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Synthesis of water-soluble multidentate aminoalcohol β-cyclodextrin derivatives via epoxide opening

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ABSTRACT

New highly soluble β-aminoalcohol β-cyclodextrin (β-CD) derivatives have been synthesized via nucleophilic epoxide opening reactions with mono-6-amino mono-6-deoxy-permethyl-β-CD and mono-6-amino mono-6-deoxy-β-CD. The binding properties of the β-CD were enhanced by linking aminoalcohol subunits which caused its solubility to improve markedly. The reaction conditions were optimised using microwave irradiation giving moderate-to-good yields with a series of epoxides. A regioselective epoxide opening reaction was observed in the reaction with styrene oxide while the stereoselectivity was strictly dependent on substrate structure.

1. Introduction

Cyclodextrins (CDs) possess a well-studied ability to act as hosts for hydrophobic guests in water.[1] Due to their homochirality, CDs may be used as molecular receptors and constitute examples of supramolecular chemistry.[2] Chromatographic[3] and electrophoretic[4] methods as well as stereoselective reactions mediated by CDs exploit this peculiar property which has been widely explored by calorimetric, X-ray diffraction, NMR and computational studies.[5]

Because of the regularity of the β-CD ring, the substitution of one or more hydroxyl groups affects the annular asymmetry, increasing solubility and influencing its binding properties.

It has been observed that the substituents on the CD's wider side, exhibit different host properties than those on the narrower, primary hydroxyl side. Therefore the synthesis of monosubstituted CDs has become important over the years and complex procedures are generally required to obtain regioselectively substituted derivatives.[6] Monosubstituted derivatives have been used in the synthesis of dimers and oligomers.[7]

As has already been reported,[8] the solubility of β-CD can be markedly improved with the attachment of suitable moieties. Even a random and low degree of substitution with hydrophilic hydroxyethyl- or oligo(ethylene glycol)- groups disrupts the hydrogen bond molecular network and dramatically improves water solubility. This solubilising effect has been observed in the reaction of β-CD with propylene oxide and, as a consequence, 6-*O*(2-hydroxypropyl) β-CD showed higher solubility than the 2-*O* substituted derivative.[9]

The ring opening of epoxides by nucleophiles is one of the most versatile and well established reactions of all 'click chemistry' protocols. This reaction is typically carried out in the presence of a catalyst and a large excess of amines at elevated temperatures. For this reason, non-conventional techniques, besides the more classical procedures, have been used to promote the reaction.[10] The reaction of epoxides with amines affords β-aminoalcohols which are important intermediates for carbohydrate and nucleoside synthesis. When linked to β-CD, the β-aminoalcohol moiety can enhance the CD's binding property and favourably affects its solubility. These derivatives can efficiently form metal complexes with β-CD which can then be applied as supramolecular catalysts in regio- or stereoselective reactions.[11] These chemically reactive subunits interact with the bound guests making a complementary metal coordination effect. Furthermore, aminoalcohol derivatives of β-CD may be very attractive as powerful chiral selectors in capillary electrophoresis, as charged β-CDs they are endowed with a high resolution ability without interfering with the detection of analytes.[12]

To the best of the authors' knowledge, there are very few reports on the synthesis of β-CD aminoalcohols and, in these studies, they are usually obtained by displacement of the tosyl group from

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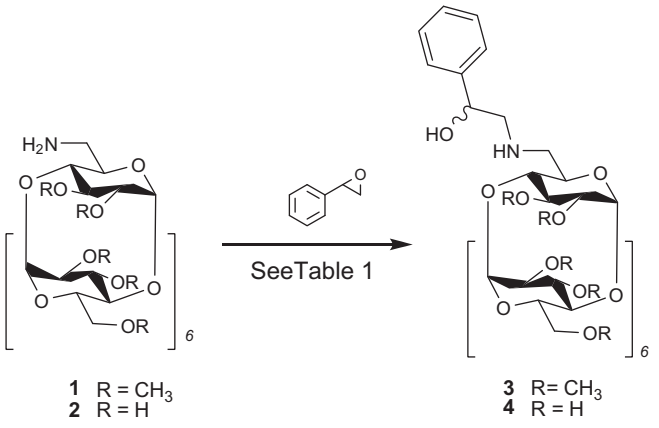
the 6-monodeoxy-6-mono-(*p*-tolylsulfonyl)-β-CD with an amino-alcohol.[10,12c] The direct etherification of β-CD with epoxides was reported by Pitha et al.[9] and confirmed by Wenz et al.[13] They demonstrated that in aqueous alkali and the presence of propylene oxide, β-CD is alkylated on the primary or the secondary face which results in a mixture of 2-*O*, 3-*O*, 6-*O* substituted CDs. After long reaction times, the desired product is isolated in very low yield. Furthermore native β-CD and derivatives have been used to initiate the polymerization with ethylene oxide, with the aim to obtain new biomimetic synthetic pores.[14] There are no publications that refer to the ring opening of epoxides by monoamino β-CD. In the light of the widespread applications of aminoalcohol β-CD derivatives, we have systematically studied the nucleophilic opening of epoxides with monoamino β-CD: a straightforward way of obtaining a range of multidentate and water-soluble aminoalcohol β-CD derivatives. In this paper the alkylation of monoamino β-CD has been achieved with various epoxides and with the aim of exploring the relationship between structure and reactivity. Mono-6-amino mono-6-deoxy-permethyl-β-CD was compared to the mono-6-amino mono-6-deoxy-β-CD in such a way as to evaluate the reactivity of the hydroxyl group and the influence of epoxide inclusion. The optimization of these reactions was studied under microwave (MW) irradiation. The regioselectivity of the attack was studied when the reaction was performed with styrene oxide, whereas cyclohexene oxide was chosen as a symmetrically substituted epoxide which could report on whether its inclusion into CD yields stereoselective effects.

