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Diisobutylaluminium-promoted regioselective de-*O*-methylation of cyclodextrins: an expeditious entry to selectively modified cyclodextrins

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Abstract—Substituted cyclodextrins carrying methyl groups on the primary rim undergo highly regioselective de-*O*-methylation in the presence of benzyl groups, using diisobutylaluminium. This gave access to AD or AB di-6-*O*-demethylated derivatives, which were fully characterised by NMR, MS and chemical degradation using the hex-5-enose method. Direct functionalisation of these derivatives, for example by glycosylation, makes this method an attractive procedure for the preparation of modified cyclodextrins. © 2001 Elsevier Science Ltd. All rights reserved.

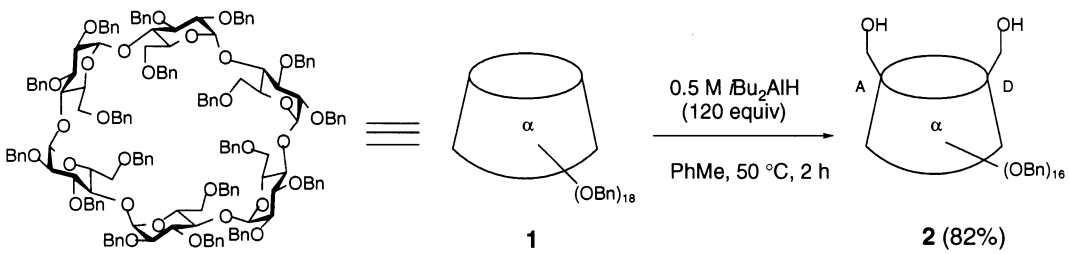
1. Introduction

Selectively modified cyclodextrins (CDs) are in high demand for applications ranging from supramolecular building blocks to drug delivery systems.[1–5] However, despite several well-defined protocols, methods for the synthesis of modified cyclodextrins are only slowly responding to this demand and, furthermore, usually involve tedious and laborious routes.[6,7] An attractive alternative is the regioselective deprotection of perfunctionalised cyclodextrins. For example, we recently reported[8] that perbenzylated cyclodextrins such as **1** undergo regioselective de-*O*-benzylation at the primary rim with DIBAL (diisobutylaluminium) to afford AD-diols such as **2** in excellent yield (Scheme 1).

Herein, we report the first regioselective de-*O*-methylation of CDs containing methyl groups at the primary rim. This method is simple, remarkably regioselective and synthetically convenient, and the cyclodextrin obtained is selectively protected for direct further elaboration. Furthermore, the benzyl protecting groups render the CDs non-polar and the products can therefore be readily purified by standard silica gel chromatography.

2. Results and discussion

When the known benzylated and AD-bis-methylated α-cyclodextrin **3**[8] was treated with excess DIBAL in toluene at 50°C, we observed the preferential AD type



Scheme 1.

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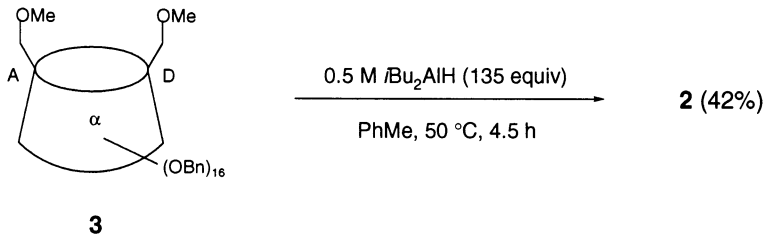


Scheme 2.

O-demethylation reaction and the diol **2** was isolated in 42% purified yield. Minor *O*-debenzylation products were also formed (about 15%), but were not analysed further (Scheme 2).

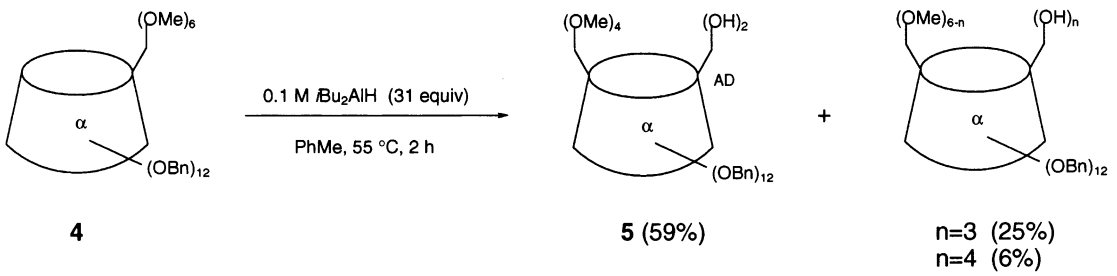
To the best of our knowledge this is the first example of selective *O*-demethylation in the presence of a benzyl ether. Furthermore, this de-*O*-alkylation reaction occurs exclusively at the primary rim. We therefore aimed to exploit these observations using other CDs containing methyl groups at the primary rim and benzyl groups at the secondary rim.

