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Note

Synthesis of regioselectively and uniformly modified maltoheptaose derivatives from cyclomaltoheptaose precursors

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Abstract—Heptadeoxy-$6^{I–VII}$-halo, -azido, and hepta-$6^{I–VII}$ *S*-hepta(*N*-Boc-2-amino)ethyl-$6^{I–VII}$-heptathiomaltoheptaose derivatives were prepared by acetolysis of the corresponding per-C-6-modified β-cyclodextrin derivatives. The rapid and convenient structural characterisation of all of the modified oligosaccharides by ESIMS is described.

Keywords: Acetolysis; Cyclodextrins; $6^{I–VII}$-Heptadeoxyhalomaltoheptaose derivatives; $6^{I–VII}$-Heptaazidodeoxymaltoheptaose derivatives; $6^{I–VII}$-*S*-Heptacysteaminylmaltoheptaose derivatives

Since natural and modified oligosaccharides have found increasing interest in cosmetic and pharmaceutical applications, the need for modified homologous oligosaccharides by more convenient and efficient routes has evolved. Up to now however, there has been relatively few published work to reflect such demand due to: (i) the difficulty of achieving good regioselectivity by chemical modification of linear oligosaccharides; (ii) the extreme difficulty of accessing to pure homologous linear oligosaccharides on a large scale.

Thus, the cost of obtaining the higher maltooligosaccharides of dp 6 and 7 is prohibitive on a gram scale and those of dp 8 are not yet commercially available. Moreover, their chemical synthesis is not suitable for operating at a preparative scale. Nevertheless, their acetylated and benzoylated derivatives can be obtained readily from cyclomaltooligosaccharides (α-, β-, and γ-cyclodextrins, α-, β- and γ-CDs), respectively. The H_2SO_4-catalysed acetolysis of per-*O*-acetylated α-, β- and γ-CDs has been reported by Farkas et al.[1] and Sakairi et al.[2] They obtained fully acetylated maltohexaose, -heptaose and -octaose derivatives in about 45% yield. Similarly, Sakairi et al.[3] used acetolysis of a single glycosidic bond of per-*O*-benzoylated α-, β- and γ-CDs to afford comparable yields of the corresponding linear derivatives. Recently, this procedure has been improved by Hoffmann et al.[4] and per-*O*-acetylated maltohexaose was obtained from α-CD in 95% yield using 70% $HClO_4$. The concept has been extended to the acetolysis of permethylated α-CD by Kida et al.[5] by the use of 30% $HClO_4$ resulting in the maltohexaose derivative in 31% yield.

Previously reported chemical modifications of such maltooligosaccharides have been carried out mainly at the anomeric position[1,2,4,6–8] or at the terminal non-reducing end through a 4,6-*O*-benzylidene acetal intermediate.[1–4,9] To our knowledge, selective modification at primary hydroxyl groups of maltooligosaccharides has not yet been reported. Synthesis of regioselectively and uniformly halogenated oligosaccharides can lead to potentially interesting compounds in only few steps.

Since the selective halogenation of primary hydroxyl groups of CDs is now well established,[10–16] we have chosen to use halogenated CDs as starting materials to explore routes to regioselectively derivatised maltooligosaccharides by acetolysis of appropriate CDs. Heptakis(2,3-di-*O*-acyl-6-bromo-6-deoxy)-β-CDs[10] were selected for this study since the subsequent linear products would be suitably substituted for further chemical

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modification. We report therein an approach to homologous series of regioselectively C-6 derivatised maltooligosaccharides in high purity and yield.

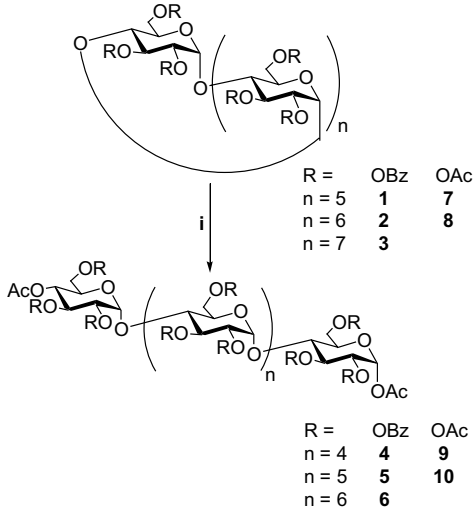
In our initial experiments, the known acetolysis procedures for α-, β- and γ-CDs were repeated (Scheme 1). Per-*O*-benzoylated α-, β- and γ-CD[17] **1**, **2** and **3** were reacted with Ac_2O–H_2SO_4 according to Ref. 3. In our hands, the expected di-*O*-acetylated maltohexaose, -heptaose and -octaose derivatives **4**, **5** and **6** were obtained in high yield (82%, 76% and 70%, respectively). The unreacted CDs and the corresponding maltooligosaccharide products were readily separated by flash chromatography.

Hoffmann et al. procedure,[4] which has only been described for α-CD, was used for the acetolysis of both hexakis(2,3,6-tri-*O*-acetyl)-α-CD **7** and heptakis(2,3,6-tri-*O*-acetyl)-β-CD **8**. Unfortunately, we were not able to reproduce the high yields reported with the consequence that the corresponding acetylated maltohexaose **9** and -heptaose **10** derivatives were only obtained in 60% and 35% yields, respectively. Nevertheless, both Sakairi et al.[3] and Hoffmann et al.[4] methods were explored to open the macrocycle in heptakis(2,3-di-*O*-acyl-6-bromo-6-deoxy)-β-CD.