Given the fact that most terminal epoxides are inexpensive and easily available, we also decided to apply this synthetic approach to the preparation of bifunctional molecules by reacting monoamino β-CD with diethylene glycol diglycidyl ether and octadiene dioxide.

2. Results and discussion

Mono-6-amino mono-6-deoxy-permethyl-β-CD was chosen as a preliminary β-CD substrate and was reacted with styrene oxide in a series of reactions carried out with the aim of optimising conditions (Scheme 1 and Table 1).

The reactions were performed at 60 °C or 85 °C in DMF under conventional heating or MW irradiation. The epoxide ratio was varied from 1 to 5 equiv and in some experiments LiBr was added. We monitored reaction conversion by TLC and the product was isolated by silica gel column chromatography. The optimised procedure was setup at 85 °C, under MW irradiation with 1 equiv of styrene oxide, the presence of LiBr points to the catalyst lack of



Scheme 1. Reaction of mono-6-amino mono-6-deoxy-permethyl-β-CD (**1**) and mono-6-amino mono-6-deoxy-β-CD (**2**) with styrene oxide.

Table 1
Assessment of alkylation of mono-6-amino mono-6-deoxy-permethyl-β-CD (**1**) and mono-6-amino mono-6-deoxy-β-CD (**2**) with styrene oxide

Entry	Reagent	Eq. Epoxide	Reaction condition, time	Yield[a,b] %
1	1	5	LiBr, DMF, 60 °C, 24 h	18
2	1	5	LiBr, DMF, 85 °C, 4 h, MW	35
3	1	1	LiBr, DMF, 60 °C, 24 h	18
4	1	1	LiBr, DMF, 85 °C, 24 h	38
5	1	1	LiBr, DMF, 85 °C, 4 h, MW	50
6	1	1	DMF, 85 °C, 4 h, MW	52
7	2	1	DMF, 85 °C, 4 h, MW	—
8	2	5	LiBr, DMF, 85 °C, 19 h	18
9	2	5	LiBr, DMF, 85 °C, 4 h, MW	19
10	2	5	DMF, 85 °C, 4 h, MW	32
11	2	5	H_2O, 85 °C, 4 h, MW	Traces

[a] All the products were characterized by ^{1}H NMR, 2D NMR (^{1}H–^{13}C HMQC, ^{1}H–^{1}H COSY), IR spectroscopy and mass spectrometry.
[b] Isolated yield obtained after flash chromatography.

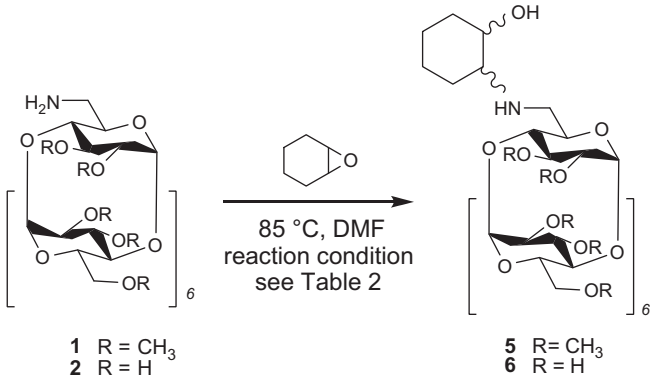
effect on the conversion and yield. As already observed in reported derivatizations of CDs,[7a,b,d,15] MW irradiation promotes the reaction cutting down reaction times from 24 to 4 h. As regards the regiochemistry of the ring opening, styrene oxide displays a general tendency for regioselective attack at the benzylic position when less nucleophilic aromatic amines are employed. In the presence of aliphatic amines a lower degree of regioselectivity is observed and the reaction is controlled by steric factors. The preferential reaction at the non-benzylic position is achieved only with a catalyst.[16] When permethyl β-CD was reacted with styrene oxide a single regioisomers was isolated. Using a combination of ^{1}H NMR and 2D NMR experiments (^{1}H–^{13}C HMQC, ^{1}H–^{1}H COSY), we were able to discover that the product that resulted from the nucleophilic attack at the less-hindered epoxide carbon was the obtained regioisomer. Likewise, the same reaction with mono-6-amino mono-6-deoxy-β-CD (Table 1, entries 7–10) selectively attacks the β position (**5**) but differently from the reaction with permethyl β-CD (**1**), 5 equiv of epoxide were required to achieve conversion. Turning to stereochemistry, when styrene oxide was reacted with 6-monoamino β-CD derivatives **2**, TLC showed two spots with different intensities and R_f values. Reverse phase separation yielded an inseparable mixture of the two products (same molecular weights by MS spectrometry and same ^{1}H NMR spectra). For this reason, we assume that the mixture was composed of two epimers with slightly different polarities. The diastereomeric ratio of product **4** was measured by HPLC and was found to be 9:1 for the stereoisomeric secondary alcohol. To evaluate the influence of the solvent on the stereoselectivity, the reaction was repeated in water but only traces of product were observed by TLC and HPLC. By HPLC we could not separate the two epimers of products **3**, the two spots were evidenced only by bidimensional TLC.