Thus, the known methylated α-cyclodextrin **4**[9] was conveniently prepared from **1** (67% from **1**) by acetolysis[10,11] followed by de-*O*-acetylation with NaOMe/MeOH and methylation using MeI/NaH in DMF. Reaction of **4** with excess DIBAL in toluene at 55°C gave the C_2-symmetric AD-diol **5** in 59% yield, resulting from regioselective de-*O*-methylation at the primary rim (Scheme 3). Mixtures of triols (25%) and tetrols (6%) resulting from further de-*O*-methylation, as identified by FAB-MS, were also isolated, but not analysed further.

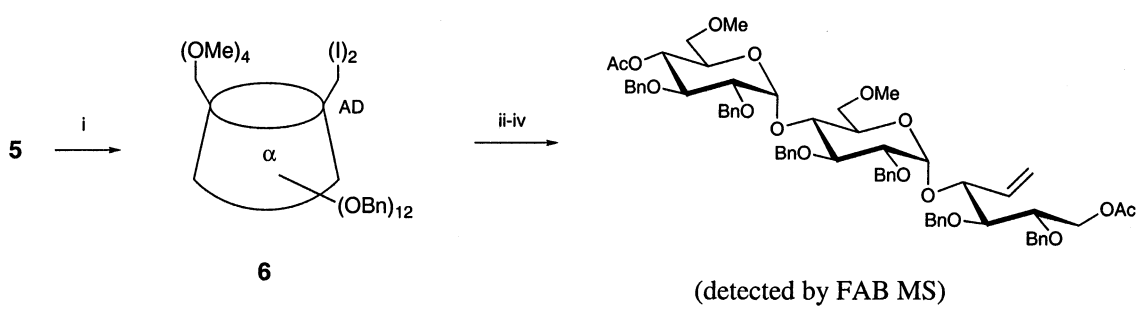
The structure of **5** was identified as the AD-regioisomer by ^{1}H and ^{13}C NMR, which clearly showed the presence of the expected twofold symmetry. This was further confirmed by chemical degradation using the hex-5-enose method[12–15] in which the diol **5** was first converted into bis iodide **6** by iodination according to Garegg's procedure[16] and then fragmented with activated zinc, reduced with $NaBH_4$ and finally acetylated. Analysis of the product by FAB-MS identified a sole fragment {*m*/*z* (%): 1147.4 (100) [M+Na$^+$]} arising from the AD-regioisomer and hence diol **5** was assigned AD-regiochemistry (Scheme 4).

Due to its differential protection, compound **5** is an attractive starting material for subsequent multiple synthetic modifications. For example, it undergoes smooth glycosylation with the thioglucosyl donor **7**[17] to give the protected glycoconjugate **8** in 85% yield (Scheme 5).

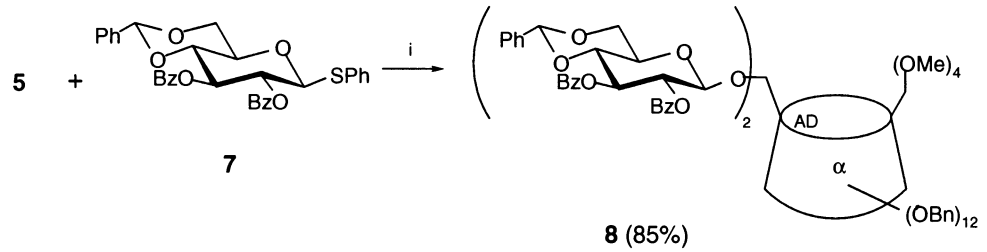
Modifiying the reaction conditions also allowed access to products of mono de-*O*-methylation. Thus, when **4** was treated with 2 equivalents of DIBAL under more dilute conditions, we isolated the mono-de-*O*-methylated product **9** in 30% yield, together with recovered



Scheme 3.



Scheme 4. Reagents and conditions: (i) I_2, PPh_3, Im, toluene, 70°C, 1 h, quant.; (ii) Zn, PrOH, H_2O, reflux, 1 h (iii) $NaBH_4$, MeOH, H_2O; (iv) Ac_2O, pyridine.



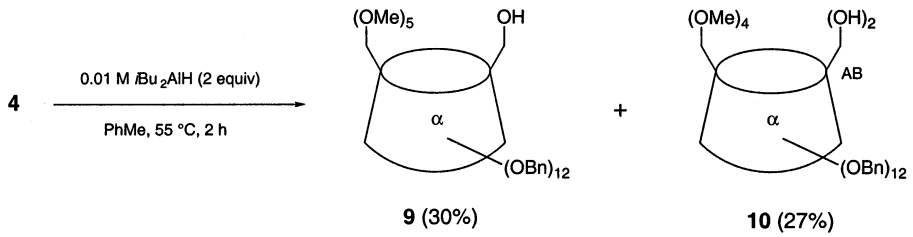
Scheme 5. Reagents and conditions: (i) 6 equiv. **7**, NIS, TfOH, DCM, 4 Å MS, –40 to –20°C, 1 h.

starting material **4** in 34% yield. Surprisingly, we also isolated the AB-diol **10** in 27% yield, whilst only trace amounts of the diol **5** and triols were recovered (Scheme 6).

