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ORIGINAL ARTICLE

Regioselective difunctionalization of cyclodextrins

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Abstract An efficient route for selective functionalization of cyclodextrin diols ($2^{A–F}$,$3^{A–F}$,$6^{B,C,E,F}$-hexadeca-*O*-benzyl-α-cyclodextrin or $2^{A–G}$,$3^{A–G}$,$6^{B,C,E–G}$-nonadeca-*O*-benzyl-β-cyclodextrin) is reviewed here. It has been reported that these diols can be transformed into 6^{A},6^{D}-cyclic sulfites, which can be oxidized to 6^{A},6^{D}-cyclic sulfates in good yields. The latter can be regioselectively opened by nucleophilic attack from one side of the bridge. This behavior allowed the synthesis of various potential artificial glycosidases and phosphorylases in which one moiety would work as the catalyst, the other one would be investigated as assisting group. The synthesis of new hetero-functionalized cyclodextrins is presented here.

Keywords Supramolecular · Cyclodextrins · Difunctionalization · Artificial enzymes · Catalysis

Introduction

Cyclodextrin molecules are fascinating because of their wonderful properties and applicability. Their accessibility at low cost, nontoxicity and hydrophobic/hydrophilic features make them versatile compounds in various applications: food, pharmaceutical, cosmetic and perfume industry [1] as well as for drug formulation or in biomimetic chemistry [2–5]. Cyclodextrins are characterized by a truncated cone-shaped structure which has a lipophilic cavity and a hydrophilic exterior. The internal hydrophobicity is mainly caused by 3- and 5-sugar hydrogens pointing into the cavity. This characteristic makes them particularly fit for forming enzyme-like host–guest complexes. The external hydrophilicity is caused by the numerous hydroxyl groups, pointing away from the cavity and towards the aqueous environment. This feature makes them useful molecules in physiological water environment.

Cyclodextrins have been successfully used in synthesis of artificial enzymes. But, we are not yet fully aware of what requirements a molecule should have in order to rival the activity and selectivity of native enzymes. Although the structure of the enzymes determines their function, it is not trivial to predict their activity only by the functionalities at the active site. This is the case also with cyclodextrins. Nevertheless more studies and more synthetic work are needed in order to transform these supramolecular hosts into powerful catalytic devices and that is what this paper is trying to do: new hetero-functionalized cyclodextrin derivatives.

It is known that in their interior, lipophilic residues are bound with a binding constant in the range of 10^2–10^4 [6]. Therefore the interest in selective modifications of cyclodextrin molecules is high, but certainly not a straightforward task since the molecule contains 18, 21 and 24 similar alcohol functionalities, respectively for α-, β- and γ-cyclodextrin [7]. However, new synthetic methods for selective functionalization of only few of the hydroxyl groups are still needed.

Normally, mono- or di-functionalization of cyclodextrin can be carried out by preparing different sulfonyl esters [8]. So far, there are many problems with those methods because of poor regioselectivity, tedious separation of the mixtures and low yields even with highly selective

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sulfonylation reagents [9]. It was therefore a very important progress when Sinaÿ and coworkers [10] discovered that DIBAL-H can liberate by choice one or two primary hydroxyls on opposite sides (A and D sugar moieties) of the upper, primary rim of a perbenzylated cyclodextrin. Sollogoub and coworkers [11, 12] have subsequently shown multiple possibilities to provide various debenzylation patterns at the primary rim through oriented deprotections. Also, compounds **1** and **2** have been important precursors in synthesis of several artificial enzymes [13–22]. The free OH groups could be functionalized further in order to catalyse a desired reaction and the rest of the cyclodextrin molecule could act as an active site to specifically bind the substrate in the cavity. Artificial glycosidases and oxidases have been created in this way [13–22] (Fig. 1).

