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# Synthesis of C6$^A$-to-C6$^A$ and C3$^A$-to-C3$^A$ diamide linked γ-cyclodextrin dimers

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ABSTRACT

The syntheses of three new diamide-linked γ-cyclodextrin dimers joined by substitution at either a glucopyranose C6$^A$ or C3$^A$ carbon are reported. The syntheses involve the reaction of either C6$^A$ or C3$^A$ amino-substituted γ-cyclodextrin with bis(4-nitrophenyl)succinate to form succinamide linked γ-cyclodextrin dimers or reaction of C6$^A$ azide-substituted γ-cyclodextrin with carbon dioxide to form a urea linked γ-cyclodextrin dimer.



## 1. Introduction

Host–guest complexation by native and modified cyclodextrin (CD) hosts often alters the solubility, chemical reactivity and other properties of the ground and excited states of the guest species and is an area of substantial supramolecular chemical interest.[1,2] Prominent in such studies are linked βCD dimers in which the linker is substituted onto two βCD at either the C6$^A$ or C3$^A$ carbon of a glucopyranose unit.[3–9] The nature of the linker can significantly influence the stabilities of the host–guest complexes formed by the linked βCD dimer. In some cases their stability constants are substantially greater than those expected statistically on the basis of native βCD complex, which is evidence for cooperativity between the linked βCD in complexing the guest species.[3–6,9] While guests such as adamantane-1-carboxylate[3] and 6-(4-toluidino)naphthalene-2-sulfonate[6] fit the annuli of βCD and linked βCD dimers closely, the γCD annulus better accommodates larger guest exemplified by fullerenes[10] and porphyrins.[11] In principle, understanding of the host–guest complexation of these and other large guests may be enhanced through studies of their complexation by linked γCD dimers. Accordingly, we have synthesised two linked γCD dimers linked through either two C3$^A$ or two C6$^A$ by succinamide and a third γCD dimer linked through two C6$^A$ by urea (Fig. 1) which to the best of our knowledge are the first reported examples of diamide-linked γCD dimers.

## 2. Results and discussion

The modification of native CDs may be achieved through substitution of either a OH$^2$, OH$^3$ or OH$^6$ (Fig. 1) but their similarity and number (6, 7 and 8 of each in αCD, βCD and γCD, respectively) renders selective modification challenging.[12] The OH$^6$ are the most basic and usually the most nucleophilic, the OH$^2$ are the most acidic and the OH$^3$ are sterically the most difficult to access. Substitution of OH$^6$ in βCD is usually most readily achieved through 6$^A$-*O*-(4-methylbenzenesulfonyl)-β-cyclodextrin,[13] while substitution of OH$^2$ and OH$^3$ is often achieved through 2$^A$-*O*-(4-methylbenzenesulfonyl)-β-cyclodextrin.[14] However, using the literature reaction of βCD and 4-toluenesulfonylchloride in aqueous solution[13] for γCD results in polysubstitution at C6 probably because of the larger γCD annulus.[15] Larger arenesulfonyl chlorides have been used to achieve mono C6$^A$ substitution,[16] but the yields are low and the cost of the arenesulfonyl chlorides is greater than that of 4-toluenesulfonylchloride.

A modification of the method of Murakami[14] for the synthesis of 2$^A$-*O*-(4-methylbenzenesulfonyl)-β-cyclodextrin was selected as the simplest and most economical simultaneous route to 2$^A$- and 6$^A$-*O*-(4-methylbenzenesulfonyl)-γ-cyclodextrin although the yields are modest. The reaction of γCD and 4-toluenesulfonylchloride in dimethylformamide (DMF) in the presence of dibutyltin oxide gave a mixture of 2$^A$- and 6$^A$-*O*-(4-methylbenzenesulfonyl)-γ-cyclodextrin (2γCDTs and 6γCDTs), which were readily separated on a Diaion HP-20 column in 5–10% yields of each.