In the second part of this study, cyclohexene oxide was taken as a symmetrically substituted epoxide and reacted with permethyl mono-6-amino β-CD in DMF.

As with the experiment above, the influence of LiBr catalysis, the heating conditions and the number of equivalents of epoxides were compared (Scheme 2 and Table 2). The reaction was monitored by TLC and the hydroxycyclohexylamino β-CD derivative (**5**) was isolated by flash chromatography.

Differently to styrene oxide, 4 equiv of cyclohexene oxide were added to obtain the desired product in satisfactory yields. The reaction required a long reaction time when performed under conventional heating and more than 5 equiv of epoxide did not provide higher yields (Table 2, entry 4). The reaction was optimised by heating under MW at 85 °C for 4 h and the final product was obtained in 27% yield.

The reaction was repeated on mono-6-amino-mono-6-deoxy-β-CD. The reaction showed the best results when performed with



1 R = CH_3
2 R = H

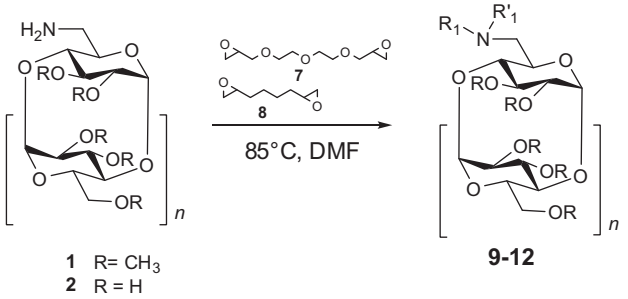
5 R= CH_3
6 R = H

Scheme 2. Reaction of mono-6-amino-mono-6-deoxy-permethyl-β-CD (**1**) and mono-6-amino-mono-6-deoxy-β-CD (**2**) with cyclohexene oxide.

Table 2
Assessment of alkylation of mono-6-amino-mono-6-deoxy-permethyl-β-CD (**1**) and mono-6-amino-mono-6-deoxy-β-CD (**2**) with cyclohexene oxide

Entry	Reagent	Eq. epoxide	Reaction condition[a]	Yield[b,c] %
1	1	1	LiBr, 24 h	5
2	1	4	LiBr, 24 h	12
3	1	4	LiBr, 48 h	16.8
4	1	7	LiBr, 26 h	15
5	1	4	LiBr, 4 h, MW	26
6	1	4	4 h, MW	27
7	2	1	48 h	Failed
8	2	10	LiBr, 36 h	9.2
9	2	4	4 h, MW	Failed
10	2	10	4 h, MW	30
11	2	10	LiBr, 4 h, MW	28

[a] The reaction was performed at 85 °C in DMF.
[b] All the products were characterized by ^{1}H NMR, 2D NMR (^{1}H–^{13}C HMQC, ^{1}H–^{1}H COSY) and mass spectrometry.
[c] Isolated yield obtained after column chromatography.



1 R= CH_3
2 R = H

9-12

9 R = CH_3, R_1 = H R'$_1$ =

10 R = H, R_1 = H R'$_1$ =

11 R = CH_3, R_1 = H R'$_1$ =

12 R = H R_1 , R'1 =

Scheme 3. Reaction of mono-6-amino-mono-6-deoxy-β-CD (**1**) and mono-6-amino-mono-6-deoxy-permethyl-β-CD (**2**) with terminal epoxides **7** and **8**.

10 equiv of cyclohexene oxide under the optimal conditions found for the permethyl derivatives. The influence of MW in promoting the reaction was confirmed as had been observed for the permethyl derivative.

Regarding the stereochemistry, nucleophilic ring epoxide opening almost certainly involves an SN_2 reaction and occurs with an inversion in configuration at the point of attack. Bearing this in mind, it has been assumed that this opening method would give trans-diaxial rather than trans-diequatorial products. Trans-diaxial cleavage proceeded via a transition state which is more energetically favourable than in the trans-diequatorial epoxide opening.[17] Assignment of the relative configuration of the β-aminoalcohol derivative is possible via a comparison of the coupling constants ^3J.

When cyclohexene oxide was reacted with **1** neither TLC nor HPLC revealed stereospecificity. But when we monitored the synthesis of product **6**, TLC showed two spots as had been previously observed with styrene oxide. Reverse phase separation yielded only the major isomer because the minor was present in a negligible amount. A ^{1}H NMR spectrum of the isolated compound **6** (see Fig. 1) was characteristic because the cyclohexyl moiety was found to be strongly influenced by the presence of CD. All the cylohexanol diasterotopic methylene groups were seen to split each other. 2D-NMR experiments (^{1}H–^{13}C HMQC, ^{1}H–^{1}H COSY) were employed to assign the peaks and remove any doubt. From this spectrum it was seen that the complexity of CD derivative **6** renders *J* coupling measurement impossible so that we were unable to verify whether the final product had been isolated in the trans-diaxial or the trans-diequatorial form. The strong interaction between the CD core and the substituent, as shown in the NMR, has promoted the hypothesis of a stereoselective ring opening.

