacuo. The residue was subjected to flash chromatography (eluent: CH_2Cl_2/CH_3OH=30:1) to give 29.3 mg (86%) of compound **5** as a white foam. R_f=0.40 (CH_2Cl_2/CH_3OH=10:1); $[\alpha]_D$ +140.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H, CH_3CO), 2.22 (s, 3H, CH_3CO), 3.12–3.21 (m, 4H, 4× H_2), 3.22 (dd, 1H, $J_{1,2}$=3.1 Hz, $J_{2,3}$=10.1 Hz, $H_2{}^B$), 3.40 (s, 3H, OCH_3 (C_6)), 3.41 (2× s, 15H, 5× OCH_3 (C_6)), 3.44 (s, 3H, OCH_3 (C_2)), 3.48 (s, 6H, 2× OCH_3 (C_2)), 3.51 (s, 6H, 2× OCH_3 (C_2)), 3.57 (s, 3H, OCH_3 (C_3)), 3.58 (m, 1H, H_5), 3.59 (s, 3H, OCH_3 (C_3)), 3.62 (s, 3H, OCH_3 (C_3)), 3.65 (s, 3H, OCH_3 (C_3)), 3.67 (m, 1H, $H_3{}^A$), 3.70 (s, 3H, OCH_3 (C_3)), 3.72 (m, 1H, $H_4{}^B$), 3.53–3.96 (m, 25H, 4× H_3, 5× H_4, 5× H_5, 6× H_{6a}, 5× H_{6b}), 4.08 (dd, 1H, $J_{5,6b}$=2.2 Hz, $J_{6a,6b}$=10.8 Hz, H_{6b}), 4.70 (dd, 1H, $J_{1,2}$=2.6 Hz, $J_{2,3}$=10.3 Hz, $H_2{}^A$), 4.99 (d, 1H, $J_{1,2}$=2.6 Hz, $H_1{}^A$), 5.03–5.06 (m, 3H, 3× H_1), 5.09 (d, 1H, $J_{1,2}$=3.1 Hz, H_1), 5.12 (d, 1H, $J_{1,2}$=3.1 Hz, $H_1{}^B$), 5.47 (t, $J_{2,3}$=10.1 Hz, $J_{3,4}$=9.0 Hz, $H_3{}^B$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.45, 21.68 (2C, 2× *C*H_3CO), 57.52, 57.70, 57.78, 57.95, 58.24 (5C, 5× OCH_3 (C_2)), 58.78, 58.91, 58.95, 59.02, 59.04 (6C, 6× OCH_3 (C_6)), 61.46, 61.59, 61.71, 61.85, 62.06 (5C, 5× OCH_3 (C_3)), 70.69, 71.42, 71.45, 71.58, 71.87 (6C, 6× C_6), 70.84, 71.12, 71.14, 71.50, 71.61 (6C, 6× C_5), 71.66 ($C_3{}^B$), 74.38 ($C_2{}^A$), 79.87 ($C_2{}^B$), 78.40, 78.98, 80.80, 80.92, 80.93, 80.99, 82.18, 82.23, 82.31, 82.35, 82.56, 82.60, 82.62, 82.65, 82.83 (15C, 4× C_2, 5× C_3, 6× C_4), 98.45 ($C_1{}^A$), 99.83, 99.88, 100.01, 100.22, 100.42 (5C, 5× C_1), 170.39 (2C, 2× C=O); HRMS calcd for $C_{56}H_{96}NaO_{32}$ $[M+Na]^+$: 1303.5777. Found 1303.5763.

4.5. 3^B-Hydroxyl-per-*O*-methyl-α-cyclodextrin (6)

To a solution of **3** (97.4 mg, 0.081 mmol) in anhydrous THF (5 mL) was added 3.3 mg (60%, 0.081 mmol, 1.0 equiv) of NaH at 0 °C under nitrogen. After the reaction mixture was stirred at 0 °C for 1 h, 5.0 μL of CH_3I (0.081 mmol, 1.0 equiv) was added. The reaction mixture was stirred at 0 °C for 6 h and then kept at room temperature for another 12 h under nitrogen. CH_3OH was added dropwise to quench the reaction and the solvent was removed in vacuo. The residue dissolved with CH_2Cl_2, washed with brine, dried with $MgSO_4$, filtrated, and the solvent was removed in vacuo. The residue was subjected to flash chromatography (eluent: CH_2Cl_2/EtOAc/CH_3OH=10:10:1) to give 15.0 mg (15%) of **7** firstly, then 76.4 mg (78%) of **6** as white foam. R_f=0.38 (CH_2Cl_2/CH_3OH/EtOAc=5:1:5); $[\alpha]_D$ +126.5 (*c* 1.0, $CHCl_3$); the NMR data of **6** are in agreement with those reported previously.[9a]

4.6. 3^B-*O*-Acetyl-per-*O*-methyl-α-cyclodextrin (8)

