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Chemical Clockwise Tridifferentiation of α- and β-Cyclodextrins: Bascule-Bridge or Deoxy-Sugars Strategies

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Abstract: The selective and efficient functionalisation of large concave molecules is a chemical challenge opening the door to various applications, such as artificial enzymes. We propose here a method, based on deprotection of benzylated cyclodextrins, to selectively access a variety of complex structures with two or three new different functionalities on the primary platform. Our strategy is based on a mechanistic hypothesis involving the approach of an aluminium reagent between the primary oxygen atom and the endocyclic one of the same sugar unit. Due to its cyclic directionality, a change in steric hindrance on a given position of the cyclodextrin has a different effect on the clockwise or the counterclockwise directions. This concept is illustrated and exploited in two complementary ways: deoxygenation of the primary position of two diametrically opposed sugars induces a debenzylation reaction on the neighbouring clockwise sugars of α- and β-cyclodextrins. Reversible capping, or bascule-bridging, of the same pair of sugars has the same effect on the debenzylation of α-cyclodextrin, but induces an important change of the geometry of β-cyclodextrin, hence allowing the selective access to yet another functionalisation pattern. A combined use of deoxygenation and bascule-bridging allows the access to an α-cyclodextrin with its three pairs of primary functions differentiated and ready for further modifications. Bascule-bridge or deoxy-sugars are two complementary means to operate steric decompression and induce selective reactions to efficiently access a number of new patterns of functionalities on concave molecules.

Keywords: aluminum · concave molecules · cyclodextrins · oligosaccharides · regioselectivity

Introduction

Concave molecules are at the root of host–guest chemistry,[1] which bears great promises as well as stimulating challenges for chemists. The analogy of their cavities with those naturally occurring in proteins, the role of which is not only to host but also to transform, qualify concave molecules as potential artificial enzymes.[2] Common concave molecules, such as cyclodextrins (CDs), calixarenes and resorcinarenes, are cyclic oligomers made of identical repeating units, mainly aromatics or sugars in the case of CDs. This uniformity is inherent to the difficulty to topologically differentiate distinct positions of the cavity, a classical problem in the development of artificial enzymes. The design of the now classical CD–diimidazole ribonuclease enzyme mimic[3] was indeed intimately related to the possibility of functionalizing two adjacent positions on the primary rim of CDs.[4] Two major problems are encountered when one wants to functionalise a cyclic structure formed of *n* identical subunits: the control on one hand of the number of similar functionalities introduced, and, on the other hand, of the regioselectivity of the functionalisation of this structure. Due to clear symmetry reasons, incorporating a new functionality on a single site is rather straightforward through control of the reagent's quantity,[5] but when two or more sites need to be transformed, then the number of possibilities implies more sophisticated techniques. So far, two strategies have been developed to selectively polyfunctionalise the primary rim of CDs. The first one is based on the use of sterically hindered reagents and proved for geometrical reasons to be mainly efficient on α-CDs.[6] The second one, more efficient on β-CDs, consists in capping the CD with bifunctional re-

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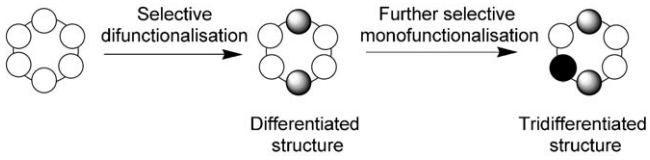
agents.[7,8] When one wants to go one step further and introduce a second functional group different from the first one in order to get a tridifferentiated cycle (Scheme 1) the same

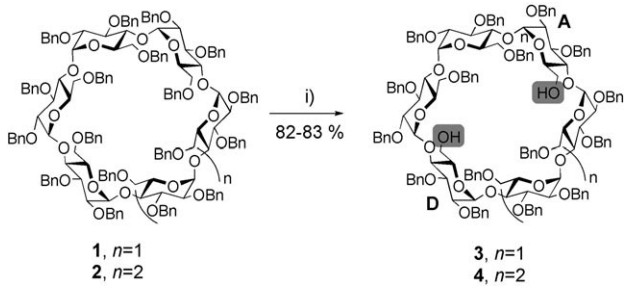


Scheme 1. Schematic representation of differentiated and tridifferentiated cyclic oligomers.

problems are encountered, with even more possible regioisomers formed. For the sake of clarity, we wish to define these terms. A cyclic structure based on the assembly of *n* monomeric units bearing two different functionalities will be called a differentiated structure. If it contains three different functionalities, this structure will be tridifferentiated, and so on.

As a consequence, only very few examples of tridifferentiated macrocycles are reported.[9] In the case of the primary rim of CDs only two patterns of tridifferentiation are so far selectively accessible: a tridifferentiated β-CD based on the regioselective opening of a $6^A,6^B$-cap[10] and an asymmetric $6^A,6^B$-capping of γ-CD.[11] We wish to present herein a full account of our work on the sequential functionalisation of the upper rim of α- and β-cyclodextrins efficiently affording previously inaccessible tridifferentiation patterns.

The starting point of this story is the discovery of an original blueprint strategy to regioselectively deprotect sugars[12] that allowed the spectacular differentiation of cyclodextrins.[13] A fully benzyl-protected CD is selectively bis-deprotected by using diisobutylaluminium hydride (DIBAL-H) to afford $6^A,6^D$-diols **3** and **4** in 82 and 83% yield from α- and β-CDs **1** and **2**, respectively (Scheme 2).[13] A remarkable



Scheme 2. Debenzylation of α- and β-CDs **1** and **2**. i) DIBAL-H (15 equiv, 1.5 M, or 30 equiv, 1 M), toluene, 50 °C, 2 h.[15]

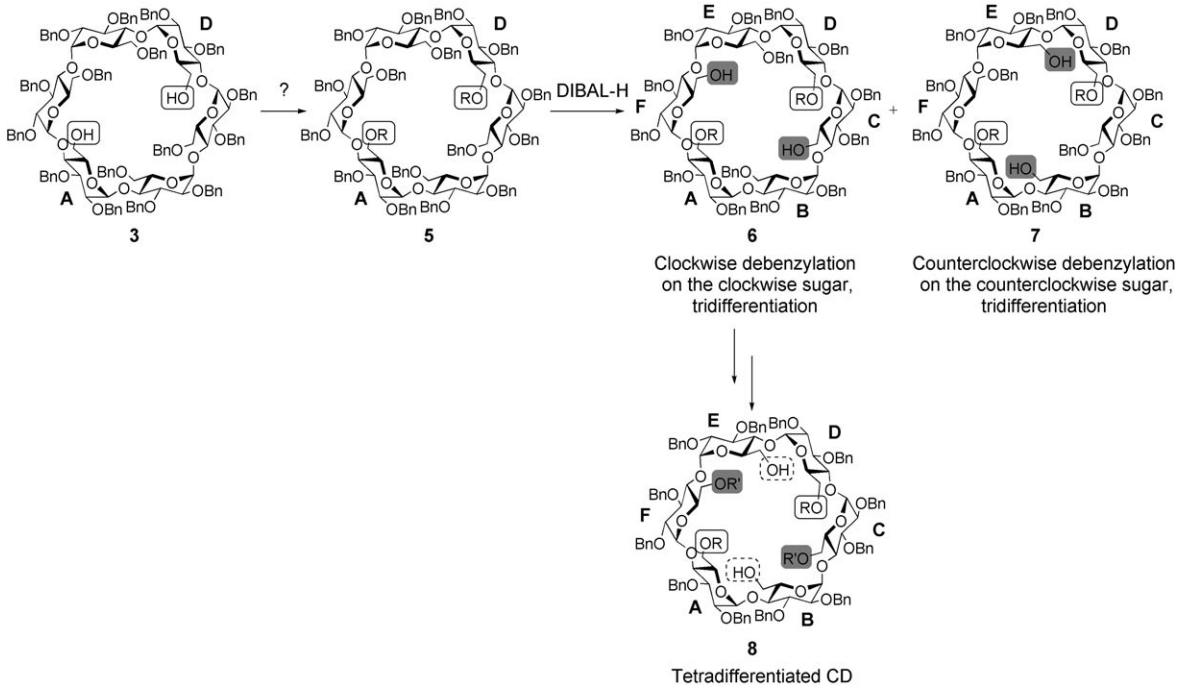
feature of this reaction is that it is a rare example of selective CD bis-functionalisation being as efficient on α- and β-CDs.[8] As an illustration of our previous assumption on the link between easy functionalisation and access to novel artificial enzymes, M. Bols et al. nicely used this methodology to build up a series of efficient artificial enzymes.[14]

We would now like to give the full account of the duplication of this process that allows the tridifferentiation of the upper rim of α- and β-CDs.

Abstract in French: *La fonctionnalisation sélective et efficace de grosses molécules concaves constitue un défi ouvrant la voie à de nombreuses applications, notamment dans le domaine des enzymes artificielles. Nous proposons dans ce travail une méthode, basée sur la déprotection de cyclodexyrines benzylées, donnant un accès sélectif à une variété de structures complexes possédant deux ou trois fonctionnalités nouvelles et différentes sur la plateforme primaire. Notre stratégie repose sur une hypothèse mécanistique impliquant l'approche d'un réactif aluminique entre l'atome d'oxygène primaire et celui inclus dans le cycle d'une même unité glucosidique. Par suite de la directionalité cyclique d'une cyclodextrine, une modification de l'encombrement stérique sur une position primaire donnée a un effet différent sur l'unité voisine selon sa position dans le cycle: horaire ou trigonométrique. Ce concept a été illustré et exploité de deux façons complémentaires: une désoxygénation des positions primaires de deux sucres diamétralement opposés induit une réaction de débenzylation de l'α- et de la β-cyclodextrine sur les deux sucres voisins dans le sens horaire. Un pontage réversible, ou pont à bascule, de la même paire de sucres oriente la débenzylation de la même façon dans le cas de l'α-cyclodextrine, mais produit un changement important dans la conformation de la β-cyclodextrine, permettant ainsi un accès sélectif à un autre type de substitution. Un emploi combiné de la désoxygénation et du pont à bascule sur l'α-cyclodextrine permet l'accès à une cyclodextrine ayant trois paires de groupements protecteurs orthogonaux. Le pont à bascule ou les sucres désoxygénés constituent ainsi deux moyens complémentaires de décompression stérique induisant des réactions sélectives donnant un accès efficace à de nombreux profils de substitution de molécules concaves.*

Results and Discussion

α-Cyclodextrin: Our strategy is based on our ability to synthesise an α-CD (**5**) functionalised on positions $6^A,6^D$ by an appropriate OR group resistant to DIBAL-H (Scheme 3). The question we wish to address here is whether it is possible to duplicate the DIBAL-H deprotection in a regioselective manner on this functionalised $6^A,6^D$-cyclodextrin **5**, that is, to operate a clockwise (**6**) or counterclockwise (**7**) double debenzylation reaction, considering the CD as seen from the primary rim. Only two diametrically opposed hydroxyl groups are expected to be deprotected, by analogy with the first deprotection process. CDs **3** and **5** bearing two different functionalities will be defined as differentiated CDs; CDs **6** and **7** possessing three different functionalities will be defined as tridifferentiated CDs. Finally, another DIBAL-H resistant functionalisation followed by a final debenzylation



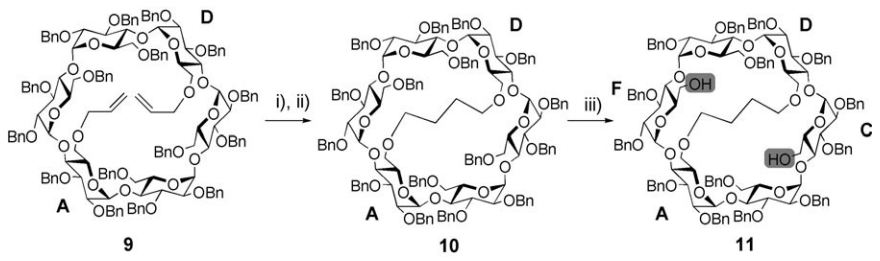
Scheme 3. Principles of the duplication of the DIBAL-H process.

would lead to a tetradifferentiated CD such as **8** with four different functionalities, three on the primary rim, one on the secondary rim (Scheme 3). To the best of our knowledge, these compounds would be the first examples of tri- and tetradifferentiated α-cyclodextrins.

Bascule-bridged CD—tridifferentiation: During the course of the elucidation of the reaction mechanism,[13] we had to decide whether the second debenzylation on the CD was induced by an aluminium derivative connected to the first debenzylation site, or by an independent process. To address this question, we synthesised the capped-CD **10** by means of a ring-closing metathesis (RCM) of the diallyl derivative **9** and reduction, hence reasonably preventing interaction between the two diametrically opposed potential debenzylation sites (Scheme 4). Subjected to the action of DIBAL-H the capped α-CD **10** reacted in a very informative way: not only two independent debenzylation reactions occurred, thus answering our question, but a most remarkable regioselectivity was observed resulting in the formation of the single diol **11**.

Considering our mechanistic hypothesis involving the approach of two molecules of aluminium reagent on the chelate O5/O6,[13] we deduced from this result that the approach of aluminium derivatives on a glucopyranoside unit was highly sensitive to the steric hindrance exerted by the protecting group located on the primary position of the neighbouring counter-clockwise sugar, for example on sugar **D** of capped-CD **10**. Indeed, as shown on Figure 1, the approach of an aluminium derivative on the $O5^A/O6^A$ pair is kinetically hindered by the presence of a benzyl moiety on the 6-position of the counterclockwise sugar **B**. Due to the cyclic directionality of the CD, the 6-benzyloxy group of the clockwise sugar **F** seems too far away to interact with the aluminium derivative (Figure 1).

According to this hypothesis, we supposed that the methylenic bridge induced a steric modification, resulting in the regioselective clockwise debenzylation of the capped-CD **10** into diol **11**. Furthermore, we thought that this result might be independent from the nature of the bridge. Indeed, we showed by molecular modeling that the tetramethylene-capping of the CD induces the orientation of the $O6^A$ and $O6^D$ towards the inside of the cavity.[13] Very interestingly, this conformational change precludes the formation of chelates on these glucose moieties, making the



Scheme 4. Duplication of the DIBAL-H process on the capped CD **10**. i) $[Cl_2(PCy_3)_2Ru{=}CHPh]$, CH_2Cl_2, reflux, 1.5 h, then $Pb(OAc)_4$, RT, 3 h, 92%; ii) PtO_2, H_2, EtOAc, 90%; iii) DIBAL-H, toluene, 50°C, 2 h, 86%.

