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Synthesis of symmetrical cyclodextrin derivatives bearing multiple charges

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Summary – Several water-soluble symmetrical cyclodextrin derivatives bearing positively charged or negatively charged groups were synthesized to examine the possibility of obtaining stable electrostatically linked heterodimers in water. The positively charged species were obtained from per-amino functionalization of the 6-glucose positions, whereas the negative units were obtained through introduction of thioglycolate or glycolate groups at the 6- or 3-glucose positions.

symmetrically substituted cyclodextrin / polyelectrolyte / ion pair

Introduction

The design of molecular assemblies in solution is a topic of current interest [1-7]. Many strategies have been devised to observe predefined species built by assembly of conveniently designed components. Among the interactions that may be used to generate oligomeric self-assembled systems, attention has essentially focused on ligand–metal and hydrogen bonds. Although of current use in the field of self-assembly on solid supports [8-10], electrostatic interactions were only marginally envisaged to design self-assembled species in solution. This may be understood when one considers the limitations of this type of interaction to build a complex of predefined geometry. The first limitation results from the nature of the electrostatic interaction. Indeed, in the case of two central charges, it is described by a $(z_+z_-)/\varepsilon r^2$ term, where z_+ and z_- represent the number of positive and negative charges borne by the interacting species, ε is the dielectric constant of the medium and r is the distance between the application points of the charges [11, 12]. Since the interaction range is large (r^{-2} dependence) and no angular dependence appears in the interaction law, electrostatic interactions are generally considered to be non-specific [13]. The second limitation lies doubtlessly in the often incompatible requirement of designing species that would be simultaneously highly charged and soluble in a medium of low dielectric constant which generally has a poor ability to solvate ions. Despite these drawbacks for self-assembly engineering, electrostatic interactions are nevertheless recognized to play a major role in the control over molecular assemblies in biological systems.

In the present paper, we report the design and the synthesis of the components of a self-assembled system that is based on charge–charge electrostatic interactions, but should exhibit stability and selectivity features comparable to those presented by other self-assembled systems.

The basic idea underlying the design of the present self-assembled system based on electrostatic interactions between point charges was to make use of rigid bodies with several charges tightly bound to planar faces according to a similar spatial distribution in both positively and negatively charged species. It rests on energetic considerations that: i) prevent the species from reorganizing its backbone to minimize its energy through intramolecular deformations which decrease the electrostatic repulsion between identically charged groups (rigidity and absence of spacer); and ii) allow for complementarity between oppositely charged species by means of planar surfaces bearing identical charge distribution. In order to avoid the solubility problems associated with the solvation of individual charged components, we decided to concentrate our attention on the use of water as a solvent. We therefore had to work with highly charged species to overcome the effect of the high

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dielectric constant of water. However, since the neutralization accompanying the association would be reasonably expected to induce aggregation or precipitation, each interacting species was chosen to be hydrophilic, independently of the presence of charges.

Cyclodextrins appeared suitable candidates to fulfil these various requirements. They are cyclic oligomers of α-(1-4)-linked D-glucose displaying a toroidal shape presenting six, seven or eight primary hydroxyl groups on one rim and twice as many secondary ones on the other rim for α, β and γ-cyclodextrin respectively [14-17]. Their reactivity has been extensively investigated and numerous water-soluble cyclodextrins have already been synthesized [18]. The high symmetry and degree of functionalization, the rigidity of the cyclodextrin torus and the possibility of introducing positive and negative functionalities without a long spacer on the primary rim make cyclodextrins suitable units for generating in water heterodimers based on two components of opposite charges. Furthermore, because of the circular distribution of charges on the primary rim, face-to-face dimerization [19] may be reasonably considered as the most probable arrangement of heterodimers (fig 1). Such a dimerization strategy yields self-assembled double cyclodextrin architectures and represents an alternative to the synthetically demanding covalent dimerization of cyclodextrin [20].

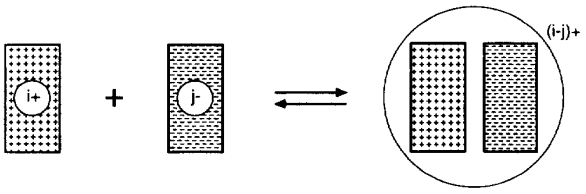


Fig 1. Hypothetical heterodimer formation resulting from interaction between two oppositely charged units.

Once the cyclodextrin backbone has been chosen, the main task of the molecular design of charged units consists of looking for the nature of charged groups to be borne on both cyclodextrin components. Ideally, the most suitable groups to be introduced for the present purpose should be pH-insensitive (like quaternary ammoniums, for instance). Indeed, since the presence of numerous charges in close proximity is required to give stable heterodimers, the most highly charged cyclodextrin derivatives will be observed at significantly different pH from the intrisic pK_a of the grafted function [21]. Hence, the final apparent acidities or basicities of the six, seven or eight acidobasic functions on cyclodextrin units will decrease by about 3–4 pH units [22]. Thus, the coexistence of the most highly positively and negatively charged species in aqueous solutions requires pH-sensitive grafted functions to be sufficiently basic and acid.

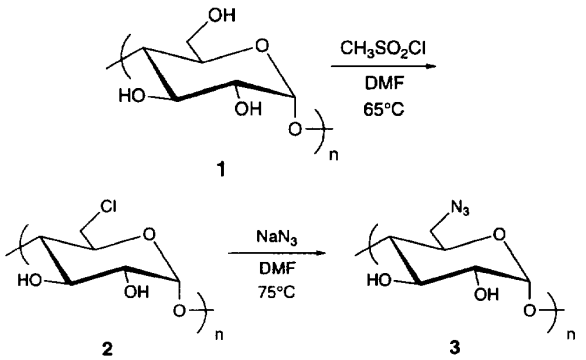
In the present paper, we report the synthesis of water-soluble symmetrical cyclodextrin derivatives which are expected to bear high opposite charges under the same conditions (pH, ionic strength, etc) in aqueous solutions.

Results

Synthesis of positively charged cyclodextrins

Ideally, the most suitable positive group to be introduced for the present purpose should either be pH-insensitive or remain positive in a wide pH range (in particular, for biological applications at neutral pH). No per-6 introduction of pH-insensitive positive groups has been reported. Indeed, only a few per-6-functionalized cyclodextrins have been described in the literature [23]. Among them, the potentially positive per-6-amino cyclodextrins (ammonium) appeared the most suitable because of the large enough basicity of the primary amine function.