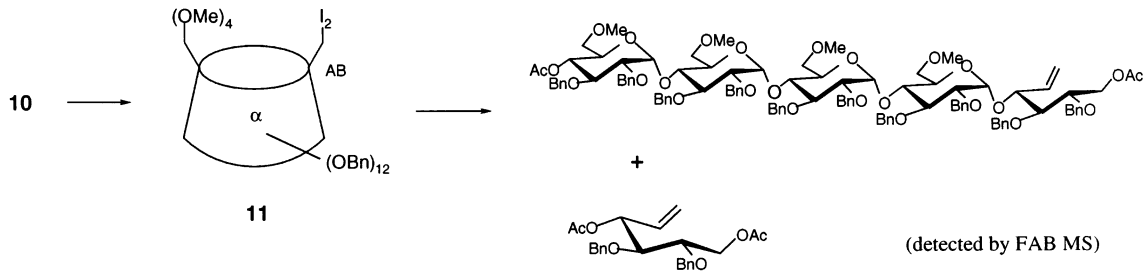
The structure of diol **10** was again confirmed by conversion to the corresponding bis iodide **11** and subsequent hex-5-enose degradation as above. FAB-MS analysis of the fragmentation products obtained {*m*/*z* (%): 1860.5 (15) [$C_{108}H_{124}O_{26}$+Na^+], 435.2 (100) [$C_{24}H_{28}O_6$+Na^+]} confirmed the AB-regiochemistry (Scheme 7).

In contrast to α-CD, the methylated β-cyclodextrin **13**, prepared in 82% yield by methylation of heptakis(2,3-di-*O*-benzyl)-β-cyclodextrin **12**,[5] gave complex product mixtures when treated with excess DIBAL (35 equivalents) in toluene at 55°C. However, reaction with 7 equivalents of DIBAL under dilute conditions gave the mono de-*O*-methylated product **14** in 40% yield (Scheme 8). Compound **13** was recovered from the reaction in 17% yield, and diols were also formed (30%), but not analysed further.

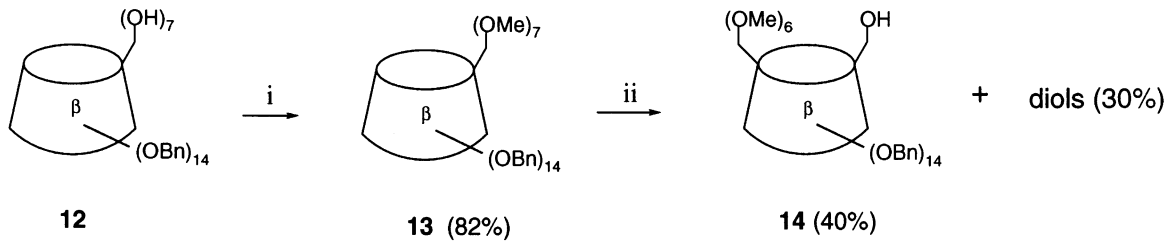
De-*O*-benzylation of **5** by catalytic hydrogenolysis followed by purification of the product on Sephadex G-15 provided, after freeze-drying, the tetra-*O*-methyl-α-cyclodextrin **15** in 97% yield (Scheme 9). Statistical calculations indicate that several hundred positional isomers are possible for a tetra-*O*-methyl-α-cyclodextrin, one of which is easily prepared by this method.



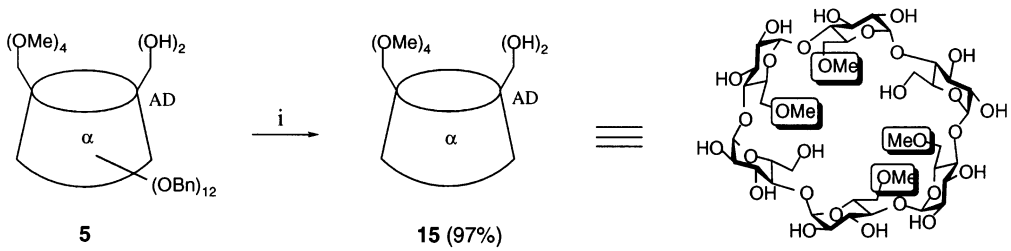
Scheme 6.



Scheme 7.



Scheme 8. Reagents and conditions: (i) NaH, DMF, 0°C, 1 h, then MeI, 0°C to rt, 40 h; (ii) 0.1 M iBu_2AlH (7 equiv.), toluene, 55°C, 20 min.



Scheme 9. Reagents and conditions: H_2, Pd/C, EtOAc/MeOH (1/1), rt, 3 h.

3. Conclusion

We have demonstrated that DIBAL-promoted de-*O*-methylation of partially methylated cyclodextrins occurs regioselectively, giving access to mono-6-*O*-demethylated, AD or AB di-6-*O*-demethylated derivatives, which are selectively protected for further functionalisation. This simple method illustrates the use of the de-*O*-alkylation strategy in the preparation of selectively modified cyclodextrins. Extension of this process to permethylated CDs, of interest due to their enhanced water solubility compared to unprotected CDs, is under investigation.