By the same procedure described in 4.2, compound **8** was obtained by flash chromatography (eluent: cyclohexane/acetone=2:1) as a white foam in 87% yield. R_f=0.32 (cyclohexane/acetone=1:1); $[\alpha]_D$ +129.7 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 2.14 (s, 3H, CH_3CO), 3.10–3.20 (m, 5H, 5× H_2), 3.25 (dd, 1H, $J_{1,2}$=3.0 Hz, $J_{2,3}$=10.5 Hz, $H_2{}^B$), 3.41 (s, 3H, OCH_3 (C_6)), 3.42 (2× s, 15H, 5× OCH_3 (C_6)), 3.44 (s, 3H, OCH_3 (C_2)), 3.47 (s, 3H, OCH_3 (C_2)), 3.48 (s, 3H, OCH_3 (C_2)), 3.49 (s, 3H, OCH_3 (C_2)), 3.50 (s, 3H, OCH_3 (C_2)), 3.51 (s, 3H, OCH_3 (C_2)), 3.58 (s, 3H, OCH_3 (C_3)), 3.60 (m, 1H, H_5), 3.62 (s, 6H, 2× OCH_3 (C_3)), 3.63 (s, 3H, OCH_3 (C_3)), 3.70 (s, 3H, OCH_3 (C_3)), 3.80 (m, 1H, $H_4{}^B$), 3.47–3.94 (m, 26H, 5× H_3, 5× H_4, 5× H_5, 6× H_{6a}, 5× H_{6b}), 4.02 (dd, 1H, $J_{5,6b}$=2.8 Hz, $J_{6a,6b}$=10.5 Hz, H_{6b}), 4.96 (d, 1H, $J_{1,2}$=2.8 Hz, H_1), 5.01 (d, 1H, $J_{1,2}$=3.3 Hz, H_1), 5.04–5.05 (m, 2H, 2× H_1), 5.09 (d, 1H, $J_{1,2}$=3.3 Hz, H_1), 5.11 (d, 1H, $J_{1,2}$=3.0 Hz, $H_1{}^B$), 5.45 (dd, 1H, $J_{2,3}$=10.5 Hz, $J_{3,4}$=9.0 Hz, $H_3{}^B$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.39 (CH_3CO), 57.52, 57.71, 57.73, 57.79, 58.21, 58.72, 58.88, 58.95, 58.98, 59.08 (12C, 6× OCH_3 (C_2), 6× OCH_3 (C_6)), 61.56, 61.69, 61.77, 61.89, 62.09 (5C, 5× OCH_3 (C_3)), 70.75, 71.35, 71.39, 71.48, 71.71, 71.84 (6C, 6× C_6), 70.99, 71.09, 71.13, 71.15, 71.23, 71.32 (6C, 6× C_5), 71.67 ($C_3{}^B$), 79.54, 80.75, 80.87, 80.92, 80.93, 82.19, 82.27, 82.29, 82.52, 82.54, 82.60, 82.62, 82.67, 82.73, 82.84 (16C, 5× C_2, 5× C_3, 6× C_4), 79.78 ($C_2{}^B$), 99.68, 99.88, 100.15, 100.22, 100.31, 100.33 (6C, 6× C_1), 170.84 (C=O); HRMS calcd for $C_{55}H_{96}NaO_{31}$ $[M+Na]^+$: 1275.5828. Found 1275.5816.

4.7. 3^B-*O*-Phenoxythiocarbonyl-per-*O*-methyl-α-cyclodextrin (9)

To a solution of **6** (170.3 mg, 0.14 mmol) in pyridine (2 mL) was added 4-dimethylaminopyridine (34.2 mg, 0.28 mmol) and *O*-phenyl chlorothioformate (290 μL, 2.1 mmol). The reaction mixture was degassed under vacuum and urged with nitrogen three times, then stirred under nitrogen balloon at 50 °C for 10 h and concentrated. The residue dissolved with CH_2Cl_2, washed with brine, dried with $MgSO_4$, filtrated, and the solvent was removed in vacuo. The residue was subjected to flash chromatography (eluent: petroleum ether/acetone=3:2) to recover **6** (48.5 mg), and then to give the mixture of compound **9** and **10** (109.2 mg, 68%) as a white foam. Compound **9**: ^{13}C NMR (125 MHz, $CDCl_3$): 122.24, 126.47, 129.41, 153.42 (6C, 6× arom-C); compound **10**: ^{13}C NMR (125 MHz, $CDCl_3$): 121.17, 125.67, 129.19, 153.87 (6C, 6× arom-C), 151.49 (C=O).

HPLC indicate that compound **9**:**10**=55:45.

4.8. 3^B-*O*-Phenoxycarbonyl-per-*O*-methyl-β-cyclodextrin (10) and 3^B-deoxy-per-*O*-methyl-β-cyclodextrin (11)

The mixture of compound **9** and **10** (54.3 mg) was dissolved in anhydrous toluene (2 mL) and AIBN (3.3 mg, 0.02 mmol) was added. The solution was degassed under vacuum and urged with nitrogen three times, then tributylstannane (150 μL, 0.52 mmol) was added. The mixture was stirred at 100 °C for 2 h. After evaporation of toluene, the residue was dissolved in dichloromethane (10 mL) then washed with brine, dried with $MgSO_4$, filtrated, and the solvent was removed in vacuo. The residue was subjected to flash chromatography (eluent: CH_2Cl_2/CH_3OH=60:1–40:1) to recover 21.7 mg **10** (40%) firstly, and then to give 25.2 mg (49%) of **11** as a white foam.