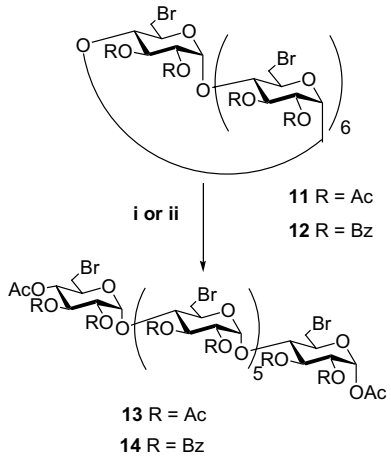
Heptakis(2,3-di-*O*-acetyl-6-bromo-6-deoxy)-β-CD **11**[10] and heptakis(2,3-di-*O*-benzoyl-6-bromo-6-deoxy)-β-CD **12** were each prepared in two steps from native β-CD. The primary hydroxyl groups of β-CD were first halogenated using the in situ generation of bromodimethyliminium bromide (Vilsmeier reagent) via the triphenylphosphine–bromine system in DMF according to lit.[11] The resulting heptakis(6-bromo-6-deoxy)-β-CD was esterified in the presence of acetic anhydride and benzoyl bromide, respectively, to afford the desired heptakis(2,3-di-*O*-acetyl-6-bromo-6-deoxy)-β-CD, **11**[10] and the previously unknown heptakis(2,3-di-*O*-benzoyl-6-bromo-6-deoxy)-β-CD, **12**, each in 90% overall yield. It is worth of note that the use of benzoyl chloride, which is cheaper than the corresponding bromide, gives heptakis(2,3-di-*O*-benzoyl-6-chloro-6-deoxy)-β-CD as the exclusive product under the present conditions.

Our initial attempts to acetolyse heptakis(2,3-di-*O*-acyl-6-bromo-6-deoxy)-β-CDs **11** and **12** employed acetic anhydride and sulfuric acid as catalyst. Both **11** and **12** proved to be more resistant to acid catalysed ring opening than their per-*O*-esterified analogues. In contrast, halogenated maltoheptaose per-esters were shown to be more susceptible to acetolysis when subjected to longer reaction times, thus resulting in maltooligosaccharides of dp 5 and 6. The optimum reaction conditions (Scheme 2) found for the acetolysis of **11** and **12** gave $1^{I},2^{I–VII},3^{I–VII},4^{VII}$-hexadeca-*O*-acetyl-$6^{I–VII}$-heptabromo-$6^{I–VII}$-heptadeoxy-α-maltoheptaose (**13**) and $1^{I},4^{VII}$-di-*O*-acetyl-$2^{I–VII},3^{I–VII}$-tetradeca-*O*-benzoyl-$6^{I–VII}$-heptabromo-$6^{I–VII}$-heptadeoxy-α-maltoheptaose (**14**) in 16% and 32% yields, respectively. For these two heptabromo compounds, a good agreement was found in ESIMS between the experimental isotopic patterns of the $[M+Na]^+$ ions and those predicted by theoretical means.

As has already been observed for the fully esterified CDs **1**–**3**, the unchanged halo-CDs **11** and **12** could be recovered in 78% and 58% yields showing that no degradation occurred despite the harsh reaction conditions used. It should be pointed out that the use of harsher conditions or longer reaction times lead to a depolymerisation of the acyclic product rather than an increase of the amount of opened CDs. At this stage of the synthesis, compounds **13** and **14** could not be obtained with very high purity. Even after purification by means of



Scheme 1. Reagents and conditions (yields): (i) 49:1 Ac_2O–H_2SO_4, 50–60 °C, 30–40 h, 70–82%.



Scheme 2. Reagents and conditions (yields): (i) 97:3 Ac_2O–H_2SO_4, 57 °C, 28 h (16% of **13**) or 96:4 Ac_2O–H_2SO_4, 57 °C, 30 h (32% of **14**); (ii) Ac_2O, 4.6 equiv $HClO_4$, 0 °C, 20 h then 36 °C, 20 h (30% of **14**).