The third part of this study focused on the application of the epoxide ring opening reaction to terminal epoxides.

Monoamino CD derivatives **1** and **2** were reacted with diethylene glycol diglycidyl ether (**7**) to give a new highly soluble and functionalized CD derivative (Scheme 3, Table 3). The reaction required 10 equiv to obtain satisfactory conversion rates. However, product **9** was only obtained in a 4% yield and derivative **10** was isolated in a slightly better 9% yield. As has already been mentioned, nucleophilic epoxide opening with CD does not afford complete conversion but, differently from the reactions already described, diethylene glycol diglycidyl ether gave a mixture of side products and so the desired products were difficult to isolate.

As expected, product **10** showed higher solubility in water than the starting material. Therefore, to reach our objective, we evaluated a new epoxide substrate from which the desired β-aminoalcohol CD derivative was obtained in a higher yield. 1,7-Octadiene was epoxidated with MCPBA and isolated in a 95% yield to obtain 1,7-octadiene dioxide (**8**). The reaction was repeated, with the same conditions as for diethylene glycol diglycidyl ether, and the products **11** and **12** were obtained with 30% and 52% yields, respectively Table 3.

After NMR and MS analysis we found that the ring opening reaction with the octadiene dioxide occurred twice so that product **12** is a disubstituted β-CD. When repeated with fewer equivalents

Table 3
Results of reaction of mono-6-amino-mono-6-deoxy-β-CD (**1**) and mono-6-amino-mono-6-deoxy-permethyl-β-CD (**2**) with terminal epoxides **7** and **8**

Entry	Reagent	Epoxide	Reaction condition	Yield[a,b] %
1	1	7	7 (10 equiv), DMF, 65–85 °C, 4 h, MW	4
2	2	7	7 (10 equiv), DMF, 85 °C, 4 h, MW	9
3	1	8	8 (10 equiv), DMF, 65–85 °C, 4 h, MW	30
4	2	8	8 (10 equiv), DMF, 65–85 °C, 4 h, MW	52

[a] All the products were characterized by ^{1}H NMR, 2D NMR (^{1}H–^{13}C HMQC, ^{1}H–^{1}H COSY) and mass spectrometry.
[b] Isolated yield obtained after column chromatography.

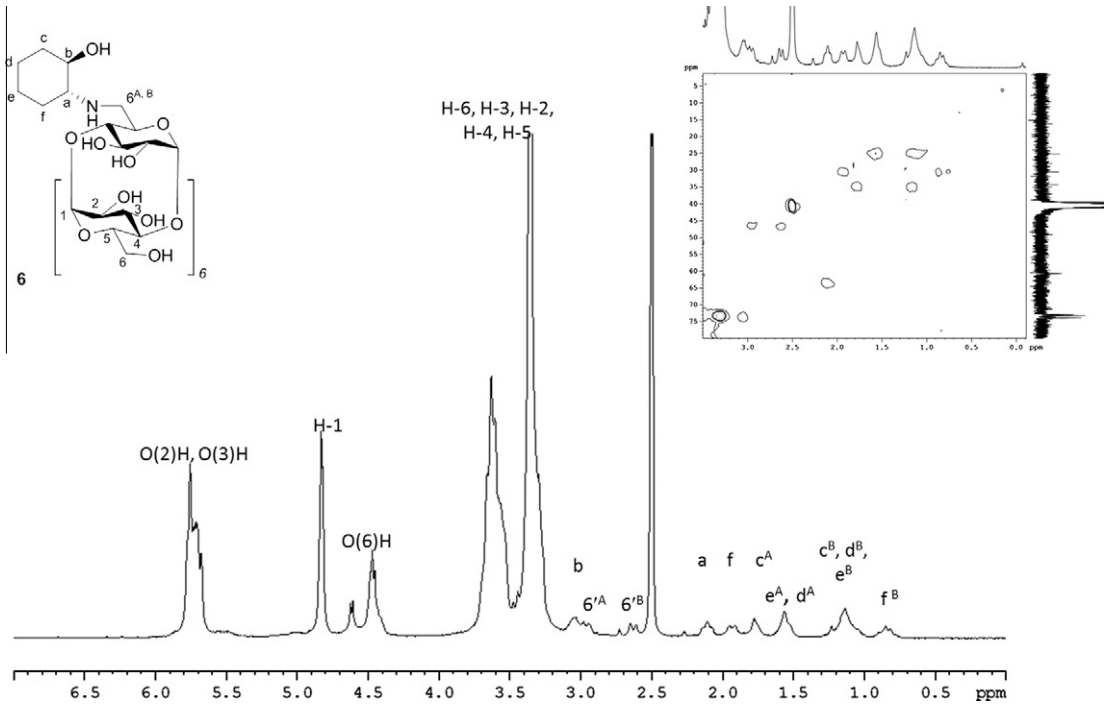


Figure 1. ^{1}H NMR (300 MHz, DMSO-d_6) spectrum of 6-mono(2-hydroxycyclohexylamino)-6-monodeoxy-β-CD (**6**); on the left, the complete product structure; on the right, a particular of the bidimensional ^{1}H–^{13}C HSQC spectrum.

of 1,7-octadiene dioxide (**8**) the reaction with β-CD **2** did not afford the desired monosubstituted derivative in satisfactory yields.