4. Experimental

4.1. General

Optical rotation measurements were obtained at 22°C with a Perkin–Elmer Model 241 digital polarimeter, using a 10 cm, 1 mL cell. Fast atom bombardment mass spectra (FAB-MS) were obtained with a JMS-700 spectrometer using an *m*-nitrobenzyl alcohol (NBA) matrix. Elemental analyses were performed by Service de Microanalyse de l'Université Pierre et Marie Curie, 4 Place Jussieu, 75005 Paris, France. ^{1}H NMR spectra were recorded with a Bruker DRX 400 spectrometer at ambient temperature. Assignments were aided by COSY experiments. ^{13}C NMR spectra were recorded at 100.6 MHz with a Bruker DRX 400 spectrometer. Assignments were aided by J-mod technique and proton–carbon correlation. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of silica gel 60 F_{254} (layer thickness 0.2 mm; E. Merck, Darmstadt, Germany) and detection by charring with sulfuric acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh, E. Merck).

4.2. Hexakis(2,3-di-*O*-benzyl)-6^B,6^C,6^E,6^F-tetra-*O*-methyl-α-cyclodextrin 5

Hexakis(2,3-di-*O*-benzyl)-6^A,6^B,6^C,6^D,6^E,6^F-hexa-*O*-methyl-α-cyclodextrin **4** (125 mg, 0.058 mmol) was dissolved in anhydrous toluene (16 mL), then DIBAL (1.5 M, 1.2 mL, 31 equiv.) was added dropwise into the stirred solution over 1 min at room temperature under argon. The reaction mixture was stirred at 55–58°C for 1 h, when TLC ($CHCl_3$/MeOH, 38/1) indicated a new product (R_f 0.45) and disappearance of starting material. The reaction mixture was cooled to 0°C, and water (10 mL) was carefully added dropwise. The solidified mixture was then filtered through Celite® in vacuo and washed with hot EtOAc (30 mL). The filtrate was combined, washed with water (3×10 mL), then the organic phase was separated and dried with $MgSO_4$. After evaporation, the residue was purified by flash column chromatography (CH_2Cl_2/acetone, 9/1–5/1) to give **5** as an amorphous powder (73 mg, 59%): $[\alpha]_D$ +28 (*c* 3.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.06–7.40 (m, 60H, arom. H), 5.84 (d, 2H, $J_{1,2}=3.9$ Hz, 2×H-1), 5.53, 4.96 (2d, 4H, $J=10.3$ Hz, 2×PhCH_2), 5.26, 4.82 (2d, 4H, $J=10.6$ Hz, 2×PhCH_2), 4.97, 4.80 (2d, 4H, $J=11.8$ Hz, 2×PhCH_2), 4.82, 4.50 (2d, 4H, $J=11.9$ Hz, 2×PhCH_2), 4.66, 4.56 (2d, 4H, $J=12.6$ Hz, 2×PhCH_2), 4.43, 4.38 (2d, 4H, $J=12.6$ Hz, 2×PhCH_2), 4.65 (bs, 4H, 4×H-1), 4.25 (dd, 2H, $J_{2,3}=9.8$ Hz, $J_{3,4}=7.7$ Hz, 2×H-3), 3.60 (dd, 2H, $J_{1,2}=3.9$ Hz, $J_{2,3}=9.8$ Hz, 2×H-2), 3.53 (dd, 2H, $J_{1,2}=3.5$ Hz, $J_{2,3}=9.5$ Hz, 2×H-2), 3.50 (dd, 2H, $J_{1,2}=3.3$ Hz, $J_{2,3}=9.8$ Hz, 2×H-2), 3.37, 3.35 (2s, 12H, 4×OMe); ^{13}C NMR ($CDCl_3$): δ 139.24, 139.21, 139.15, 138.54, 138.17, 137.94 (12C, Ph), 128.37–126.16 (60C, arom. C), 98.7, 97.8, 97.4 (372C-1), 81.8 (2C-3), 81.6 (2C-4), 81.4 (2C-4), 80.8 (2C-3), 80.5 (2C-3), 80.1 (2C-2), 79.1 (2C-2), 77.5 (2C-2), 76.5 (2Ph*C*H_2), 76.2 (2Ph*C*H_2), 73.9 (2Ph*C*H_2), 73.33 (2Ph*C*H_2), 73.31 (2Ph*C*H_2), 72.7 (2Ph*C*H_2), 72.6 (2C-4), 72.0 (2C-6), 71.8 (2C-6), 60.6 (2C-6), 59.0 (2OMe), 58.9 (2OMe). MS: *m*/*z* 2132.4 (100%, M+Na$^+$). Anal. calcd for $C_{124}H_{140}O_{30}$: C, 70.57; H, 6.69. Found: C, 70.51; H, 6.78%.