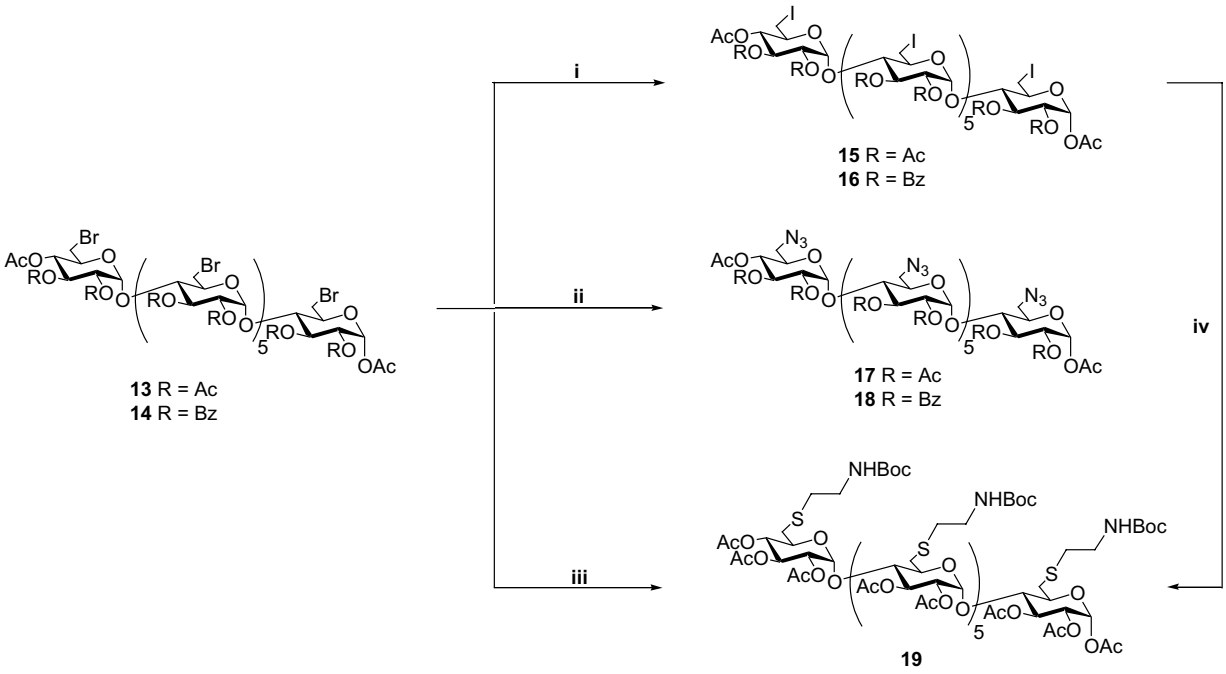
silica gel column chromatography, some traces of the corresponding maltohexaose derivative could be observed by mass spectrometry.

Optimisation of the Hoffmann et al.[4] methodology was applied to cleave heptakis(2,3-di-*O*-acetyl-6-bromo-6-deoxy)-β-CD, **11**. It was found that a higher reaction temperature was required (40 °C vs 23 °C) to obtain the desired maltoheptaose derivative **13** in an optimum yield of 30%, but this was achieved at the expense of a lower purity. In this case, a certain amount of the corresponding maltohexaose and also maltopentaose derivatives could be observed by mass spectrometry.

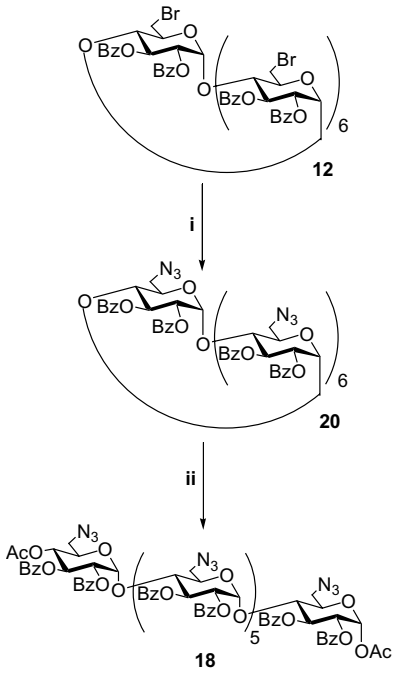
With the key acyclic maltooligosaccharides **13** and **14** in hand, nucleophilic substitution of the bromide groups was examined. As depicted in Scheme 3, these were easily substituted sequentially, by iodide, azide and 2-(Boc-amino)ethanethiolate to afford, accordingly, **15**–**19** in yields ranging from 70% to 90%. Interestingly, all of the compounds, $1^{I},2^{I–VII},3^{I–VII},4^{VII}$-hexadeca-*O*-acetyl-$6^{I–VII}$-heptadeoxy-$6^{I–VII}$-heptaiodo-α-maltoheptaose (**15**), $1^{I},4^{VII}$-di-*O*-acetyl-$2^{I–VII},3^{I–VII}$-tetradeca-*O*-benzoyl-$6^{I–VII}$-heptadeoxy-$6^{I–VII}$-heptaiodo-α-maltoheptaose (**16**), 1^{I}, $2^{I–VII},3^{I–VII},4^{VII}$-hexadeca-*O*-acetyl-$6^{I–VII}$-heptaazido-$6^{I–VII}$-heptadeoxy-α-maltoheptaose (**17**) and $1^{I},4^{VII}$-di-*O*-acetyl-$6^{I–VII}$-heptaazido-$2^{I–VII},3^{I–VII}$-tetradeca-*O*-benzoyl-$6^{I–VII}$-heptadeoxy-α-maltoheptaose (**18**), could be readily separated from the contaminating maltohexaose derivatives by flash chromatography. In contrast, similar attempts to remove $1^{I},2^{I–VII},3^{I–VII},4^{VII}$-hexadeca-*O*-acetyl-$6^{I–VII}$-*S*-[hepta-(*N*-Boc-2-amino)ethyl]-$6^{I–VII}$-heptathio-α-maltoheptaose (**19**) from the contaminating maltohexaose derivative proved unsuccessful. However, an alternative was found to give the desired product **19** in high purity from the precursor **15** in 89% yield. Moreover, it should be pointed out that the use of Na_2CO_3 instead of NaH to generate the thiolate ion from 2-(Boc-amino)ethanethiol allowed to avoid the partial *O*-deacetylation of the product and formation of maltooligosaccharides of lower dp.