The next step in building up a synthetic strategy for artificial enzymes was to find a method for hetero-functionalization of the primary rim. Since compound **1** is a symmetrical diol, the next challenge was to differentiate between the two equivalent hydroxyl groups at the primary rim. Usual mono-silylation procedure (with TBSCl) gave low selectivity, forming mixtures and consequently low yields of mono-silylated derivative [23]. Mono-alkylation was also an unsatisfactory process ending with mixtures of compounds after long reaction times [24]. Guieu and Sollogoub [25] reported, that DIBAL-H can effect a regioselective debenzylation of a monoazide-cyclodextrin in good yields. On the other hand, the synthesis of the monoazide was based on substitution of the low yielding precursor **2**, which is a drawback of this method.

Herein we present the preparation of several hetero-functionalized cyclodextrin derivatives where one of the moieties is designed to work as a catalyst, while the other one would be investigated as an assisting group.

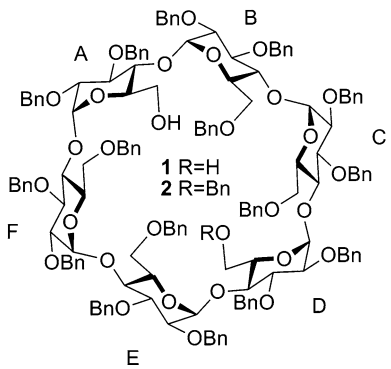


Fig. 1 Partially 6-*O*-debenzylated cyclodextrins obtained by DIBAL-H reaction on perbenzylated α-cyclodextrin

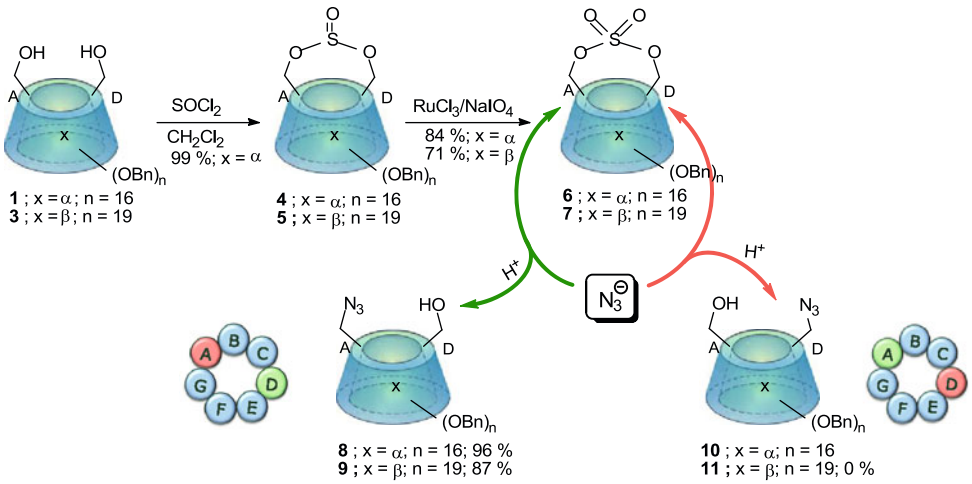
Results and discussion

Recently, a new approach has given very good results in the synthesis of cyclodextrin derivatives. The selective mono-functionalization has been successfully achieved and an azido-alcohol has been synthesized from the readily available α- and *β*-cyclodextrin diols **1** and **3** as outlined in Scheme 1 [26].

The synthesis of hetero-functionalized cyclodextrins **8** and **9** proceeded smoothly via a thionyl chloride substitution that gave very good yields of cyclic sulfites **4** and **5**. It is noteworthy to mention that the bridge formation on the *β*-cyclodextrin diol **3** was more difficult, probably due to longer distance between the two hydroxyl groups. This led to longer reaction time and slightly lower yield of the sulfite **5**. The problem was overcome by doing the bridge formation and oxidation in one pot reaction. To our knowledge this was the first time that the A, D-diol was capped with a short, single atom bridge. Nevertheless, several bridged derivatives of **1** and **3** have been previously reported [13–22]. Oxidation with $RuCl_3/NaIO_4$ provided the 6A,6D-cyclic sulfates **6** in 84% yield and **7** in 71% yield after two steps. The cyclic sulfates **6** and **7** are key intermediates for the synthesis of various hetero-functionalized cyclodextrin derivatives, since they can react with a series of nucleophiles that will cause a ring opening [26]. Reaction of **6** with NaN_3 followed by acidic hydrolysis of the remaining sulfate gave the mono-azide **8** in 96% yield. When working with α-cyclodextrin, compounds **8** and **10** are equivalent due to the symmetry of the molecule. Substitution reaction on the *β*-cyclodextrin analogue **7** may afford two products, **9** and **11**. Since *β*-cyclodextrin diol is asymmetric, the two alcohols are not equivalent therefore two products can be obtained by their displacement (see Scheme 1). Substitution of **7** with NaN_3 and subsequent acidic hydrolysis only afforded the mono-azido derivative **9** in 87% yield with no traces of the isomer **11**. This regioselectivity was further investigated by spectral data and molecular models. The substitution only from the A residue direction was explained by the position of the ring oxygen from the E residue that obstructs the S_N2 attack from the D residue direction, resulting in a nucleophilic reaction only at the A residue direction which provides compound **9**.