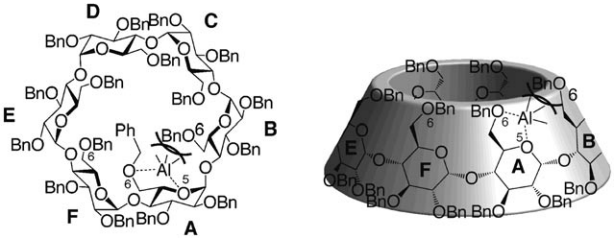
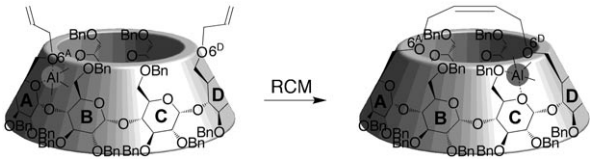


Figure 1. Approach of the aluminium atom on the perbenzylated CD.

cap DIBAL-H resistant, and also relieves steric hindrance on sugar units **C** and **F** (Scheme 5).

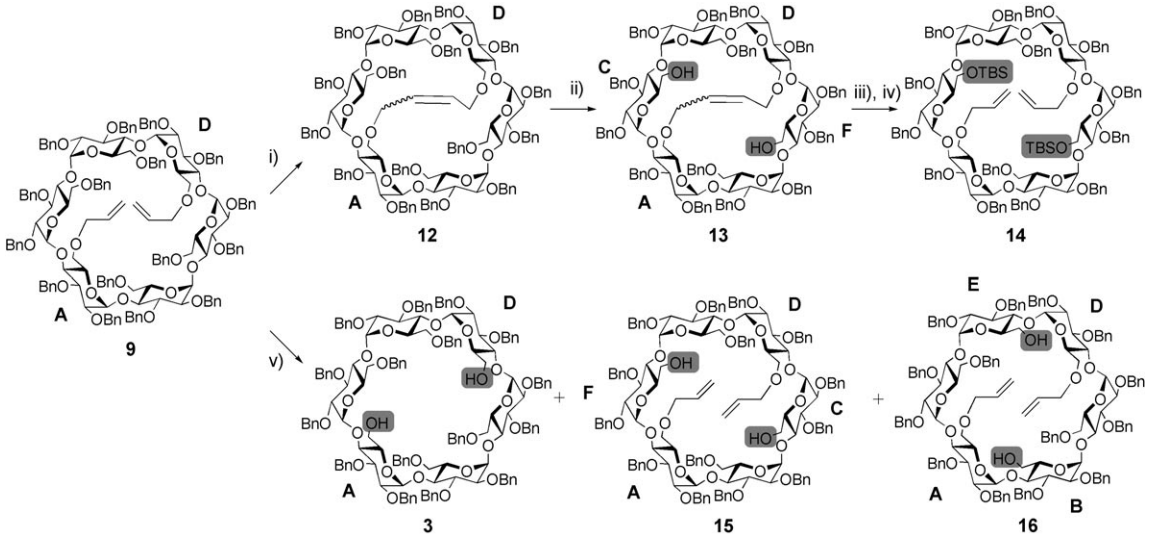


Scheme 5. Capping of the CD induces regioselectivity.

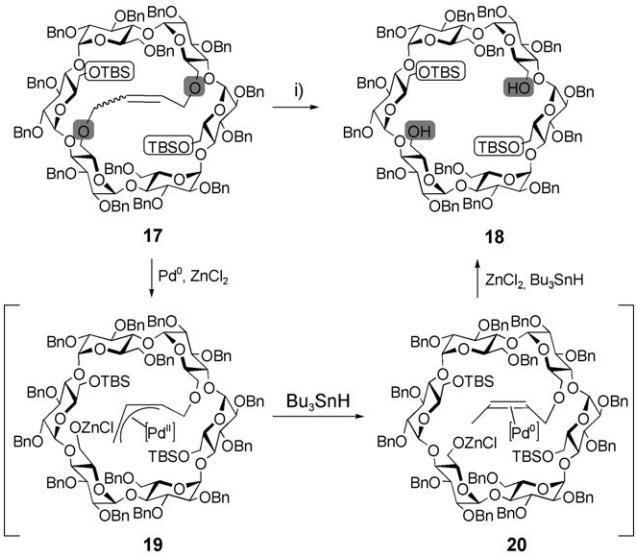
We hence supposed that the difference in reactivity between the bridge and a pair of benzyl groups is independent from the nature and electronic properties of these two ethers. We therefore capped the diallylic CD **9** by means of a RCM using Grubbs catalyst, but did not reduce the formed double bond, and submitted this unsaturated capped-CD **12** to the action of DIBAL-H.[16] As hoped, the nature of the bridge did not change the outcome of the reaction, which afforded the diol **13** in 79% yield. The structure of this regioisomer was confirmed by selective hydrogenation of the alkene and comparison of the spectroscopic data of the resulting compound with that of CD **11**. The remaining double bond critically allowed the reopening of the bridge and the restoration of the allyl protecting groups through another metathesis reaction in the presence of Grubbs catalyst under an atmosphere of ethylene (Scheme 6). This reversible process clearly reminds of the machinery of a bascule-bridge allowing regioselectivity through its closing. To illustrate the importance of the capping step, we also submitted the diallylic CD **9** to the action of DIBAL-H and not surprisingly obtained a mixture of the three possible regioisomers. This way to temporarily turn off the reactivity of an allyl group through a conformational bias is quite noticeable.

The re-opening of the bridge nicely illustrated the utility of the reversibility of the metathesis reaction in an original way, but its direct removal would alleviate the synthesis. To this purpose, we designed a new double de-allylation process involving the successive formation of two π-allyl complexes. When placed in the presence of Pd^0, a Lewis acid ($ZnCl_2$) and a hydride donor (Bu_3SnH) CD **17** afforded diol **18** in 75% yield. The Lewis acid on the allyl ether helps the formation of the *p*-allyl **19**, which is reduced on its less hindered side, restoring an allylic ether **20** cleaved in the same way to afford diol **18** (Scheme 7).[17]

This double de-allylation allowed us to use another capping: the methallyl bridge introduced by Bols in another context.[18] It has been introduced in one step using 3-chloro-2-(chloromethyl)-1-propene and sodium hydride, affording CD **21** in 92% yield. This bridge also promotes the regioselective debenzylation reaction in the presence of DIBAL-H in 90% yield. Silylation of the obtained diol **22** followed by Pd^0-catalysed double de-allylation then gives the diol **17** in 88% yield. This synthetic scheme provides an efficient access to the doubly tridifferentiated CD **18**, thus obtained in six steps and in 58% overall yield from native α-CD (Scheme 8).[19]



Scheme 6. Action of DIBAL-H on bis-allylated CD **9**. Reagents and conditions: i) $[Cl_2(PCy_3)_2Ru{=}CHPh]$, CH_2Cl_2, reflux, 1.5 h then $Pb(OAc)_4$, RT, 3 h, 92%; ii) DIBAL-H, toluene, 50°C, 1 h, 84% ; iii) TBSOTf, pyr, CH_2Cl_2, RT, 2 h, 95%; iv) $[Cl_2(PCy_3)_2Ru{=}CHPh]$, $CH_2{=}CH_2$, CH_2Cl_2, RT, 3 days then $[Pb(OAc)_4]$, RT, 3 h, 70%; v) DIBAL-H, toluene, 50°C, 2 h, 79% (**3:15:16**, 51:18:9).



Scheme 7. Direct synthesis of diol **18** through double de-*O*-allylation. Reagents and conditions: i) $[Pd(PPh_3)_4]$, $ZnCl_2$, Bu_3SnH, THF, RT→reflux, 12 h, 75%.

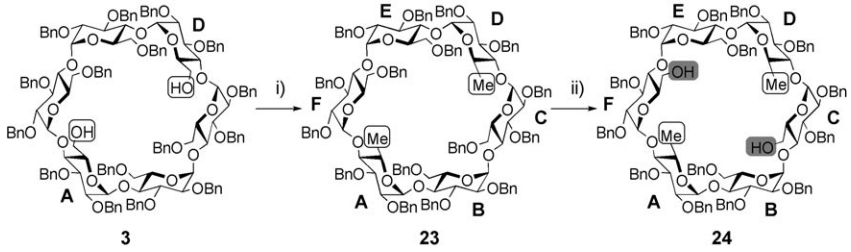
Hence, we have demonstrated that the reversible bridging of CD diol **3** allows the duplication of the DIBAL-H-promoted debenzylation reaction in a fully regioselective counterclockwise manner and the synthesis of a useful tridifferentiated CD synthon in high yield. The proposed explanation for the regioselectivity lies in the steric decongestion induced by the bridge of the O5/O6 pair of the glucose units located clockwise to it. This is a rather sophisticated way to achieve steric decompression and we decided to simplify this process while sustaining this hypothesis.

Deoxy sugars—tridifferentiation: An obvious way to decrease the steric hindrance induced by a benzyloxy group is to remove it. We therefore synthesised 6^A,6^D-dideoxy CD **23**, through mesylation and reduction of the diol **3**, and submitted it to the action of DIBAL-H. Much to our delight, the outcome of the reaction was the expected clockwise di-debenzylation of compound **23** affording the diol **24** in 75% yield (Scheme 9).[20]

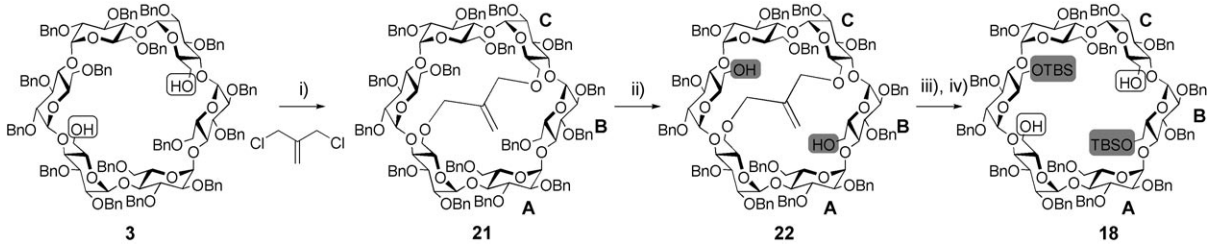
We hereby confirmed that a steric decompression on the 6^A,6^D-positions could explain and induce the clockwise 6^C,6^F-duplication of the DIBAL-H deprotection. As illustrated on Scheme 10, the aluminium reagent approaches the $O5^C/O6^C$ pair more easily than the $O5^B/O6^B$ one due to the difference of steric hindrance between a hydrogen and a benzyloxy group. However, the drawback of this concept is the impossibility to further functionalise the deoxy sugars **A** and **D**.

We therefore synthesised 6^A,6^D-dideoxy CD **26** bearing vinyl groups, because they can be reversibly converted into alcohols. This deoxy CD **26** is obtained from diol **3** by an oxidation–Wittig olefination sequence. When submitted to the action of DIBAL-H, it readily afforded the expected clockwise diol **27** in 90% yield. This diol can be converted into the tridifferentiated CD **18**, previously synthesised using the capping strategy, by means of a silylation and reductive ozonolysis in 61% yield over three steps (Scheme 11). This conversion also confirms the regioselectivity of the debenzylation reaction. This reaction pathway gives a new access to the tridifferentiated CD **18** by using the concept of deoxy sugars. It also illustrates the versatility of the vinyl protection of hydroxyl groups, the importance of which will vividly appear in the next section, as well as in that on β-cyclodextrins.

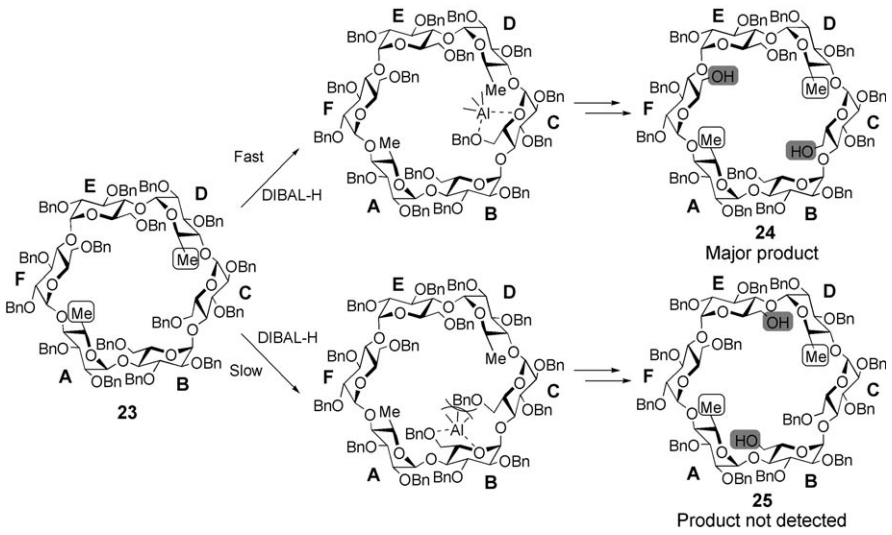
A combination of both techniques—tetradifferentiation: A last pair of benzyl groups on the primary rim remains to be removed preferentially to the ones on the secondary rim.



Scheme 9. Dehydroxylation and regioselective clockwise de-*O*-benzylation. Reagents and conditions: i) a) MsCl, Et_3N, DCM, 0°C→RT, 1 h; b) $LiAlH_4$, THF, RT, 2 h, 78% over two steps; ii) DIBAL-H, toluene, 50°C, 1 h, 75%.



Scheme 8. Synthesis and regioselective de-*O*-benzylation of capped-CD **21**. Reagents and conditions: i) 3-chloro-2-(chloromethyl)-1-propene, NaH, RT, 2 h, 92%; ii) DIBAL-H, toluene, 50°C, 1 h, 90%; iii) TBSOTf, pyr, CH_2Cl_2, RT, 2 h, 95%; iv) $[Pd(PPh_3)_4]$, $ZnCl_2$, Et_3SiH, THF, reflux, 6 h, 88%.



Scheme 10. Approach of the aluminium atom on the deoxy-CD **23**

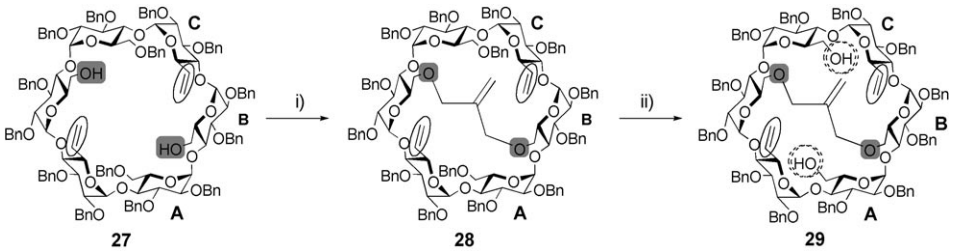
We would then get the first CD bearing four different functional groups: three pairs on the primary rim and a different one on the secondary rim.

An orderly sequential use of the two previously described strategies fulfilled the purpose in view. The tridifferentiated CD diol **27**, collected through the use of deoxysugar approach was bridged to capped-CD **28**. This compound was submitted to the action of DIBAL-H for the third time. It solely afforded the CD **29** in a rewarding 93% yield. This molecule is the first example of a tetradifferentiated CD bearing three pairs of orthogonal functionalities on the primary rim and benzyl groups on the secondary positions (Scheme 12). The use of this strategy was made necessary by the reactivity of esters, silyl groups or methyl and allyl ethers, with the aluminium reagent.