The modest yields obtained for the macrocycle opening of heptakis(2,3-di-*O*-acyl-6-bromo-6-deoxy)-β-CDs **11** and **12** (Scheme 2) prompted us to modify our strategy by reversing the order of the latter two steps of the sequence 'bromination–acetolysis–substitution' thus performing acetolysis as the last step. Thus, heptakis(2,3-di-*O*-benzoyl-6-bromo-6-deoxy)-β-CD (**12**) was allowed to react with sodium azide in DMF to give heptakis(6-azido-2,3-di-*O*-benzoyl-6-deoxy)-β-CD (**20**) in 90% yield. Acetolysis of **20** was performed according to Sakairi et al.[3] (49:1 Ac_2O–H_2SO_4) to afford $1^{I},4^{VII}$-di-*O*-acetyl-$6^{I–VII}$-heptaazido-$2^{I–VII},3^{I–VII}$-tetradeca-*O*-benzoyl-$6^{I–VII}$-heptadeoxy-α-maltoheptaose **18** in 30% yield and in high purity. Once again, an esterified per-(6-substituted-6-deoxy)-β-CD proved to be the more resistant to macrocycle opening in acidic conditions than its corresponding fully esterified analogue (Scheme 4).

All of the maltooligosaccharides obtained were fully characterised by mass spectrometry. Accurate mass measurements were obtained on the $[M+Na]^+$ ions of the products at a resolution of 10,000, using appropriate



Scheme 3. Reagents and conditions (yields): (i) NaI, butanone, 90 °C, 12 h, 72% of **15**, 83% of **16**; (ii) LiN_3 (20% in water), DMF, 48 h, rt, 91% of **17**, 91% of **18**; (iii) 2-(Boc-amino)ethanethiol, Na_2CO_3, DMF, N_2, rt, 4 days, 70%; (iv) 2-(Boc-amino)ethanethiol, Na_2CO_3, DMF, N_2, rt, 48 h, 89%.



Scheme 4. Reagents and conditions (yields): (i) NaN_3, DMF, 100 °C, 24 h, 90%; (ii) 49:1 Ac_2O–H_2SO_4, 55 °C, 30 h, 30%.

cluster ions of sodium iodide $[(NaI)_n+Na]^+$ as the internal lock mass.

We have opened the way to novel C-6 modified maltooligosaccharides in excellent yield and high purity and shown that nucleophilic substitution of bromide groups can be easily performed leading in very few steps to potentially interesting linear oligosaccharides. Indeed the synthesis of regioselectively and uniformly modified oligosaccharide derivatives such anionic, cationic or amphiphilic oligosaccharides is in progress in our laboratory.

1. Experimental

1.1. General methods

Optical rotations were measured with a JASCO DIP-370 digital polarimeter, using a sodium lamp (λ = 589 nm) at 20 °C. All NMR experiments were performed at 300.13 MHz using a Bruker DMX300 spectrometer equipped with a Z-gradient unit for pulsed-field gradient spectroscopy. Me_4Si was used as an external standard and calibration was performed using the signal of the residual protons or of the carbon of the solvents as a secondary reference. Measurements were performed at 300 K with careful temperature regulation. The length of the 90° pulse was approximately 7 μs. 1D NMR data spectra were collected using 16K data points. Elemental analysis were performed at the Service de Microanalyse de l'Université de Champagne-Ardennes in Reims, France. Preparative HPLC was carried out with a Waters Prep LC 4000 System chromatograph fitted with an evaporative light scattering detector PL-ELS 1000 (Polymer Laboratories) and a Prevail C-18 column (5μ, 22×250 mm). Thin-layer chromatography was performed on E. Merck glass plates silica gel sheets (Silica Gel F_{254}) followed by charring with vanilin. Column chromatography was performed on Kieselgel (E. Merck 230–400 mesh). Stepwise control of the reaction and structure elucidation of the final products has been readily achieved using mass spectrometry ESI-MS in the positive ion mode and high resolution (HR) along with the tandem mass spectrometric (MS/MS) capabilities of a quadrupole orthogonal time-of-flight mass spectrometer (Q-TOF).[18] High-resolution electrospray mass spectra in the positive ion mode were obtained on Waters-Micromass Q-TOF *Ultima Global* hybrid quadrupole/time-of-flight instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Waters-Micromass, Manchester, UK). The source and solvation temperatures were kept at 80 and 150 °C, respectively. Nitrogen was used as the drying and nebulising gas at flow rates of 350 and 50 L/h, respectively. The capillary voltage was 3.5 kV, the cone voltage 100 V and the RF lens1 energy was optimised for each sample (50–200 V). For collision-induced dissociation (CID) experiments, argon was used as collision gas at an indicated analyser pressure of 5×10^{-5} Torr and the collision energy was set to 80 V. For accurate mass measurements, an internal lock mass correction, using appropriate cluster ions of sodium iodide $[(NaI)_n+Na]^+$ was applied. The mass range was typically 50–4450 amu and spectra were recorded at 4 s/scan in the profile mode at a resolution of 10,000 (FWMH). Data acquisition and processing were performed with MassLynx 4.0 software. Samples of maltooligosaccharides derivatives were dissolved (0.01 mg mL^{-1}) in 1:1 MeOH–water and the solns directly introduced (5 μL mn^{-1}) through an integrated syringe pump into the electrospray source.