6$^A$-Azido-6$^A$-deoxy-γ-cyclodextrin, (6γCDN$_3$) was prepared as described in the literature,[16] through reaction of 6γCDTs with sodium azide in DMF, and 66γCD$_2$ur was prepared in 53% yield by reacting 6γCDN$_3$ in $CO_2$ saturated DMF in the presence of

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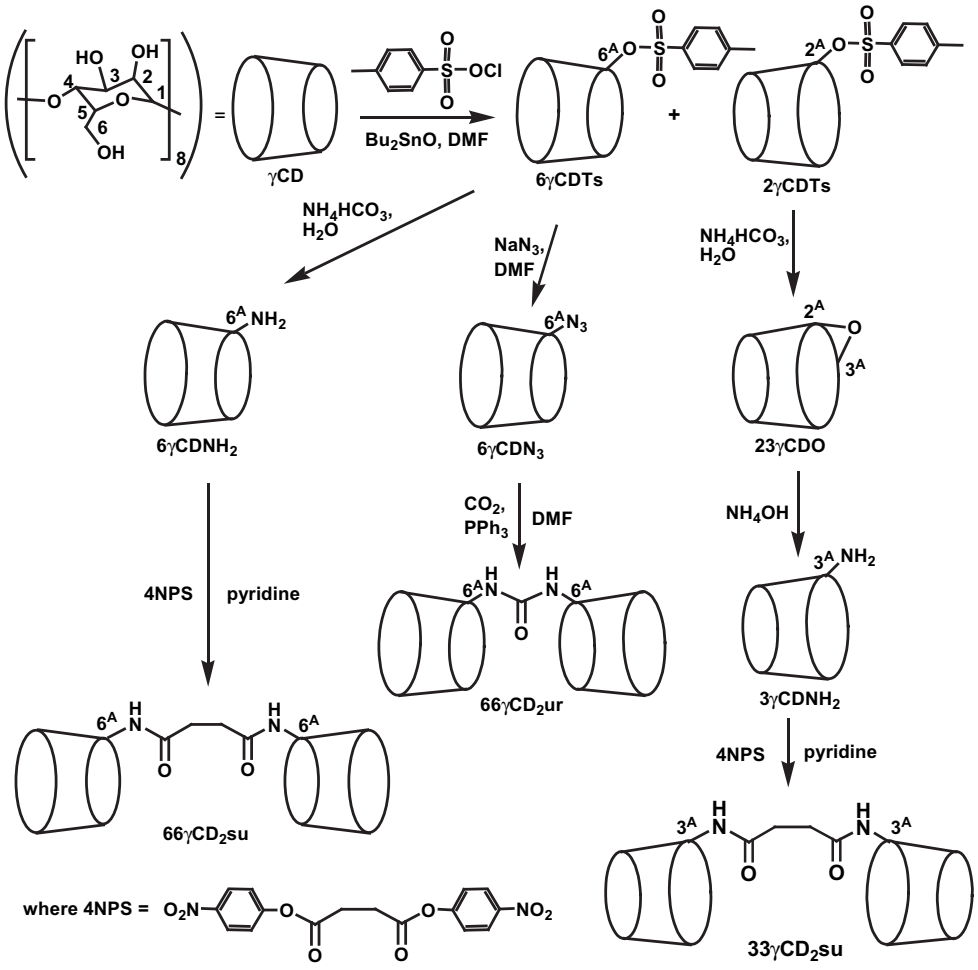


**Figure 1.** Synthetic routes from γCD to the diamide-linked γCD dimers: 66γCD$_2$ur, 33γCD$_2$su and 66γCD$_2$su.

triphenylphosphine. The preparation of 33γCD$_2$ur was not attempted as previous studies show that linking C3$^A$ to C3$^A$ of two CDs through the short urea linker is severely inhibited by steric crowding of the adjacent CDs and the inversion at C3$^A$ in both CDs.[6]

Bis-4-nitrophenyl succinate[6,17] required in the preparation of 33γCD$_2$su and 66γCD$_2$su was synthesised by reaction of succinyl chloride with 4-nitrophenol in a similar manner to that described in the literature.