Compound **10**: R_f=0.39 (CH_2Cl_2/CH_3OH=20:1); $[\alpha]_D$ +138.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.14–3.18 (m, 5H, 5× H_2), 3.36 (dd, 1H, $J_{1,2}$=3.2 Hz, $J_{2,3}$=10.0 Hz, $H_2{}^B$), 3.41 (s, 12H, 4× OCH_3 (C_6)), 3.42 (s, 3H, OCH_3 (C_6)), 3.43 (s, 3H, OCH_3 (C_6)), 3.46 (s, 6H, 2× OCH_3 (C_2)), 3.47 (s, 3H, OCH_3 (C_2)), 3.48 (s, 3H, OCH_3 (C_2)), 3.51 (s, 3H, OCH_3 (C_2)), 3.52 (s, 3H, OCH_3 (C_2)), 3.55 (s, 3H, OCH_3 (C_3)), 3.58 (s, 3H, OCH_3 (C_3)), 3.59 (2× s, 6H, 2× OCH_3 (C_3)), 3.65 (s, 3H, OCH_3 (C_3)), 3.87 (m, 1H, $H_4{}^B$), 3.46–3.88 (m, 27H, 5× H_3, 5× H_4, 6× H_5, 6× H_{6a}, 5× H_{6b}), 3.97 (m, 1H, H_{6b}), 5.02–5.06 (m, 5H, 5× H_1), 5.14 (d, 1H, $J_{1,2}$=3.2 Hz, $H_1{}^B$), 5.33 (m, 1H, $H_3{}^B$), 7.20–7.22 (m, 1H, arom-H), 7.35–7.36 (m, 4H, arom-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.56, 57.60, 57.70, 57.81, 58.05, 58.31 (6C, 6× OCH_3 (C_2)), 58.90, 58.93, 58.96, 59.05 (6C, 6× OCH_3 (C_6)), 61.67, 61.71, 61.84, 61.93, 61.98 (5C, 5× OCH_3 (C_3)), 70.70, 71.38, 71.69 (6C, 6× C_6), 70.99, 71.10, 71.13, 71.21 (6C, 6× C_5), 76.71 ($C_3{}^B$), 79.60 ($C_2{}^B$), 79.93 ($C_4{}^B$), 80.71, 80.87, 80.94, 82.15, 82.21, 82.25, 82.40, 82.50, 82.65, 82.73 (15C, 5× C_2, 5× C_3, 5× C_4), 99.90, 99.94, 100.05, 100.16, 100.31 (6C, 6× C_1), 121.12, 125.61, 129.13, 153.37 (6C, 6× arom-C), 151.45 (C=O); HRMS calcd for $C_{60}H_{98}NaO_{32}$ $[M+Na]^+$: 1353.5933. Found 1353.5935.

Compound **11**: R_f=0.37 (CH_2Cl_2/CH_3OH=20:1); $[\alpha]_D$ +133.5 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.96–2.05 (m, 1H, $H_{3a}{}^B$), 2.31–2.39 (m, 1H, $H_{3b}{}^B$), 3.12 (dd, 1H, $J_{1,2}$=2.8 Hz, $J_{2,3}$=9.6 Hz, H_2), 3.16–3.19 (m, 4H, 4× H_2), 3.28–3.32 (m, 1H, $H_2{}^B$), 3.41 (s, 12H, 4× OCH_3 (C_6)), 3.43 (s, 3H, OCH_3 (C_6)), 3.44 (s, 3H, OCH_3 (C_6)), 3.48 (s, 6H, 2× OCH_3 (C_2)), 3.50 (br s, 12H, 4× OCH_3 (C_2)), 3.61 (s, 3H, OCH_3 (C_3)), 3.63 (s, 3H, OCH_3 (C_3)), 3.65 (s, 6H, 2× OCH_3 (C_3)), 3.66 (s, 3H, OCH_3 (C_3)), 3.71 (m, 1H, $H_4{}^B$), 3.48–3.90 (m, 28H, 5× H_3, 5× H_4, 6× H_5, 6× H_{6a}, 6× H_{6b}), 4.94 (d, 1H, $J_{1,2}$=3.2 Hz, H_1), 5.03 (d, 1H, $J_{1,2}$=3.2 Hz, $H_1{}^B$), 5.06–5.07 (m, 4H, 4× H_1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.24 ($C_3{}^B$), 56.57, 57.62, 57.70, 57.79, 58.76, 58.93, 58.95, 59.00, 59.02, 59.10 (12C, 6× OCH_3 (C_2), 6× OCH_3 (C_6)), 61.59, 61.80, 61.82, 61.89 (5C, 5× OCH_3 (C_3)), 71.11, 71.15, 71.19, 71.51 (6C, 6× C_5), 71.36, 71.46, 71.79 (6C, 6× C_6), 76.13 ($C_4{}^B$), 76.51 ($C_2{}^B$), 81.12, 81.14, 81.19, 81.26, 81.87, 81.91, 81.98, 82.10, 82.17, 82.21, 82.29, 82.45, 82.50 (15C, 5× C_2, 5× C_3, 5× C_4), 99.14 ($C_1{}^B$), 99.72, 99.91, 100.03, 100.21 (5C, 5× C_1); HRMS calcd for $C_{53}H_{94}NaO_{29}$ $[M+Na]^+$: 1217.5773. Found 1217.5778.