4.3. Hexakis(2,3-di-*O*-benzyl)-6^A,6^D-dideoxy-6^A,6^D-diiodo)-6^B,6^C,6^E,6^F-tetra-*O*-methyl-α-cyclodextrin 6

Diol **5** (100 mg, 0.05 mmol), triphenylphosphine (80 mg, 0.31 mmol), imidazole (40 mg, 0.59 mmol) and I_2 (76 mg, 0.3 mmol) were dissolved in anhydrous toluene (10 mL), and the mixture was heated at 70°C for 1 h, when TLC (cyclohexane/EtOAc, 2/1) showed that **5** was completely consumed. The mixture was concentrated and the residue purified by flash column chromatography (cyclohexane/EtOAc, 3/1) to give **6** as an amorphous powder (110 mg, 100%): $[\alpha]_D$ +21 (*c* 3.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.40–7.10 (m, 60H, arom. H), 5.30, 4.96 (2d, 4H, $J=11.1$ Hz, 2×PhCH_2), 5.22, 4.91 (2d, 4H, $J=11.0$ Hz, 2×PhCH_2), 5.16 (d, 2H, $J_{1,2}=3.15$ Hz, 2×H-1), 5.14, 4.88 (2d, 4H, $J=11.0$ Hz, 2×PhCH_2), 4.58, 4.46 (2d, 4H, $J=12.6$ Hz, 2×PhCH_2), 4.56, 4.48 (2d, 4H, $J=12.4$ Hz, 2×PhCH_2), 4.51, 4.47 (2d, 4H, $J=12.7$ Hz, 2×PhCH_2), 3.39 (s, 6H, 2×OMe), 3.37 (s, 6H, 2×OMe); ^{13}C NMR ($CDCl_3$): δ 139.4,

139.3, 139.2, 138.3, 138.1, 138.1 (12C, Ph), 128.2–126.9 (60C, arom. C), 99.6, 99.4, 98.8 (3×2C-1), 75.6, 75.5, 75.3 (3×2PhCH_2), 72.92, 72.92, 72.86 (3×2PhCH_2), 71.6, 71.4 (C-6^B,6^C,6^E,6^F), 9.0 (C-6^A,6^D), 59.2, 59.1 (2×2OMe). MS: m/z 2352.7 (100%, M+Na^+). Anal. calcd for $C_{124}H_{138}I_2O_{28}$: C, 63.91; H, 5.97. Found: C, 63.93; H, 6.09%.

4.4. 6^A,6^D-[Di-*O*-(2,3-di-*O*-benzoyl-4,6-*O*-benzylidene)-β-D-glucopyranosyl]-hexakis(2,3-di-*O*-benzyl)-6^B,6^C,6^E,6^F-tetra-*O*-methyl-α-cyclodextrin 8

A mixture of **5** (41 mg, 0.02 mmol), phenyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside **7** (70 mg, 0.12 mmol) and powdered 4 Å molecular sieves (100 mg) in dry CH_2Cl_2 (6 mL) was stirred at room temperature for 30 min. *N*-Iodosuccinimide (81 mg, 0.36 mmol) was added at room temperature. The reaction mixture was cooled to −60°C, and triflic acid (5 μL, 0.06 mmol) was added dropwise. The reaction mixture was stirred at −60°C for 1 h, neutralised with Et_3N and filtered through a layer of Celite®. The filtrate was washed with aqueous thiosulfate, water and brine, and then dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (eluent gradient, cyclohexane/EtOAc, 4/1 to 3/1) to give **8** as an amorphous powder (51 mg, 85%): $[\alpha]_D$ +17 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.00–7.10 (m, 90H, arom. H), 5.83 (t, 2H, $J_{2,3}=J_{3,4}=9.4$ Hz, H-3′), 5.57 (dd, 2H, $J_{1,2}=7.8$ Hz, $J_{2,3}=9.4$ Hz, H-2′), 5.56 (s, 2H, 2×PhCH), 5.16, 4.78 (2d, 4H, $J=11.2$ Hz, 2×PhCH_2), 5.14, 4.87 (2d, 4H, $J=11.3$ Hz, 2×PhCH_2), 5.06, 4.85 (2d, 4H, $J=11.2$ Hz, 2×PhCH_2), 5.02 (d, 2H, $J_{1,2}=3.4$ Hz, 2×H-1), 4.98 (d, 2H, $J_{1,2}=7.8$ Hz, H-1′), 4.97 (d, 2H, $J_{1,2}=3.5$ Hz, 2×H-1), 4.80 (d, 2H, $J_{1,2}=3.2$ Hz, 2×H-1), 4.48, 4.39 (2d, 4H, $J=12.6$ Hz, 2×PhCH_2), 4.42, 4.37 (2d, 4H, $J=12.6$ Hz, 2×PhCH_2), 4.21, 3.92 (2d, 4H, $J=12.7$ Hz, 2×PhCH_2), 4.01 (t, 2H, $J_{3,4}=J_{4,5}=9.4$ Hz, H-4′), 3.46, 3.39 (2s, 12H, 4×OMe), 3.13 (dd, 2H, $J_{1,2}=3.2$ Hz, $J_{2,3}=9.9$ Hz, 2×H-2); ^{13}C NMR ($CDCl_3$): δ 165.6, 165.0 (2O=C, Bz), 139.4, 139.33, 139.26, 138.4, 138.24, 138.22, 136.7, 129.30, 129.00 (18C, Ph), 133.2–126.8 (90C, arom. C), 101.4 (2Ph*C*H), 101.2 (2C, 2×C-1′), 99.8, 99.7, 99.1 (6C, C-$1^{A\text{-}F}$), 75.9, 75.3, 75.2, 73.0, 72.7, 71.6 (12PhCH_2), 72.3, 71.7, 68.4, 68.2 (8C-6), 59.0, 58.9 (4OMe). MS: m/z 3049.7 (100%, M+Na^+). Anal. calcd for $C_{178}H_{184}O_{44}$: C, 70.62; H, 6.13. Found: C, 70.51; H, 6.20%.