1.2. $1^{I},4^{VI}$-Di-*O*-acetyl-$2^{I–VI},3^{I–VI},6^{I–VI}$-octadeca-*O*-benzoyl-α-maltohexaose (4)

Hexakis(2,3,6-tri-*O*-benzoyl)cyclomaltohexaose[17] **1** (2 g, 0.7 mmol) was dried at 60 °C for 2 h under diminished pressure and dissolved in 49:1 Ac_2O–H_2SO_4 (20 mL). The mixture was stirred at 60 °C for 30 h, cooled, quenched by the addition of pyridine (4 mL), concentrated under diminished pressure and then co-evaporated with toluene (×3). The residue was subjected to silica gel column chromatography (15:1 toluene–EtOAc) affording unreacted **1** (0.3 g, 15%) and the diacetate **4** (1.7 g, 82%): $[\alpha]_D$ +89 (*c* 2.5, EtOAc); lit.[3] $[\alpha]_D$ +76 (*c* 0.26, $CHCl_3$). ^{13}C NMR identical with lit.[3]

1.3. $1^{I},4^{VII}$-Di-*O*-acetyl-$2^{I–VII},3^{I–VII},6^{I–VII}$-heneicosa-*O*-benzoyl-α-maltoheptaose (5)

Heptakis(2,3,6-tri-*O*-benzoyl)cyclomaltoheptaose[17] **2** (9 g, 2.71 mmol) in 49:1 Ac_2O–H_2SO_4 (34 mL) was heated at 55 °C for 42 h. Workup as described for the preparation of **4**, gave unreacted **2** (1.5 g, 17%) and the diacetate **5** (7 g, 76%) as an amorphous solid: $[\alpha]_D$ +79 (*c* 2.3, EtOAc); lit.[3] $[\alpha]_D$ +67 (*c* 0.47, $CHCl_3$). ^{13}C NMR identical with lit.[3]

1.4. $1^{I},4^{VIII}$-Di-*O*-acetyl-$2^{I–VIII},3^{I–VIII},6^{I–VIII}$-tetracosa-*O*-benzoyl-α-maltooctaose (6)

Octakis(2,3,6-tri-*O*-benzoyl)cyclomaltooctaose[17] **3** (2.9 g, 0.77 mmol) was treated with 49:1 Ac_2O–H_2SO_4 (50 mL) at 50 °C for 35 h. The workup was as described for the preparation of **7**, which gave unreacted **3** (0.5 g, 17%) and the diacetate **6** (2.13 g, 70%) as an amorphous solid: $[\alpha]_D$ +75 (*c* 5.95, EtOAc); lit.[3] $[\alpha]_D$ +72 (*c* 0.19, $CHCl_3$). ^{13}C NMR identical with lit.[3]

1.5. $1^{I},2^{I–VI},3^{I–VI},4^{VI},6^{I–VI}$-Eicosa-*O*-acetyl-α-maltohexaose (9)

Under N_2 and with vigorous stirring, compound **7** (1 g, 0.56 mmol) was dissolved in Ac_2O (30 mL) at room temperature. The soln was cooled to 0 °C and 70% $HClO_4$ (0.4 mL, 2.57 mmol) was added. The soln was stirred for 20 h, and allowed to warm to room temperature. After 2 h at rt, the soln was cooled to 0 °C and neutralised by the addition of a 10% aq $NaHCO_3$ soln (24 mL). The mixture was concentrated to 1/4 of its original volume (15 mL) under diminished pressure. The remaining soln was diluted with EtOAc and washed with water. The aq layer was extracted with EtOAc. The residue was subjected to silica gel column chromatography (4:1 EtOAc–hexane) to afford unreacted **7** (0.3 g, 30%) and the diacetate **9** (0.63 g, 60%): $[\alpha]_D$ +107 (*c* 1.85, EtOAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.61, 170.31, 169.80, 169.49, 168.94 ($OCOCH_3$), 95.59 (C-1II–VII), 88.75 (C-1I), 73.04, 72.12, 71.53, 70.33, 69.93, 69.69, 68.83, 68.32, 67.77 (C-2I–VII, C-3I–VII, C-4I–VII, C-5I–VII), 62.17, 61.22 (C-6I–VII), 20.79, 20.50 ($OCOCH_3$); ESI-HRMS: *m*/*z* 1853.5332 ($[M+Na]^+$), ($C_{76}H_{102}NaO_{51}$ requires 1853.5286).

1.6. $1^{I},2^{I–VII},3^{I–VII},4^{VII},6^{I–VII}$-Tricosa-*O*-acetyl-α-maltoheptaose (10)

Under N_2 and with vigorous stirring, **8** (2 g, 0.99 mmol) was dissolved in Ac_2O (54 mL) at room temperature. The soln was cooled to 0 °C and 70% $HClO_4$ (0.7 mL, 4.56 mmol) was added. The soln was stirred for 20 h, and allowed to warm to rt. The workup was as described for the preparation of **9**, which gave unreacted **8** (1.1 g, 55%) and the diacetate **10** (0.7 g, 35%): $[\alpha]_D$ +121 (*c* 1.33, EtOAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.64, 170.36, 169.85, 169.55, 169.45 ($OCOCH_3$), 95.62 (C-1II–VII), 88.78 (C-1I), 73.03, 72.15, 71.64, 70.37, 69.96, 69.70, 69.27, 68.85, 68.35, 67.81 (C-2I–VII, C-3I–VII, C-4I–VII, C-5I–VII), 62.20, 61.25 (C-6I–VII), 20.83, 20.54 ($OCOCH_3$); ESI-HRMS: *m*/*z* 2141.6113 ($[M+Na]^+$), ($C_{88}H_{118}NaO_{59}$ requires 2141.6131).