The per-6-amino α- and β-cyclodextrins [24, 25] and the per-6-methylamino-β-cyclodextrin [26] have been already reported. The syntheses of the per-6-amino cyclodextrins proceed via i) the synthesis of the intermediate per-6-azido derivatives either from the direct transformation of the commercially available cyclodextrins using triphenylphosphine sodium azide as a reagent [25] or from nucleophilic substitution on perhalogeno derivatives [27]; and ii) the reduction of the corresponding intermediate per-6-azido derivatives, either by catalytic hydrogenation [28] or reduction with triphenylphosphine [25]. Although the syntheses based on triphenylphosphine have high yields, they require either tedious repetitive precipitations to eliminate the excess phosphine and the triphenylphosphine oxide formed during the reaction or to prepare some easily tractable derivative, for instance, the per-2,3-di-*O*-acetyl-6-azido-cyclodextrins [29], from which the per-6-azido cyclodextrins can be regenerated. In order to avoid these drawbacks, we looked for other methods to synthesize the per-6-amino cyclodextrins while keeping a purification step before the transformation of the azide into the amine. Our strategy was based on the synthesis of the per-6-azido-2,3-di-*O*-benzyl cyclodextrins 4 in which a final hydrogenation should directly lead to the expected



α n = 6

β n = 7

γ n = 8

Fig 2. Synthesis of per-6-azido cyclodextrins.

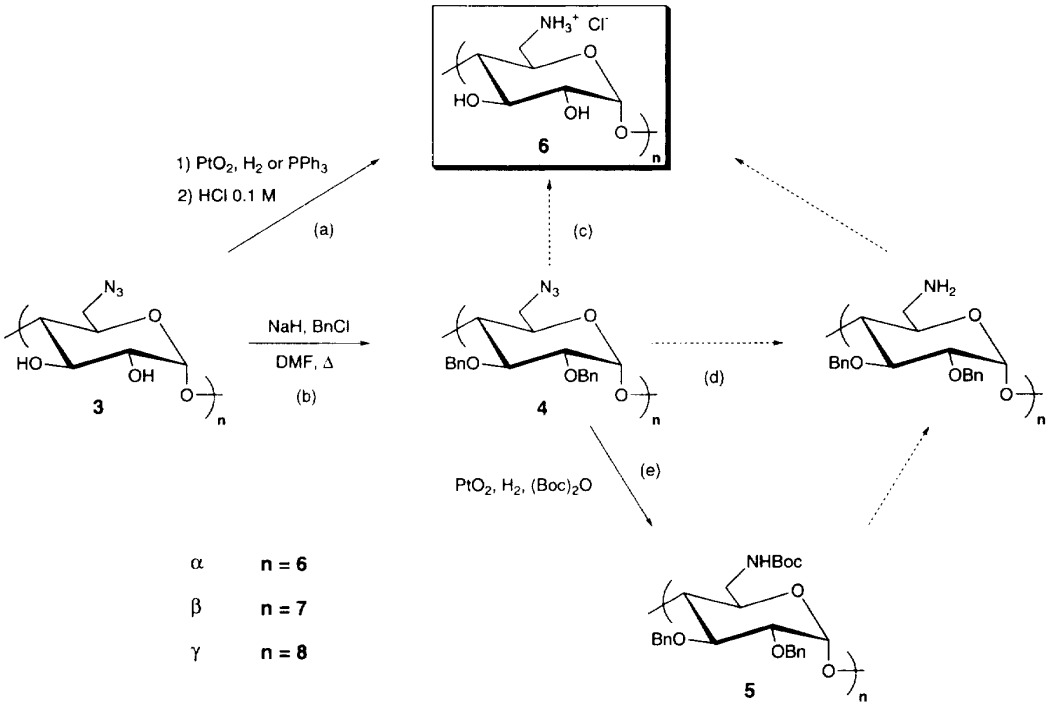


Fig 3. Synthetic routes to access per-6-ammonium chlorhydrate β-cyclodextrin **6**β.

per-6-amino derivatives (fig 3; route c). Indeed, we have previously shown that hydrogenolysis of per-2,3-di-*O*-benzyl β-cyclodextrin derivatives smoothly remove the protecting benzyl groups [30]. Furthermore, the transformation of azide to amine by hydrogenation in the cyclodextrin series was previously reported [24, 28]. The per-6-azido cyclodextrins were synthesized in two steps (fig 2): i) the cyclodextrins **1**α, **1**β and **1**γ were first transformed into the per-6-chloro cyclodextrins **2**α, **2**β [31] and **2**γ by reaction with mesyl chloride in DMF [32-33]; ii) nucleophilic substitution by sodium azide in DMF afforded the expected per-6-azido cyclodextrins **3**α [25], **3**β [24] and **3**γ. Compound **3**β was then alkylated (NaH, BnCl, DMF) [30] to give the per-6-azido-2,3-di-*O*-benzyl-β-cyclodextrin **4**β (fig 3). Numerous attempts were made to reduce **4**β by hydrogenation to directly reach **6**β, but none of them provided pure **6**β (fig 3; route c). Catalytic hydrogenation on platinum oxide does not cleave the benzyl groups, whereas with palladium on charcoal it does remove the benzyl groups but leads to palladium complexes from which it is impossible to extract pure **6**β [34]. Consequently, we tried first to reduce the azido groups before cleaving the benzyl ethers (fig 3; route d). We failed to reduce **4**β cleanly by hydrides ($LiAlH_4$ or $NaBH_4$, $NiCl_2$ [35]). Eventually, we tried to simultaneously reduce the azido groups and protect the amino groups produced (fig 3; route e). We succeeded in isolating the pure per-6-*N*-Boc-protected β-cyclodextrin **5**β by hydrogenation on platinum oxide in the presence of excess di-*tert*-butyl dicarbonate [36] but the low yield of this reaction led us to give up this strategy. Therefore, we synthesized the per-6-amino cyclodextrins **6**α, **6**β and **6**γ according to previously described procedures [25], the iminophosphorane route appearing more convenient since the absence of metal avoids complex formation and allows the isolation of the free amine instead of the corresponding ammonium salt (fig 3; route a).

Synthesis of negatively charged cyclodextrins

The same criteria as for the positively charged units apply for the negatively charged ones. Ideally, we would prefer to work with pH-insensitive species. Persulfate cyclodextrins have been reported [37] and would be ideal in view of the low intrisic pK_a of the sulfuric function. Unfortunately, their synthesis does not allow easy purification of the final compounds and their chemical stability may be limited. Therefore, the carboxylic group appeared more suitable. When it is activated by electron-withdrawing substituent, the intrisic pK_a of the carboxylic group would still be low enough to observe the coexistence of perammonium and percarboxylate cyclodextrins at neutral pH.