This high yielding and regiospecific chemistry opened an efficient route for the synthesis of new difunctional cyclodextrin derivatives with potential enzymatic activity for a wide variety of reaction types.

Cyclodextrins containing aldehydes at the primary rim have previously been used as artificial enzymes in oxidation of aminophenols and benzyl alcohols with H_2O_2 in buffer pH 7 with rate increases up to 12000 in the best case [27]. Carboxylic acid functionalities on cyclodextrin provide catalytic activity as artificial glycosyl phosphorylases



Scheme 1 Synthesis of α- and β-azido-alcohol cyclodextrins **8** and **9**

[13–22], while cyanohydrin-modified cyclodextrins gave four orders of magnitude rate increase in aryl glycoside hydrolysis [13–22], and the research in this field is still in progress. In order to make an even better comparison between modified cyclodextrins and enzymes, we prepared cyclodextrins derivatives **16**, **19**, **21**. They contain an amino functionality together with catalytic groups that have shown good activity in various reactions.

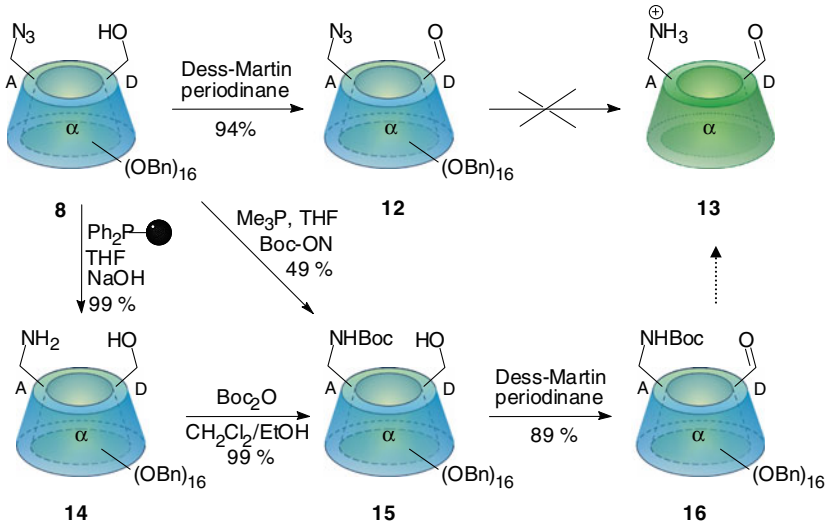
Encouraged by the promising results obtained by capping cyclodextrin diols with a sulfate bridge, we investigated other methods that could give access to novel protective group strategy in our synthesis. Dibutylstannylene acetals [28] and *p*-methoxybenzylidene acetals [29, 30] are widely used in carbohydrate chemistry as protective groups, known to react with various nucleophiles to give almost exclusively mono-substitution products and to provide regioselective reductive ring opening, respectively. Therefore the reaction between α-cyclodextrin diol and di-*n*-butyltin oxide in methanol has been tried. Only traces of product could be seen by MALDI-TOF examinations of the reaction mixtures. The same unsatisfactory result was obtained when compound **1** was reacted with 4-methoxybenzaldehyde dimethyl acetal in DMF. A catalytic amount of toluene-*p*-sulphonic acid was added and methanol was continuously distilled off at room temperature in vacuo. However, it was found that the formation of these bridged cyclodextrin derivatives, resulted only in low conversions due to the instability of the products during the reaction conditions.