3. Conclusions

Overall it can be concluded that nucleophilic epoxide opening with mono-6-amino mono-6-deoxy-β-CD and mono-6-amino mono-6-deoxy-permethyl β-CD, promoted by MW, can be considered a versatile way to obtain β-aminoalcohol derivatives of β-CD in acceptable yields. The selective formation of the β regioisomer was observed when the reaction was performed with styrene oxide and excellent stereoselectivity was achieved in the nucleophilic epoxide cleavage of styrene and cyclohexene oxides with mono-6-amino mono-6-deoxy-β-CD. These newly prepared compounds showed high water solubility and the linked aminoalcohol subunits enhanced the CD binding properties. Using monoamino β-CD and terminal diepoxides this protocol afforded new functionalized β-CD derivatives, versatile intermediates which can be exploited for further modifications.

4. Experimental

Commercially available reagents and solvents were used without further purification. Native CDs were kindly provided by Wacker Chemie. 6-Amino-mono-6-deoxy-β-CD (**1**) and mono-6-amino-mono-6-deoxy-permethyl-β-CD (**2**) were prepared in accordance with the well established procedure.[18,19] Diethylene glycol diglycidyl ether was purified from a commercially available 50% pure solution (column chromatography DCM/MeOH). Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates. Spot detection was carried out by staining with 5% H_2SO_4 in ethanol or with phosphomolybdic acid stain. IR spectra were recorded with a Shimadzu FT-IR 8001 spectrophotometer. NMR spectra were recorded with a Bruker 300 Avance (300 MHz and 75 MHz for ^{1}H and ^{13}C, respectively) at 25 °C; chemical shifts are calibrated to the residual proton and carbon resonances of the solvent: DMSO-d_6 (δ_H = 2.54, δ_C = 39.5). Chemical shifts (δ) are given in ppm, coupling constants (J) in Hertz. ESI-mass spectra were performed on a Waters Micromass ZQ spectrometer equipped with ESI source.

4.1. 6-Mono(2-hydroxyl-2-phenyl)ethylamino-6-monodeoxy-permethyl-β-CD (3)

The reaction was carried out under magnetic stirring in a professional MW oven; the temperature was monitored with a fibre-optic thermometer. Mono-6-amino mono-6-deoxy-permethyl-β-CD (130 mg, 0.09 mmol) was dissolved in anhydrous DMF (2 mL) and styrene oxide (10.5 μL, 0.09 mmol) was added. The mixture was irradiated with MW (160 W) at 85 °C for 4 h. The reaction was monitored by TLC ($CHCl_3$/MeOH 9:1) and spots were visualized with a phosphomolybdic acid stain. The solvent was partially evaporated and the reacted mixture was diluted with CH_2Cl_2, washed with water and finally dried (Na_2SO_4). The crude residue was purified by CC (CH_2Cl_2/CH_3OH) to yield 73 mg (52% yield) of the desired product.

Compound **3** is a white powder; R_f = 0.61 ($CHCl_3$/CH_3OH 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36–7.27 (m, 5H, H-Ar), 5.12 (m, 7H, H-1), 4.75 (m, 1H, Ph-C*H*(OH)), 3.84–3.81 (m, 14H, H-5, H-6^{A}), 3.64–3.502 (m, 63H, 3-OCH_3, 2-OCH_3, H-4,H-6^{B}, H-3), 3.302 (m, 18H, 6-OCH_3), 3.29 (m, 7H, H-2), 2.95 (m, 1H, C*H*$_2$–NH), 2.78 (m, 1H, C*H*$_2$–NH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.6 (C_{ipso}), 128.72–126.2 (C_{ortho}, C_{meta}, C_{para}), 99.3 (C1), 82.4–82.06 (C2, C3) 80.81–80.51 (C4), 71.75–71.47 (C6, PhCHOH), 71.31–71.17 (C5), 61.86–61.76 (3-OCH_3), 59.27–59.24 (2-OCH_3), 59.01–58.69 (6-OCH_3), 57.84 (*C*H$_2$NH) ppm; MS (ESI): *m/z* calcd for $C_{70}H_{119}NO_{35}$ $[M+H]^+$ 1535.7 found 1535.87, $C_{70}H_{119}NO_{35}$ $[M+H+Na]^{2+}$ 779.35 found 779.25.

4.2. 6-Mono(2-hydroxyl-2-phenyl)ethylamino-6-monodeoxy-β-CD (4)

The reaction was carried out under magnetic stirring in a professional MW oven, the temperature was monitored with a

fibre-optic thermometer. Mono-6-amino-mono-6-deoxy-β-CD (100 mg, 0.09 mmol) was dissolved in anhydrous DMF (2 mL) and styrene oxide (50.2 μL, 0.44 mmol) was added. The mixture was irradiated with MW (160 W) at 85 °C for 4 h. It was partially evaporated, dissolved with 800 μL of water then precipitated with cold acetone. The precipitate was purified by reverse phase column chromatography (H_2O/CH_3OH gradient from 97:3 to methanol 100%) to yield 36 mg (32% yield) of the desired product.