4.5. Hexakis(2,3-di-*O*-benzyl)-6^B,6^C,6^D,6^E,6^F-penta-*O*-methyl-α-cyclodextrin 9 and hexakis(2,3-di-*O*-benzyl)-6^C,6^D,6^E,6^F-tetra-*O*-methyl-α-cyclodextrin 10

To a stirred solution of **4** (180 mg, 0.084 mmol) in anhydrous toluene (16 mL) was dropwise added DIBAL (0.11 mL, 1.5 M in toluene, 2 equiv.) over 0.5 min at room temperature under argon. The stirring mixture was heated to 55°C for 2 h under argon. The reaction mixture was quenched and treated by the same procedure as described for the preparation of **5**. The residue was purified by flash column chromatography (eluent gradient, CH_2Cl_2/acetone, 9/1 to 6/1) to give the mono-de-*O*-methylation product **9** as an amorphous powder (54 mg, 30%): $[\alpha]_D$ +15 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.39–7.15 (m, 60H, arom. H), 5.70 (d, 1H, $J_{1,2}=3.7$ Hz, H-1), 5.62 (d, 1H, $J_{1,2}=3.7$ Hz, H-1), 5.53, 5.02 (2d, 2H, $J=10.6$ Hz, PhCH_2), 5.45, 4.95 (2d, 2H, $J=10.5$ Hz, PhCH_2), 5.28, 4.85 (2d, 2H, $J=10.6$ Hz, PhCH_2), 5.21, 4.86 (2d, 2H, $J=10.9$ Hz, PhCH_2), 4.98, 4.89 (2d, 2H, $J=11.6$ Hz, PhCH_2), 4.92 (bs, 2H, PhCH_2), 4.78, 4.47 (2d, 2H, $J=11.6$ Hz, PhCH_2), 4.77, 4.46 (2d, 2H, $J=12.5$ Hz, PhCH_2), 4.63, 4.53 (2d, 2H, $J=12.6$ Hz, PhCH_2), 4.61, 4.52 (2d, 2H, $J=12.7$ Hz, PhCH_2), 4.56, 4.53 (2d, 2H, $J=12.3$ Hz, PhCH_2), 4.40, 4.36 (2d, 2H, $J=12.6$ Hz, PhCH_2), 3.38, 3.37, 3.36, 3.35, 3.30 (5s, 15H, 5×OMe); ^{13}C NMR ($CDCl_3$): δ 139.5, 139.27, 139.25, 139.25, 139.22, 139.11, 138.6, 138.4, 138.3, 138.1, 138.0, 138.0 (12C, Ph), 128.3–126.3 (60C, arom. C), 99.1, 98.4, 98.3, 98.00, 97.97, 97.5 (6C-1), 76.3, 76.1, 75.85, 75.79, 74.4, 74.1, 73.3, 73.2, 73.14, 73.12, 72.8, 72.5 (12PhCH_2), 71.78, 71.77, 71.77, 71.5, 71.2 (C-6^B, 6^C,6^D,6^E,6^F), 60.6 (C-6^A), 59.2, 59.0, 59.0, 58.93, 58.92 (5OMe). MS: m/z 2146.9 (100%, M+Na^+). Anal. calcd for $C_{125}H_{142}O_{30}$: C, 70.67; H, 6.74. Found: C, 70.60; H, 6.76%.

Compound **10** was then eluted as an amorphous powder (49 mg, 27%): R_f 0.48 for TLC ($CHCl_3$/MeOH, 38/1); $[\alpha]_D$ +24 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.40–7.10 (m, 60H, arom. H), 5.41 (d, 1H, $J_{1,2}=3.7$ Hz, H-1), 5.38, 4.90 (2d, 2H, $J=10.6$ Hz, PhCH_2), 5.32, 4.90 (2d, 2H, $J=10.6$ Hz, PhCH_2), 5.30, 4.97 (2d, 2H, $J=10.8$ Hz, PhCH_2), 5.31 (d, 1H, $J_{1,2}=3.8$ Hz, H-1), 5.23, 4.97 (2d, 2H, $J=10.8$ Hz, PhCH_2), 5.19 (d, 1H, $J_{1,2}=3.5$ Hz, H-1), 5.12 (d, 1H, $J_{1,2}=3.5$ Hz, H-1), 5.03, 4.88 (2d, 2H, $J=11.4$ Hz, PhCH_2), 5.01, 4.92 (2d, 2H, $J=11.2$ Hz, PhCH_2), 4.75 (d, 1H, $J_{1,2}=3.4$ Hz, H-1), 4.71 (d, 1H, $J_{1,2}=3.3$ Hz, H-1), 4.70, 4.62 (2d, 2H, $J=12.2$ Hz, PhCH_2), 4.70, 4.54 (2d, 2H, $J=12.5$ Hz, PhCH_2), 4.69, 4.50 (2d, 2H, $J=12.3$ Hz, PhCH_2), 4.63, 4.42 (2d, 2H, $J=12.2$ Hz, PhCH_2), 4.61, 4.50 (2d, 2H, $J=12.3$ Hz, PhCH_2), 4.47, 4.41 (2d, 2H, $J=12.6$ Hz, PhCH_2), 3.40, 3.37, 3.36, 3.32 (4s, 12H, 4×OMe); ^{13}C NMR ($CDCl_3$): δ 139.4, 139.3, 139.21, 139.18, 139.09, 139.08, 138.5, 138.2, 138.14, 138.14, 138.12, 138.0 (12C, Ph), 128.3–126.7 (60C, arom. C), 98.8, 98.6, 98.4, 97.9, 97.54, 97.49 (6C-1), 76.1, 76.1, 76.0, 75.3, 75.1, 75.1, 74.8, 73.24, 73.16, 73.04, 73.00, 73.00, 72.8, 72.2, 71.8, 71.5 (12PhCH_2, C-6^B,6^C,6^D,6^E), 62.2, 61.3 (C-6^A,6^B), 59.12, 59.09, 59.02, 58.9 (4OMe). MS: m/z 2132.9 (100%, M+Na^+). Anal. calcd for $C_{124}H_{140}O_{30}$: C, 70.57; H, 6.69. Found: C, 70.49; H, 6.89%.