1.7. Heptakis(2,3-di-*O*-acetyl-6-bromo-6-deoxy)cyclomaltoheptaose (11)

Heptakis(6-bromo-6-deoxy)cyclomaltoheptaose[15] (8 g, 5.07 mmol) was dissolved in pyridine (100 mL) and Ac_2O (30.5 mL, 325 mmol) was added. The mixture was stirred for 48 h, quenched with MeOH at 0 °C and evaporated under diminished pressure. The residue was subjected to silica gel column chromatography (4:1 EtOAc–hexane) to afford **11** (10.5 g, 96%): $[\alpha]_D$ +79.0 (*c* 2.3, EtOAc); lit.[10] $[\alpha]_D$ +98 (*c* 1.6, $CHCl_3$). ^{13}C NMR identical with lit.[10]

1.8. Heptakis(2,3-di-*O*-benzoyl-6-bromo-6-deoxy)-cyclomaltoheptaose (12)

To a soln of dried heptakis(6-bromo-6-deoxy)cyclomaltoheptaose[15] (8.33 g, 5,28 mmol) in pyridine (100 mL) was added dropwise benzoyl bromide (22 mL, 222 mmol) at 0 °C. The mixture was stirred at room temperature for 16 h, quenched with MeOH at 0 °C and concentrated under diminished pressure. The residue was subjected to silica gel column chromatography (2:3 EtOAc–hexane), to give the per-benzoyl derivative **12** (15.8 g, 99%): $[\alpha]_D$ +72 (*c* 5.4, EtOAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.41, 164.85 ($OCOC_6H_5$), 133.06, 132.86, 130.17, 128.27, 128.11 ($OCOC_6H_5$), 97.53 (C-1I–VII), 79.47 (C-4I–VII), 71.87, 71.29, 71.07 (C-2I–VII, C-3-I–VII, C-4I–VII), 34.21 (C-6I–VII); ESI-HRMS: *m*/*z* 3055.1339 ($[M+Na]^+$), ($C_{140}H_{119}$-$^{79}Br_3{}^{81}Br_4NaO_{42}$ requires 3055.1275). Anal. Calcd for $C_{140}H_{119}Br_7O_{42}$: C, 55.44; H, 3.95. Found: C, 55.40; H, 3.87.

1.9. $1^{I},2^{I–VII},3^{I–VII},4^{VII}$-Hexadeca-*O*-acetyl-$6^{I–VII}$-heptabromo-$6^{I–VII}$-heptadeoxy-α-maltoheptaose (13)

Heptakis(2,3-di-*O*-acetyl-6-bromo-6-deoxy)cyclomaltoheptaose **11** (9 g, 0.41 mmol) was dried at 60 °C for 24 h under diminished pressure and dissolved in 97:3 Ac_2O–H_2SO_4 (20 mL). The mixture was stirred at 57 °C for 28 h, cooled, and the reaction mixture was quenched by the addition of pyridine (4 mL). The soln was evaporated under diminished pressure. The residue was subjected to silica gel column chromatography (3:2 EtOAc–hexane then EtOAc) to afford unchanged **11** (7 g, 78%) and **13** (1.5 g, 16%): $[\alpha]_D$ +115 (*c* 0.5, EtOAc);

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.48, 170.05, 169.83, 169.68, 169.25, 168.92 ($OCOCH_3$), 95.45, 95.27 (C-1II–VII), 88.94 (C-1I), 73.55, 73.43, 71.95, 71.50, 71.38, 71.18, 70.33, 69.99, 69.63, 69.04, 68.82, 68.56 (C-2I–VII, C-3I–VII, C-4I–VII, C-5I–VII), 34.42, 34.06, 33.67 (C-6I–VII), 20.89, 20.56, 20.47 ($OCOCH_3$), ESI-MS: *m/z* 2288.9446 ($[M+Na]^+$), ($C_{74}H_{97}{}^{79}Br_3{}^{81}Br_4NaO_{45}$ requires 2288.9401). Anal. Calcd for $C_{74}H_{97}Br_7O_{45}$: C, 39.23; H, 4.31. Found: C, 39.33; H, 4.17.

1.10. 1^{I},4^{VII}-Di-*O*-acetyl-$2^{I–VII}$,$3^{I–VII}$-tetradeca-*O*-benzoyl-$6^{I–VII}$-heptabromo-$6^{I–VII}$-heptadeoxy-α-maltoheptaose (14)

The β-cyclodextrin derivative **12** (6 g, 1.97 mmol) was dried at 60 °C for 24 h under diminished pressure and dissolved in 28:1 Ac_2O–H_2SO_4 (20 mL). The mixture was stirred at 57 °C for 30 h, cooled, quenched by the addition of pyridine (4 mL) and evaporated under diminished pressure. The residue was subjected to silica gel column chromatography (20:1 then 10:1 toluene–EtOAc) to afford unchanged **12** (3.5 g, 58%) and **14** (2 g, 32%): $[\alpha]_D$ +51 (*c* 1.135, EtOAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.25, 168.92 ($OCOCH_3$), 165.47, 164.85, 164.65, 164.32, 164.00 ($OCOC_6H_5$), 133.14, 132.72, 132.11, 131.91, 129.63, 129.37, 129.23, 129.04, 128.64, 128.28, 127.93, 127.67, 127.58, 127.47, 127.32, 127.16 ($OCOC_6H_5$), 96.57, 96.19, 95.56 (C-1II–VII), 88.88 (C-1I), 78.53, 73.78, 73.51, 71.08, 70.94, 70.35, 70.14, 69.32, 68.88, 68.57 (C-2I–VII,C-3I–VII, C-4I–VII, C-5I–VII), 34.39, 33.26, 31.38 (C-6I–VII), 20.47, 20.13 ($OCOCH_3$), ESI-HRMS: *m/z* 3157.1848 ($[M+Na]^+$), ($C_{144}H_{125}{}^{79}Br_3{}^{81}Br_4NaO_{45}$ requires 3157.1769). Anal. Calcd for $C_{144}H_{125}Br_7O_{45}$: C, 55.17; H, 4.02. Found: C, 54.99; H, 3.95.