Compound **5** is a white powder; R_f = 0.45 (*i*PrOH/H_2O/EtOAc/NH_4OH = 5:3:1:1); ^1H NMR (300 MHz, DMSO-d_6) δ = 7.37–7.27 (m, 5H, H-Ar), 5.82–5.71 (m, 14H, O(2)H, O(3)H), 4.88 (br s 7H, H-1), 4.66 (m, 1H, PhC*H*(OH)), 4.53 (m, 6H, O(6)H), 3.7–3.6 (m, 28H, H-6, H-3), 3.5–3.2 (m, overlaid with water, H-2, H-4, H-5), 2.61 (m, 2H, CH_2–NH) ppm; ^{13}C NMR (75 MHz, DMSO) δ = 145.47 (C_{ipso}), 128.76 (C_{meta}), 126.72 (C_{ortho}, C_{para}), 102.84 (C1), 82.4 (C4), 73.3 (C3), 73.28 (C2), 72.88 (C5), 70.48 (PhCH(OH)), 57.5 (C6), 57.35 (CH_2NH) 49.64 (C6′) ppm; MS (ESI): *m/z* calcd for $C_{50}H_{79}NO_{35}$ $[M+H]^+$ 1254.4 found 1255.45.

4.3. 6-Mono(2-hydroxycyclohexyl)amino-6-monodeoxy-permethyl-β-CD (5)

The reaction was carried out under magnetic stirring in a professional MW oven, the temperature was monitored with a fibre-optic thermometer. Mono-6-amino mono-6-deoxy-permethyl-β-CD (150 mg, 0.11 mmol) was dissolved in anhydrous DMF (1 mL) and cyclohexene oxide (43 μL, 0.42 mmol) was added. The mixture was irradiated with MW (160 W) at 85 °C for 4 h. The reaction was monitored by TLC ($CHCl_3$/MeOH 9:1) and spots were visualized with a phosphomolybdic acid stain. The solvent was partially evaporated and the reacted mixture was diluted with CH_2Cl_2, washed with water and finally dried (Na_2SO_4). The crude residue was purified by CC (CH_2Cl_2/CH_3OH) to yield 50 mg (27% yield) of the desired product.

Compound **6** is a white powder; R_f = 0.54 ($CHCl_3/CH_3OH$ 9:1); ^1H NMR ($CDCl_3$, 300 MHz) δ = 5.18–5.03 (m, 7H, H-1), 4.05–3.98 (m, 1H, H-$6^{A\prime}$), 3.87–3.82 (m, 14H, H-5, H-6^A), 3.64–3.52 (m, 64H, 3-OCH_3,2-OCH_3, H-4,H-6^B, H-3, H-a), 3.40 (m, 19H, 6-OCH_3, H-$6^{B\prime}$), 3.22–3.18 (m, 7H, H-2), 1.27 (m, 4H, H-c, H-f), 0.081 (m, 4H, H-d, H-e) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 98.7 (C-1), 82.15, 81.87, 81.66 (C-2, C-3), 80.70, 80.30, 80.14 (C-4), 72.42, 71.64, 71.3 (C-5, C-6), 62.9, 61.84, 61.62 (3-OCH_3), 58.73 (2-OCH_3), 57.73 (6-OCH_3), 42.9 (C-6′), 30.01 (C-c), 23.6 (C-f), 21.7, 21.2 (C-d, C-e) ppm; MS (ESI): *m/z* calcd for $C_{68}H_{121}NO_{35}$ $[M+H]^+$ 1511.77, found 1512.03.

4.4. 6-Mono(2-hydroxycyclohexylamino)-6-monodeoxy-β-CD (6)

The reaction was carried out under magnetic stirring in a professional MW oven, the temperature was monitored with a fibre-optic thermometer. Mono-6-amino mono-6-deoxy-β-CD (100 mg, 0.09 mmol) was dissolved in anhydrous DMF (2 mL) and cyclohexene oxide (100 μL, 0.88 mmol) was added. The mixture was irradiated with MW (160 W) at 85 °C for 4 h. It was partially evaporated, dissolved with 800 μL of water then precipitated with cold acetone. The precipitate was purified by reverse phase column chromatography (H_2O/CH_3OH gradient from 97:3 to methanol 100%) to yield 33 mg (30% yield) of the desired product.