In the same way as other workers [38], we first tried to directly oxidize the primary alcohol into the corresponding carboxylic acid but we failed to extract any pure material from these trials. It was thus necessary to introduce the shortest possible spacer for attaching the carboxylic groups onto the cyclodextrin backbone. Since it has been reported that it was impossible to obtain the homologated percarboxylic acid [39], we decided to synthesize several glycolate derivatives of the β-cyclodextrin. These can be obtained *a priori* from either condensation on perhalogeno cyclodextrins or direct carboxymethylation of the cyclodextrins. Two different routes were first identified to give the per-6- or per-3-glycolate cyclodextrins. Introduction of many functionalities in the 6-position of

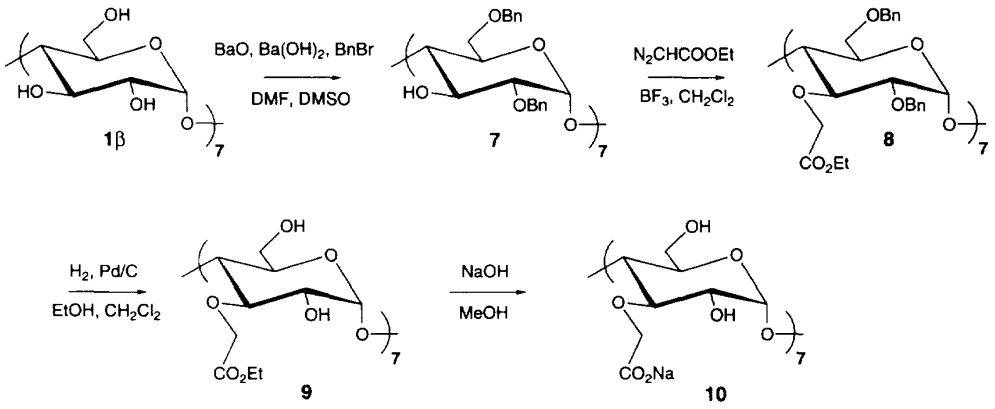


Fig 4. Synthesis of per-3-glycolic acid β-cyclodextrin **10**.

the cyclodextrins may be achieved either via the *tert*-butyldimethylsilyl protection [40, 41] or halogenation of all 6-positions [42, 43], whereas the main entry to the functionalization of the 3-positions goes through the protection of the 2- and 6-positions followed by the removal of the protecting groups [44]. We first chose to introduce the glycolate group by reacting the corresponding benzyl-protected hydroxy derivatives with ethyldiazoacetate; the condensation of the diazoester in methylene chloride is catalyzed by the boron trifluoride ether complex and generally occurs smoothly with high yields on aliphatic and polyoxyethylenic alcohols [45]. The two per-2,6-di-*O*-benzyl and per-2,3-di-*O*-benzyl β-cyclodextrins **7** [46] and **11** [30, 47] were first obtained in one and three steps respectively from **1**. The diazo-condensation proceeded successfully onto the per-2,6-di-*O*-benzyl β-cyclodextrin **7** to yield the per-2,6-di-*O*-benzyl-3-ethylglycolate ester β-cyclodextrin **8** (fig 4). Compound **8** was then debenzylated by hydrogenolysis on palladium/charcoal to give the per-3-ethylglycolate ester **9** which was then hydrolyzed to give the corresponding heptaacid **10**. Surprisingly, the similar reaction onto the per-2,3-di-*O*-benzyl β-cyclodextrin **11** was unsuccessful despite the use of various conditions of temperatures and work-up. It is likely that this unexpected reactivity is related to the sensitivity of the per-2,3-di-*O*-benzyl β-cyclodextrin **11** to acidic conditions [48]. Therefore, we tried to condense **11** onto bromoacetate derivatives under Williamson conditions. We eventually managed to isolate the per-2,3-di-*O*-benzyl-3-*tert*-butyl glycolate ester β-cyclodextrin **12** in low yield after extensive purification (14%; fig 5). Finally, we decided to synthesize the thioglycolate derivative, which appeared to be more easily accessible from the nucleophilic substitution of the thiolester onto the per-6-halogeno derivatives. The final target molecule **15** was obtained either by direct condensation of the methylthioglycolate ester with the per-6-bromo β-cyclodextrin **13** to give the per-6-methylthioglycolate β-cyclodextrin **14**, which was subsequently hydrolyzed under basic conditions (fig 6), or by reaction of the ethylthioglycolate ester with the per-2,3-di-*O*-acetyl-6-iodo β-cyclodextrin **17** obtained from **1** in three steps: i) per chlorination of the 6-positions to give **2β**; ii) acetylation of the remaining 2- and 3-positions to afford **16**; and iii) halogen exchange to provide **17** (fig 7). The condensation product **18** was then hydrolyzed under basic conditions to yield **15**.

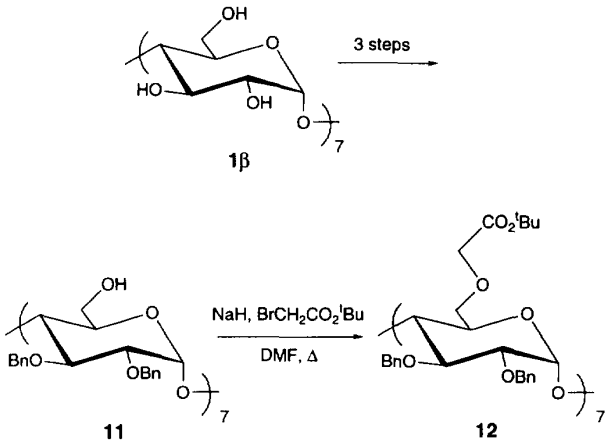


Fig 5. Synthesis of per-2,3-dibenzyl-3-*tert*-butyl glycolate ester β-cyclodextrin **12**.

Conclusion

Two series of highly charged, water-soluble α, β and γ-cyclodextrin derivatives have been synthesized. The three homologous positively charged per-6-ammonium cyclodextrins chlorhydrates constitute the first series. The γ compound has been obtained according to described methods for α and β cyclodextrin derivatives. The second series of negatively charged β-cyclodextrins was obtained by introduction of carboxylate groups on the cyclodextrin backbone; the first derivative was synthesized by grafting a glycolate group on all the 3-positions whereas the second derivative was obtained by appending thioglycolate groups on the 6-positions. In a forthcoming paper [21], we will report the interaction between cyclodextrins bearing opposite charges and their assembly into electrostatically bound supramolecular architectures.

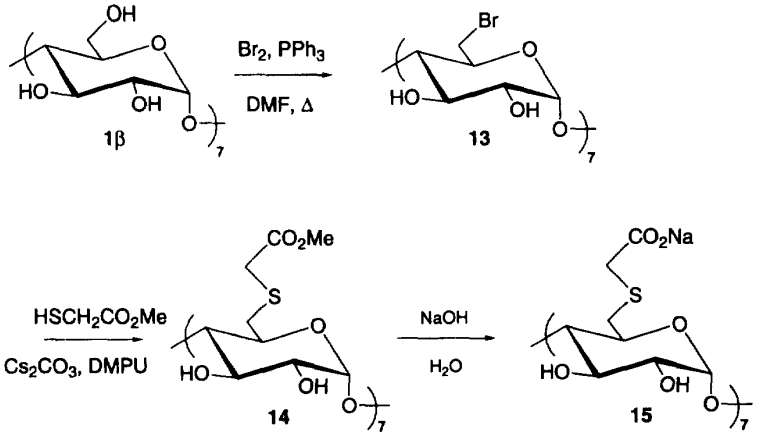


Fig 6. Synthesis of per-6-thioglycolic acid-β-cyclodextrin **15** (first route).