1.11. 1^{I},$2^{I–VII}$,$3^{I–VII}$,4^{VII}-Hexadeca-*O*-acetyl-$6^{I–VII}$-heptadeoxy-$6^{I–VII}$-heptaiodo-α-maltoheptaose (15)

To a soln of **13** (0.4 g, 0.18 mmol) in butanone (40 mL) was added NaI (1.85 g, 12.4 mmol). The reaction mixture was stirred at 90 °C for 12 h. The solvent was removed by concentration under diminished pressure and the residue was purified by flash chromatography (1:1 then 3:2 EtOAc–hexane), to afford **15** (0.33 g, 72%): $[\alpha]_D$ +85 (*c* 0.65, EtOAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.84, 170.74, 170.15, 169.69, 169.31 ($OCOCH_3$), 95.86, 95.65 (C-1II–VII), 89.16 (C-1I), 77.09, 76.97, 76.87, 72.65, 72.13, 71.50, 71.42, 71.27, 71.10, 70.69, 70.08, 69.55, 69.42, 69.32, 69.20, 68.81, 68.57 (C-2I–VII, C-3I–VII, C-4I–VII, C-5I–VII), 21.39, 21.28, 21.10, 20.92, 20,79 ($OCOCH_3$), 9.99, 9.19, 8.68, 5.57 (C-6I–VII); ESI-HRMS: *m/z* 2616.8428 ($[M+Na]^+$), ($C_{74}H_{97}I_7NaO_{45}$ requires 2616.8513). Anal. Calcd for $C_{74}H_{97}I_7O_{45}$: C, 34.25; H, 3.77. Found: C, 34.83; H, 3.83.

1.12. 1^{I},4^{VII}-Di-*O*-acetyl-$2^{I–VII}$,$3^{I–VII}$-tetradeca-*O*-benzoyl-$6^{I–VII}$-heptadeoxy-$6^{I–VII}$-heptaiodo-α-maltoheptaose (16)

To a soln of **14** (0.33 g, 0.10 mmol) in butanone (40 mL) was added NaI (1.1 g, 7.4 mmol). The reaction mixture was stirred at 90 °C for 12 h, then concentrated under diminished pressure. The residue was purified by flash chromatography (2:3 then 1:1 EtOAc–hexane), to afford **16** (0.3 g, 83%): $[\alpha]_D$ +59 (*c* 0.5, EtOAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.13 ($OCOCH_3$), 165.67, 165.32, 165.05, 164.71 ($OCOC_6H_5$), 133.03, 129.80, 129.59, 129.41, 128.73, 128.32, 127.88, 127.74 ($OCOC_6H_5$), 97.03, 96.54, 96.21, 95.87 (C-1II–VII), 88.88 (C-1I), 72.25, 71.14, 70.78, 70.49, 69.51, 68.80, 68.39 (C-2I–VII, C-3I–VII, C-4I–VII, C-5I–VII), 20.95, 20.60 ($OCOCH_3$), 10.38, 10.06, 9.61, 8.72, 5.50 (C-6I–VII); ESI-HRMS: *m/z* 3485.0750 ($[M+Na]^+$), ($C_{144}H_{125}I_7NaO_{45}$ requires 3485.0704). Anal. Calcd for $C_{144}H_{125}I_7O_{45}$: C, 49.93; H, 3.64. Found: C, 50.75; H, 3.72.

1.13. 1^{I},$2^{I–VII}$,$3^{I–VII}$,4^{VII}-Hexadeca-*O*-acetyl-$6^{I–VII}$-heptaazido-$6^{I–VII}$-heptadeoxy-α-maltoheptaose (17)

To a soln of **13** (0.25 g, 0.11 mmol) in DMF (10 mL) was added a LiN_3 (0.2 mL, 4.64 mmol, 20% in water). The reaction mixture was stirred at room temperature for 48 h and concentrated under diminished pressure. The residue was purified by flash chromatography (1:1 then 3:2 EtOAc–hexane), to afford **17** (0.2 g, 91%): $[\alpha]_D$ +154 (*c* 0.85, EtOAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.23, 169.71, 169.63, 169.45, 169.15, 168.65 ($OCOCH_3$), 95.14, 94.90 (C-1II–VII), 88.60 (C-1I), 71.83, 71.43, 71.29, 70.38, 69.91, 69.53, 69.14, 68.86 (C-2I–VII, C-3I–VII, C-4I–VII, C-5I–VII), 50.82, 51.50 (C-6I–VII), 20.66, 20.31, 20.18 ($OCOCH_3$); ESI-HRMS: *m/z* 2022.5773 ($[M+Na]^+$), ($C_{74}H_{97}N_{21}NaO45$ requires 2022.5845). Anal. Calcd for $C_{74}H_{97}N_{21}O_{45}$: C, 44.42; H, 4.89; N, 14.7. Found: C, 44.80; H, 4.84; N, 12.99.