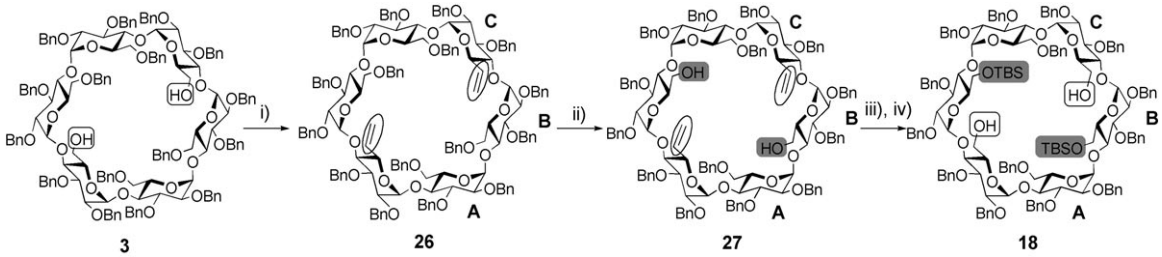
To demonstrate that the successive liberation of the three pairs of hydroxyl groups on the primary rim of CD **29** is possible, the two free primary alcohols were first silylated, the cap being next removed using Pd^0 to afford diol **30**. This compound was classically acetylated. Finally, the double bonds were transformed back into hydroxyl groups by ozonolysis/reduction sequence, affording the diol **31**. We thus obtained a new CD **31** from CD **29** for which all three pairs of functionalities on primary positions of the sugars were changed into another one, showing the orthogonality of the original protections on compound **29** (Scheme 13).

In summary, the principle of steric decompression induced by dehydroxylation and bridging allows the functionalisation of all three pairs of hydroxyl groups on the primary rim of α-CD in a fully selective manner, completing the stripping of this rim. We next turned our attention to the β-CD.

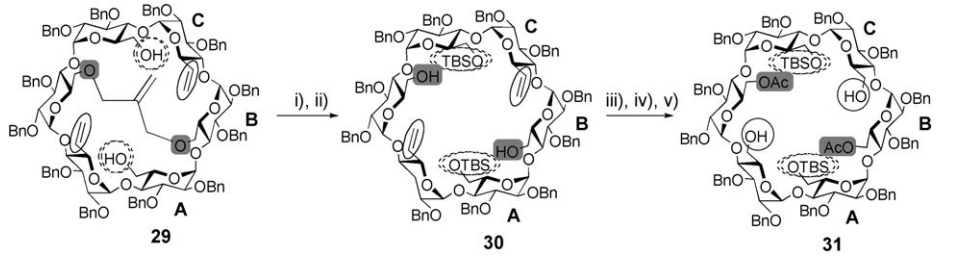
β-Cyclodextrin: As we previously mentioned, a remarkable feature of the debenzylation reaction lies in its equal efficiency on both α- and β-CDs. We therefore had to show that the regioselective duplication of this process could also be performed on β-CD. The challenge here is even more stimulating, because of lack of symmetry: the duplication of



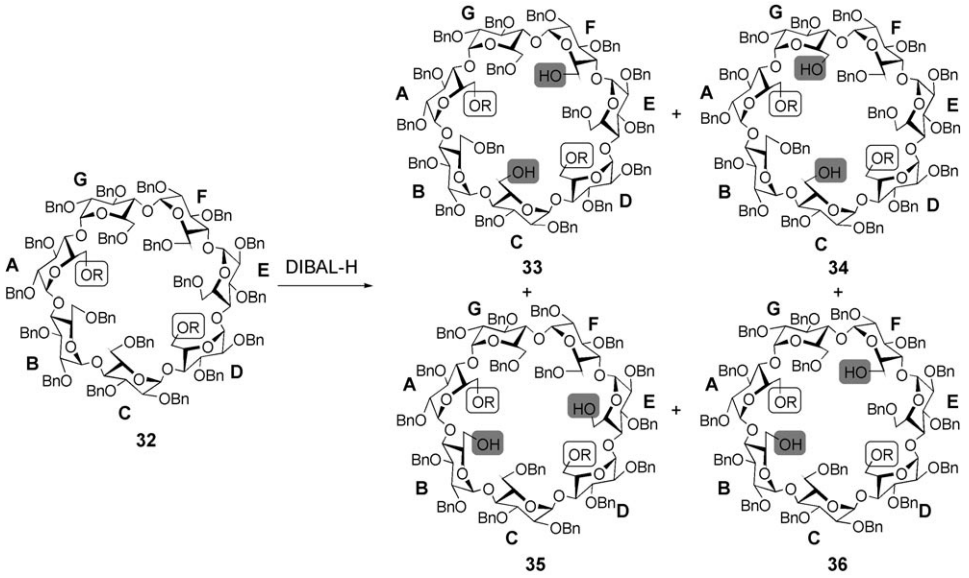
Scheme 12. Tetradifferentiation of the α-CD - i) NaH, **26**, DMF, RT, 2 h 30, 89%; ii) DIBAL-H, toluene, 50°C, 30 min, 93%.



Scheme 11. Synthesis of the tridifferentiated α-CD **18**. i) a) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, RT; b) Ph_3PCH_3Br, *n*BuLi, THF, −40°C → RT, 4 h, 70% (over two steps); ii) DIBAL-H, toluene, 50°C, 1 h 20, 90%; iii) TBSOTf, pyr, CH_2Cl_2, RT, 2 h; iv) 1) O_3, CH_2Cl_2, −78°C, then Me_2S, RT; 2) $NaBH_4$, CH_2Cl_2/MeOH, RT, 61% over three steps.



Scheme 13. Synthesis of the tetradifferentiated α-CD **31**. i) TBSOTf, pyr, CH_2Cl_2, RT, 1 h, quant.; ii) [Pd^0-(PPh_3)$_4$], $ZnCl_2$, Et_3SiH, THF, RT→reflux, 2 h, 80%; iii) Ac_2O, DMAP, Pyr, RT, 1 h, quant.; iv) a) O_3, CH_2Cl_2, −78°C, b) Me_2S, RT; v) $NaBH_4$, CH_2Cl_2/MeOH, RT, 55% over three steps.



Scheme 14. Duplication of the DIBAL-H process on β-CD—four possible regioisomers.

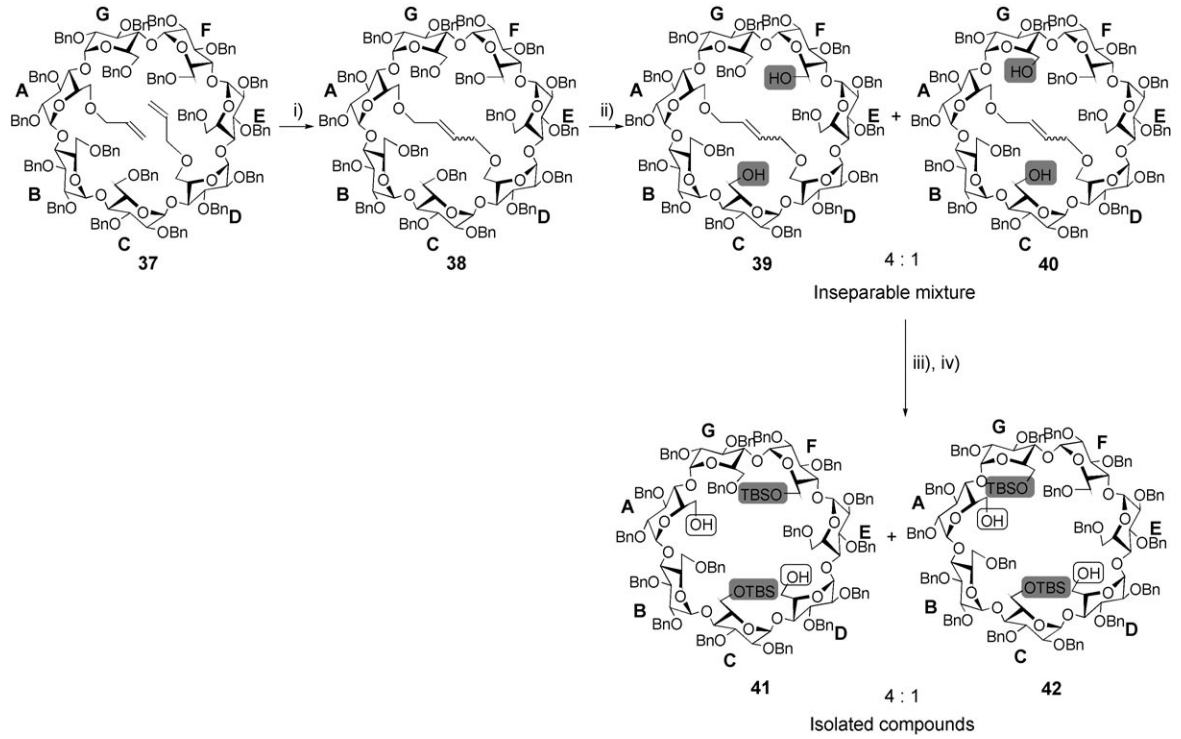
the debenzylation process can lead to four different diametrically opposed diols (Scheme 14).

Bascule-bridged CD—tridifferentiation: We first investigated the bascule-bridge strategy, with capped-CD **38**, synthesised as previously described, through bis-allylation and RCM. Subjected to the action of DIBAL-H, capped-CD **38** afforded an inseparable mixture of two diols that we finally identified, as it will be explained later on, as CD **39** and **40** in a 4:1 ratio. After silylation and removal of the bridge tridifferentiated CDs **41** and **42** could be separately isolated. Very surprisingly, the major product of the duplicate debenzylation on the capped-CD **38** is not the expected 6^C,6^G-clockwise diol **40**, but the unexpected 6^C,6^F-diol **39**, as a result of a debenzylation clockwise to the bridge on 6^C and one on unit **F** clockwise to a sugar bearing a benzyl group on its primary position (Scheme 15). We hypothesised that, due to the capping, the conformation of CD **38** is such that the $O5^F$/$O6^F$ pair—the central pair of the triad **EFG**—must be less hindered than the one borne by glucose unit **G**. Molecular modeling, described in a following section, will confirm that assumption.

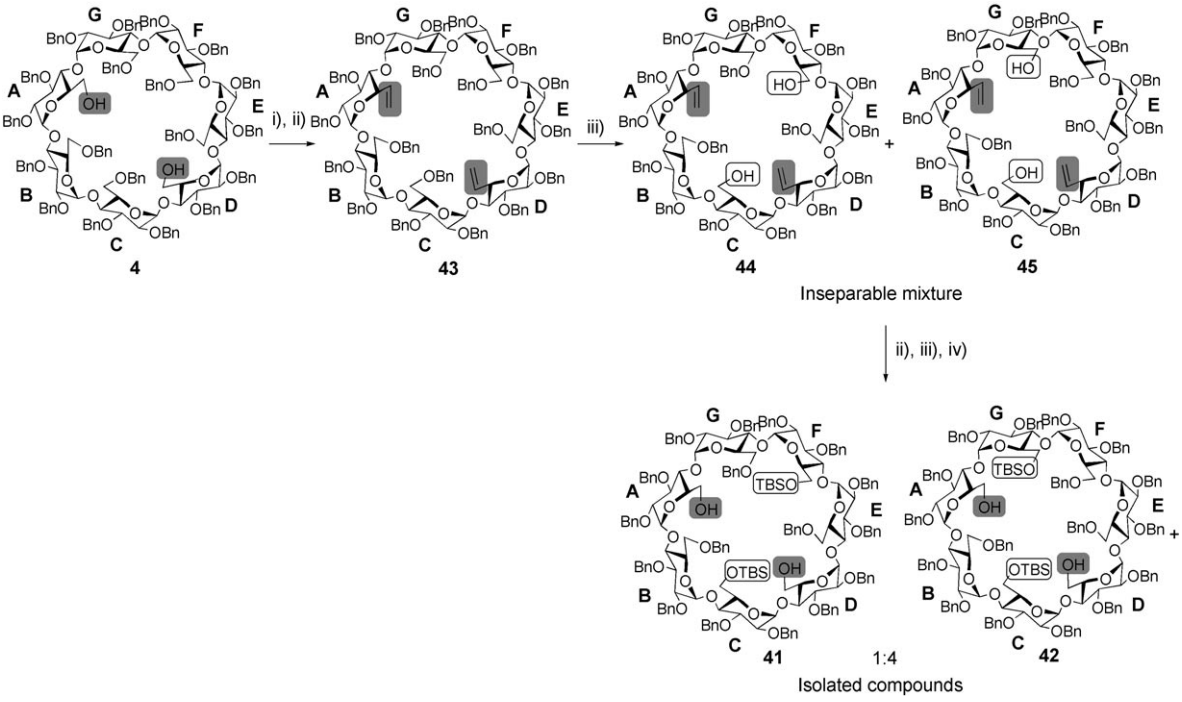
Deoxy sugars—tridifferentiation: The unexpected and surprising result obtained with the bascule-bridge process led us to investigate the deoxy-sugar concept on β-CD. Indeed, in this case no distortion of the CD should be observed, and a simple clockwise debenzylation outcome is expected. Hence, diol **4** was easily converted into the divinyl compound **43** by means of a Swern oxidation and a Wittig olefination in 65% yield. The dideoxy CD **43** was then treated with DIBAL-H and also afforded a mixture of two diols, which appeared to be compounds **44** and **45**, as demonstrated after silylation and reductive ozonolysis, delivering CDs **41** and **42**, in an approximately inverse ratio to the one obtained previously with bridged CD **38**. Much to our delight and according to our expectation, the outcome of the debenzylation reaction was indeed the 6^C,6^G-clockwise process, together with a small amount of the other 6^C,6^F-diol (Scheme 16).

The complementary features of the two concepts, bascule-bridge and deoxy-sugars, is therefore strongly highlighted here. We now have a regioselective access to two different tridifferentiated β-CDs **41** and **42** with totally unprecedented patterns of functionality.