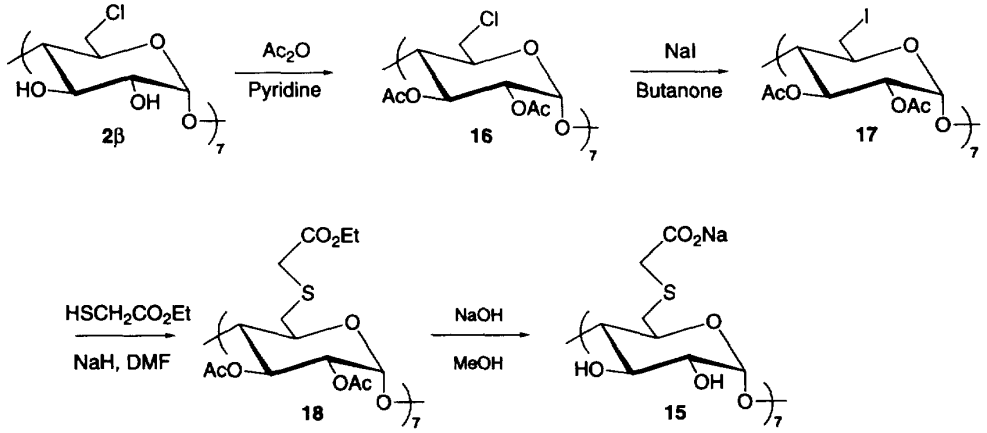


Fig 7. Synthesis of per-6-thioglycolic acid-β-cyclodextrin **15** (second route).

Experimental section

Anhydrous solvents (SDS) were kept on molecular sieves (3–4 Å) and were used as obtained. All catalytic hydrogenations were performed at 1 bar pressure. Column chromatography (CC): silica gel 60 (0.040-0.063 mm) Merck. Analytical and preparative thin layer chromatography (TLC): silica gel plates Merck; detection by UV (254 nm), I_2, 5% H_2SO_4 or a mixture of $MoO_4(NH_4)_2$ (2.5 g), $(NH_4)_2Ce(NO_3)_6$ (1.2 g) and H_2SO_4 (100 mL, 3.6 M). Melting points (uncorrected): Kofler hot-stage.

^{1}H-NMR spectra: AM-200-SY-Bruker (4.7 T) recorded at room temperature; Aspect 3000 calculator; chemical shifts in ppm related to protonated solvent as internal reference (^{1}H: $CHCl_3$ in $CDCl_3$, 7.26 ppm; CHD_2OD in CD_3OD, 3.30 ppm; CHD_2SOCD_3 in CD_3SOCD_3, 2.49 ppm; CHD_2COCD_3 in CD_3COCD_3, 2.04 ppm; C_5HD_4N in C_5D_5N, 8.65, 7.5 and 7.14 ppm. ^{13}C: $^{13}CDCl_3$ in $CDCl_3$, 76.9 ppm, $^{13}CD_3OD$ in CD_3OD, 49.0 ppm, $^{13}CD_3SOCD_3$ in CD_3SOCD_3, 39.6 ppm; $^{13}CD_3COCD_3$ in CD_3COCD_3, 29.8 ppm, $^{13}CC_4D_5N$ in C_5D_5N, 149.0, 134.6 and 122.6); coupling constants J in Hz.

Mass spectrometry: FAB-MS (positive mode) were performed by the Service de spectrométrie de masse du CNRS, Vernaison, by Dr O Laprévote in the Laboratoire de spectrométrie de masse of ICSN (CNRS) and/or at CERMAV by Dr C Rossso. Microanalyses were performed by the Service de microanalyses de l'Université Pierre-et-Marie-Curie, Paris or CNRS, Vernaison. The commercial cyclodextrins were dried under vacuum (1 mmHg) at 100°C for 24 h before use. Compounds **7** [46] and **11** [30] were synthesized as described previously. Except for **6α** and **6β**, which were fully characterized for physicochemical purposes, previously reported compounds (**3α**, **3β**, **13**, **16** and **17**) are not described again. Their characteristics were in agreement with those given in the corresponding quoted reference.

6^A,6^B,6^C,6^D,6^E,6^F,6^G-Heptachloro-6^A,6^B,6^C,6^D,6^E,6^F,6^G-heptadeoxy-β-cyclodextrin **2β** *[31]*

Mesyl chloride (12.4 mL, 18.3 g; 160 mmol, 5.2 equiv) was added dropwise into a solution of β-cyclodextrin **1β** (5.0 g; 4.4 mmol) in dry DMF (90 mL). After stirring for 2 d at 65°C, the solvent was evaporated, the residue was dissolved into methanol (25 mL) and the resulting solution was neutralized with a 3 M solution of sodium methylate in methanol. After stirring for 30 min at room temperature, the mixture was poured onto ice and the resulting precipitate was filtered, thoroughly rinsed with methanol and dried. The white powder of **2β** (5.17 g; 92%) was used without further purification for the next step.

MP decomposition T > 265°C.

^{1}H NMR (DMSO-d_6): δ 5.99 (d, ^2J = 6, 1H), 5.85 (s, 1H), 4.94 (d, ^3J = 3, 1H), 4.07 and 3.59 (AB, ^2J = 10, 2H); 3.8–3.3 (m, 4H).

^{13}C NMR (DMSO-d_6): δ 102.0, 83.5, 72.4, 71.9, 71.1, 44.9.

$6^A,6^B,6^C,6^D,6^E,6^F$-Hexachloro-$6^A,6^B,6^C,6^D,6^E,6^F$-hexadeoxy-α-cyclodextrin **2**α

Compound **2**α was prepared as for **2**β using mesyl chloride (13.5 mL, 20.0 g; 0.17 mol; 5 equiv), **1**α (5.65 g; 6 mmol) and DMF (75 mL); **2**α was isolated as a white powder (6.50 g; 90%).

^{1}H NMR (DMSO-d_6): δ 4.91 (d, ^3J = 2.5, 1H), 4.1–3.7 (m, 4H), 3.6–3.2 (m, 3H).

^{13}C NMR (DMSO-d_6): δ 101.9, 83.6, 72.6, 71.6, 70.9, 45.2.