4.9. 2^A-*O*-Benzyl-3^B-hydroxyl-per-*O*-methyl-α-cyclodextrin (12)

To a solution of **3** (437.8 mg, 0.37 mmol) in anhydrous THF (20 mL) was added 14.6 mg (60%, 0.37 mmol, 1.0 equiv) of NaH at 0 °C under nitrogen. After the reaction mixture was stirred at 0 °C for 1 h, 43.8 μL BnBr (0.37 mmol, 1.0 equiv) was added. The reaction mixture was stirred at 0 °C for 6 h and then kept at room temperature for 12 h under nitrogen. CH_3OH was added dropwise to quench the reaction and the solvent was removed in vacuo. The residue was dissolved with CH_2Cl_2, washed with brine, dried with $MgSO_4$, filtrated, and the solvent was removed in vacuo. The residue was subjected to flash chromatography (eluent: CH_2Cl_2/EtOAc/CH_3OH=10:10:1) to give 407.6 mg (87%) of **12** as a white foam. R_f=0.44 (CH_2Cl_2/EtOAc/CH_3OH=5:5:1); $[\alpha]_D$ +134.8 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.15–3.18 (m, 4H, 4× H_2), 3.29 (dd, 1H, $J_{1,2}$=3.3 Hz, $J_{2,3}$=10.3 Hz, $H_2{}^B$), 3.35 (s, 3H, OCH_3 (C_6)), 3.36 (s, 3H, OCH_3 (C_6)), 3.37 (m, 1H, $H_2{}^A$), 3.39 (2× s, 9H, 3× OCH_3 (C_6)), 3.41 (s, 3H, OCH_3 (C_6)), 3.47 (s, 3H, OCH_3 (C_2)), 3.48 (br s, 6H, 2× OCH_3 (C_2)), 3.50 (s, 3H, OCH_3 (C_2)), 3.52 (m, 1H, $H_4{}^B$), 3.55 (s, 3H, OCH_3 (C_2)), 3.62 (s, 3H, OCH_3 (C_3)), 3.63 (s, 3H, OCH_3 (C_3)), 3.64 (br s, 6H, 2× OCH_3 (C_3)), 3.68 (m, 1H, $H_3{}^A$), 3.69 (s, 3H, OCH_3 (C_3)), 3.44–3.86 (m, 27H, 4× H_3, 5× H_4, 6× H_5, 6× H_{6a}, 6× H_{6b}), 4.10 (t, 1H, $J_{2,3}$=9.8 Hz, $J_{3,4}$=9.0 Hz, $H_3{}^B$), 4.62 (d, 1H, $J_{1,2}$=3.3 Hz, $H_1{}^A$), 4.73 (d, 1H, J_{gem}=12.5 Hz, PhCH_2), 4.88 (d, 1H, J_{gem}=12.5 Hz, PhCH_2), 5.00 (d, 1H, $J_{1,2}$=3.3 Hz, H_1), 5.03–5.05 (m, 3H, 3× H_1), 5.10 (d, 1H, $J_{1,2}$=3.3 Hz, $H_1{}^B$), 5.20 (s, 1H, D_2O exchangeable, OH), 7.28–7.35 (m, 3H, 3× arom-H), 7.39–7.41 (m, 2H, 2× arom-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.55, 57.64, 57.78, 57.94 (5C, 5× OCH_3 (C_2)), 58.89, 58.90, 58.97, 59.01 (6C, 6× OCH_3 (C_6)), 61.74, 61.78, 61.87, 61.91 (5C, 5× OCH_3 (C_3)), 69.91, 71.09, 71.21, 71.30, 71.49 (6C, 6× C_6), 71.12, 71.15, 71.35, 71.57 (6C, 6× C_6), 71.61 ($C_3{}^B$), 73.70 ($PhCH_2$), 78.51 ($C_2{}^A$), 80.75 ($C_2{}^B$), 81.04, 81.10, 81.27, 82.03, 82.12, 82.15, 82.25, 82.42, 82.48, 82.52, 83.68 (14C, 4× C_2, 4× C_3, 6× C_4), 82.71 ($C_3{}^A$), 99.94, 99.99, 100.04, 100.21, 100.26 (5C, 5× C_1), 101.72 ($C_1{}^A$), 128.20, 128.51, 128.75, 137.07 (6C, 6× arom-C); HRMS calcd for $C_{59}H_{98}NaO_{30}$ $[M+Na]^+$: 1309.6035. Found 1309.6018.