Structural assignment: A rather difficult part in this work has been the structural assignment of the obtained regioisomeric β-CDs **41** and **42**. For proper NMR analysis we first needed to simplify the NMR spectra of our molecules **41** and **42**: it was necessary to get rid of the benzylic protons that overlap some of the proton sugar signals. We hence chose to convert the benzyl groups into acetyl moieties. We also needed reliable tags to be able to clearly identify the different groups on the 6-position of the sugar units. We selected a methyl ether, a deoxygenation of the 6-position and acetyl groups. Indeed, the deoxygenated 6-positions will be very easily detected through their chemical shifts, H6 next to an acetyl group will be deshielded and the remaining H6 will be next to the methyl ethers. Diol **41** was therefore methylated, affording diol **46** after standard desilylation. The



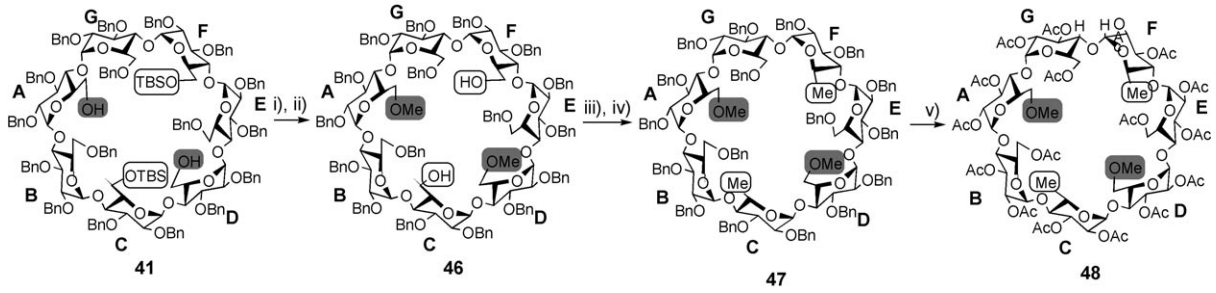
Scheme 15. Tridifferentiation of the β-CD via the capped β-CD **38.** i) DIBAL-H, toluene, 50 °C, 2 h, 74 % ; ii) TBSOTf, pyr, CH_2Cl_2, RT, 2 h, quant.; iii) $[Pd(PPh_3)_4]$, $ZnCl_2$, $n$$Bu_3SnH$, THF, RT→reflux, 20 h, 75 %.



Scheme 16. Tridifferentiation of the β-CD via the di-vinyl β-CD **43**. i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, RT; ii) Ph_3PCH_3Br, nBuLi, THF, −40 °C→RT, 4 h, 65 % (over two steps); iii) DIBAL-H, toluene, 50 °C, 1 h, 56 %; iv) TBSOTf, pyr, CH_2Cl_2, RT, 1 h ; v) O_3, CH_2Cl_2, −78 °C, then Me_2S, RT; vi) $NaBH_4$, CH_2Cl_2/MeOH, RT, 60 % (over three steps).

obtained diol was dehydroxylated by mesylation and reduction to give CD **47**, which was fully debenzylated and acetylated to give CD **48** (Scheme 17).

This compound **48** was analysed by NMR spectroscopy by using a Bruker 600 MHz spectrometer by using COSY, TOCSY, and NOESY experiments as well as the program



Scheme 17. Synthesis of compound **48**. i) NaH, MeI, DMF, 0 °C→RT, 1 h 30, 88 %; ii) nBu$_4$NF, THF, RT, 3 h, 74 %; iii) a) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C→RT, 2 h; b) LiAlH$_4$, THF, RT, 1 h 30, 53 % over two steps; iv) a) H$_2$, Pd/C, THF/H$_2$O, RT, 15 h; b) Ac$_2$O, Pyr., DMAP, RT, 24 h, 65 % over two steps.

TOPSPIN for spectrum analysis. First of all, we had to assign H6 protons of the different glucose units. We clearly identified three sets of H6 protons: the more deshielded ones (over 4 ppm) were assigned to the acetylated O6 of units **B,E,G**, the most shielded ones were attributed to the deoxy sugars **C,F** (Figure 2a). Furthermore, a NOE correlation between the methyl ethers and the H6 clearly pointed out the **A,D** methyl ethers (Figure 2b). The COSY and TOCSY experiments then allowed the assignment of all signals on each cycle; the ones bearing the deoxy function are unambiguously identified as illustrated by Figure 2a. Finally, the sequence of the cycles was reconstituted through H1/H4 NOE cross correlations between different cycles, as shown on Figure 2c.

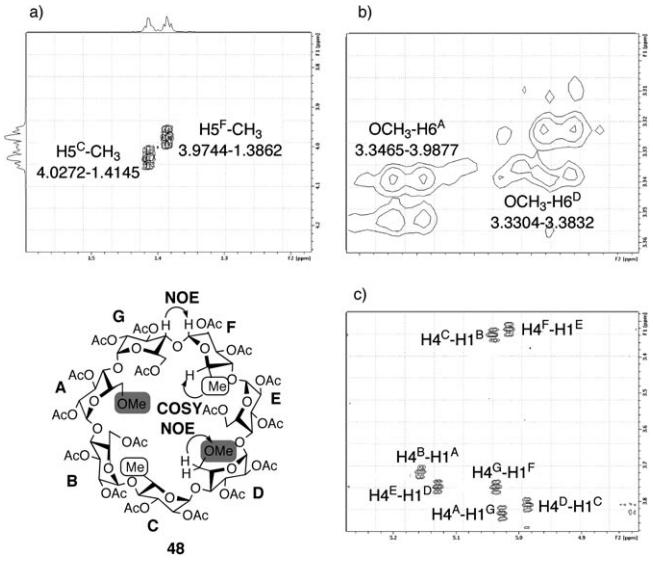


Figure 2. Structural assignment of compound **48**: a) COSY spectrum, b) NOE spectrum, c) NOE spectrum.

Considering the complexity of the NMR spectra, we proposed to use another spectroscopic method to confirm our first deduction. The "hex-5-enose degradation" method proved to be useful in related cases.[21] We therefore substituted the four hydroxyl groups of desilylated CD **41**, affording tetraiodinated-CD **49**, which was further degraded by Zn-mediated reductive cleavage.[22] The resulting mixture was reduced for stability reasons, and analysed as such by mass spectrometry. Two peaks indicated the presence of two sets of fragments of 760 and 328 molecular mass, which confirmed our NMR analysis (Scheme 18).

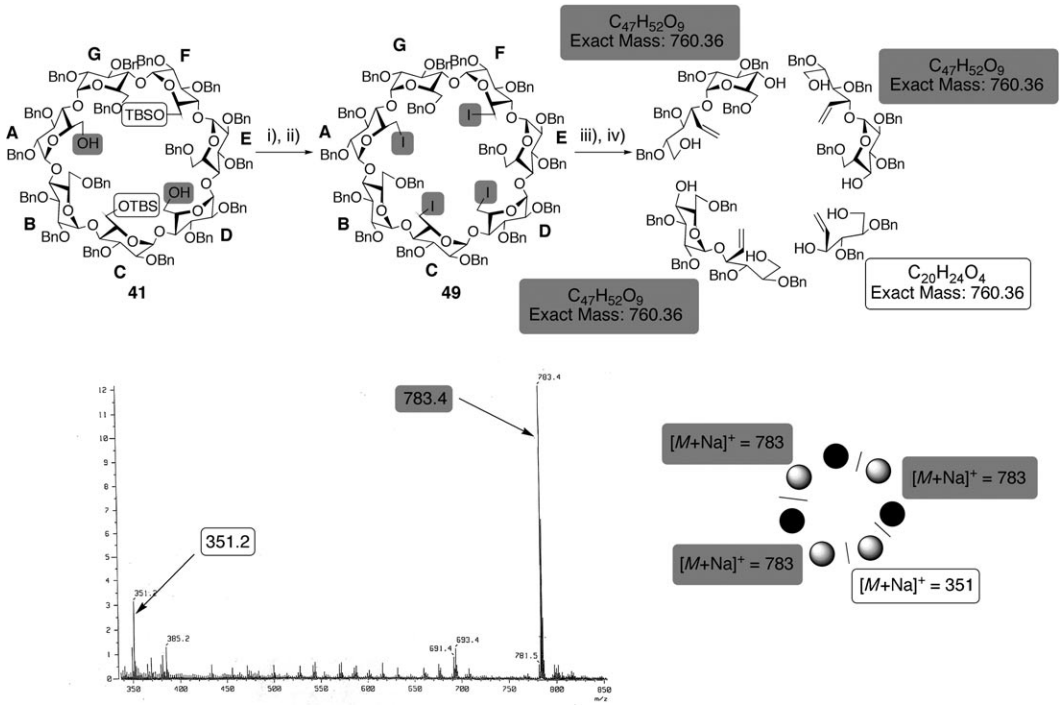
The same set of transformations on the other regioisomer **42** afforded the acetylated compound **52** (Scheme 19). The same NMR analytical techniques, illustrated on Figure 3, clearly allowed the structure elucidation of this compound.

Figure 3a shows the coupling between protons H5 and the deoxy positions on units **C,G**. In this case, we also observed a NOE correlation between H6 protons and OMe groups of cycles **A** and **D** (Figure 3b). Cross correlations between H1 and H4 protons of successive glucose units finally allows the reconstitution of the order of substitutions (Figure 3c).

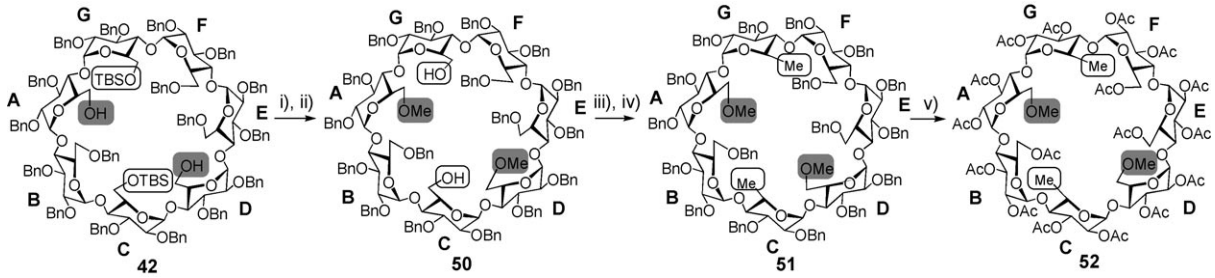
CD **42** was also transformed into tetraiodinated CD **53**, which was subjected to reductive fragmentation, affording a mixture analysed as such by mass spectroscometry (Scheme 20). The three expected molecular peaks were detected, allowing the confirmation of the structural assignment of CD **42**.

Extensive NMR and MS measurements indicated that the major product of the debenzylation of the capped β-CD **38** was the unexpected diol **39**. As we said, we could only presume at this point that O5^F,O6^F-chelate was less hindered than the one on sugar **G**.

Regioselectivity rational: To sustain this hypothesis, we performed molecular modelling. Molecular mechanics calculations were performed with the MM3* program[23] as integrated in the MACROMODEL 7.0 package.[24] First, X-ray structure of permethylated β-CD was used to build the desired compounds **38** by constructing the ethylene bridge between the primary hydroxyl groups of α-Glc units **A** and **D** of the macrocycle and adding the benzyl groups, by using the BUILDER option of MACROMODEL. After the bridge was set, energy optimisations were carried out by using standard conjugate gradient minimisations until convergence was reached. A bulk dielectric constant of 10 Debyes was employed. The resulting simplified structure is shown in the upper part of Figure 4, for sake of clarity we erased the secondary benzyloxy groups and schematised the



Scheme 18. Hex-5-enose degradation applied to compound **41**. i) nBu$_4$NF, THF, RT, 3 h; ii) I_2, PPh_3, imidazole, toluene, 70 °C, 15 h, 51 % over two steps; iii) Zn, nPrOH/H_2O, reflux; iv) $NaBH_4$, MeOH, RT.



Scheme 19. Synthesis of compound **52**. i) NaH, MeI, DMF, 0 °C→ RT, 1 h 30, 77 %; ii) nBu$_4$NF, THF, RT, 3 h, 100 %; iii) a) MsCl, Et_3N, CH_2Cl_2, 0 °C→ RT, 1 h 30; b) $LiAlH_4$, THF, RT, 1 h 30, 40 % over two steps; iv) a) H_2, Pd/C, THF/H_2O, RT, 15 h; b) Ac_2O, Pyr., DMAP, RT, 24 h, 49 % over two steps.

3D structures in the lower part of Figure 4. First of all, it seems clear that the bridging of the β-CD by a tetramethylenic bridge induces a major conformational disruption on the regular structure of the CD. Two major consequences of the capping are the orientation of cycles **A** and **D** towards the inside of the cavity and the exclusion of glucose **F** from the median plan of the CD. This last fact seems to account for the easier access of aluminium derivatives to the $O5^F$,$O6^F$-chelation site. Molecular modelling experiments hence confirm our initial hypothesis concerning the particular steric availability of cycle **F** induced by the CD-capping.

Conclusion

We have presented herein a full account of our work on the sequential regioselective stripping of the upper rim of perbenzylated α- and β-cyclodextrins by pairs of benzyl groups (Scheme 21). To that purpose we developed two techniques to duplicate a first DIBAL-H double deprotection, a first one so-called bascule-bridging based on the consequences of a conformational change induced by a reversible capping of the CD, and a second one based on the steric decompression induced by dehydroxylation of primary positions. These two tricks allow regioselective clockwise debenzylation of α-CDs, and give access to two different patterns of tridifferentiated β-CD. We have also combined those two techniques to obtain, through a third DIBAL-H reaction, the first tetradifferentiated α-CD possessing three functionalities on the primary rim different from that on the secondary rim. This work also strongly supports our proposed mechanism based on the approach of a pair of aluminium derivatives on the less hindered O5/O6 pair of the same glucose subunit.[13] Hence we can say that DIBAL-H is able to read the cyclic