Anal calc for $(C_6H_9O_4Cl)_6$ (1 083.5): C, 39.90; H, 5.02. Found : C, 39.72; H 5.19.

$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-Octachloro-$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-octadeoxy-$\gamma$-cyclodextrin **2**$\gamma$

Compound **2**γ was prepared as for **2**β using mesyl chloride (3.0 mL, 4.4 g; 3.8 mmol, 4.7 equiv), **1**γ (1.30 g; 1.0 mmol) and DMF (20 mL); **2**γ was isolated as a white powder (1.40 g; 97%).

^{1}H NMR (DMSO-d_6): δ 4.97 (d, ^3J = 3.1, 1H), 4.1–3.9, 3.9–3.7, 3.7–3.3 (m, 6H).

^{13}C NMR (DMSO-d_6): δ 102.0, 82.9, 72.3, 72.2, 71.1, 44.9.

Anal calc for $(C_6H_9O_4Cl)_8$ (1 444.7): C. 39.90; H 5.02. Found: C, 39.53; H, 5.40.

A sample of **2**γ was acetylated for analysis.

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,2^H,3^A,3^B,3^C,3^D,3^E,3^F,3^G,3^H$-hexadeca-O-acetyl-$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-octachloro-$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-octadeoxy-$\gamma$-cyclodextrin

^{1}H NMR ($CDCl_3$): δ 5.33 (dd, ^3J = 10, 1H, H3), 5.25 (d, ^3J = 3.7, 1H, H1), 4.74 (dd, ^3J = 3.7, 10, 1H, H2), 4.10 (m, 1H, H5), 3.95 (m, 2H, H6), 3.81 (dd, ^3J = 10, 1H, H4).

^{13}C NMR ($CDCl_3$): δ 170.2, 169.3, 95.8, 75.6, 70.5 (2), 70.0, 44.3, 20.6, 20.5.

Anal calc for $(C_{10}H_{13}O_6Cl)_8$ (2 117.3): C, 45.38; H 4.95. Found: C, 45.31; H, 4.95.

$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-Heptaazido-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-heptadeoxy-$\beta$-cyclodextrin **3**$\beta$ *[24]*

A mixture of **2**β (1.98 g; 1.56 mmol) and sodium azide (7.2 g; 0.11 mol, 10 equiv) in dry DMF (90 mL) was stirred for 2 d at 75°C. After cooling at room temperature, the suspension was poured into water and the precipitate was filtered. After drying, **3**β was obtained as a white powder (1.91 g; 93%).

Mp decomposition 240–245°C (lit, slow decomposition T > 230°C [24]).

$6^A,6^B,6^C,6^D,6^E,6^F$-Hexaazido-$6^A,6^B,6^C,6^D,6^E,6^F$-hexadeoxy-α-cyclodextrin **3**α *[25]*

Compound **3**α was prepared as for **3**β using **2**α (3.00 g; 2.8 mmol), NaN_3 (10.0 g; 0.15 mol, 9 equiv) and DMF (50 mL); **3**α was isolated as a white powder (2.36 g; 76%).

$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-Octaazido-$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-octaadeoxy-$\gamma$-cyclodextrin **3**$\gamma$

Compound **3**γ was prepared as for **3**β using **2**γ (1.24 g; 0.86 mmol), NaN_3 (6.0 g; 92 mmol, 14 equiv) and DMF (25 mL); **3**γ was prepared as a white powder (839 mg; 65%).

^{1}H NMR (DMSO-d_6): δ 4.86 (d, ^3J = 3, 1H), 3.9–3.2 (m, 6H).

^{13}C NMR (DMSO-d_6): 102.0, 82.6, 72.4, 72.3, 70.4, 51.2.

Anal calc for $[(C_6H_9N_3O_4)_8 \cdot 3.3\ H_2O]$ (1 556.7): C, 37.03; H, 5.09. Found: C, 36.81; H, 4.88.

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G$-Tetradeca-O-benzyl-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-heptaazido-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-heptadeoxy-$\beta$-cyclodextrin **4**$\beta$

NaH (80% suspension in mineral oil; 2.42 g; 81 mmol, 5 equiv) was added at 0°C into a solution of **3**β (1.50 g; 1.14 mmol) in dry DMF (40 mL). After 1 h at 0°C, benzyl chloride (7.5 mL, 8.25 g; 65 mmol, 4 equiv) was added and the mixture was further stirred for 1 h at 0°C and then 2 h at room temperature. After hydrolysis with water, the solution was extracted with ethyl acetate. The organic phase was washed with water, dried over Na_2SO_4 and evaporated. The crude residue was washed twice with pentane. The decanted yellow oil was purified by CC on silica gel (200 g; elution: CH_2Cl_2/pentane (95:5) then CH_2Cl_2) to give **4**β as a colorless resin (1.35 g; 45%).

^{1}H NMR ($CDCl_3$): δ 7.39–7.18 (m, 10H), 5.01 (d, ^3J = 3, 1H), 5.05 and 4.77 (AB, ^2J = 11, 2H), 4.61 and 4.41 (AB, ^2J = 12, 2H), 4.0–3.6 (m, 5H), 3.53 (dd, ^2J = 9, ^3J = 3, 1H).

^{13}C NMR ($CDCl_3$): δ 138.8, 137.9, 128.2, 127.9, 127.8, 127.6, 127.1, 127.0, 98.4, 80.1, 79.8, 78.6, 75.3, 73.1, 71.2, 52.0.

Anal calc for $(C_{20}H_{21}O_4N_3)_7$ (2 571.7): C, 65.38; H, 5.76; N, 11.44. Found: C, 65.58; H, 5.85; N, 11.43.

TLC: silica, CH_2Cl_2/pentane (95:5), R_f = 0.4.

$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G$-Tetradeca-O-benzyl-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-heptakis[(tert-butoxycarbonyl)amino]-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-heptadeoxy-$\beta$-cyclodextrin **5**$\beta$

A suspension of platinum oxide (46 mg) in a solution of **4**β (99 mg; 0.038 mmol), $(Boc)_2O$ (87 mg; 0.40 mmol, 1.3 equiv) in MeOH (10 mL) and dioxane (2 mL) was hydrogenated for 6.5 h at 40–50°C. After filtration, the filtrate was evaporated and the residue was purified by preparative TLC (elution: CH_2Cl_2/ether 95:5) to yield **5**β as a colorless resin (25 mg; 21%).

^{1}H NMR ($CDCl_3$): δ 7.26–7.00 (m, 10H), 5.66 (broad s, 1H), 5.27 (unresolved d, 1H), 4.73–4.42 (m, 4H), 4.01–3.47 (m, 6H), 1.41 (s, 9H).