Compound **7** is a white powder; R_f = 0.41 (*i*PrOH/H_2O/EtOAc/NH_4OH = 5:3:1:1); ^1H NMR (DMSO-d_6, 300 MHz) δ = 5.72 (m, 14H, O(2)H, O(3)H), 4.83 (m, 7H, H-1), 4.62–4.45 (m, 6H, O(6)H), 3.63–3.48 (m, 28H, H-6, H-3), 3.40–3.2 (m, overlaid with water, H-2, H-4, H-5), 3.04–2.98 (m, 2H, H-b, H-$6^{A\prime}$), 2.64 (d, J = 11.4 Hz, H-$6^{B\prime}$), 2.11 (m, 1H, H-a), 1.91 (d, 1H, H-f), 1.77 (m, 1H, H-c), 1.56 (m, 2H, H-e, H-d), 1.17 (m, 3H, H-c, H-d, H-e), 0.85 (m, 1H, H-f) ppm; ^{13}C NMR (DMSO, 75 MHz): δ = 102.84 (C1), 82.5 (C4), 73.87 (C3), 73.32 (C-b), 73.27 (C2), 72.90 (C5), 63.16 (C-a), 60.7 (C-6), 46.23 (C-6′), 34.54 (C-c), 30.03 (C-f), 24.86 (C-d, C-e) ppm; MS (ESI): *m/z* calcd for $C_{48}H_{81}NO_{35}$ $[M+H]^+$ 1232.46 found 1233.14.

4.5. 1,7-Octadiene dioxide (8)

Octadiene (1.37 mL, 9.07 mmol) was dissolved in 25 mL of DCM and stirred at 0 °C. MCPBA (4.68 g, 18.08 mmol) dissolved in 45 mL of DCM was added dropwise. The solution was left at 0 °C under stirring overnight. The reaction was monitored by TLC (PE/EtOAc 8:2) and spots were visualized with a phosphomolybdic acid stain. The solution was washed three times with water and finally dried (Na_2SO_4). 1.39 g (95% yield) of the desired product was recovered and employed without further purifications. Analytical data were in accordance with reported values.[20]

4.6. 6-Mono(2-hydroxy-3-(2-(2-(oxiran-2-ylmethoxy)ethoxy)ethoxy) propylamino)-6-monodeoxy-permethyl-β-CD (9)

The reaction was carried out under magnetic stirring in a professional MW oven, the temperature being monitored with a fibre-optic thermometer. Mono-6-amino mono-6-deoxy-permethyl-β-CD (300 mg, 0.212 mmol) was dissolved in anhydrous DMF (2 mL) and diethylene glycol diglycidyl ether (292 μL, 2.12 mmol) was added. The mixture was irradiated with MW (160 W) at 65 °C for 1 h then 85 °C for 3 h. The reaction was monitored by TLC ($CHCl_3$/MeOH 95:5) and spots were visualized with phosphomolybdic acid stain. The solvent was partially evaporated and the reacted mixture was diluted with CH_2Cl_2, washed with brine and finally dried (Na_2SO_4). The crude residue was purified by column chromatography (CH_2Cl_2/CH_3OH) to yield 14 mg (4% yield) of the desired product.

Compound **10** is white powder; R_f = 0.54 ($CHCl_3/CH_3OH$ 9:1); ^1H NMR ($CDCl_3$, 300 MHz) δ = 5.14 (br s 7H, H-1), 4.01 (m, 1H, H-$6^{A\prime}$), 3.86–3.81 (m, 14H, H-5, H-6^A), 3.65–3.51 (m, 64H, 3-OCH_3,2-OCH_3, H-4,H-6^B, H-3, C*H*–NH), 3.41 (m, 18H, 6-OCH_3, H-$6^{B\prime}$), 3.21–3.18 (m, 23H, H-2, H-e, H-a, H-b, H-c, H-d), 2.81 (m, 1H, H-f), 2.63 (m, 1H, H-f), ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 98.9 (C-1), 80.04 (C-2), 81.67 (C-3), 80.50 (C-4), 71.45, 71.47 (C-c, C-d), 71.83, 71.51, 71.22 (C-5, C-6), 61.28 (3-OCH_3), 58.92 (2-OCH_3), 58.41 (6-OCH_3), 59.3 (CH_2NH), 52.17 (C-e), 47.35 (C-f); MS (ESI): *m/z* calcd for $C_{72}H_{129}NO_{39}$ $[M+H]^+$ 1632.81 found 1633.36.

4.7. 6-Mono(2-hydroxy-3-(2-(2-(oxiran-2-ylmethoxy)ethoxy)ethoxy) propylamino)-6-monodeoxy-β-CD (10)

The reaction was carried out under magnetic stirring in a professional MW oven, the temperature being monitored with a fibre-optic thermometer. Mono-6-amino mono-6-deoxy-β-CD (300 mg, 0.26 mmol) was dissolved in anhydrous DMF (2 mL) and diethylene glycol diglycidyl ether (363 μL, 2.64 mmol) was added. The mixture was irradiated with MW (160 W) at 85 °C for 4 h. It was partially evaporated, dissolved with 800 μL of water then precipitated with cold acetone. The precipitate was purified by reverse phase column chromatography (H_2O/CH_3OH gradient from 97:3 to methanol 100%) to yield 26 mg (9% yield) of the desired product.