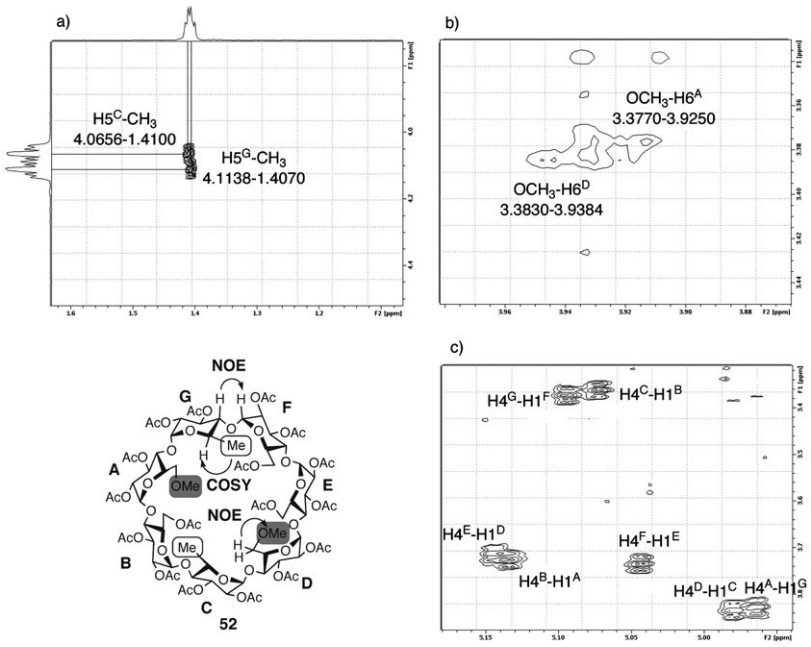


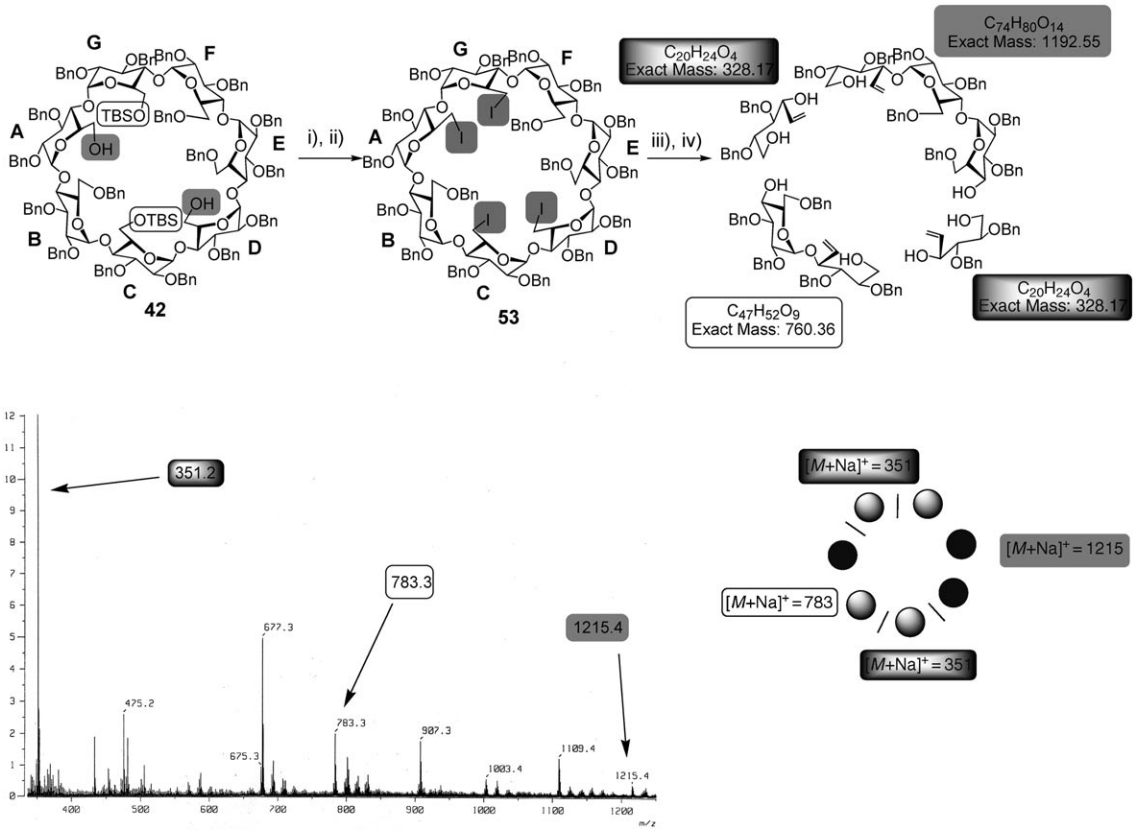
Figure 3. Structural assignment of compound **52**: a) COSY spectrum, b) NOE spectrum, c) NOE spectrum.

directionality and, as a consequence, can promote, in a rather unique manner, a regioselective chemistry at the upper rim of cyclodextrins.

The next step is the use of this novel access to unprecedented complexity in the pattern of functions on the CDs. A few of the possible tracks are currently being explored, for example, asymmetric catalysis and functional materials.

Experimental Section

General: Solvents were freshly distilled from Na/benzophenone (THF, toluene), or P_2O_5 (CH_2Cl_2). Reactions were carried under Ar. Optical rotations were measured on a Perkin–Elmer 241 digital polarimeter with a path length of 1 dm. Fast atom bombardment mass spectra (FAB-MS) were obtained with a JMS-700 spectrometer. Elemental analyses were performed by the Service de Microanalyse de l'ICSN (Gif sur Yvette, France) and Centre Régional de Mesures Physiques de l'Ouest (Rennes, France). ^{1}H NMR spectra were recorded with a Bruker DRX 400 for solutions of the samples in $CDCl_3$ at ambient temperature. Assignments were aided by COSY experiments. ^{13}C NMR spectra were recorded at 100.6 MHz with a Bruker DRX 400 spectrometer for solutions of samples



Scheme 20. Hex-5-enose degradation applied to compound **42**. i) nBu$_4$NF, THF, RT, 3 h; ii) I_2, PPh_3, imidazole, toluene, 70 °C, 15 h, 49% over two steps; iii) Zn, nPrOH/H_2O, reflux; iv) $NaBH_4$, MeOH, RT.

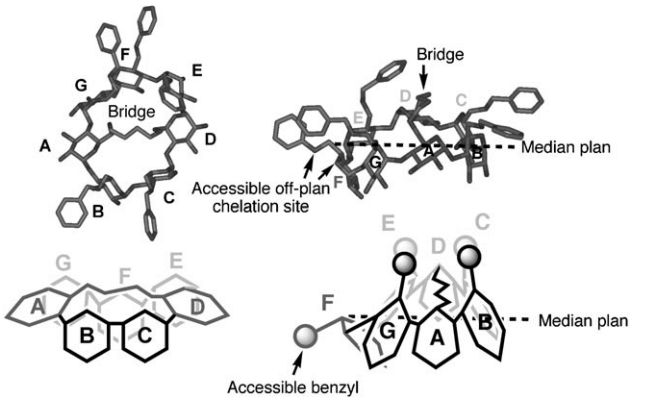
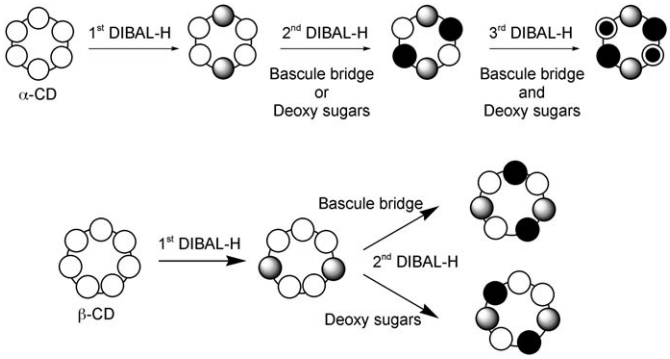


Figure 4. Molecular modelling of the capped β-CD **38.**



Scheme 21. New accessible functionalisation patterns through DIBAL-H reactions.

in $CDCl_3$ adopting 77.00 ppm for the central line of $CDCl_3$. Assignments were aided by J-mod technique and HMQC. C_2-Symmetric CDs such as **13, 14, 15, 16, 18, 22, 23, 24, 26, 27, 28, 29, 30** and **31** are described as trisaccharides to avoid confusion between overlapping signal and those corresponding to equivalent carbons or protons due to the compound symmetry. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of silica gel 60 F_{254} (layer thickness 0.2 mm; Merck, Darmstadt, Germany) and detection by charring with sulfuric acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh, E. Merck). Diisobutylaluminium was purchased from Aldrich as a 1.5 M solution in toluene.

Deprotection of CD 9: DIBAL-H (1.5 M in toluene, 1.8 mL, 2.7 μmol) was slowly added to a solution of **9** (230 g, 92 mmol) in toluene (1 mL) under argon at room temperature. The reaction mixture was heated at 50 °C for 2 h, then cooled to room temperature and poured on ice. The aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Silica gel chromatography of the residue (cyclohexane/EtOAc, 3:1 then 2:1) gave **15** (38 mg, 19%), **16** (19 mg, 9%), and diol **3** (113 mg, 51%), as white foams.

Diol ***15***: $[\alpha]_D^{20} = +39$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 3.44 (dd, $^3J_{2,1} = 3.2$ Hz, $^3J_{2,3} = 9.9$ Hz, 1H; 2-H), 3.51 (dd, $^3J_{2,1} = 3.4$ Hz, $^3J_{2,3} = 9.7$ Hz, 1H; 2-H), 3.61 (dd, $^3J_{1,2} = 3.9$ Hz, $^3J_{2,3} = 9.7$ Hz, 1H; 2-H), 3.72 (dd, $^3J_{4,3} = {}^3J_{4,5} = 8.9$ Hz, 1H; 4-H), 3.78–4.03 (m, 13H; 2×4-H, 3×5-H, 6×6-H, 2× $OCH_2CH{=}CH_2$), 4.05 (dd, $^3J_{3,2} = {}^3J_{3,4} = 9.1$ Hz, 1H; 3-H), 4.15 (dd, $^3J_{3,2} = {}^3J_{3,4} = 8.8$ Hz, 1H; 3-H), 4.25 (dd, $^3J_{3,2} = 9.6$ Hz, $^3J_{3,4} =$ 7.5 Hz, 1H; 3-H), 4.38 (d, $^2J = 12.8$ Hz, 1H; 1×CHPh), 4.41 (d, $^2J =$ 12.8 Hz, 1H; 1×CHPh), 4.48 (d, $^2J = 12.2$ Hz, 1H; 1×CHPh), 4.50 (d, $^2J = 11.9$ Hz, 1H; 1×CHPh), 4.54 (d, $^2J = 12.6$ Hz, 1H; 1×CHPh), 4.58 (d, $^2J = 12.6$ Hz, 1H; 1×CHPh), 4.65 (d, $^2J = 12.2$ Hz, 1H; 1×CHPh), 4.72 (d, $^3J_{1,2} = 3.3$ Hz, 1H; 1-H), 4.76 (d, $^3J_{1,2} = 3.4$ Hz, 1H; 1-H), 4.79 (d, $^2J =$ 9.8 Hz, 2H; 2×CHPh), 4.82 (d, $^2J = 9.0$ Hz, 1H; 1×CHPh), 4.93 (d, $^2J =$ 11.0 Hz, 1H; 1×CHPh), 5.18 (d, $^2J = 1.0$ Hz, $J_{cis} = 10.4$ Hz, 1H; $OCH_2CH{=}CH_2$), 5.22 (d, $^2J = 10.8$ Hz, 1H; 1×CHPh), 5.25 (d, $^2J =$ 1.5 Hz, $J_{trans} = 17.3$ Hz, 1H; $OCH_2CH{=}CH_2$), 5.49 (d, $^2J = 10.3$ Hz, 1H; 1× CHPh), 5.79 (d, $^3J_{1,2} = 3.9$ Hz, 1H; 1-H), 5.85 (ddt, $J_{cis} = 10.8$ Hz, $J_{trans} =$ 16.3 Hz, $^3J = 5.8$ Hz, 1H; $OCH_2CH{=}CH_2$), 7.10–7.32 ppm (m, 35H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 61.4$, 69.5, 69.9 (3×C-6), 71.2, 71.7, 72.0 (3×C-5), 72.4 ($OCH_2CH{=}CH_2$, 2×CH_2Ph), 72.9 (CH_2Ph), 73.4 (2×CH_2Ph), 73.7 (C-4), 73.9, 76.1, 76.4 (3×CH_2Ph), 77.6 (C-2), 79.0 (C-2), 79.8 (C-2), 80.6 (C-3), 80.9 (C-3), 81.2 (C-4), 81.7 (C-3), 81.9 (C-4), 97.6 (C-1), 97.7 (C-1), 98.4 (C-1), 117.6 ($OCH_2CH{=}CH_2$), 126.3–128.3 (35×CH arom.), 134.3 ($OCH_2CH{=}CH_2$), 137.8, 137.9, 138.3, 138.6, 139.2 (5×C arom.quat.), 139.25 ppm (2×C arom.quat.); MS (FAB): *m/z*: 2337.4 $[M+Na]^+$; elemental analysis calcd (%) for $C_{140}H_{152}O_{30}$: C 72.64, H 6.62; found: C 72.29, H 6.91.

Diol ***16***: $[\alpha]_D^{20} = +35$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 3.46 (dd, $^3J_{2,1} = 3.3$ Hz, $^3J_{2,3} = 9.6$ Hz, 1H; 2-H), 3.50 (dd, $^3J_{2,1} = 3.2$ Hz, $^3J_{2,3} = 9.9$ Hz, 1H; 2-H), 3.60 (dd, $^3J_{1,2} = 3.9$ Hz, $^3J_{2,3} = 9.8$ Hz, 1H; 2-Ha), 3.68 (br d, $^2J = 11.4$ Hz, 1H; 6-H), 3.75–4.03 (m, 13H; 3×4-H, 3×5-H, 5×6-H, 2× $OCH_2CH{=}CH_2$), 4.06 (dd, $^3J = 6.9$ Hz, $^3J = 8.4$ Hz, 1H; 3-H), 4.14 (dd, $^3J = 8.0$ Hz, $^3J = 9.3$ Hz, 1H; 3-H), 4.24 (dd, $^3J = 7.0$ Hz, $^3J =$ 9.6 Hz, 1H; 3-H), 4.34 (d, $^2J = 12.6$ Hz, 1H; 1×CHPh), 4.40 (d, $^2J =$ 12.6 Hz, 1H; 1×CHPh), 4.48 (d, $^2J = 11.9$ Hz, 1H; 1×CHPh), 4.49 (d, $^2J = 12.1$ Hz, 1H; 1×CHPh), 4.56 (d, $^2J = 12.6$ Hz, 1H; 1×CHPh), 4.62 (d, $^2J = 11.9$ Hz, 1H; 1×CHPh), 4.74 (d, $^3J_{1,2} = 3.4$ Hz, 1H; 1-H), 4.76 (d, $^3J_{1,2} = 3.4$ Hz, 1H; 1-H), 4.78 (d, $^2J = 11.7$ Hz, 1H; 1×CHPh), 4.80 (d, $^2J =$ 11.0 Hz, 1H; 1×CHPh), 4.81 (d, $^2J = 11.4$ Hz, 1H; 1×CHPh), 4.93 (d, $^2J = 11.9$ Hz, 1H; 1×CHPh), 4.94 (d, $^2J = 10.3$ Hz, 1H; 1×CHPh), 5.20 (d, $^2J = 1.5$ Hz, $J_{cis} = 10.5$ Hz, 1H; $OCH_2CH{=}CH_2$), 5.23 (d, $^2J = 11.0$ Hz, 1H; 1×CHPh), 5.27 (d, $^2J = 1.6$ Hz, $J_{trans} = 17.0$ Hz, 1H; $OCH_2CH{=}CH_2$), 5.51 (d, $^2J = 10.4$ Hz, 1H; 1×CHPh), 5.79 (d, $^3J_{1,2} = 4.0$ Hz, 1H; 1-H), 5.89 (ddt, $J_{cis} = 10.5$ Hz, $J_{trans} = 16.3$ Hz, $^3J = 5.8$ Hz, 1H; $OCH_2CH{=}CH_2$), 7.09–7.33 ppm (m, 35H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 61.3$, 69.4, 69.7 (3×C-6), 71.2, 71.6, 72.0 (3×C-5), 72.2, 72.4 (CH_2Ph, $OCH_2CH{=}CH_2$), 73.1, 73.3, 73.4 (3×CH_2Ph), 73.6 (C-4), 73.8 (CH_2Ph), 76.1, 76.5 (2×CH_2Ph), 77.6, 79.0, 79.8 (C-2), 80.6 (C-3), 80.9 (C-3), 81.3 (C-4), 81.6 (C-4), 81.65 (C-3), 97.7, 97.8, 98.4 (C-1), 117.6 ($OCH_2CH{=}CH_2$), 126.2–128.4 (35×CH arom.), 134.4 ($OCH_2CH{=}CH_2$), 137.8, 137.9, 138.2, 138.6, 139.2, 139.25, 139.3 ppm (7×C arom.quat.); MS (FAB): *m/z*: 2337.1 $[M+Na]^+$; elemental analysis calcd (%) for $C_{140}H_{152}O_{30}$: C 72.64, H 6.62; found: C 72.29, H 6.91.