Since the bridged-sulfate formation is a very high yielding method, it remains the best synthetic solution in our applications. As previously shown, a variety of nucleophiles can afford nucleophilic opening of the bridged sulfate-cyclodextrin **6.** N-nucleophiles performed better than O-nucleophiles, while reactions with halides are very poor. The yields are in most cases not as high as in the reaction with the azide; for that reason derivative **8** was used as the main intermediate for the synthesis of compounds **13**, **19** and **21**.

Oxidation of the free hydroxyl group with Dess–Martin periodinane gave the aldehyde **12** in 94% yield (Scheme 2). Since a direct one step reduction-hydrogenolysis reaction is not the best choice in this case, the synthesis of compound **13** was planned in a stepwise methodology. In the first step the reduction of the azido moiety was performed by a Staudinger reaction of **8** with 1 M solution trimethylphosphine in THF at reflux. After 1 h and subsequent hydrolysis of the iminophosphorane intermediate compound **14** was obtained in 58% yield. The low yield was due to the high instability of the trimethylphosphine reagent.

We hence resonated that an optimization of the reaction is necessary. Virtually any trivalent phosphorus compound can undergo this type of reaction. Triphenylphosphine and tributylphosphine in THF followed by basic hydrolysis gave slightly better yields but the best reagent to use was the triphenylphospine on solid support which after basic work up afforded the amino-alcohol **14** in 99% yield. A protection of the amino group was necessary in order to avoid problems during the last deprotection step. The amino-alcohol **14** dissolved in a 1:1 mixture of dichloromethane/ethanol at room temperature was treated with 1 eq. Boc_2O to give the Boc-protected amino-alcohol **15** in 99% yield. Compounds **14** and **15** have been analyzed by ^{1}H, ^{13}C-NMR and the spectral data have been compared with the literature [25]. A tandem reduction-protection reaction has been tried by a direct addition of 6 eq. of Boc-ON reagent (2-(*tert*-Boc-Oxyimino)-2-phenylacetonitrile) over a THF solution of the azido-alcohol **8** and trimethylphosphine. After overnight reaction at room temperature, Boc-aminoalcohol **15** could be isolated from the reaction mixture in 49% yield. Compound **14** has been previously prepared in 74% yield by a tandem DIBAL-H reduction-deprotection of the mono-azido perbenzylated α-cyclodextrin [25], but considerably

Scheme 2 Synthesis of amino aldehyde derivative **13**



lower yield is obtained in this manner, considering that the starting material, α-cyclodextrin monoalcohol, comes from a low yielding reaction.

Dess–Martin oxidation of the hydroxyl group gave the corresponding aldehyde **16** in 89% yield. The structure was supported by spectroscopic data; thus ^{1}H-NMR spectrum showed a broad singlet at 9.39 ppm and ^{13}C NMR a signal at 195.2 ppm. Deprotection of the benzyl groups has to follow, according to the procedure already tested for compound **19** (Scheme 3).

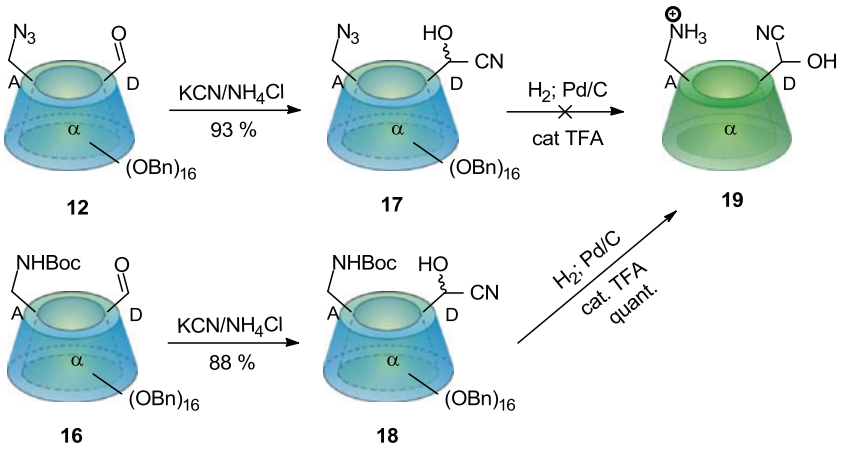
By treatment with excess of KCN and NH_4Cl in 1:1 diethyl ether/methanol mixture, compound **12** was successfully transformed into azido-cyanohydrin **17** in 93% yield (Scheme 3). The spectroscopic data certified the presence of the cyano moiety (^{13}C NMR: 119.2, 120.4 ppm), compound **17** being a mixture of isomers.