4.6. Hexakis(2,3-di-*O*-benzyl)-6^A,6^B-dideoxy-6^A,6^B-diiodo-6^C,6^D,6^E,6^F-tetra-*O*-methyl-α-cyclodextrin 11

Compound **11** was prepared from **10** using the same procedure as described for **6**, and obtained as an amorphous powder (100%): $[\alpha]_D$ +18 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.31–7.17 (m, 60H, arom. H), 5.27 (d, 1H, $J_{1,2}=2.9$ Hz, H-1), 5.24, 4.89 (2d, 2H, $J=10.7$ Hz, PhCH_2), 5.24, 4.90 (2d, 2H, $J=10.5$ Hz, PhCH_2), 5.23, 4.94 (2d, 2H, $J=10.8$ Hz, PhCH_2), 5.21, 4.92 (2d, 2H, $J=10.7$ Hz, PhCH_2), 5.16, 4.90 (2d, 2H, $J=11.3$ Hz, PhCH_2), 5.06, 4.87 (2d, 2H, $J=11.0$ Hz, PhCH_2), 5.08 (d, 1H, $J_{1,2}=3.2$ Hz, H-1), 5.07 (d, 1H, $J_{1,2}=3.7$ Hz,

H-1), 4.98 (d, 1H, $J_{1,2}=3.5$ Hz, H-1), 4.97 (d, 2H, $J_{1,2}=3.4$ Hz, 2×H-1), 4.68, 4.50 (2d, 2H, $J=12.4$ Hz, $PhCH_2$), 4.58, 4.47 (2d, 2H, $J=12.5$ Hz, $PhCH_2$), 4.56, 4.45 (2d, 2H, $J=12.1$ Hz, $PhCH_2$), 4.53, 4.47 (2d, 2H, $J=12.5$ Hz, $PhCH_2$), 4.52, 4.41 (2d, 2H, $J=12.6$ Hz, $PhCH_2$), 4.48, 4.42 (2d, 2H, $J=12.4$ Hz, $PhCH_2$), 3.38, 3.36, 3.35, 3.34 (4s, 12H, 4×OMe); ^{13}C NMR ($CDCl_3$): δ 139.5, 139.5, 139.38, 139.34, 139.07, 139.00, 138.4, 138.3, 138.28, 138.17, 138.12, 138.0 (12C, Ph), 128.3–126.8 (60C, arom. C), 99.55, 99.50, 99.4, 98.9, 98.5, 98.4 (6C-1), 75.6, 75.6, 75.6, 75.34, 75.29, 75.2, 73.11, 73.08, 72.97, 72.88, 72.84, 72.84 (12Ph*C*H_2), 71.79, 71.76, 71.6, 71.3 (C-6^C,6^D,6^E,6^F), 9.7, 9.2 (C-6^A,6^B), 59.2, 59.08, 59.06, 59.06 (4OMe). MS: m/z 2352.7 (100%, M+Na^+). Anal. calcd for $C_{124}H_{138}I_2O_{28}$: C, 63.91; H, 5.97. Found: C, 63.94; H, 5.94%.