Diol 13: DIBAL-H (1.5 M in toluene, 36 mL, 54 mmol) was slowly added to a solution of **12** (4.4 g, 1.8 mmol) in toluene (18 mL) under argon at room temperature. The reaction mixture was heated at 50 °C for 2 h, then cooled to room temperature and poured on ice. The aqueous layer was extracted with EtOAc (3×60 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Silica gel flash chromatography of the residue (cyclohexane/EtOAc, 2:1) gave **13** (3.43 g, 84%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.32$ (dd, $^3J = 7.9$ Hz, $^3J =$ 9.5 Hz, 1H; 2-H), 3.37–3.62 (m, 9H; 5×2-H, 4×6-H), 3.70–3.77 (m, 1H; $OCH_2CH{=}CH{-}CH_2O$), 3.82–4.27 (m, 29H; 6×3-H, 6×4-H, 6×5-H, 8×6-H, 3×$OCH_2CH{=}CH{-}CH_2O$), 4.36 (d, $^2J = 12.5$ Hz, 1H; 1×CHPh), 4.43–4.60 (m, 14H; 14×CHPh), 4.62 (d, $^2J = 12.1$ Hz, 1H; 1×CHPh), 4.66 (d, $^2J = 12.3$ Hz, 1H; 1×CHPh), 4.77 (d, $^2J = 10.4$ Hz, 1H; 1×CHPh), 4.78 (d, $^3J_{1,2} = 3.8$ Hz, 1H; 1-H), 4.82 (d, $^3J_{1,2} = 3.1$ Hz, 1H; 1-H), 4.83 (d, $^3J_{1,2} =$ 3.3 Hz, 1H; 1-H), 4.86–4.91 (m, 2H; 2×CHPh), 4.92 (d, $^2J = 10.1$ Hz, 1H; 1×CHPh), 4.95 (d, $^2J = 10.3$ Hz, 1H; 1×CHPh), 4.98 (d, $^2J = 11.8$ Hz, 1H; 1×CHPh), 4.99 (d, $^3J_{1,2} = 3.4$ Hz, 1H; 1-H), 5.03 (d, $^2J = 11.8$ Hz, 1H; 1× CHPh), 5.09 (d, $^2J = 10.9$ Hz, 1H; 1×CHPh), 5.27 (d, $^2J = 10.4$ Hz, 1H; 1×CHPh), 5.28 (d, $^2J = 11.0$ Hz, 1H; 1×CHPh), 5.33 (d, $^3J_{1,2} = 3.9$ Hz, 1H; 1-H), 5.44 (d, $^2J = 10.1$ Hz, 1H; 1×CHPh), 5.48 (d, $^3J_{1,2} = 3.7$ Hz, 1H; 1-H), 5.69 (t, $^3J = 4.3$ Hz, 2H; $OCH_2CH{=}CH{-}CH_2O$), 5.95 (t, $^3J = 3.0$ Hz, 2H; $OCH_2CH{=}CH{-}CH_2O$), 7.00–7.30 ppm (m, 70H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 66.1$, 69.3, 69.4 (6×C-6), 70.8, 71.0 (2×$OCH_2CH{=}CH{-}CH_2O$), 70.7, 70.85, 71.2, 71.7, 71.9, 73.5 (6×C-5), 72.1, 72.4, 72.8, 72.9, 73.05, 73.1, 73.2, 73.3, 74.4, 74.7, 75.6, 75.8, 76.3, 76.4 (14×CH_2Ph), 77.9, 78.1, 78.2, 79.1, 79.15, 79.2 (6×C-2), 79.7, 80.0, 80.4, 80.5, 80.6, 83.0 (6×C-4), 80.7, 80.9, 81.1, 81.6, 81.7, 81.8 (6×C-3), 96.7, 97.1, 98.8, 99.2, 99.3, 99.35 (6×C-1), 126.6–128.3 (70×CH arom.), 129.5,

131.5 (2×OCH_2CH=CH−CH_2O), 137.9, 137.95, 138.0, 138.05, 138.1, 138.2, 138.3, 138.6, 139.15, 139.2, 139.25, 139.3, 139.4, 139.45 ppm (14×C arom.quat.); MS (FAB): *m/z*: 2309.1 $[M+Na]^+$; elemental analysis calcd (%) for $C_{138}H_{148}O_{30}$: C 72.49, H 6.52; found: C 71.97, H 6.58.

Tridifferentiated α-CD 14: A solution of **13** (145 mg, 63 μmol), pyridine (41 μL, 0.5 mmol) and *tert*-butyldimethylsilyltrifluoromethanesulfonate (116 μL, 0.5 mmol) in dichloromethane (2.5 mL) was stirred at room temperature for 2 h, diluted with dichloromethane (10 mL), washed with sat. aq. NH_4Cl (2×5 mL), dried ($MgSO_4$), filtered and concentrated. Silica gel flash chromatography (cyclohexane/EtOAc, 6:1) on silica gel gave a disilylated compound **17** (150 mg, 95%) directly used in the next step. Grubbs catalyst (9.8 mg, 12 μmol) was added to stirred solution of this compound (150 mg, 60 μmol) in degassed dichloromethane (3.6 mL), under ethylene at room temperature. The reaction mixture was stirred at room temperature under ethylene atmosphere for 18 h, then Grubbs catalyst (9.8 mg, 12 μmol) was added and the reaction mixture was stirred for additional 30 h at room temperature, then treated with $Pb(OAc)_4$ (16 mg, 36 μmol), stirred under argon for 3 h, concentrated and purified by silica gel flash chromatography (cyclohexane/EtOAc, 10:1) to give **14** (112 mg, 70%) as a white foam. $[\alpha]_D^{20}=+35$ ($c=1.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.01$ (s, 6H; CH_3Si), 0.04 (s, 6H; CH_3Si), 0.90 (s, 18H; $(CH_3)_3Si$), 3.35–3.50 (m, 6H; 6×2-H), 3.55–4.05 (m, 28H; 4×OCH_2CH=CH_2, 6×4-H, 6×5-H, 12×6-H), 4.10–4.25 (m, 6H; 6×3-H), 4.30 (br d, 4H; 4×CHPh), 4.42–4.70 (m, 12H; 12×CHPh), 4.80–4.95 (m, 6H; 6×CHPh), 5.00 (d, $^3J_{1,2}=3.2$ Hz, 2H; 2×1-H), 5.08–5.30 (m, 16H; 6×CHPh, 4×1-H, 4×OCH_2CH=CH_2), 5.74–5.84 (ddt, $^3J_{cis}=10.5$ Hz, $^3J_{trans}=16.0$ Hz, 2H; 2×OCH_2CH=CH_2), 7.18–7.31 ppm (m, 70H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.1$ (2×CH_3Si), −4.9 (2×CH_3Si), 18.3 (2×$(H_3C)_3CSi$), 25.9 (3×$(H_3C)_3CSi$), 26.0 (3×$(H_3C)_3CSi$), 62.4 (2×C-6), 68.85 (2×C-6), 69.0 (2×C-6), 71.3, 71.4, 72.5 (6×C-6), 72.2, 72.4, 72.8, 72.9, 73.3 (2×CH_2Ph, 2×OCH_2CH=CH_2), 75.1, 75.4, 75.7 (6×CH_2Ph), 78.1 (2×C-4), 78.75 (4×C-4), 78.8, 79.0, 79.1 (6×C-2), 80.7, 81.1, 81.2 (6×C-3), 98.0, 98.3, 98.4 (6×C-1), 116.9 (2×OCH_2CH=CH_2), 126.8–138.6 (70×CH arom.), 132.2 (2× OCH_2CH=CH_2), 138.1, 138.2, 138.25, 138.3 (8×C arom.quat), 139.25, 139.3, 139.4 ppm (6×C arom.quat.); MS (FAB): *m/z*: 2565.2 $[M+Na]^+$; elemental analysis calcd (%) for $C_{152}H_{180}O_{30}Si_2$: C 71.78, H 7.13; found: C 71.81, H 7.15.

Tridifferentiated α-CD 18: $[Pd^0(PPh_3)_4]$ was prepared according to the Rosevear methodology: PPh_3 (13.1 g, 0.05 mol) was dissolved in warm ethanol (200 mL). Na_2PdCl_4 (2.94 g, 0.01 mol) dissolved in ethanol (50 mL) and water (5 mL) was added. The reaction mixture was cooled to room temperature and $NaBH_4$ (1 g, 0.04 mol) in water (25 mL) and ethanol (25 mL) was added. The yellow solid was filtered off, washed with ethanol, dried under vacuum and stored at 4°C under argon. $[Pd^0(PPh_3)_4]$ (53 mg, 46 μmol) was added to a solution of compound **17** (1.15 g, 460 μmol) in THF (12 mL). A 1M solution of anhydrous $ZnCl_2$ in THF (6.9 mL, 6.9 mmol) was added dropwise to the reaction mixture at room temperature 10 min later, Bu_3SnH (1.85 mL, 6.9 mmol) was added slowly. The reaction mixture was refluxed for 20 h under argon and concentrated. The crude was dissolved in toluene and purified by silica gel flash chromatography (cyclohexane/EtOAc, 4:1) to give **18** (849 mg, 75%) as a white foam. $[\alpha]_D^{20}=+43$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.11$ (s, 3H; CH_3Si), 0.12 (s, 3H; CH_3Si), 0.96 (s, 9H; $(CH_3)_3Si$), 3.42 (dd, 1H; $^3J_{2,1}=3.5$ Hz, $^3J_{2,3}=9.6$ Hz, 1H; 2-Hc), 3.51–3.57 (m, 2H; 2×2-H), 3.62–3.75 ppm (m, 2H; 2×6-H), 3.78–3.87 (m, 4H; 2×4-H, 5-H, 6-H), 3.90 (br d, $^2J=11.0$ Hz, 1H; 6-H), 3.93–4.05 (m, 4H; 4-H, 2×5-H, 6-H), 4.09 (t, $^3J_{3,2}=^3J_{3,4}=9.7$ Hz, 1H; 3-H), 4.11 (t, $^3J_{3,2}=^3J_{3,4}=9.5$ Hz, 1H; 3-H), 4.21 (dd, $^2J=11.5$ Hz, $^3J_{6,5}=4.1$ Hz, 1H; 6-H), 4.27 (dd, $^3J_{3,2}=7.8$ Hz, $^3J_{3,4}=9.7$ Hz, 1H; 3-H), 4.32 (d, $^2J=12.6$ Hz, 1H; 1×CHPh), 4.38 (d, $^2J=12.6$ Hz, 1H; 1×CHPh), 4.47 (d, $^2J=12.0$ Hz, 1H; 1×CHPh), 4.52 (d, $^2J=11.9$ Hz, 1H; 1×CHPh), 4.62 (d, $^2J=12.7$ Hz, 1H; 1×CHPh), 4.65 (d, $^2J=12.2$ Hz, 2H; 2×CHPh), 4.73 (d, $^3J_{1,2}=3.4$ Hz, 1H; 1-H), 4.80 (d, $^2J=10.6$ Hz, 2H; 2×CHPh), 4.84 (d, $^2J=11.2$ Hz, 1H; 1×CHPh), 4.87 (d, $^2J=10.9$ Hz, 1H; 1×CHPh), 4.92 (d, $^2J=10.3$ Hz, 1H; 1×CHPh), 4.98 (d, $^3J_{1,2}=3.3$ Hz, 1H; 1-H), 5.20 (d, $^2J=10.8$ Hz, 1H; 1×CHPh), 5.49 (d, $^2J=10.3$ Hz, 1H; 1×CHPh), 5.68 (d, $^3J_{1,2}=3.8$ Hz, 1H; 1-H), 7.10–7.33 ppm (m, 35H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.2$ (1×CH_3Si), −5.0 (1×CH_3Si), 18.5 (($(H_3C)_3CSi$), 26.0 (($(H_3C)_3CSi$), 61.9, 63.1, 69.6 (3×C-6), 71.2 (C-5), 72.0 (C-5), 72.2 (CH_2Ph), 72.7 (C-5), 72.8, 73.3, 73.4 (3×CH_2Ph), 74.0 (CH_2Ph), 74.05 (C-4c), 76.1, 76.2 (2×CH_2Ph), 77.9 (C-2), 79.0 (C-2), 79.7 (C-2), 80.6 (C-3), 80.65 (C-4), 80.8 (C-3), 81.7 (C-3, C-4), 97.3 (C-1), 97.7 (C-1), 98.3 (C-1), 126.5–128.3 (35×CH arom.), 137.8, 138.0, 138.3, 138.5, 139.2, 139.25, 139.3 ppm (7×C arom.quat.); MS (FAB): *m/z*: 2485.2 $[M+Na]^+$; elemental analysis calcd (%) for $C_{146}H_{172}O_{30}Si_2$: C 71.19, H 7.04; found: C 70.81, H 7.04.

Capped α-CD 21: Sodium hydride (60% w/w in oil, 400 mg, 10 mmol) was added at room temperature under argon to a solution of diol **3** (3 g, 1.24 mmol) in dry DMF (188 mL). The reaction mixture was stirred for 30 min, then 3-chloro-2-chloromethyl-1-propene (158 μL, 1.40 mmol) was added. After 2 h of stirring, MeOH (10 mL) was slowly added and the solvents were removed in vacuo. The residue was dissolved in EtOAc (70 mL) and washed with a saturated aqueous solution of NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (3×30 mL) and the organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. Silica gel flash chromatography of the residue (cyclohexane/EtOAc, 6:1) gave **21** (2,82 g, 92%) as a white foam. $[\alpha]_D^{20}=+30$ ($c=1.0$ in $CHCl_3$), lit. [18] $[\alpha]_D^{20}=+31.4$ ($c=1.1$ in $CHCl_3$); MS (FAB): *m/z*: 2490.0 $[M+Na]^+$.