^{13}C NMR ($CDCl_3$): δ 156.4, 139.0, 138.2, 128.1, 127.9, 127.7, 127.3, 127.2, 126.9, 98.1, 80.0, 78.6, 78.3, 74.7, 72.4, 70.9, 41.1, 29.4, 28.5.

MS (FAB$^+$): m/z 3 097 [M + Li$^+$] (calc: 3 098).

$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-Heptaamino-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-heptadeoxy-β-cyclodextrin-heptachlorhydrate **6β**

• *By hydrogenation [24]*

A suspension of platinum oxide (160 mg) in a solution of **3β** (350 mg; 0.27 mmol) in a mixture methanol/water 3:1 (30 mL) was hydrogenated for 4 h at room temperature. After filtration, the filtrate was evaporated to give 316 mg of a grey powder containing platinum; 60 mg of this powder was dissolved in HCl 0.1 M. The solution was filtered over a glass microfibre filter and lyophilized to give **6β** as a white powder (50 mg; 61%).

Mp 185–190°C (decomposition) (lit 182–185°C dec [24]).

^{1}H NMR (D_2O): δ 5.10 (d, ^3J = 2, 1H), 4.1 (m, 1H), 3.9 (dd, ^3J = 8, 1H), 3.6 (dd, ^3J = 10, 1H), 3.5–3.2 (m, 3H).

^{13}C NMR (D_2O): δ 101.4, 82.2, 72.1, 71.6, 67.8, 40.3.

Anal calc for $[(C_6H_{12}O_4NCl)_7 \cdot 13H_2O]$: C, 31.18; H, 6.85; N, 6.06. Found: C, 31.23; H, 6.82; N, 5.65.

• *By the iminophosphorane route [25]*

A mixture of **3β** (1.00 g; 0.76 mmol), triphenylphosphine (4.2 g; 1.6 mmol; 3 equiv) in methanol (25 mL) and dioxane (130 mL) was stirred at room temperature for 2 h. Water (1.75 mL) was then added and the solution was further stirred for 60 h. After evaporation, the residue was suspended in toluene (100 mL) and the resulting suspension was sonicated and centrifugated. This operation was repeated five times. The solid was extracted for 2 d with a Soxhlet extractor (toluene). After drying, the heptaamine was isolated as a white powder (765 mg; 85%) contaminated with a small amount of phosphine which was detected by ^{1}H NMR (the microanalysis should agree with the formula $(C_6H_{11}O_4N)_7 \cdot 10\ H_2O$, $(Ph)_3PO$; anal calc: C, 45.42; H, 7.11; N, 6.17; found: C, 45.63; H, 7. 09; N, 6.37). This white solid (200 mg) was suspended in 10 mL water. After acidification with HCl 0.1 M to pH 2, the aqueous solution was extracted with methylene chloride. The lyophilization of the aqueous phase gave **6β** as a white powder (200 mg; 82%).

Anal calc for $[(C_6H_{12}NO_4)_7 \cdot 6.5\ HCl \cdot 11\ H_2O]$: C, 32.28; H, 6.81; N, 6.27; Cl, 14.78. Found: C, 32.00; H, 6.51; N, 5.86; Cl, 14.71.

$6^A,6^B,6^C,6^D,6^E,6^F$-Hexaamino-$6^A,6^B,6^C,6^D,6^E,6^F$-hexadeoxy-α-cyclodextrin-hexachlorhydrate **6α**

This was synthesized as described in reference 25 (yield 78%).

^{1}H NMR (D_2O): δ 5.07 (d, ^3J = 3, 1H), 4.1 (m, 1H), 3.9 (dd, ^3J = 9, 1H), 3.7–3.3 (m, 3H), 3.18 (dd, ^3J = 6 and 13, 1H).

^{13}C NMR (D_2O, internal reference CD_3OD at 49.0 ppm): δ 102.2, 83.2, 73.4, 72.1, 68.7, 41.1.

Despite extensive extraction, it was impossible to remove some residual triphenylphosphine [49]. NMR spectra and analysis agreed with the formula: $[(C_6H_{12}O_4NCl)_6 \cdot 0.17\ PPh_3 \cdot 5.1\ H_2O]$ (1 322.09): C, 35.50; H, 6.46; N, 6.36; Cl, 16.09. Found: C, 35.53; H, 6.63; N, 6.15; Cl, 16.16.

$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-Octaamino-$6^A,6^B,6^C,6^D,6^E,6^F,6^G,6^H$-octadeoxy-γ-cyclodextrin **6γ**

A mixture of **3γ** (690 mg; 0.46 mmol), triphenylphosphine (3.31 g; 12.6 mmol, 3.4 equiv) in methanol (10 mL) and dioxane (50 mL) was stirred at room temperature for 6 h. Concentrated NH_3 (3.5 mL) was then added and the solution was further stirred for 18 h. The suspension was filtered and the solid was thoroughly rinsed with MeOH and then dried to yield **6γ** as a white powder (639 mg; 91%).

^{1}H NMR (D_2O): δ 5.26 (d, ^3J = 3, 1H), 4.2 (m, 1H), 4.0 (dd, ^3J = 9, 1H), 3.8–3.2 (m, 4H).

^{13}C NMR (D_2O, internal reference CD_3OD at 49.0 ppm): δ 101.5, 81.9, 72.8, 72.6, 68.6, 41.2.

As for **6α**, the presence of residual triphenylphosphine was detected by ^{1}H NMR. NMR spectra and analysis agreed with the formula: $[(C_6H_{12}O_4N)_8 \cdot 0.33\ PPh_3 \cdot 8.5\ H_2O]$ (1 529.06): C, 42.35; H, 7.25; N, 7.33. Found: C, 42.63; H, 7.46; N, 7.32.

Cyclohepta 3-O-(1→4)-(2,6-di-O-benzyl-α-D-glucopyranosyl) ethyl glycolate **8** *[$2^A,2^B,2^C,2^D,2^E,2^F,2^G$-$6^A,6^B,6^C,6^D,6^E,6^F,6^G$-tetradeca-O-benzyl-$3^A,3^B,3^C,3^D,3^E,3^F,3^G$-hepta-O-(ethyl glycolate)-β-cyclodextrin]*

A solution of ethyl diazoacetate (330 μL; 3.1 mmol, 3 equiv) in methylene chloride (15 mL) was added dropwise at 0°C into a solution of **7** (358 mg; 0.15 mmol), boron trifluoride/ethyl ether (one drop) in dry methylene chloride (25 mL). After stirring overnight at room temperature, the organic solution was washed with aqueous solutions of sodium hydrogen carbonate, sodium chloride and was then dried over Na_2SO_4. After evaporation of the solvent, the crude residue was purified by column chromatography (elution: gradient of acetone in methylene chloride) to yield **8** as a colorless resin (283 mg; 63%).