4.10. 2^{A}-*O*-Benzyl-3^{B}-*O*-acetyl-per-*O*-methyl-α-cyclodextrin (13)

By the same procedure described in Section 4.2, compound **13** was obtained by flash chromatography (eluent: cyclohexane/acetone=2:1) as a white foam in 92% yield. R_f=0.38 (cyclohexane/acetone=1:1); $[\alpha]_D$ +130.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H, CH_3CO), 3.12–3.19 (m, 4H, 4× H_2), 3.25 (dd, 1H, $J_{1,2}$=2.8 Hz, $J_{2,3}$=9.9 Hz, $H_2{}^A$), 3.29 (dd, 1H, $J_{1,2}$=3.3 Hz, $J_{2,3}$=10.5 Hz, $H_2{}^B$), 3.33 (s, 3H, OCH_3 (C_6)), 3.37 (s, 3H, OCH_3 (C_6)), 3.40 (s, 3H, OCH_3 (C_6)), 3.41 (2× s, 9H, 3× OCH_3 (C_6)), 3.45 (s, 3H, OCH_3 (C_2)), 3.47 (s, 3H, OCH_3 (C_2)), 3.50 (s, 6H, 2× OCH_3 (C_2)), 3.51 (s, 3H, OCH_3 (C_2)), 3.54 (m, 1H, $H_3{}^A$), 3.57 (s, 3H, OCH_3 (C_3)), 3.61 (s, 3H, OCH_3 (C_3)), 3.64 (s, 3H, OCH_3 (C_3)), 3.68 (s, 3H, OCH_3 (C_3)), 3.70 (s, 3H, OCH_3 (C_3)), 3.76 (m, 1H, $H_4{}^B$), 3.48–3.97 (m, 27H, 4× H_3, 5× H_4, 6× H_5, 6× H_{6a}, 6× H_{6b}), 4.62 (d, 1H, $J_{1,2}$=2.8 Hz, $H_1{}^A$), 4.63 (d, 1H, J_{gem}=12.5 Hz, Ph*CH*$_2$), 4.76 (d, 1H, J_{gem}=12.5 Hz, Ph*CH*$_2$), 5.00 (d, 1H, $J_{1,2}$=3.3 Hz, H_1), 5.04–5.05 (m, 2H, 2× H_1), 5.08 (d, 1H, $J_{1,2}$=3.0 Hz, H_1), 5.12 (d, 1H, $J_{1,2}$=3.0 Hz, $H_1{}^B$), 5.45 (dd, 1H, $J_{2,3}$=10.1 Hz, $J_{3,4}$=9.0 Hz, $H_3{}^B$), 7.30–7.31 (m, 1H, arom-H), 7.34–7.38 (m, 2H, 2× arom-H), 7.41–7.43 (m, 2H, 2× arom-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.25 (*C*H_3CO), 57.47, 57.68, 57.78, 57.98, 58.20 (5C, 5× OCH_3 (C_2)), 58.74, 58.91, 58.93, 58.95, 59.01 (6C, 6× OCH_3 (C_6)), 61.50, 61.65, 61.77, 61.86, 62.07 (5C, 6× OCH_3 (C_3)), 70.61, 71.29, 71.46, 71.64, 71.82 (6C, 6× C_6), 70.92, 71.10, 71.17 (6C, 6× C_5), 71.34 ($C_3{}^B$), 73.51 (Ph*C*H$_2$), 79.27 ($C_4{}^B$), 79.79 ($C_2{}^B$), 77.21, 80.86, 80.89, 80.91, 81.00, 82.16, 82.23, 82.29, 82.44, 82.53, 82.57, 82.62, 82.66, 82.84 (15C, 5× C_2, 5× C_3, 5× C_4), 99.82, 100.08, 100.17, 100.29, 100.45 (6C, 6× C_1), 127.88, 128.06, 128.41, 138.57 (6C, 6× arom-C), 170.95 (C=O); HRMS calcd for $C_{61}H_{100}NaO_{31}$ $[M+Na]^+$: 1351.6141. Found 1351.6130.

4.11. 2^{A}-*O*-Benzyl-per-*O*-methyl-α-cyclodextrin (14)