The first step in the synthesis of previously unreported (2$^A$S,3$^A$S)-3$^A$-amino-3$^A$-deoxy-γ-cyclodextrin (3γCDNH$_2$) was achieved through reaction of 2γCDTs with aqueous ammonium bicarbonate to give 2$^A$,3$^A$-manno-epoxide-γ-cyclodextrin (23γCDO), which was isolated through chromatography on Diaion HP-20 and BioRex 70 (H$^+$) in 78.6% yield. The product was then reacted with ammonium hydroxide (25%, 60 cm$^3$) at 60 °C for 4 h to give 3γCDNH$_2$ after chromatographic separation on BioRex 70 (H$^+$) in 56.7% yield. $^{13}$C and $^1$H NMR spectra indicate that the C2$^A$ and C3$^A$ carbons of a glycopyranose unit in γCD moiety are inverted to form an altropyranose ring during the synthesis, as is also the case for 3βCDNH$_2$.[18,19] The new 6$^A$-amino-6$^A$-deoxy-γ-cyclodextrin (6γCDNH$_2$) was converted from 6γCDTs by treatment with ammonium hydroxide over five days and was isolated through chromatography on BioRex 70 (H$^+$) in 18% yield.

The 33γCD$_2$su and 66γCD$_2$su linked γCD dimers were synthesised through a general method with yields of 75.7 and 91.6%, respectively. The succinate diester was stirred with 2.5 equiv of either 3γCDNH$_2$ or 6γCDNH$_2$ in pyridine for 48 h at room temperature to give 33γCD$_2$su and 66γCD$_2$su, which were separated on Biorex 70 (H$^+$).

## 3. Conclusion

The preparative methods described herein for 33γCD$_2$su, 66γCD$_2$su and 66γCD$_2$ur are both facile and economic such that multigram quantities may be prepared. The preparative methodology for the first two are potentially applicable to a range linked γ-cyclodextrin dimers of varying diamide linker length. The products are chemically stable with no degradation observed in samples stored at −5 to 0 °C for several years. In aqueous solution the diamide linkers are stable over a wide pH range.

In preliminary complexation studies 600 MHz 2D $^1$H NOESY NMR spectra of $10^{-3}$ mol dm$^{-3}$ sodium 6-(4-toluidino)naphthalenesulfonate, NaTNS, and either equimolar 66γCD$_2$ur, 33γCD$_2$su, or 66γCD$_2$su in D$_2$O at pD 7.0 and 25 °C reveal strong cross-peaks arising from dipolar interactions between the H[3,5,6] protons of the linked γCD annuli and the aromatic protons of TNS$^-$ consistent with complexation of this guest by the diamide-linked γCD dimers. Quantitative studies of the complexation the substantially larger porphyrins and also of complexation in hydrophobe substituted poly(acrylate)s[20] are in progress.

## 4. Experimental

### 4.1. General

Proton and $^{13}$C NMR spectra were recorded with a Varian Gemini ACP-300 spectrometer operating at 300.145 MHz ($^1$H) or 75.4 MHz ($^{13}$C). 2D $^1$H NOESY NMR spectra were recorded with

a Varian-Inova 600 spectrometer operating at 599.957 MHz using a standard pulse sequence with a mixing time of 0.3 s. Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 $F_{254}$ on aluminium-backed sheets. For analysis of cyclodextrin derivatives, plates were developed with 7:7:5:4 v/v ethyl acetate/propan-2-ol/ammonium hydroxide/water and the compounds were visualised by drying the plate and then dipping it into a 1% sulfuric acid in ethanol solution and heating it with a heat-gun. To visualise amino bearing cyclodextrins plates were dried prior to dipping into 0.5% ninhydrin in ethanol and heated with a heat-gun, before dipping in 1% sulfuric acid in ethanol. For the preparations described below $R_c$ represents the $R_f$ of a substituted cyclodextrin relative to the $R_f$ of the parent cyclodextrin, $R_f$(γCD)=0.42. Melting points were measured using a Kofler hot-stage apparatus viewed through a Reichert microscope and are uncorrected. As cyclodextrin derivatives decompose without melting above 180 °C, melting points were not determined. Elemental analyses were performed by the Microanalytical Service of the Chemistry Department, University of Otago, Dunedin, New Zealand. Mass spectrometry was carried on a Micromass Q-TOF2 instrument. Samples were dissolved in HPLC grade methanol, Milli-Q water or a mixture of the two at a concentration of 0.5 mg $cm^{-3}$.