4.7. Heptakis(2,3-di-*O*-benzyl-6-*O*-methyl)-β-cyclodextrin 13

Sodium hydride (60% dispersion in mineral oil, 1.1 g, 42 equiv.) was added portion-wise to a stirred solution of heptakis(2,3-di-*O*-benzyl)-β-cyclodextrin **12**[10,11] (1.6 g, 0.66 mmol) in anhydrous DMF (100 mL) at 0°C. The mixture was stirred for 1 h at 0°C, and methyl iodide (1.46 mL) was added dropwise into the solution. The reaction mixture was allowed to warm to room temperature and stirred for 2 days, when TLC analysis (CH_2Cl_2/acetone, 9/1) showed completion of the reaction. The reaction mixture was cooled to 0°C and methanol (2 mL) was added dropwise. The solvent was evaporated in vacuo and the residue was diluted with CH_2Cl_2 and filtered through a layer of Celite®. The filtrate was diluted with CH_2Cl_2 and washed with water. The organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (CH_2Cl_2/acetone, 9/1) to give **13** as a white foam (1.37 g, 82%): $[\alpha]_D$ +20 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.30–7.10 (m, 70H, arom. H), 5.15, 4.86 (2d, 14H, $J=11.0$ Hz, 7×PhCH_2), 5.13 (d, 7H, $J_{1,2}=3.6$ Hz, 7×H-1), 4.59, 4.52 (2d, 14H, $J=12.4$ Hz, 7×PhCH_2), 4.11–4.05 (m, 7H, 7×H-3), 3.99–3.90 (m, 21H, 7×H-4, 7×H-5, 7×H-6a), 3.60–3.50 (m, 14H, 7×H-2, 7×H-6b), 3.35 (s, 21H, 7×OMe); ^{13}C NMR ($CDCl_3$): δ 98.4 (7C-1), 80.9 (7C-3), 78.7 (7C-2), 78.2 (7C-4), 75.4 (7Ph*C*H_2), 72.9 (7Ph*C*H_2), 71.2 (7C-6), 71.0 (7C-5), 58.9 (7OMe). MS: m/z 2517.0 (100%, M+Na^+). Anal. calcd for $C_{147}H_{168}O_{35}$: C, 70.77; H, 6.79. Found: C, 70.67; H, 6.84%.

4.8. Heptakis(2,3-di-*O*-benzyl)-6^B,6^C,6^D,6^E,6^F,6^G-hexa-*O*-methyl-β-cyclodextrin 14

Compound **13** (68 mg, 0.027 mmol) was dissolved in anhydrous toluene (8 mL) with stirring. DIBAL (1.5 M in toluene, 0.62 mL, 35 equiv.) was added dropwise into the solution over 0.5 min at room temperature under argon. The reaction mixture was heated at 50°C for 10 min and then quenched and treated by the same procedure as described for the preparation of **5**. The residue was purified by flash column chromatography (CH_2Cl_2/acetone, 9/1) to give **14** (27 mg, 40%) as an amorphous powder: $[\alpha]_D$ +22 (*c* 3.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.30–7.19 (m, 70H, arom. H), 5.45 (d, 1H, $J_{1,2}=3.8$ Hz, H-1), 5.28 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 5.22 (d, 1H, $J_{1,2}=3.8$ Hz, H-1), 4.96 (d, 1H, $J_{1,2}=3.4$ Hz, H-1), 4.91 (d, 2H, $J_{1,2}=3.4$ Hz, 2×H-1), 4.86 (d, 1H, $J_{1,2}=3.8$ Hz, H-1), 3.37, 3.35, 3.33, 3.33, 3.32, 3.31 (6s, 18H, 6×OMe); ^{13}C NMR ($CDCl_3$): δ 98.9, 98.77, 98.75, 98.6, 98.5, 98.1, 97.7 (7C-1), 61.18 (C-6^A), 58.99, 58.96, 58.91, 58.90, 58.88, 58.84 (6OMe). MS: m/z 2503.2 (100%, M+Na^+). Anal. calcd for $C_{146}H_{166}O_{35}$: C, 70.68; H, 6.74. Found: C, 70.52; H, 6.75%.

4.9. 6^B,6^C,6^E,6^F-Tetra-*O*-methyl-α-cyclodextrin 15

A solution of **5** (30 mg, 0.014 mmol) in EtOAc/MeOH (1/1, 6 mL) was stirred in the presence of Pd/C (10%, 50 mg) at room temperature under H_2 for 3 h, when TLC (EtOAc/*i*-Propanol/H_2O, 3/2/1) showed completion of the reaction. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified on a Sephadex G-15 column, using water as eluent. After freeze-drying, compound **15** was obtained as a white amorphous powder (14 mg, 97%): $[\alpha]_D$+105 (*c* 0.6, MeOH); ^{1}H NMR (D_2O): δ 5.03 (d, 2H, $J_{1,2}=3.7$ Hz, 2×H-1), 5.02 (d, 2H, $J_{1,2}=3.7$ Hz, 2×H-1), 5.01 (d, 2H, $J_{1,2}=3.4$ Hz, 2×H-1), 3.38 (s, 12H, 4×OMe); ^{13}C NMR (D_2O): δ 101.80, 101.77, 101.62 (3×2C-1), 81.62, 81.59, 81.56, 73.60, 73.57, 72.35, 71.96, 71.03, 70.88 (ring C), 71.03, 70.98 (C-6^B,6^C,6^E,6^F), 60.70 (C-6^A,6^D), 58.80, 58.75 (4OMe). HRMS: m/z for $C_{40}H_{68}O_{30}$: calcd, 1051.3693 (100%, M+Na^+); found, 1051.3673 (100%, M+Na^+). Anal. calcd for $C_{40}H_{68}O_{30}\cdot 25\ H_2O$: C, 32.48; H, 8.04. Found: C, 32.63; H, 8.24%.

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