Compound **11** is a white powder; R_f = 0.49 (*i*PrOH/H_2O/EtOAc/NH_4OH = 5:3:1:1); ^1H NMR (DMSO-d_6, 300 MHz) δ = 5.87–5.68 (m, 14H, O(2)H, O(3)H), 4.83 (m, 7H, H-1), 4.48–4.46 (m, 6H, O(6)H), 3.77–3.25 (m, 28H), 3.35–3.31 (m, overlaid with water, H-2, H-4, H-5, H-6, H-3, H-b, H-c. H-d), 2.92 (m, 1H, H-e), 2.75 (m, 1H, H-f), 2.47 (m, 2H, H-f, H-a) 2.35 (m, 1H, H-a), ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 102.8 (C1), 82.38 (C4), 73.88 (C3),

73.27 (C2), 72.89 (C5), 70.15, 70.77(C-c, C-d), 66.27 (C-b) 62.42 (C-a), 60.76 (C6), 52.42 (C-e), 47.85 (C-f) ppm; MS (ESI): *m/z* calcd for $C_{52}H_{89}NO_{39}$ $[M+H]^+$ 1352.50 found 1353.03, $[M+Na+H]^{2+}$ 688.24 found 688.10.

4.8. 6-Mono(2-hydroxy-6-(oxyran2-yl)hexylamino)-6-monodeoxy-permethyl-β-CD (11)

The reaction was carried out under magnetic stirring in a professional MW oven, the temperature was monitored with a fibre-optic thermometer. Mono-6-amino mono-6-deoxy-permethyl-β-CD (150 mg, 0.11 mmol) was dissolved in anhydrous DMF (1.5 mL) and 1,7-octadiene dioxide (150 mg, 1.06 mmol) was added. The mixture was irradiated with MW (160 W) at 85 °C for 4 h. The reaction was monitored by TLC ($CHCl_3$/MeOH 9:1) and spots were visualized with a phosphomolybdic acid stain. The solvent was partially evaporated and the reacted mixture was diluted with CH_2Cl_2, washed with water and finally dried (Na_2SO_4). The crude residue was purified by column chromatography (CH_2Cl_2/CH_3OH) to yield 47 mg (30% yield) of the desired product.

Compound **12** is a white powder; $R_f = 0.55$ ($CHCl_3$/CH_3OH = 9:1); ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 5.11$ (m, 7H, H-1), 3.99 (m, 1H, H-6^{A_V}), 3.87 (m, 14H, H-5, H-6^A), 3.62–3.49 (m, 64H, 3-OCH_3,2-OCH_3, H-4,H-6^B, H-3, C*H*–NH), 3.45 (m, 18H, 6-OCH_3), 3.18 (m, 7H, H-2), 2.89 (m, H-g), 2.73 (m, 1H, H-h), 2.44 (m, 1H, H-h), 2.04 (m, 2H, CH_2 aliphatic chain), 1.50 (m, 6H, CH_2 aliphatic chain) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 98.65, 98.56 (C-1), 82.08, 81.53 (C-2, C-3), 80.23, 80.11 (C-4), 71.69, 71.27, 71.01 (C-5, C-6), 61.59 (3-OCH_3), 59.15 (2-OCH_3), 58.59 (6-OCH_3), 42.47 (C-6′), 51.85 (C-g), 47.58 (C-h), 33.87 (CH_2 aliphatic chain) 29.8 (CH_2 aliphatic chain) ppm; MS (ESI): *m/z* calcd for $C_{70}H_{125}NO_{36}$ $[M+H]^+$ 1556.8 found 1557.1.

4.9. 6-Mono(di-2-hydroxy-6-(oxyran2-yl) hexylamino)-6-monodeoxy-β-CD (12)

The reaction was carried out under magnetic stirring in a professional MW oven, the temperature was monitored with a fibre-optic thermometer. Mono-6-amino mono-6-deoxy-β-CD (400 mg, 0.35 mmol) was dissolved in anhydrous DMF (3 mL) and 1,7-octadiene dioxide (501 mg, 3.52 mmol) was added. The mixture was irradiated with MW (160 W) at 85 °C for 4 h. It was partially evaporated, dissolved with 800 μL of water then precipitated with cold acetone. The precipitate was purified by reverse phase column chromatography (H_2O/CH_3OH gradient from 97:3 to methanol 100%) to yield 234 mg (52% yield) of the desired product.

Compound **13** is a white powder; $R_f = 0.46$ (*i*PrOH/H_2O/EtOAc/NH_4OH = 5:3:1:1); ^1H NMR (DMSO-d_6, 300 MHz) $\delta = 5.87–5.68$ (m, 14H, O(2)H, O(3)H), 4.86 (m, 7H, H-1), 4.64–4.51 (m, 6H, O(6)H), 3.66–3.21 (m, overlaid with water, H-2, H-4, H-5, H-6, H-3, H-b), 2.87 (m, 1H, H-g), 2.72 (m, 1H, H-h), 2.44 (m, 2H, H-h, H-a) 2.32 (m, 1H, H-a) 1.5–1.15 (m, 16H, H-c, H-d, H-e, H-f) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 103.04 (C1), 82.49 (C4), 74.03 (C3), 73.05 (C2), 72.85 (C5), 66.58 (C-b) 62.16 (C-a), 60.31 (C6), 52.43 (C-g), 47.13 (C-h), 31.9 (C-c, C-f), 26.82, 26.38, 26.47, 25.82 (C-d, C-e) ppm; MS (ESI): *m/z* calcd for $C_{58}H_{99}NO_{38}$ $[M+H]^+$ 1418.58 found, $[M+Na+H]^{2+}$ 721.29 found 721.12.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2011.09.018.

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