^{1}H NMR ($CDCl_3$): δ 7.42–7.16 (m, 10H), 4.96 (d, ^3J = 3, 1H), 4.80–4.74 (m, 3H), 4.37–4.28 (m, 3H), 4.03 (m, 2H), 3.7 (m, 4H), 3.45–3.40 (m, 2H), 1.13 (t, ^3J = 7, 3H).

^{13}C NMR ($CDCl_3$): δ 169.8, 138.3, 138.1, 128.1, 127.9, 127.4, 99.2, 81.3, 79.7, 78.5, 73.1, 73.0, 71.2, 70.9, 69.0, 60.1, 14.0.

Anal calc for $(C_{24}H_{28}O_7)_7$ (2 999.2): C, 67.27; H, 6.59. Found: C, 67.03; H, 6.61.

TLC CH_2Cl_2/acetone 95:5; R_f = 0.5.

Cyclohepta (1→4)-(3-O-α-D-glucopyranosyl) ethyl glycolate **9** *[$3^A,3^B,3^C,3^D,3^E,3^F,3^G$-hepta-O-(ethyl glycolate)-β-cyclodextrin]*

A suspension of Pd/C (Aldrich E101NE/W; 640 mg), **8** (350 mg; 0.12 mmol) in ethanol 95% (35 mL) and CH_2Cl_2 (15 mL) was stirred for 24 h under a hydrogen atmosphere at room temperature. After filtration, the solution was decolorized on active charcoal and then evaporated to yield **9** as a colorless resin (216 mg; 86%).

^{1}H NMR (CD_3OD): δ 5.02 (d, ^3J = 3, 1H), 4.82 and 4.61 (AB, ^2J = 23, 2H), 4.21 (m, 2H), 4.1–3.7 (m, 4H), 3.56 (dd, ^2J = 9, ^3J = 3, 1H), 1.28 (t, ^3J = 7, 3H).

^{13}C NMR (CD_3OD): δ 173.0, 102.8, 82.9, 80.1, 74.9, 73.6, 70.1, 62.0 (2), 14,0.

Anal calc for $[(C_{10}H_{16}O_7)_7 \cdot 7\ H_2O]$ (1 863.7): C, 45.09; H, 6.82. Found: C, 44.86; H, 6.50.

MS (FAB^+): m/z 1 759 [M + Na^+] (calc: 1 761).

Cyclohepta (1→4)-(3-O-α-D-glucopyranosyl) glycolic acid sodium salt **10** *[$3^A,3^B,3^C,3^D,3^E,3^F,3^G$-hepta-O-(glycolic acid)-β-cyclodextrin]*

A mixture of **9** (60 mg; 0.032 mmol), 1 M NaOH (380 μL; 0.38 mmol, 1.5 equiv) and MeOH (10 mL) was stirred at room temperature for 1 h. A white precipitate formed. Water was added and the aqueous solution was extracted with CH_2Cl_2. The aqueous phase was lyophilized to yield

a mixture of NaOH and the sodium salt of **10** (60 mg; estimated yield: quantitative).

^{1}H NMR (D_2O): δ 5.01 (bs, 1H), 4.54 (bs, 2H), 4.18 (bs, 2H), 3.9–3.5 (m, 4H).

^{13}C NMR (D_2O + CD_3OD): δ 181.0, 102.7, 84.4, 80.6, 74.6, 74.2, 66.4, 63.4.

Cyclohepta 6-O-(1→4)-(2,3-di-O-benzyl-α-D-glucopyranosyl) tert-*butyl glycolate* **12** *[2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G-tetradeca-O-benzyl-6^A,6^B,6^C,6^D,6^E,6^F,6^G-hepta-O-(*tert*-butyl glycolate) β-cyclodextrin]*

NaH 80% (16 mg; 0.5 mmol, 2 equiv) was added at 0°C to a solution of **11** (100 mg; 0.042 mmol) in freshly distilled DMF on CaH_2 (5 mL). After stirring for 1 h at 0°C, *tert*-butyl bromoacetate (156 mg, 118 μL; 0.80 mmol, 2.5 equiv) was added. The solution was stirred for 1 h at 0°C and then overnight at room temperature. After quenching with water, the mixture was extracted with ethylacetate. After washing with water, the organic phase was dried over Na_2SO_4 and concentrated. The crude residue was treated again as above. Preparative TLC (SiO_2; elution: CH_2Cl_2/acetone 97:3) provided **12** as a colorless resin (23 mg; 17%).

^{1}H NMR ($CDCl_3$): δ 7.19–7.00 (m, 10H), 5.26 (d, ^3J = 3, 1H), 5.03 and 4.74 (AB, ^2J = 11, 2H), 4.47 (broad s, 2H), 4.1–3.8 (m, 7 H), 3.5 (m, 1H), 1.45 (s, 9H).

^{13}C NMR ($CDCl_3$): δ 169.2, 139.4, 138.4, 128.0, 127.8, 127.2, 126.8, 98.4, 80.8, 78.8, 75.2, 72.5, 71.6, 70.5, 69.3, 68.6, 29.4, 28.2.

MS (FAB$^+$): m/z 3 203 [M + Li^+] (calc: 3 202).

TLC (CH_2Cl_2/acetone 95:5); R_f = 0.6.

6^A,6^B,6^C,6^D,6^E,6^F,6^G-Heptabromo-6^A,6^B,6^C,6^D,6^E,6^F,6^G-heptadeoxy-β-cyclodextrin **13** *[42]*

Bromine (4.7 mL, 91.7 mmol) was carefully added over 15 min to a solution of triphenylphosphine (24.3 g, 92.7 mmol) in dry DMF (90 mL) (evolution of heat; the solution reached approximately 50°C) [43]. β-Cyclodextrin **1** (5.4 g; 4.76 mmol) was then added and the resulting solution was stirred for 15 h at 80°C. After cooling and evaporation of about 40 mL DMF under reduced pressure, sodium methoxide in methanol (3 M, 30 mL) was added to the reaction vessel with cooling until pH 8–9 and the mixture was stirred for 30 min. The product was precipitated with ice water then filtered, washed with water (500 mL) and then with CH_2Cl_2 (500 mL). The precipitate was dissolved into a small amount of DMF and precipitated again by addition of methanol. The precipitate was filtered off and dried under high vacuum (6.47 g, 86%).

Cyclohepta (1→4)-(6-S-α-D-glucopyranosyl) methyl glycolate **14** *[6^A,6^B,6^C,6^D,6^E,6^F,6^G-hepta(methyl 2-thioglycolate ester)-6^A,6^B,6^C,6^D,6^E,6^F,6^G-heptadeoxy-β-cyclodextrin]*

Dry **13** (1.00 g, 0.63 mmol) in DMPU (4 mL) was added under argon to a suspension of cesium carbonate (2.00 g, 6.1 mmol) and methyl thioglycolate ester (0.6 mL; 6.7 mmol; 1.5 equiv). After stirring for 12 h at 60°C, **14** was obtained after precipitation in water as a light yellow solid and dried under high vacuum (0.63 g; 57%).