By the same procedure described in Section 4.4, compound **14** was obtained by flash chromatography (eluent: cyclohexane/acetone=2:1) as a white foam in 80% yield. R_f=0.42 (cyclohexane/acetone=3:2); $[\alpha]_D$ +143.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.16–3.21 (m, 5H, 5× H_2), 3.36 (dd, 1H, $J_{1,2}$=3.3 Hz, $J_{2,3}$=10.1 Hz, $H_2{}^A$), 3.38 (s, 3H, OCH_3 (C_6)), 3.39 (s, 3H, OCH_3 (C_6)), 3.41 (s, 12H, 4× OCH_3 (C_6)), 3.49 (s, 9H, 3× OCH_3 (C_2)), 3.50 (s, 3H, OCH_3 (C_2)), 3.54 (s, 3H, OCH_3 (C_2)), 3.60 (m, 1H, $H_3{}^A$), 3.63 (s, 3H, OCH_3 (C_3)), 3.64 (s, 3H, OCH_3 (C_3)), 3.65 (s, 3H, OCH_3 (C_3)), 3.66 (s, 3H, OCH_3 (C_3)), 3.71 (s, 6H, 2× OCH_3 (C_3)), 3.44–3.86 (m, 29H, 5× H_3, 6× H_4, 6× H_5, 6× H_{6a}, 6× H_{6b}), 4.65 (d, 1H, J_{gem}=12.5 Hz, $PhCH_2$), 4.80 (d, 1H, J_{gem}=12.5 Hz, $PhCH_2$), 4.92 (d, 1H, $J_{1,2}$=3.3 Hz, $H_1{}^A$), 5.05–5.06 (m, 5H, 5× H_1), 7.24–7.27 (m, 1H, arom-H), 7.31–7.34 (m, 2H, 2× arom-H), 7.43–7.45 (m, 2H, 2× arom-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.79, 57.83, 58.08 (5C, 5× OCH_3 (C_2)), 58.88, 58.93 (6C, 6× OCH_3 (C_6)), 61.75, 61.95 (6C, 6× OCH_3 (C_3)), 71.01, 71.16, 71.18, 71.28 (6C, 6× C_5), 71.40, 71.43 (6C, 6× C_6), 72.16 ($PhCH_2$), 80.01 ($C_2{}^A$), 81.12, 81.20, 81.22, 81.54, 82.06, 82.15, 82.20, 82.39, 82.43, 82.47 (17C, 6× C_2, 6× C_3, 6× C_4), 100.03, 100.07, 100.08, 100.14, 100.31 (5C, 5× C_1), 100.75 ($C_1{}^A$), 127.35, 127.64, 128.17, 138.82 (6C, 6× arom-C); HRMS calcd for $C_{60}H_{100}NaO_{30}$ $[M+Na]^+$: 1323.6192. Found 1323.6183.

4.12. 2^{A}-Hydroxyl-per-*O*-methyl-α-cyclodextrin (7)

To a solution of compound **14** (125.7 mg, 0.097 mmol) in methanol (10 mL) was added 21.2 mg (10%, 0.02 mmol, 0.2 equiv) of Pd–C under nitrogen. The suspension was degassed under vacuum and urged with H_2 three times, then stirred under H_2 balloon at room temperature for 16 h. The suspension was filtered through a pad of Celite and the pad cake was washed with CH_3OH (5 mL×3). The combined filtrate was concentrated to dryness. The residue was subjected to flash chromatography (eluent: cyclohexane/acetone=2:1) to give 113.0 mg (97%) of compound **7** as a white foam. R_f=0.27 (cyclohexane/acetone=3:2); $[\alpha]_D$ +147.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.16–3.22 (m, 4H, 4× H_2), 3.27 (dd, 1H, $J_{1,2}$=3.0 Hz, $J_{2,3}$=9.8 Hz, H_2), 3.41 (s, 3H, OCH_3 (C_6)), 3.42 (3× s, 15H, 5× OCH_3 (C_6)), 3.49 (s, 6H, 2× OCH_3 (C_2)), 3.50 (2× s, 9H, 3× OCH_3 (C_2)), 3.53 (m, 1H, $H_2{}^A$), 3.63 (s, 3H, OCH_3 (C_3)), 3.64 (s, 3H, OCH_3 (C_3)), 3.65 (s, 3H, OCH_3 (C_3)), 3.66 (s, 3H, OCH_3 (C_3)), 3.73 (s, 6H, 2× OCH_3 (C_3)), 3.88 (m, 1H, H_3), 3.47–3.91 (m, 29H, 5× H_3, 6× H_4, 6× H_5, 6× H_{6a}, 6× H_{6b}), 4.27 (d, 1H, $J_{2,OH}$=10.5 Hz, D_2O exchangeable, OH), 4.90 (d, 1H, $J_{1,2}$=3.0 Hz, $H_1{}^A$), 5.05–5.08 (m, 5H, 5× H_1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.48, 57.62, 57.67, 57.77, 57.82 (5C, 5× OCH_3 (C_2)), 58.97, 59.00, 59.02, 59.07, 59.08 (6C, 6× OCH_3 (C_6)), 60.13, 61.47, 61.77, 61.80, 62.10 (6C, 6× OCH_3 (C_3)), 70.66, 71.28, 71.45, 71.61, 71.63 (6C, 6× C_6), 71.11, 71.17, 71.19, 71.23, 72.10 (6C, 6× C_5), 73.90 ($C_2{}^A$), 80.47 (C_3), 79.36, 81.15, 8.17, 81.21, 81.28, 82.10, 82.13, 82.19, 82.23, 82.42, 82.61, 82.69, 83.81 (16C, 5× C_2, 5× C_3, 6× C_4), 99.94, 99.99, 100.18, 100.32 (5C, 5× C_1), 102.72 ($C_1{}^A$); HRMS calcd for $C_{53}H_{94}NaO_{30}$ $[M+Na]^+$: 1233.5722. Found 1233.5725.