Bio-Rex 70 resin was purchased from Bio-Rad Laboratories, Inc, CA and converted to the acid form using 3 mol $dm^{-3}$ hydrochloric acid. γ-Cyclodextrin (Nihon Shokuhin Kako Co.), *N*,*N*′-dicyclohexylcarbodiimide (DCC) (Merck), 4-toluenesulfonylchloride (Aldrich) and 4-nitrophenol (BDH) were used without further purification. All other reagents and solvents were of good quality reagent grade. $6^A$-Azido-$6^A$-deoxy-γ-cyclodextrin[16] and bis-4-nitrophenyl succinate[6,17] were prepared by literature methods.

## 4.2. Synthesis

*4.2.1. $2^A$-O-(4-Methylbenzenesulfonyl)-γ-cyclodextrin, 2γCDTs and its $6^A$- analogue, 6γCDTs.* γ-Cyclodextrin (51.9 g, 40.0 mmol) was added to anhydrous DMF (150 $cm^3$) and the mixture was stirred for two hours at 0 °C under dry nitrogen until dissolution was complete. After heating to 100 °C, dibutyltin oxide (25.1 g, 100.9 mmol) was added and stirred for another 2 h. The mixture was then cooled to 0 °C, triethylamine (12.2 g, 120.6 mmol) was added, followed by dropwise addition of 4-toluenesulfonylchloride (20 g, 105 mmol) in DMF (50 $cm^3$). The mixture was stirred for 2 h before another portion of 4-toluenesulfonylchloride (9.7 g, 50.9 mmol) in DMF (20 $cm^3$) was added dropwise. The resultant solution was stirred for a further 10 h at room temperature and then concentrated to a yellow syrup. This was added to 2 $dm^3$ of vigorously stirred acetone and stirring was continued for 30 min. The precipitate formed was collected by filtration, washed with acetone and diethylether and dried under vacuum to give 62 g of crude product, which was recrystallised from ca. 200 ml water. The precipitate was collected and dried under vacuum to give ca. 9 g of crude 6γCDTs, while the filtrate was evaporated to dryness to give ca. 47 g of crude 2γCDTs.

The crude 2γCDTs was dissolved in water (1 $dm^3$) and loaded onto a Diaion HP-20 column (5×30 cm). After flushing with ca. 3 $dm^3$ of water, followed by 10–15% aqueous methanol solvent gradient elution of unreacted γCD, 2γCDTs was eluted with 20–25% aqueous methanol (ca. 400 $cm^3$ fractions). The fractions containing the product were combined, the methanol was removed and the product was dried under vacuum to give the 2γCDTs as a white powder. Yield: 4.37 g (7.5%). TLC: $R_c$=1.67. $^1$H NMR $\delta_H$ (DMSO-$d_6$): 7.83, 7.47 (ABq, *J*=8.2 Hz, 4H, ArH), 5.91–5.69 (m, 15H, $OH^2$, $OH^3$), 4.88 (s, 8H, H1), 4.30–3.30 (m, 56H, H2-6, $OH^6$), 2.41 (s, 3H, Ar–$CH_3$). $^{13}$C NMR, $\delta_C$ (DMSO-$d_6$): 133.4, 129.9, 128.2, 125.7 (Ar–C); 101.9–101.1 ($C1^{B-H}$), 97.3 ($C1^A$); 82.3–78.2 (C4); 73.1–69.2 (C2, C3, C5); 60.2 (C6); 40.9–38.4 (DMSO); 21.3 (Ar–$CH_3$).