Final deprotection of the benzyl groups under standard hydrogenolysis conditions afforded only partially debenzylated analogues of **19** which contain amino functionality. This problem was overcome by starting the synthesis from protected amino-aldehyde **16** which gave the Boc-amino cyanohydrin derivative **18** in 88% isolated yield. Removal of the benzyl groups under hydrogen atmosphere using Pd/C and TFA, provided the final amino-cyanohydrin **19** in quantitative yield (Scheme 3).

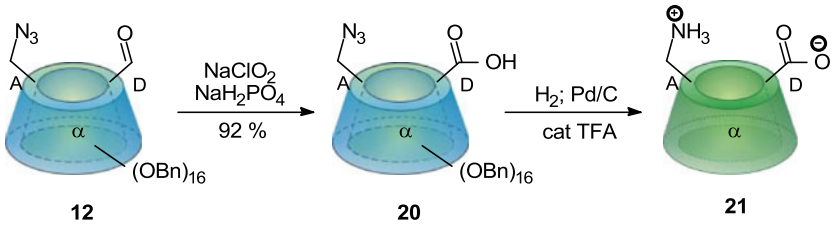
Another compound of interest was the α-cyclodextrin aminoacid **21**. The synthesis starts with an in situ oxidation of the aldehyde moiety of compound **12** with sodium chlorite in a buffered medium (Scheme 4). This procedure gave access to the carboxylic acid derivative **20** in 92% yield. The ^{13}C NMR spectrum showed the corresponding peak for the carboxylic residue (171.2 ppm).

It is noteworthy to mention that the Staudinger reduction of the azide group of derivative **20** has been also performed in good yields. Direct deprotection of benzyl groups and reduction of the azide functionality under standard conditions succeeded giving quantitative yield of the final α-cyclodextrin amino-acid **21** (Scheme 4).

Scheme 3 Synthesis of amino-cyanohydrin **19**



Scheme 4 Synthesis of aminoacid derivative **21**



Conclusions

We have successfully prepared a series of hetero-functionalized cyclodextrin derivatives in very good yields and optimized the problematic steps of the synthesis. Our synthetic routes were extended applications of the new discriminating method that have been previously developed in our group. We proved once again the usefulness of this method that gives access to highly versatile difunctionalized cyclodextrins derivatives that can be intermediates in other complex syntheses. Aminoacid and aminoaldehyde derivatives of cyclodextrins are versatile species that open the way to many applications, for example: peptide syntheses, asymmetric catalysis, etc. The future the work will be continued by investigating the effect of compounds like **19**, **21** and eventually **13** for enzyme-like reactivity in a variety of reactions.

Experimental section

General information

Solvents were distilled under anhydrous conditions. All reagents were used as purchased without further purification, α- and β-cyclodextrins were purchased by Fluka. All reactions were performed under inert atmosphere. Evaporation was carried out in a rotatory evaporator. Glassware used for water-free reactions was dried for 2 h at 130 °C before use. Flash chromatography was performed using silica gel 60 (230–400 mesh) as the stationary phase. TLC plates (Merck, 60, F_{254}) were visualized by spraying with cerium sulfate (1%) and molybdic acid (1.5%) in 10% H_2SO_4 and heating until coloured spots appeared. ^{1}H-, ^{13}C-NMR were carried out with a Varian Mercury 300 instrument. Monoisotopic mass spectra (MALDI-TOF) were obtained on a Bruker Daltonics mass spectrometer using α-cyanohydroxycinnamic acid matrix. Spectra were calibrated using a peptide calibration standard solution.