1.14. 1^{I},4^{VII}-Di-*O*-acetyl-$6^{I–VII}$-heptaazido-$2^{I–VII}$,$3^{I–VII}$-tetradeca-*O*-benzoyl-$6^{I–VII}$-heptadeoxy-α-maltoheptaose (18)

Method a: Compound **20** (5 g, 1.8 mmol) was dried at 60 °C for 24 h under diminished pressure and dissolved in 49:1 Ac_2O–H_2SO_4 (17.6 mL). The reaction mixture was stirred at 55 °C for 30 h, cooled, quenched by the addition of pyridine (4 mL) and concentrated under diminished pressure. The residue was subjected to silica gel column chromatography (20:1 then 10:1 toluene–EtOAc) giving unreacted **20** (3.3 g, 66%) and compound **18** (1.5 g, 30%).

Method b: Compound **14** (0.25 g, 0.08 mmol) was dissolved in DMF (10 mL). To this soln was added LiN_3

(0.15 mL, 3.35 mmol, 20% in water) and the reaction mixture was stirred at room temperature for 48 h. After concentration under diminished pressure, the residue was subjected to silica gel column chromatography (3:2 EtOAc–hexane) to afford **18** (0.21 g, 91%): $[\alpha]_D$ +114 (*c* 2.25, EtOAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.34, 168.89 ($OCOCH_3$), 165.72, 165.16, 164.80 ($OCOC_6H_5$), 133.18, 133.05, 132.59, 132.36, 129.84, 129.72, 129.60, 129.40, 128.96, 128.61, 128.34, 128.11, 128.03, 127.80, ($OCOC_6H_5$), 97.05, 96.23, 95.99 (C-1II–VII) 88.97 (C-1I), 77.38, 71.98, 71.90, 71.76, 71.05, 70.75, 70.50, 69.78, 69.07 (C-2I–VII, C-3I–VII, C-4I–VII, C-5I–VII), 51.83, 51.33, 51.10 (C-6I–VII), 21.37, 20.88, 20.53 ($OCOCH_3$); ESI-HRMS: *m*/*z* 2890.8115 ($[M+Na]^+$), ($C_{144}H_{125}N_{21}NaO_{45}$ requires 2890.8036). Anal. Calcd for $C_{144}H_{125}N_{21}O_{45}$: C, 60.27; H, 4.39; N, 10.25. Found: C, 60.32; H, 4.58; N, 9.23.

1.15. 1^{I},$2^{I–VII}$,$3^{I–VII}$,4^{VII}-Hexadeca-*O*-acetyl-$6^{I–VII}$-*S*-[hepta-(*tert*-butoxycarbonyl-2-amino)ethyl]-$6^{I–VII}$ hepta-thio-α-maltoheptaose (19)

A soln of 2-(Boc-amino)ethanethiol (2.40 mL, 13.5 mmol) and Na_2CO_3 (1.41 g, 13.5 mmol) in DMF (15 mL) was stirred for 30 min. Then **15** (1 g, 0.38 mmol) was added and the mixture stirred under N_2 at 40 °C for 48 h. After concentration under diminished pressure, the residue was subjected to silica gel column chromatography (3:2 then 7:3 EtOAc–hexane) to afford **19** (1 g, 89%): $[\alpha]_D$ +98 (*c* 0.8, EtOAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.46, 169.72 (OCOCH3), 155.76 (CONH), 95.73, 95.25 (C-1II–VII), 88.70 (C-1I), 79.04 ($C(CH_3)_3$), 73.87, 72.11, 71.61, 70.83, 70.51, 70.03, 69.80, 69.16 (C-2-I–VII, C-3I–VII, C-4I–VII, C-5I–VII), 39.81 (SCH_2CH_2NH), 33.93, 33.56, 32.85 (C-6I–VII, SCH_2CH_2NH), 28.33 ($C(CH_3)_3$), 20.82, 20.60, 20.46 ($OCOCH_3$); ESI-HRMS: *m*/*z* 2961.0513 ($[M+Na]^+$), ($C_{123}H_{195}N_7NaO_{59}S_7$ requires 2961.0416). Anal. Calcd for $C_{123}H_{195}N_7O_{59}$: C, 50.25; H, 6.68; N, 3.33. Found: C, 49.19; H, 6.90; N, 3.19.

1.16. Heptakis(6-azido-2,3-di-*O*-benzoyl-6-deoxy)-cyclomaltoheptaose (20)

Compound **12** (5 g, 1.65 mmol) was dissolved in DMF (25 mL). Then NaN_3 (3 g, 46 mmol) was added. The mixture was stirred vigorously for 24 h at 100 °C, then concentrated under diminished pressure. The crude product was precipitated by addition of 10:1 MeOH–water, filtered, washed with water, and dried. Heptakis(6-azido-2,3-di-*O*-benzoyl-6-deoxy)cyclomaltoheptaose **20** (4.1 g, 90%) was isolated as a white powder: $[\alpha]_D$ +134 (*c* 1.2, EtOAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.94, 164.52 ($OCOC_6H_5$), 132.63, 132.38, 129.71, 129.15, 128.11, 127.82, 127.66 ($OCOC_6H_5$), 97.04 (C-1I–VII), 77.35 (C-4I–VII), 71.39, 71.15, 71.04 (C-2I–VII, C-3I–VII, C-5I–VII), 51.81 (C-6I–VII); ESI-HRMS: *m*/*z* 2788.7708 ($[M+Na]^+$), ($C_{140}H_{119}N_{21}NaO_{42}$ requires 2788.7719). Anal. Calcd for $C_{140}H_{119}N_{21}O_{45}$: C, 60.76; H, 4.33; N, 10.63. Found: C, 59.85; H, 4.15; N, 10.13.

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