Diol 22: DIBAL-H (1.5M in toluene, 12 mL, 18 mmol) was slowly added to a solution of **21** (1.5 g, 0.6 mmol) in toluene (6 mL) under argon at room temperature. The reaction mixture was heated at 50°C for 2 h, then cooled to room temperature and poured onto ice. The aqueous layer was extracted with EtOAc (3×60 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Silica gel flash chromatography of the residue (cyclohexane/EtOAc, 2:1) gave **22** (1.25 g, 90%) as a white foam. The regioselectivity of this reaction was deduced when the known product **18** was obtained from this compound. $[\alpha]_D^{20}=+32$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.95$ (br s, 1H; OH), 3.39 (dd, $^3J_{2,1}=3.3$ Hz, $^3J_{2,3}=9.6$ Hz, 1H; H-2), 3.42–3.62 (m, 4H; 2×H-2, H-4, H-5), 3.71–4.05 (m, 9H; 2×H-4, 2×H-5, 3×H-6, 2×OCH_2C=), 4.08–4.16 (m, 4H; 2×H-3, 2×H-6), 4.25–4.42 (m, 6H; 3×CHPh, H-3, H-5, H-6), 4.43–4.55 (m, 4H; 4×CHPh), 4.72 (d, $^3J_{1,2}=3.3$ Hz, 1H; H-1), 4.80 (d, $^3J_{1,2}=3.3$ Hz, 1H; H-1), 4.81 (d, $^2J=11.8$ Hz, 1H; CHPh), 4.85 (d, $^2J=10.0$ Hz, 1H; CHPh), 4.87 (d, $^2J=11.5$ Hz, 1H; CHPh), 4.90 (d, $^2J=11.7$ Hz, 1H; CHPh), 5.01 (d, $^2J=10.4$ Hz, 1H; CHPh), 5.13 (s, 1H; CH_2=C), 5.28 (d, $^2J=10.6$ Hz, 1H; CHPh), 5.55 (d, $^3J_{1,2}=4.1$ Hz, 1H; H-1), 5.59 (d, $^2J=10.5$ Hz, 1H; CHPh), 7.09–7.34 ppm (m, 35H; H arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=62.2$ (2×C-6), 69.05 (C-6), 69.1 (C-5), 71.7 (OCH_2C=), 71.9 (C-5), 71.95 (CH_2Ph), 72.6 (C-5), 72.9, 73.2, 73.4, 73.7, 76.1, 76.5 (6× CH_2Ph), 77.6 (C-4), 78.7, 79.2, 79.9 (3×C-2), 80.5, 80.8, 81.1 (3×C-3), 81.6–82.1 (2×C-4), 97.7, 99.5, 99.6 (3×C-1), 114.5 (CH_2C=), 123.3–125.9 (CH arom.), 137.8, 137.9, 138.3, 138.6, 139.2, 139.25, 139.6 (7×Cquat. arom.), 142.8 ppm (C=CH_2); MS (FAB): *m/z*: 2309.1 $[M+Na]^+$; elemental analysis calcd (%) for $C_{138}H_{148}O_{30}$: C 72.49, H 6.52; found: C 72.13, H 6.68.

Tridifferentiated α-CD 18 from diol 22: A solution of **22** (1.94 g, 850 μmol), pyridine (411 μL, 5 mmol) and *tert*-butyldimethylsilyltrifluoromethanesulfonate (1.17 mL, 5 mmol) in dichloromethane (30 mL) was stirred at room temperature for 2 h. The reaction mixture is then diluted with dichloromethane (10 mL), washed with a saturated aqueous solution of NH_4Cl (2×5 mL), dried ($MgSO_4$), filtered and concentrated. Silica gel flash chromatography of the residue (cyclohexane/EtOAc, 6:1) afforded the bis-silylated cyclodextrine (2.10 g, 98%) directly used in the next step. $[Pd^0(PPh_3)_4]$ (7 mg, 6 μmol) was added to a solution of bis-silylated compound (150 mg, 60 μmol) in degassed THF (2.5 mL). A 1M solution of $ZnCl_2$ in degassed THF (900 μL, 900 μmol) was added and the reaction mixture was stirred at room temperature under argon for 10 min. After addition of Et_3SiH (144 μL, 900 μmol), the reaction mixture was refluxed under argon for 6 h, diluted with EtOAc (10 mL), poured on water (10 mL). Layers were separated and the aqueous layer was extracted with EtOAc (3×10 mL). Organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Silica gel flash chromatography of the residue (cyclohexane/EtOAc, 6:1 then 4:1) afforded the diol **18** (129 mg, 88%) as white foam. $[\alpha]_D^{20}=+43$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.11$ (s, 3H; CH_3Si), 0.12 (s, 3H; CH_3Si), 0.96 (s, 9H; $(CH_3)_3Si$), 3.42 (dd, $^3J_{2,1}=3.5$ Hz, $^3J_{2,3}=9.6$ Hz , 1H; H-2), 3.51–3.57 (m, 2H; 2×H-2), 3.62–3.75 (m, 2H; 2×H-6), 3.78–3.87 (m, 4H; 2×H-4, H-5,

H-6), 3.90 (br d, ^2J=11.0 Hz, 1H; H-6), 3.93–4.05 (m, 4H; H-4, 2×H-5, H-6), 4.09 (t, $^3J_{3,2}$=$^3J_{3,4}$=9.7 Hz, 1H; H-3), 4.11 (t, $^3J_{3,2}$=$^3J_{3,4}$=9.5 Hz, 1H; H-3), 4.21 (dd, ^2J=11.5 Hz, $^3J_{6,5}$=4.1 Hz, 1H; H-6), 4.27 (dd, $^3J_{3,2}$= 7.8 Hz, $^3J_{3,4}$=9.7 Hz, 1H; H-3), 4.32 (d, ^2J=12.6 Hz, 1H; CHPh), 4.38 (d, ^2J=12.6 Hz, 1H; CHPh), 4.47 (d, ^2J=12.0 Hz, 1H; CHPh), 4.52 (d, ^2J= 11.9 Hz, 1H; CHPh), 4.62 (d, ^2J=12.7 Hz, 1H; CHPh), 4.65 (d, ^2J= 12.2 Hz, 2H; 2×CHPh), 4.73 (d, $^3J_{1,2}$=3.4 Hz, 1H; H-1), 4.80 (d, ^2J= 10.6 Hz, 2H; 2×CHPh), 4.84 (d, ^2J=11.2 Hz, 1H; CHPh), 4.87 (d, ^2J= 10.9 Hz, 1H; CHPh), 4.92 (d, ^2J=10.3 Hz, 1H; CHPh), 4.98 (d, $^3J_{1,2}$= 3.3 Hz, 1H; H-1), 5.20 (d, ^2J=10.8 Hz, 1H; CHPh), 5.49 (d, ^2J=10.3 Hz, 1H; CHPh), 5.68 (d, $^3J_{1,2}$=3.8 Hz, 1H; H-1), 7.10–7.33 ppm (m, 35H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ=−5.2 (CH_3Si), −5.0 (CH_3Si), 18.5 ((H_3C)$_3$*C*Si), 26.0 ((H_3C)$_3$*C*Si), 61.9, 63.1, 69.6 (3×C-6), 71.2 (C-5), 72.0 (C-5), 72.2 (CH_2Ph), 72.7 (C-5), 72.8, 73.3, 73.4 (3×CH_2Ph), 74.0 (CH_2Ph), 74.05 (C-4), 76.1, 76.2 (2×CH_2Ph), 77.9 (C-2), 79.0 (C-2), 79.7 (C-2), 80.6 (C-3), 80.65 (C-4), 80.8 (C-3), 81.7 (C-3, C-4), 97.3 (C-1), 97.7 (C-1), 98.3 (C-1), 126.5–128.3 (35×CH arom.), 137.8, 138.0, 138.3, 138.5, 139.2, 139.25, 139.3 ppm (7×C quat. arom.); MS (FAB): *m*/*z*: 2485.2; elemental analysis calcd (%) for $C_{146}H_{172}O_{30}Si_2$: C 71.19, H, 7.04; found: C 70.81, H 7.04.

Bis-deoxy α-CD 23: Et_3N (41 μL, 0.5 mmol) and MsCl (116 μL, 0.5 mmol) were added to a solution of diol **3** (235 mg, 97 μmol) in CH_2Cl_2 (2.5 mL) at 0°C. The reaction mixture was stirred at room temperature for 1 h under argon, diluted with CH_2Cl_2 (10 mL), washed with water (2×5 mL), dried over $MgSO_4$, filtered and concentrated. Silica gel flash chromatography of the residue (cyclohexane/EtOAc, 6:1) afforded the bis-mesylated cyclodextrin, which was dissolved in THF (1.8 mL) and treated with $LiAlH_4$ (870 μmol). EtOAc (5 mL) was added at 0°C and the mixture was filtered through a Celite pad, concentrated and purified by silica gel flash chromatography (cyclohexane/EtOAc, 4:1) to afford the compound **23** (150 mg, 78% over two steps) as a white foam. $[\alpha]_D^{20}$= +49 (*c*=1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.25 (d, ^3J= 6.3 Hz, 3H; CH_3), 3.42 (dd, $^3J_{2,1}$=3.4 Hz, $^3J_{2,3}$=9.7 Hz , 1H; 2-H), 3.47 (dd, $^3J_{2,1}$=3.7 Hz, $^3J_{2,3}$=9.5 Hz, 1H; 2-H), 3.60 (dd, $^3J_{2,1}$=3.5 Hz, $^3J_{2,3}$= 9.9 Hz, 1H; 2-H), 3.61 (br d, ^2J=9.9 Hz, 1H; 6-H), 3.67 (br d, ^2J= 10.2 Hz, 1H; 6-H), 3.90 5 m, 2H; 4-H, 5-H), 3.95–4.18 (m, 8H; 2×3-H, 2×4-H, 2×5-H, 2×6-H), 4.24 (dd, $^3J_{3,2}$=9.9 Hz, $^3J_{3,4}$=8.0 Hz, 1H; 3-H), 4.36 (d, ^2J=12.6 Hz, 1H; 1×CHPh), 4.39 (d, ^2J=11.9 Hz, 1H; 1×CHPh), 4.43 (d, ^2J=12.6 Hz, 1H; 1×CHPh), 4.46–4.60 (m, 6H; 6×CHPh), 4.75 (d, $^3J_{1,2}$=3.5 Hz, 1H; 1-H), 4.77 (d, ^2J=12.1 Hz, 1H; 1×CHPh), 4.82 (d, ^2J=10.8 Hz, 1H; 1×CHPh), 4.86 (d, $^3J_{1,2}$=3.4 Hz, 1H; 1-H), 4.87 (d, ^2J= 11.3 Hz, 1H; 1×CHPh), 4.91 (d, ^2J=11.0 Hz, 1H; 1×CHPh), 4.94 (d, ^2J=10.4 Hz, 1H; 1×CHPh), 5.23 (d, ^2J=10.8 Hz, 1H; 1×CHPh), 5.46 (d, ^2J=10.5 Hz, 1H; 1×CHPh), 5.64 (d, $^3J_{1,2}$=3.8 Hz, 1H; 1-H), 7.20–7.40 ppm (m, 40H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.4 (CH_3), 66.4 (C-5), 69.3, 69.4 (2×C-6), 71.5, 71.8 (2×C-5), 73.2, 73.0, 73.25, 73.3, 73.35, 74.3, 76.0, 76.3 (8×CH_2Ph), 78.1, 79.1, 80.0 (3×C-2), 80.5 (C-4), 80.7 (C-3), 80.9 (C-4), 81.1 (C-3), 81.3 (C-3), 81.4 (C-4), 97.7, 98.0, 98.1 (3×C-1), 126.5–128.3 (40×CH arom.), 131.4 (*C*H_2=CHC=O), 138.05, 138.1, 138.3, 138.4, 138.6, 139.25, 139.3, 139.4 ppm (8×C arom. quat.); MS (FAB): *m*/*z*: 2436.1 $[M+Na]^+$; elemental analysis calcd (%) for $C_{149}H_{158}O_{29}$: C 74.60, H 6.60; found: C 74.79, H 6.55.

Diol 24: A solution of **23** (150 mg, 63 μmol) in toluene (640 μL) was treated with DIBAL-H (1.5 M in toluene, 1.3 mL, 1.9 mmol) under argon at room temperature. The reaction mixture was stirred at 50°C for 20 min, cooled at room temperature, poured on ice and diluted with EtOAc (15 mL). The layers were separated. The aqueous layer was treated with a 1 M solution of HCl (8 mL) and extracted by EtOAc (2× 15 mL). Organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Silica gel flash chromatography of the residue (cyclohexane/EtOAc, 3:1 then 2:1) afforded the diol **24** (116 mg, 84%) as a white foam. $[\alpha]_D^{20}$=+44 (*c*=1.1 in CHCl); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.36 (d, ^3J=6.2 Hz, 3H; CH_3), 2.82 (br s, 1H; OH), 3.39 (t, $^3J_{4,3}$=$^3J_{4,5}$= 8.9 Hz, 1H; 1×4-H), 3.45 (dd, $^3J_{2,1}$=3.3 Hz, $^3J_{2,3}$=9.8 Hz, 1H; 2-H), 3.56 (dd, $^3J_{2,1}$=3.7 Hz, $^3J_{2,3}$=9.6 Hz, 1H; 2-H), 3.59 (dd, $^3J_{2,1}$=3.6 Hz, $^3J_{2,3}$= 9.5 Hz, 1H; 2-H), 3.72–4.24 (m, 12, 3×3-H, 2×4-H, 3×5-H, 4×6-H), 4.42–4.67 (m, 7H; 7×CHPh), 4.78 (d, ^2J=12.1, 1H; 1×CHPh), 4.87 (d, ^2J=11.0 Hz, 1H; 1×CHPh), 4.88 (d, ^2J=10.5 Hz, 1H; 1×CHPh), 4.94 (d, ^2J=11.2 Hz, 1H; 1×CHPh), 5.09 (d, ^2J=10.9 Hz, 2H; 2×CHPh), 5.14 (d, $^3J_{1,2}$=3.6 Hz, 1H; 1-H), 5.37 (d, ^2J=10.4 Hz, 1H; 1×CHPh), 5.43 (d, $^3J_{1,2}$=3.7 Hz, 1H; 1-H), 7.19–7.36 ppm (m, 35H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.7 (CH_3), 61.6 (C-6), 67.4 (C-5), 69.6 (C-6), 71.6, 72.1 (2×C-5), 72.6, 72.9, 73.3, 73.5, 74.8, 75.4, 76.3 (7×CH_2Ph), 78.1, 79.3, 79.6 (3×C-2), 80.6 (C-3), 80.7 (C-3), 81.3 (C-3), 81.4 (2×C-4), 85.3 (C-4), 97.7, 97.75, 98.2 (3×C-1), 126.9 −128.4 (CH arom.), 137.5–138.5 (C arom. quat.), 139.1–139.3 ppm (C arom. quat.); MS (FAB): *m*/*z*: 2225.1 $[M+Na]^+$; elemental analysis calcd (%) for $C_{134}H_{144}O_{28}$: C 73.07, H 6.59; found: C 72.68, H 6.55.