The crude 6γCDTs was dissolved in water (500–700 $cm^3$) and loaded onto a Diaion HP-20 column (3×25 cm). After flushing with water (ca. 1 $dm^3$), followed by 10–20% aqueous methanol solvent gradient elution of unreacted γCD, 6γCDTs was eluted with 30–40% aqueous methanol (ca. 250 $cm^3$ fractions). The fractions containing the product were combined and evaporated to dryness under vacuum to give 6γCDTs as a white powder. Yield: 2.47 g (4.25%). TLC: $R_c$=1.40. $^1$H NMR, $\delta_H$ (DMSO-$d_6$): 7.78, 7.46 (ABq, *J*=8.3 Hz, 4H, ArH), 6.05–5.35 (m, 16H, $OH^2$, $OH^3$), 5.09–4.81 (m, 8H, H1), 4.31–3.20 (m, 55H, H2-6, $OH^6$), 2.42 (s, 3H, Ar–$CH_3$). $^{13}$C NMR, $\delta_C$ (DMSO-$d_6$): 133.2, 130.7, 128.8, 126.2 (Ar–C); 102.9–101.8 ($C1^A$); 81.6–80.8 (C4); 73.6–69.7 (C2, C3, C5); 60.7 (C6); 40.9–38.4 (DMSO); 21.8 (Ar–$CH_3$).

*4.2.2. $2^A$,$3^A$-Manno-epoxide-γ-cyclodextrin, 23γCDO.* A solution of $2^A$-*O*-(4-methylbenzenesulfonyl)-γ-cyclodextrin (4 g, 2.76 mmol) in aqueous ammonium bicarbonate (10%, 125 $cm^3$) was stirred at 60 °C for 3 h. The solvent was removed under vacuum and the residue was redissolved in water, followed by evaporation to dryness (this procedure was repeated three times). This crude product was dissolved in water (20 $cm^3$) and added drop-wise to vigorously stirred acetone (500 $cm^3$). The precipitate formed was collected by filtration and washed with acetone and diethylether to give 4 g of crude product. The crude material was dissolved in water (125 $cm^3$) and loaded onto a Diaion HP-20 column (3×20 cm). The column was washed with water (1 $dm^3$) and 10% aqueous methanol and the washings were evaporated under vacuum to give the product as a white powder, which contained traces of $2\gamma CDNH_2$ by-product. The pure $2^A$,$3^A$-manno-epoxide was run through a column (4.5×4.5 cm) of BioRex 70 ($H^+$), 100–200 mesh (BioRad) to remove $2\gamma CDNH_2$. The fractions containing the product were combined and evaporated to dryness under vacuum to give as a white powder. Yield: 2.77 g (78.6%). TLC: $R_c$=1.15. $^1$H NMR, $\delta_H$ ($D_2O$): 5.27 (s, 1H, $H1^A$-epoxide), 5.13–5.07 (m, 7H, H1), 3.95–3.59 (m, 47H, H2-6), 3.49 (d, 1H, $H2^A$-epoxide). $^{13}$C NMR, $\delta_C$($D_2O$): 104.5–103.7 (C1), 83.7–83.0 (C4), 75.7–72.1 ($C2^{B-H}$, $C3^{B-H}$, C5), 63.6 ($C6^{B-H}$), 62.9 ($C6^A$), 57.1 ($C2^A$), 52.2 ($C3^A$).

*4.2.3. $3^A$-Amino-$3^A$-deoxy-($2^A$S,$3^A$S)-γ-cyclodextrin, $3\gamma CDNH_2$.* $2^A$,$3^A$-Mannoepoxide-γ-cyclodextrin (2.6 g, 2.03 mmol) was dissolved in aqueous ammonium hydroxide (25%, 60 $cm^3$) and the solution was stirred at 60 °C for 4 h. The mixture was then evaporated to dryness and the residual was dissolved in aqueous ammonium hydroxide (28%, 20 $cm^3$) and added to acetone (500 $cm^3$). The precipitate was collected, washed with acetone and diethylether and dried under vacuum to obtain 2.74 g of the crude product. This was dissolved in water (20 $cm^3$) and loaded onto a column (4.5×4.5 cm) of BioRex 70 ($H^+$), 100–200 mesh (BioRad). After flushing with water (ca. 500 $cm^3$), the $3\gamma CDNH_2$ product was eluted with 1 mol $dm^{-3}$ aqueous ammonium hydroxide (ca. 100 $cm^3$ fractions). Fractions containing the product were combined and evaporated to dryness under vacuum (removal of excess ammonia was achieved by dissolving the residue in water and evaporating to dryness three times) to afford $3\gamma CDNH_2$ as a white powder. Yield: 1.49 g (56.7%). TLC: $R_c$=0.76. $^1$H NMR, $\delta_H$ ($D_2O$): 5.22 (d, 2H, $H1^A$), 5.16–4.93 (m, 6H, H1), 4.20 (m, 1H, $H2^A$), 4.00–3.56 (m, 46H, H2-6), 3.10 (d, 1H, $H3^A$). $^{13}$C NMR, $\delta_C$ ($D_2O$): 103.1–99.7 (C1), 80.9–80.2 (C4), 79.2–71.1 (C2, $C3^{B-H}$, C5), 60.8–59.8 (C6), 52.2 ($C3^A$).