4.13. 2^{A}-*O*-Acetyl-per-*O*-methyl-α-cyclodextrin (15)

By the same procedure described in Section 4.2, compound **15** was obtained by flash chromatography (eluent: cyclohexane/acetone=2:1) as a white foam in 95% yield. R_f=0.31 (cyclohexane/acetone=3:2); $[\alpha]_D$ +140.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H, CH_3CO), 3.15–3.21 (m, 5H, 5× H_2), 3.40 (s, 3H, OCH_3 (C_6)), 3.41 (s, 3H, OCH_3 (C_6)), 3.42 (2× s, 12H, 4× OCH_3 (C_6)), 3.50 (4× s, 12H, 4× OCH_3 (C_2)), 3.51 (s, 3H, OCH_3 (C_2)), 3.62 (s, 3H, OCH_3 (C_3)), 3.65 (s, 6H, 2× OCH_3 (C_3)), 3.67 (s, 6H, 2× OCH_3 (C_3)), 3.67 (s, 3H, OCH_3 (C_3)), 3.72 (m, 1H, $H_3{}^A$), 3.83 (m, 1H, H_3), 3.53–3.92 (m, 28H, 4× H_3, 6× H_4, 6× H_5, 6× H_{6a}, 6× H_{6b}), 4.65 (dd, 1H, $J_{1,2}$=3.1 Hz, $J_{2,3}$=10.3 Hz, $H_2{}^A$), 5.06–5.08 (m, 5H, 5× H_1), 5.13 (d, 1H, $J_{1,2}$=3.1 Hz, $H_1{}^A$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.01 (*C*H_3CO), 57.74, 57.77, 57.84, 57.92 (5C, 5× OCH_3 (C_2)), 58.94 (6C, 6× OCH_3 (C_6)), 61.18, 61.55, 61.60, 61.72, 61.74, 61.77 (6C, 6× OCH_3 (C_3)), 71.11, 71.17, 71.21, 71.33 (6C, 6× C_5), 71.29, 71.40, 71.50, 71.52 (6C, 6× C_6), 74.25 ($C_2{}^A$), 79.55 ($C_3{}^A$), 80.68, 81.15, 81.21, 81.25, 81.37, 81.81, 82.09, 82.12, 82.15, 82.32, 82.39, 82.49 (16C, 5× C_2, 5× C_3, 6× C_4), 99.30 ($C_1{}^A$), 99.96, 100.01, 100.11, 100.22 (5C, 5× C_1), 170.76 (C=O); HRMS calcd for $C_{55}H_{96}NaO_{31}$ $[M+Na]^+$: 1275.5828. Found 1275.5834.

4.14. 2^{A}-*O*-Phenoxythiocarbonyl-per-*O*-methyl-α-cyclodextrin (16) and 2^{A}-*O*-phenoxycarbonyl-per-*O*-methyl-α-cyclodextrin (17)

By the same procedure described in Section 4.6, compound **16** and **17** were obtained by chromatography (eluent: cyclohexane/acetone=3:1) as a white foam in 83% and 10% yield, respectively.

Compound **16**: R_f=0.32 (petroleum ether/acetone=1:1); $[\alpha]_D$ +138.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.17–3.21 (m, 5H, 5× H_2), 3.40 (s, 3H, OCH_3 (C_6)), 3.42 (s, 9H, 3× OCH_3 (C_6)), 3.43 (2× s, 6H, 2× OCH_3 (C_6)), 3.50 (2× s, 6H, 2× OCH_3 (C_2)), 3.51 (3× s, 9H, 3× OCH_3 (C_2)), 3.65 (s, 6H, 2× OCH_3 (C_3)), 3.66 (s, 3H, OCH_3 (C_3)), 3.67 (s, 3H, OCH_3 (C_3)), 3.72 (s, 3H, OCH_3 (C_3)), 3.73 (s, 3H, OCH_3 (C_3)), 3.92 (m, 1H, $H_3{}^A$), 3.53–3.94 (m, 29H, 5× H_3, 6× H_4, 6× H_5, 6× H_{6a}, 6× H_{6b}), 5.06–5.08 (m, 5H, 5× H_1), 5.09 (dd, 1H, $J_{1,2}$=3.5 Hz, $J_{2,3}$=9.9 Hz, $H_2{}^A$), 5.50 (d, 1H, $J_{1,2}$=3.5 Hz, $H_1{}^A$), 7.18–7.20 (m, 2H, arom-H), 7.29–7.32 (m, 1H, arom-H), 7.41–7.45 (m, 2H, arom-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 57.77, 57.79, 57.83, 57.86, 57.99 (5C, 5× OCH_3 (C_2)), 58.97 (6C, 6× OCH_3 (C_6)), 61.63, 61.71, 61.79, 61.84 (6C, 6× OCH_3 (C_3)), 71.18, 71.29, 71.34, 71.38, 71.42, 71.55 (12C, 6× C_5, 6× C_6), 79.67 ($C_3{}^A$), 80.77, 81.15, 81.23, 82.14, 82.26, 82.39, 82.48 (17C, 6× C_2, 5× C_3, 6× C_4), 98.46 ($C_1{}^A$), 100.03, 100.11, 100.16, 100.26, 100.40 (5C, 5× C_1), 122.04, 126.49, 129.48, 153.71 (6C, 6× arom-C), 195.30 (C=S); HRMS calcd for $C_{60}H_{98}KO_{31}S$ $[M+K]^+$: 1385.5439. Found 1385.5405.