α- and β-Cyclodextrin sulphates (**6** and **7**) and azides (**8**, **9**, **10** and **11**) were prepared according to the previously published procedure [26].

Compound **15** was prepared according to literature [25].

General procedure for the azide reduction using solid supported Ph_3P:

The azido compound **8** (0.13 mmol) was dissolved in THF (20 mL) under nitrogen. The resin beads (4.6 eq.) were added and the suspension was stirred 2.5 h. After, 1 M NaOH was added and the mixture was stirred 12 h. The resin was filtrated off, washed with H_2O/EtOAc and the organic layer separated, washed with brine, dried ($MgSO_4$) and evaporated. Final compound **14** was isolated after chromatography (eluent EtOAc/pentane 1:3 → 1:1) in 99%. Spectra data were according with literature [25].

General procedure for Dess–Martin oxidation of cyclodextrin-alcohols to aldehydes

Dess–Martin reagent (3 eq.) was added to a solution of azido alcohol **8** or **15** (0.16 mmol), in dry CH_2Cl_2 (19 mL). The reaction mixture was stirred at room temperature for 2 h and then was quenched with Et_2O (19 mL) and a solution of $NaHCO_3$ sat. (19 mL) containing 0.739 g of $Na_2S_2O_3$, and was stirred for 30 min more. The organic phase was washed with $NaHCO_3$ (4 × 10 mL), water (4 × 10 mL), dried over $MgSO_4$ and concentrated. The aldehydes **12** or **16** were purified by column chromatography (4:1 mixture of pentane/EtOAc).

6^A-Oxa-6^D-azido-$2^{A–F}$,$3^{A–F}$,$6^{B,C,E,F}$-hexadecakis-*O*-benzyl-α-cyclodextrin (12)

White foam (94%). R_f (EtOAc/pentane 1:3) = 0.28. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ 9.38 (s, 1H, H-aldehyde), 7.87–7.08 (m, 80H, Ar–H), 5.48 (d, 1H, J = 1.75 Hz, H-1), 5.34 (d, 1H, J = 13.5 Hz, H-CHPh), 5.13 (d, 1H, J = 11.1 Hz, H-CHPh), 5.06 (d, 1H, J = 11.1 Hz, H-CHPh), 4.91 (d, 1H, J = 3.6 Hz, H-1), 4.87–4.64 (m, 10H), 4.56–4.24 (m, 18H), 4.18–3.65 (m, 21H), 4.18–3.33 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ 197.69 (C=O), 139.54–138.13 (C_{ipso}), 128.57–126.99 (C_{Ar}), 99.17, 98.62, 98.45, 98.13, 97.57 (C-1), 81.71–66.12, 53.69, 51.56 (CH_2, CH), 29.97 (C–N_3) ppm. MALDI-TOF–MS m/z calcd. for $C_{148}H_{153}N_3O_{29}$ 2436.05 found 2435.8.

6^A-Oxa-6^D-N-Boc-amino-$2^{A–F}$,$3^{A–F}$,$6^{B,C,E,F}$-hexadecakis-*O*-benzyl-α-cyclodextrin (16)

Transparent oil (89%); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ 9.39 (s, 1H, H-aldehyde), 7.98–7.11 (m, 80H, Ar–H), 5.64 (d, 1H, H-1), 5.28 (d, 1H, $J = 10.2$ Hz, H-CHPh), 5.18 (d, 1H, $J = 11.1$ Hz, H-CHPh), 5.10 (d, 1H, $J = 10.5$ Hz, H-CHPh), 5.04 (m, 6H), 4.89 (m, 4H), 4.75 (m, 3H), 4.60–4.26 (m, 18H), 4.22–3.92 (m, 22H), 3.74–3.44 (m, 10H), 3.71 (dd, 2H, $J_{1,2} = 3.3$, $J_{2,3} = 9.9$ Hz, 2 × H-2), 3.24 (dd, 2H, $J_{1,2} = 3.3$, $J_{2,3}$ 9.9 Hz, 2 × H-2), 3.16–3.11 (m, 2H), 1.43 (s, 9H, C–$(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ 195.17 (CH=O), 155.71 (NH–CO), 139.29–137.76 (C_{ipso}), 128.63–125.37 (C_{Ar}), 98.05, 97.73, 97.42, 97.26 (C-1), 80.78–76.58 (CH_2, CH), 75.8–68.18 (CH_2, CH), 30.21, 29.57, 28.37 ($C(CH_3)_3$). MALDI-TOF–MS *m/z* calcd. for $C_{153}H_{163}NO_{31}$ 2511.92 found 2512.0.