*4.2.4. $6^A$-Amino-$6^A$-deoxy-cyclodextrin, $6\gamma CDNH_2$.* $6^A$-*O*-(4-Methylbenzenesulfonyl)-γ-cyclodextrin, 6γCDTs (3.4 g, 2.3 mmol) was dissolved in ammonium hydroxide (28%, 250 $cm^3$) at 0 °C. The reaction vessel was closed and left in the dark with occasional stirring for five days. The ammonium hydroxide was removed under reduced pressure, after which water was added (100 $cm^3$) and removed under reduced pressure. The remaining solid was dissolved in ammonium hydroxide (28%, 20 $cm^3$) and the solution added

drop-wise to vigorously stirring acetone (450 $cm^3$) and stirred for 30 min. The resulting precipitate was dried under vacuum to give crude 6γCDNH$_2$ as a cream powder. This was dissolved in water (20 $cm^3$) and loaded onto a BioRex 70 ($H^+$) column. The column was washed with water (400 $cm^3$), and the title compound was eluted with 0.05–0.1 mol $dm^{-3}$ aqueous ammonium carbonate (4×100 $cm^3$ fractions). The 6γCDNH$_2$ containing fractions were evaporated to dryness under reduced pressure, and the residue freeze dried to give 6γCDNH$_2$ as a white solid. Yield: 0.55 g (18%). TLC: $R_c$=0.90. $^1$H NMR, δ($D_2O$) 5.37 (s, 2H, H1$^A$), 5.10 (m, 14H, H1$^{B-H}$), 3.93–3.58 (m, 48H, H2-6). $^{13}$C NMR, δ($D_2O$): 103.72–101.77 (C1); 80.50–79.0 (C4); 73.89–71.88 (C2, C3, C5); 60.33 (C6); 41.05 (C6$^A$).

*4.2.5. N,N′-Bis(6$^A$-deoxy-γ-cyclodextrin-6$^A$-yl)urea, 66γCD$_2$ur.* 6$^A$-Azido-6$^A$-deoxy-γ-cyclodextrin (1 g, 0.75 mmol) was dissolved in DMF (20 $cm^3$) and the solution was saturated with dry $CO_2$ and stirred at room temperature for 15 min. Triphenylphosphine (297 mg, 1.134 mmol) in DMF (5 $cm^3$) was added dropwise and the reaction mixture was saturated with $CO_2$ and stirred for 27 h after which it was added drop-wise to vigorously stirred acetone. The resulting precipitate was collected by centrifugation, washed acetone and diethylether, dried under vacuum and freeze dried. Yield: 520 mg (53%). TLC: $R_c$=0.40. $^1$H NMR, $\delta_H$($D_2O$): 5.09–5.07 (m, 16H, H$^1$); 3.9–3.3 (m, 96H, H$^2$-H$^6$). $^{13}$C NMR: $\delta_C$($D_2O$) 163.1 (amide C═O), 104.5 (C1), 85.5–83.0 (C4), 76.4–73 (C2, C3, C5), 63.0 (C6$^{B-H}$), 43.2 (C6$^A$). Mass spectrum *m*/*z*: 1332.8 $(M+Na)^{2+}$. Elemental analysis: $C_{97}H_{160}N_2O_{79}\cdot 21H_2O$: C, 38.8; H, 6.7; N, 1.0. Found: C, 38.6; H, 6.4; N, 1.2.