^{1}H NMR (pyr-d_5): δ 5.37 (d, ^3J = 5.2, 1H, H1), 4.5 (m, 2H, H3 and H5), 4.0 (m, 2H, H4 and H2), 3.68 (m, 2H, CH_2), 3.58 (s, 3H, CH_3), 3.36 (dd, ^2J = 14, 1H, H6a), 2.85 (dd, ^2J = 14, 1H, H6b).

^{13}C NMR (pyr-d_5): δ 170.4, 102.7, 85.1, 73.3, 72.9, 72.3, 51.3, 34.2, 33.7.

Anal calc for $[(C_9H_{14}O_6S)_7 \cdot 3\ H_2O]$: C, 41.94; H, 5.75; S, 12.44. Found: C, 41.88; H, 5.51; S, 11.69.

MS (FAB$^+$): m/z 1 773 [M + Na^+] (calc: 1 775); 1 884 [M + Cs]$^+$ (calc: 1 885).

Cyclohepta (1→4)-(6-S-α-D-glucopyranosyl) glycolic acid sodium salt **15** *[6^A,6^B,6^C,6^D,6^E,6^F,6^G-hepta (2-thioglycolic sodium salt)-6^A,6^B,6^C,6^D,6^E,6^F,6^G-heptadeoxy-β-cyclodextrin]*

Compound **14** (0.63 g; 0.37 mmol) was treated with aq NaOH (1 M; 3 mL) for 12 h at room temperature. After neutralization by 1 M HCl to neutral pH, inorganic sodium salts were removed by ultrafiltration (membrane YCO, 5 500 MW cut-off) and **15** was lyophilized (0.59 g; 99%).

^{1}H NMR (D_2O; TMS as internal reference): δ 5.10 (d, ^3J = 4.4, 1H, H1), 3.91 (m, 1H, H5), 3,81 (dd, ^3J = 8.75, 1H, H3), 3.7–3.5 (m, 2H, H2 and H4), 3.3 (broad s, 2H, CH_2), 3.2–3.0 (m, 1H, H6a), 2.9–2.7 (m, 1H, H6b).

^{13}C NMR (D_2O; TMS as internal reference): δ 179.9 (CO), 103.7 (C1), 85.8 (C4), 74.5, 73.9, 73.8 (C2, 3, 5) 40.3 (CH_2), 35.3 (C6).

Anal calc for $[(C_8H_{11}O_6SNa)_6, (C_8H_{12}O_6S)]$, 4 NaCl, 15 H_2O]: C, 29.31; H, 4.73; Na, 10.02; Cl, 6.19. Found: C, 29.39; H, 4.47; Na, 9.91; Cl, 6.29.

MS (FAB$^+$): m/z: 1 653 [M + H]$^+$ (calculated for acidic form: 1 655).

2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G-Tetradeca-O-acetyl-6^A,6^B,6^C,6^D,6^E,6^F,6^G-heptachloro-6^A,6^B,6^C,6^D,6^E,6^F,6^G-heptadeoxy-β-cyclodextrin **16** *[39]*

A mixture of **2β** (1.26 g, 1 mmol), dry pyridine (20 mL) and acetic anhydride (12.5 mL) was stirred for 30 h at room temperature. The solution was poured onto crushed ice and the resulting suspension was filtered. The precipitate was dissolved in ethyl acetate. The organic phase was washed with 0.5 M H_2SO_4, then water and dried over Na_2SO_4. After evaporation, the residue was purified by column chromatography (SiO_2; elution: CH_2Cl_2/MeOH 97.5:2.5) to yield **16** as white crystals after recrystallization from EtOH 95% (1.56 g; 84%).

Mp 180–185°C (lit 180–182°C [39]).

2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G-Tetradeca-O-acetyl-6^A,6^B,6^C,6^D,6^E,6^F,6^G-heptaiodo-6^A,6^B,6^C,6^D,6^E,6^F,6^G-heptadeoxy-β-cyclodextrin **17** *[39, 50]*

A suspension of NaI (5.25 g; 35 mmol, 10 equiv), **16** (925 mg; 0.49 mmol) in butanone (25 mL) was refluxed for 48 h. After partial evaporation of the solvent, addition of water and extraction with ethyl acetate, the organic phase was washed with water, and then dried over Na_2SO_4 and concentrated. The crude residue was dissolved in MeOH and precipitated in water to yield **17** after filtration as a white solid (925 mg; 75%).

Mp 180–184°C (lit 176–180°C [39], 172–177°C [50]).

Cyclohepta (1→4)-(2,3-di-O-acetyl-6-S-α-D-gluco-pyranosyl) ethyl glycolate **18**
[2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G-tetradeca-O-acetate-6^A,6^B,6^C,6^D,6^E,6^F,6^G-hepta (ethyl 2-thioglycolate ester)-6^A,6^B,6^C,6^D,6^E,6^F,6^G-heptadeoxy-β-cyclodextrin]

NaH (80% suspension in mineral oil; 52 mg, 1.7 mmol) was added into a solution of ethyl thioglycolate (206 μL, 226 mg; 1.9 mmol) in dry DMF (10 mL) at 0°C. After stirring for 1 h at 0°C, **17** (200 mg; 0.08 mmol) was added and the solution was stirred for 24 h at 75°C. After cooling and evaporation of the solvent, the residue was dissolved in ethylacetate, the organic phase was washed with water, saturated brine and dried over Na_2SO_4. After evaporation, the residue was purified by column chromatography and preparative TLC (elution: AcOEt/MeOH 98:2) to yield **18** as a colorless resin (123 mg; 63%).

^{1}H NMR ($CDCl_3$): δ 5.21 (d, ^3J = 10, ^3J = 8, 1H), 5.02 (d, ^3J = 4, 1H), 4.71 (dd, ^2J = 10, ^3J = 4, 1H), 4.21–4.06 (m, 3H), 3.82 (dd, ^3J = 9, 1H), 3.32 (AB, 2H), 3.2–2.9 (m, 2H), 2.02 and 1.98 (2s, 6H), 1.25 (t, ^3J = 7 Hz, 3H).

^{13}C NMR ($CDCl_3$): δ 170.3, 170.0, 169.0, 96.4, 78.4, 71.5, 70.6, 70.3, 61.2, 35.2, 34.2, 20.5, 14.0.

Anal calc for $(C_{14}H_{20}O_8S)_7$: C, 48.27; H, 5.79. Found : C, 47.86; H, 5.65.

TLC: SiO_2; elution: AcOEt/MeOH 98:2, R_f = 0.7.

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