General procedure for preparation of cyclodextrin-cyanohydrins from aldehydes:

A mixture of KCN (63 eq.) and NH_4Cl (94 eq.) in water (8 mL) was added at 0 °C to a solution of aldehyde **12** or **16** (0.13 mmol) in ether/MeOH (8 mL/8 mL). The reaction mixture was stirred overnight at room temperature. The organic solvent was removed in vacuum and the water phase was extracted with CH_2Cl_2. The organic layer was washed, dried ($MgSO_4$), filtered and concentrated in vacuo. The cyanohydrins **17** or **18** were purified by chromatography (eluent gradient, EtOAc/pentane 1:3 → 1:2).

6^A-Azido-6^D-C-cyano-$2^{A–F}$,$3^{A–F}$,$6^{B,C,E,F}$-hexadecakis-*O*-benzyl-α-cyclodextrin (17)

White foam (93%); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ 7.41–7.04 (m, 80H, Ar–H), 5.48 (d, 1H, $^3J_{1,2} = 2.7$ Hz, H-1), 5.42–5.37 (m, 2H), 5.32–5.30 (m, 4H), 5.28–5.19 (m, 2H), 5.14–5.12 (m, 2H), 5.07 (d, 2H, $^3J_{1,2} = 10.2$ Hz, H-CHPh), 5.021–5.0 (m, 3H), 4.95–4.64 (m, 12H), 4.62–4.22 (m, 22H), 4.15–3.67 (m, 12H), 3.63–3.21 (m, 12H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 139.97–137.14 (C_{ipso}), 130.0–126.0 (C_{Ar}), 120.4 (CN), 119.2 (CN), 101.1, 100.3, 99.4, 98.8, 98.6, 98.2, 98.1, 97.9, 97.5 (C-1), 82.15–74.67, 73.9, 73.97–69.44 (CH_2, CH), 63.06 (*C*H(OH)CN), 60.01 (*C*H(OH)CN), 30.59 (*C*–N_3); MALDI-TOF–MS *m/z* calcd for $C_{149}H_{154}O_{29}N_4$ 2464.83, found 2465.3.

6^A-C-cyano-6^D-N-Boc-amino-$2^{A–F}$,$3^{A–F}$,$6^{B,C,E,F}$-hexadecakis-*O*-benzyl-α-cyclodextrin (18)

White foam (88%); ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ 7.59–6.90 (m, 80H, Ar–H), 5.52 (bs, 1H, H-1), 5.39 (d, 1H, $^3J_{1,2} = 11.7$ Hz, H-CHPh), 5.31 (d, 2H, $^3J_{1,2} = 10.8$ Hz, H-CHPh), 5.23 (bs, 1H, H-1), 5.17 (d, 2H, $^3J_{1,2} = 9.6$ Hz, H-CHPh), 5.08 (d, 2H, $^3J_{1,2} = 10.2$ Hz, H-CHPh), 5.02 (d, 2H, $^3J_{1,2} = 12$ Hz, H-CHPh), 4.96–4.59 (m, 10H), 4.57–4.29 (m, 14H), 4.22–3.72 (m, 12H), 3.67–3.52 (m, 4H), 3.47–3.35 (m, 20H), 3.28–3.26 (m, 4H), 1.43 (s, 3H, C–$(CH_3)_3$), 1.40 (s, 6H, C–$(CH_3)_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 156.36 (NH–CO), 138.54–138.14 (C_{ipso}), 128.32–127.59 (C_{Ar}), 99.27–98.96 (C-1), 81.10–69.38 (CH_2, CH), 63.4 (*C*H(OH)CN), 29.95, 28.76 ($C(CH_3)_3$). MALDI-TOF–MS *m/z* calcd for $C_{154}H_{164}O_{31}N_2Na^+$ 2560.12, found 2560.2.