### 4.3. General procedure for the preparation of the succinamide linked γCD dimers

Either (2$^A$S,3$^A$S)-3$^A$-amino-3$^A$-deoxy-γ-cyclodextrin or 6$^A$-amino-6$^A$-deoxy-γ-cyclodextrin (~1 mmol) was dissolved in pyridine (20 $cm^3$) and stirred at room temperature for 15 min. Bis-4-nitrophenyl succinate (0.4 equiv) was added to this solution in two or more portions over a period of 1 h. The reaction mixture was then stirred for 48 h at room temperature before being added dropwise to diethylether (200 $cm^3$) with vigorous stirring. The resultant precipitate was collected by centrifugation, washed with acetone and diethylether and dried under vacuum. The product was dissolved in $H_2O$ and run down a BioRex 70 ($H^+$) column to remove either excess (2$^A$S,3$^A$S)-3$^A$-amino-3$^A$-deoxy-γ-cyclodextrin or 6$^A$-amino-6$^A$-deoxy-γ-cyclodextrin. The white solid products were obtained by freeze drying followed by further drying over phosphorous pentoxide.

*4.3.1. N,N′-Bis((2$^A$S,3$^A$S)-3$^A$-deoxy-γ-cyclodextrin-3$^A$-yl) succinamide, 33γCD$_2$su.* The title compound was prepared by treatment of the 3γCDNH$_2$ (1.39 g, 1.08 mmol) with bis(4-nitrophenyl) succinate (155 mg, 0.43 mmol). After the general work-up and purification procedure, the title compound was obtained as a white solid. Yield: 0.87 g (75.7%). TLC: $R_c$=0.60. $^1$H NMR, $\delta_H$ ($D_2O$): 5.39–4.94 (m, 16H, H1), 4.26–3.59 (m, 96H, H2-6), 2.6 (s, 4H, CH2). $^{13}$C NMR, $\delta_C$ ($D_2O$): 177.7 (C═O), 105.8, 104.2, 102.3 ($C_1$), 81.9, 82.7, 83.1 (C4), 72.3, 73.9, 74.4, 74.9, 74.9, 75.2, 75.6 (C2,3,5), 62.4, 62.9 (C6), 53.6 (C3$^A$), 33.6 ($CH_2$). Mass spectrum *m*/*z*: 1359.9 $(M+Na)^{2+}$. Elemental analysis: $C_{100}H_{164}N_2O_{80}\cdot 19H_2O$: C, 39.81; H, 6.75; N, 0.93. Found: C, 39.54; H, 6.39; N, 0.89.

*4.3.2. N,N′-Bis(6$^A$-deoxy-γ-cyclodextrin-6$^A$-yl) succinamide, 66γCD$_2$su.* The title compound was prepared by treatment of the 6γCDNH$_2$ (1.58 g, 1.21 mmol) with bis(4-nitrophenyl) succinate (176 mg, 0.49 mmol). After the general work-up and purification procedure, the title compound was obtained as a white solid. Yield: 1.2 g (91.6%). TLC: $R_c$=0.45. $^1$H NMR, $\delta_H$ ($D_2O$): 5.11 (m, 16H, H1), 3.42–3.93 (m, 96H, H2-H6), 2.59 (m, 4H, CH2). $^{13}$C NMR, $\delta_C$ ($D_2O$): 177.5 (C═O), 104.3 (C1), 85.7, 83.1 (C4), 75.6, 75.0, 74.4, 72.8 (C2,3,5), 62.9 (C6$^{B-H}$), 42.8 (C6$^A$), 33.7 ($CH_2$). Mass spectrum *m*/*z*: 1359.9 $(M+Na)^{2+}$. Elemental analysis: $C_{100}H_{164}N_2O_{80}\cdot 20H_2O$: C, 39.58; H, 6.78; N, 0.92. Found: C, 39.48; H, 6.40; N, 0.91.

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### Supplementary data

Supplementary 1D $^1$H and $^{13}$C NMR and 2D $^1$H NOESY NMR spectra may be found, in the online version, at doi:10.1016/j.tet.2010.02.005.

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