Compound **17**: R_f=0.31 (petroleum ether/acetone=3:2); $[\alpha]_D$ +136.7 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.18–3.22 (m, 5H, 5× H_2), 3.40 (s, 3H, OCH_3 (C_6)), 3.42 (s, 9H, 3× OCH_3 (C_6)), 3.43 (2× s, 6H, 2× OCH_3 (C_6)), 3.50 (s, 6H, 2× OCH_3 (C_2)), 3.51 (s, 6H, 2× OCH_3 (C_2)), 3.52 (s, 3H, OCH_3 (C_2)), 3.66 (s, 6H, 2× OCH_3 (C_3)), 3.67 (s, 6H, 2× OCH_3 (C_3)), 3.73 (s, 6H, 2× OCH_3 (C_3)), 3.75 (m, 1H, $H_3{}^A$), 3.50–3.90 (m, 29H, 5× H_3, 6× H_4, 6× H_5, 6× H_{6a}, 6× H_{6b}), 4.52 (dd, 1H, $J_{1,2}$=3.3 Hz, $J_{2,3}$=10.1 Hz, $H_2{}^A$), 5.05–5.08 (m, 4H, 4× H_1), 5.10 (d, 1H, $J_{1,2}$=3.2 Hz, H_1), 5.38 (d, 1H, $J_{1,2}$=3.3 Hz, $H_1{}^A$), 7.25–7.27 (m, 3H, arom-H), 7.38–7.40 (m, 2H, arom-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.81, 57.85, 58.00 (5C, 5× OCH_3 (C_2)), 58.97, 58.99 (6C, 6× OCH_3 (C_6)), 61.64, 61.73, 61.79, 62.01 (6C, 6× OCH_3 (C_3)), 71.20, 71.23, 71.33 (6C, 6× C_5), 71.42, 71.56 (6C, 6× C_6), 78.09 ($C_2{}^A$), 79.66 ($C_3{}^A$), 80.89, 81.21, 81.28, 82.17, 82.27, 82.39, 82.45, 82.52, 82.56 (16C, 5× C_2, 5× C_3, 6× C_4), 99.43 ($C_1{}^A$), 100.07, 100.11, 100.17, 100.21, 100.42 (5C, 5× C_1), 121.26, 126.04, 129.46, 153.63 (6C, 6× arom-C), 151.22 (C=O); HRMS calcd for $C_{60}H_{98}NaO_{32}$ $[M+Na]^+$: 1353.5933. Found 1369.5944.

4.15. 2^A-Deoxy-per-*O*-methyl-α-cyclodextrin (18)

By the same procedure described in Section 4.7, compound **18** was obtained by chromatography (eluent: CH_2Cl_2/CH_3OH=30:1–20:1) as a white foam in 74% yield. R_f=0.29 (CH_2Cl_2/CH_3OH=15:1); $[\alpha]_D$ +143.5 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.65–1.71 (m, 1H, $H_{2a}{}^A$), 2.27–2.32 (m, 1H, $H_{2b}{}^A$), 3.15–3.19 (m, 5H, 5× H_2), 3.40 (s, 3H, OCH_3 (C_6)), 3.41 (s, 15H, 5× OCH_3 (C_6)), 3.47 (s, 3H, OCH_3 (C_2)), 3.48 (s, 3H, OCH_3 (C_2)), 3.49 (s, 6H, 2× OCH_3 (C_2)), 3.50 (s, 3H, OCH_3 (C_2)), 3.53 (s, 3H, OCH_3 (C_3)), 3.63 (s, 3H, OCH_3 (C_3)), 3.64 (2× s, 9H, 3× OCH_3 (C_3)), 3.74 (m, 1H, $H_3{}^A$), 3.51–3.89 (m, 29H, 5× H_3, 6× H_4, 6× H_5, 6× H_{6a}, 6× H_{6b}), 5.02 (t, 1H, $J_{1,2}$=2.4 Hz, $H_1{}^A$), 5.04–5.07 (m, 5H, 5× H_1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.49 ($C_2{}^A$), 57.57, 57.79, 57.83, 57.94 (6C, 6× OCH_3 (C_3)), 58.73, 58.96, 59.00, 59.02 (6C, 6× OCH_3 (C_6)), 61.20, 61.74, 61.78, 61.81 (5C, 5× OCH_3 (C_2)), 70.99, 71.10, 71.16, 71.21, 71.34, 71.96 (6C, 6× C_5), 71.31, 71.39, 71.44, 71.98 (6C, 6× C_6), 77.47 ($C_3{}^A$), 80.96, 81.25, 81.40, 81.71, 82.10, 82.14, 82.19, 82.23, 82.35, 82.47 (16C, 5× C_2, 5× C_3, 6× C_4), 99.49, 99.85, 99.93, 100.13, 100.33 (5C, 5× C_1), 101.84 ($C_1{}^A$); HRMS calcd for $C_{62}H_{110}NaO_{34}$ $[M+Na]^+$: 1217.5773. Found 1217.5772.

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Supplementary data

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