General procedure for oxidation of cyclodextrin-aldehydes to acid:

The aldehyde **12** (0.224 g, 0.1 mmol) was dissolved in a mixture of THF (3 mL), 2-methyl-2-butene (3 mL) and *tert*-butanol (3 mL). A solution of $NaClO_2$ (18.5 eq., 1.84 mmol, 0.166 g) and NaH_2PO_4 (15 eq., 0.202 g, 1.48 mmol) in water (3 mL) was added to the reaction and the mixture was stirred at room temperature overnight. The reaction was quenched with 2 mL of 1 M HCl and extracted with EtOAc. The organic phase was separated, dried ($MgSO_4$) and evaporated. The product was purified on silica gel column with EtOAc/pentane (1:5–2:5 + 1% HCOOH) to give the corresponding azido-acid. Compound **20** was obtained in 92% yield (0.225 g), experimental datas were according to literature [31].

General procedure for global deprotection:

Compound **18** (or **20**) (1 mmol) was dissolved in an AcOEt/MeOH mixture (1:1, 200 mL). Pd/C (400 mg) and TFA (cat.) were then added and the mixture was stirred overnight under H_2 atmosphere. Filtration over a Millipore nylon membrane and evaporation of the solvent gave compound **19** (or **21**) in quantitative yield as white solid. The products were confirmed by MALDI-TOF spectra, ^{1}H- and ^{13}C-NMRs.

6^A-C-cyano-6^D-amino-α-cyclodextrin (19)

^{1}H NMR (300 MHz, D_2O, 25 °C) δ 5.10 (dd, $J = 3.6$, 7.2, 3H, H-1), 5.08–5.03 (m, 3H, H-1), 4.16–4.04 (m, 2H), 4.02–3.83 (m, 13H), 3.77 (dd, $J = 12.7$, 4.5, 4H), 3.69 (d, $J = 6.5$, 2H), 3.64 (d, $J = 6.2$, 4H), 3.61 (m, 8H), 3.35–3.27 (m, $J = 6.9$, 1H), 3.18–3.12 (m, 1H)); ^{13}C-NMR (100 MHz, D_2O): δ 119.00–117.55 (CN), 101.75–101.64 (C-1), 81.95, 81.66, 81.37, 73.48, 73.35, 72.47, 72.15, 71.95, 71.71, 60.60 (CH_2, CH); MALDI-TOF–MS *m/z* calcd for $C_{37}H_{60}O_{29}N_2Na^+$ 1019.32, found 1018.94.

6^A-Carboxy-6^D-amino-α-cyclodextrin (21)

^{1}H NMR (300 MHz, D_2O, 25 °C) $\delta = 4.99$ (d, $J = 2.3$, 1H, H-1), 4.97–4.92 (m, 3H, H-1), 4.91 (d, $J = 2.2$, 2H, H-1), 3.98–3.82 (m, 6H), 3.81–3.64 (m, 11H), 3.57 (dd, $J = 15.3$, 8.9, 14H), 3.17 (dd, $J = 13.1$, 8.3, 2H), 2.61–2.45 (m, $J = 18.5$, 1H); ^{13}C NMR (126 MHz, D_2O): δ 165.75 (COOH), 104.77–103.45 (6 C-1), 85.75–85.62, 84.17, 84.14, 83.99, 83.92, 75.91, 75.90, 75.76, 75.72, 75.10, 74.77–74.63, 74.57–74.42, 74.30–74.25, 71.89–71.85, 70.98, 68.36, 63.15–63.00, 43.20 (CH_2, CH); MALDI-TOF–MS *m/z* calcd for $C_{36}H_{59}O_{30}NNa^+$ 1008.30, found 1008.81.

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