Deoxy α-CD 26: A solution of DMSO (7.1 mL, 58 mmol) in CH_2Cl_2 (32 mL) was added dropwise to a solution of oxalyl chloride (2.5 mL, 29 mmol) in CH_2Cl_2 (32 mL) cooled to −78°C under argon. The reaction mixture was stirred at −78°C for 30 min, then a solution of diol **3** (7 g, 2.9 mmol) in CH_2Cl_2 (83 mL) was added. After 2 h at −78°C, Et_3N (8.2 mL, 58 mmol) was added, the reaction mixture was warmed to room temperature and treated with water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3×75 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give a bis-aldehyde. Ph_3PCH_3Br (24 g, 68 mmol) was suspended in THF (40 mL), cooled to −40°C and treated dropwise with *n*BuLi (2.5 M in hexane, 23 mL, 58 mmol). The reaction mixture was stirred at −40°C for 15 min, then at 0°C for 5 min, and a solution of the bis-aldehyde diluted in THF (40 mL) was added. The reaction mixture was stirred at room temperature for 4 h under Argon, diluted with Et_2O (100 mL), and poured on a saturated solution of NH_4Cl (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×70 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. After purification by silica gel chromatography (cyclohexane 100%, then cyclohexane/EtOAc 10:1, then 8:1), the olefinic CD **26** (4.85 g, 70% over two steps) was obtained as a white foam. $[\alpha]_D^{20}$=+39 (*c*=1.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.45 (dd, $^3J_{2,1}$=3.3 Hz, $^3J_{2,3}$=9.7 Hz, 1H; 2-H), 3.48 (dd, $^3J_{2,1}$=3.2 Hz, $^3J_{2,3}$=9.9 Hz, 1H; 2-H), 3.58–3.67 (m, 4H; 1×2-H, 1×4-H, 2×6-H), 3.89–3.96 (m, 2H; 1×4-H, 1×5-H), 4.06–4.22 (m, 6H; 2×3-H, 1×4-H, 1×5-H, 2×6-H), 4.27 (dd, ^3J=7.3 Hz, ^3J=9.6 Hz, 1H; 3-H), 4.34 (d, ^2J=12.7 Hz, 1H; 1×CHPh), 4.42–4.57 (m, 9H; 1×5-H, 8× CHPh), 4.77–4.97 (m, 7H; 2×1-H, 4×CHPh), 5.01 (d, ^2J=10.5 Hz, 1H; 1×CHPh), 5.04 (br d, $^3J_{cis}$=10.5 Hz, 1H; CH=CH_2), 5.28 (d, ^2J=10.6 Hz, 1H; 1×CHPh), 5.31 (br d, $^3J_{trans}$=17.2 Hz, 1H; CH=CH_2), 5.55 (d, ^2J= 10.4 Hz, 1H; 1×CHPh), 5.61 (d, $^3J_{1,2}$=3.9 Hz, 1H; 1-H), 5.98 (ddd, ^3J= 6.7 Hz, $^3J_{cis}$=10.4 Hz, $^3J_{trans}$=17.1 Hz, 1H; C*H*=CH_2), 6.46–7.36 ppm (m, 40H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ=69.0, 69.2 (2×C-6), 70.8, 70.9 (2×C-5), 71.6 (C-5), 72.0, 72.8, 73.1, 73.2, 73.3, 73.9, 76.0, 76.4 (8×CH_2Ph), 78.1, 79.0, 79.8 (3×C-2), 80.6 (C-3, C-4), 80.9 (C-4), 80.95, 81.2 (2×C-3), 81.6 (C-4), 98.0, 98.5, 98.8 (3×C-1), 118.9 (CH=CH_2), 126.1–128.2 (CH arom.), 136.6 (*C*H=CH_2), 137.9, 138.0, 138.3, 138.35, 138.6, 139.3 (6×C arom. quat.), 139.4 ppm (2×C arom. quat.); MS (FAB): *m*/*z*: 2429.1 $[M+Na]^+$, elemental analysis calcd (%) for $C_{150}H_{156}O_{28}$: C 74.85, H 6.53; found: C 74.93, H 6.65.

Diol 27: DIBAL-H (1.5 M in toluene, 40 mL, 60 mmol) was slowly added to a solution of **26** (4.80 g, 2.0 mmol) in toluene (20 mL) under argon at room temperature. The reaction mixture was heated at 50°C for 1.3 h, then cooled to room temperature and poured on ice. The aqueous layer was extracted with EtOAc (100 mL) then treated with HCl (1 M, 35 mL) and extracted again with EtOAc (2×70 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Silica gel flash chromatography of the residue (cyclohexane/EtOAc, 2:1) gave **27** (4 g, 90%) as a white foam. $[\alpha]_D^{20}$=+34 (*c*=0.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.27 (br s, 1H; OH), 3.44 (dd, $^3J_{2,1}$=3.3 Hz, $^3J_{2,3}$= 9.7 Hz, 1H; 2-H), 3.51–3.58 (m, 3H; 2×2-H, 1×4-H), 3.72 (br s, ^2J= 9.9 Hz, 1×6-H), 3.80–4.07 (m, 7H; 2×4-H, 2×5-H, 3×6-H), 4.12 (t, ^3J= 10.0 Hz, 1×3-H), 4.14 (dd, ^3J=8.3 Hz, ^3J=9.9 Hz, 1×3-H), 4.21 (dd, ^3J= 8.4 Hz, ^3J=9.6 Hz, 1×3-H), 4.35–4.49 (m, 5H; 1×5-H, 4×CHPh), 4.53 (d, ^2J=12.4 Hz, 1H; 1×CHPh), 4.60 (d, ^2J=11.9 Hz, 1H; 1×CHPh), 4.67 (d, ^2J=12.4 Hz, 1H; 1×CHPh), 4.68 (d, ^2J=12.2 Hz, 1H; 1×CHPh), 4.76 (d, $^3J_{1,2}$=3.3 Hz, 1H; 1-H), 4.87 (d, ^2J=10.7 Hz, 1H; 1×CHPh), 4.89 (d, ^2J=11.3 Hz, 1H; 1×CHPh), 4.93 (d, ^2J=10.9 Hz, 1H; 1×CHPh), 5.01 (d, ^2J=11.5 Hz, 1H; 1×CHPh), 5.14 (br d, $^3J_{cis}$=11.5 Hz, 1H; CH=CH_2), 5.18 (d, $^3J_{1,2}$=3.5 Hz, 1H; 1-H), 5.25 (d, ^2J=10.9 Hz, 1H; 1×CHPh), 5.29 (d, $^3J_{1,2}$=3.8 Hz, 1H; 1-H), 5.30 (d, ^2J=10.9 Hz, 1H; 1×CHPh), 5.34

(br d, $^3J_{trans}$ = 18.7 Hz, 1H; CH=CH_2), 6.08 (ddd, ^3J = 6.2 Hz, $^3J_{cis}$ = 10.5 Hz, $^3J_{trans}$ = 16.9 Hz, 1H; CH=CH$_2$), 7.16–7.35 ppm (m, 35H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.8, 69.2 (2×C-6), 71.0, 71.4, 71.8 (3×C-5), 72.3, 73.05, 73.1, 73.4, 74.8, 75.3, 76.1 (7×CH_2Ph), 78.5 (C-2), 78.7 (C-4), 78.8, 79.4 (2×C-2), 80.4, 80.8, 81.1 (3×C-3), 81.5 (C-4), 82.9 (C-4), 98.1, 98.3, 98.4 (3×C-1), 118.6 (CH=CH_2), 126.7–128.3 (CH arom.), 136.2 (CH=CH$_2$), 137.8, 138.15, 138.2, 138.4, 139.2, 139.25, 139.3 ppm (7×C arom. quat.); MS (FAB): m/z: 2249.0 $[M+Na]^+$; elemental analysis calcd (%) for $C_{136}H_{144}O_{28}$: C 73.36, H 6.52; found: C 73.21, H 6.73.

Tridifferenciated α-CD 18 from bis-olefinic diol 27: A solution of **27** (2.14 g, 960 μmol), pyridine (470 μL, 6 mmol) and *tert*-butyldimethylsilyltrifluoromethanesulfonate (1.3 mL, 6 mmol) in dichloromethane (25 mL) was stirred at room temperature for 2 h, diluted with dichloromethane (20 mL), washed with aqeous saturated NH_4Cl (2×40 mL), dried over $MgSO_4$, filtered and concentrated. Silica gel flash chromatography (cyclohexane/EtOAc, 6:1) afforded the silylated compound which was dissolved in CH_2Cl_2 (100 mL). The solution was cooled to −78 °C and ozone was bubbled through it for 1 min, until the solution turned slightly blue. Me_2S (15 mL, excess) was added. The reaction mixture was stirred at room temperature for 10 min and then evaporated; the residue was dissolved in CH_2Cl_2/MeOH (1:1, 100 mL) and treated at 0 °C by $NaBH_4$ (360 mg, 9.6 mmol). After 2 h stirring at room temperature, H_2O (60 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×60 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. Silica gel flash chromatography (cyclohexane/EtOAc, 3:1) afforded the tridifferenciated α-CD **18** (1.44 g, 61 % over three steps) as a white foam.

Capped-CD 28: NaH (60 % w/w, 27 mg, 670 μmol) was added to a solution of diol **27** (373 mg, 167 μmol) in DMF (26 mL). After 30 min stirring at room temperature, 1-chloro-2-chloromethylpropene (21 mL, 184 μmol) was added dropwise. The reaction mixture was stirred at room temperature for 2.5 h under argon, treated with MeOH (10 mL) then concentrated. The residue was diluted with CH_2Cl_2 (25 mL) and washed with a saturated solution of NH_4Cl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×25 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated. After purification by silica gel chromatography (cyclohexane/EtOAc, 6:1), the compound **28** (340 mg, 89 %) was isolated as a white foam. $[\alpha]_D^{20}$ = +35 (c = 0.7 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.29 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.0 Hz, 1H; 4-H), 3.40 (dd, $^3J_{2,1}$ = 3.2 Hz, $^3J_{2,3}$ = 9.9 Hz, 1H; 2-H), 3.45 (dd, $^3J_{2,1}$ = 3.3 Hz, $^3J_{2,3}$ = 9.6 Hz, 1H; 2-H), 3.57 (dd, $^3J_{4,3}$ = $^3J_{4,5}$ = 8.4 Hz, ^2J = 9.9 Hz, 2H; 1×4-H, 1×6-H), 3.67 (dd, $^3J_{2,1}$ = 4.0 Hz, $^3J_{2,3}$ = 9.8 Hz, 1H; 2-H), 3.69–3.77 (br d, 3H; 2×6-H, 1×OCH_2C(CH$_2$O)=CH$_2$), 3.92–3.98 (m, 2H; 1×5-H, 1×OCH_2C-(CH$_2$O)=CH$_2$), 4.02–4.21 (m, 4H; 2×3-H, 1×4-H, 1×6-H), 4.28–4.52 (m, 9H; 1×3-H, 2×5-H, 6×CHPh), 4.59 (d, ^2J = 11.8 Hz, 1H; 1×CHPh), 4.66 (d, $^3J_{1,2}$ = 3.3 Hz, 1H; 1-H), 4.72–4.90 (m, 5H; 1×1-H, 4×CH_2Ph), 5.02 (s, 1H; 1×OCH$_2$C(CH$_2$O)=CH_2), 5.03 (d, ^2J = 10.5 Hz, 1H; 1×CHPh), 5.09 (dd, $^3J_{cis}$ = 11.3 Hz, ^2J = 1.4 Hz, 1H; CH=CH_2), 5.26 (dd, $^3J_{trans}$ = 17.5 Hz, ^2J = 1.7 Hz, 1H; CH=CH_2), 5.28 (d, ^2J = 10.5 Hz, 1H; 1×CHPh), 5.60 (d, ^2J = 10.5 Hz, 1H; 1×CHPh), 5.64 (d, $^3J_{1,2}$ = 4.2 Hz, 1H; 1-H), 6.61 (ddd, ^3J = 4.2 Hz, $^3J_{cis}$ = 10.9 Hz, $^3J_{trans}$ = 17.1 Hz, 1H; CH=CH$_2$), 7.03–7.34 ppm (m, 35H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.9 (C-6), 69.2 (C-5), 70.6 (C-5), 71.5 (C-6), 71.6 (C-5), 71.9 (OCH_2C(CH$_2$O)=CH$_2$), 72.3, 72.7, 73.3, 73.4, 73.6, 76.1, 76.5 (7×CH_2Ph), 77.8 (C-2), 78.8 (C-2), 78.9 (C-4), 80.4 (C-2), 80.5 (C-3), 81.2 (2×C-3), 81.8 (C-4), 87.9 (C-4), 97.8, 99.1, 99.6 (3×C-1), 114.7 (OCH$_2$C(CH$_2$O)=CH$_2$), 115.4 (CH=CH_2), 125.9–128.4 (CH arom.), 135.9 (CH=CH$_2$), 137.8, 138.1, 138.4, 138.8, 139.3, 139.4, 139.5 (7×C arom. quat.), 142.4 ppm (OCH$_2$C(CH$_2$O)=CH$_2$); MS (FAB): m/z: 2300.8 $[M+Na]^+$; elemental analysis calcd (%) for $C_{140}H_{148}O_{28}$: C 73.79, H 6.55; found: C 73.79, H 6.59.

Diol 29: DIBAL-H (1.5 M in toluene, 3 mL, 4.5 mmol) was slowly added to a solution of **28** (340 mg, 150 μmol) in toluene (1.5 mL) under argon at room temperature. The reaction mixture was heated at 50 °C for 30 min, then cooled to room temperature and poured on ice. The aqueous layer was extracted with EtOAc (15 mL) then treated with HCl (1, 10 mL) and extracted again with EtOAc (2×20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Silica gel flash chromatography of the residue (cyclohexane/EtOAc, 2:1) gave **29** (290 mg, 93 %) as a white foam. $[\alpha]_D^{20}$ = +31 (c = 0.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89 (dd, J = 4.5 Hz, J = 7.9 Hz, 1H; OH), 3.34 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.0 Hz, 1H; 4-H), 3.42–3.62 (m, 5H; 3×2-H, 1×4-H, 1×6-H), 3.78 (dd, $^3J_{5,6}$ = 1.8 Hz, ^2J = 10.1 Hz, 1H; 6-H), 3.85–3.97 (m, 4H; 1×4-H, 1×5-H, 1×6-H, 1× OCH_2C(CH$_2$O)=CH$_2$), 4.04 (d, ^2J = 11.2 Hz, 1H; 1×OCH_2C(CH$_2$O)=CH$_2$), 4.08–4.17 (m, 3H; 2×3-H, 1×6-H), 4.28–4.40 (m, 5H; 1×3-H, 2×5-H, 2×CHPh), 4.46 (d, ^2J = 12.5 Hz, 1H; 1×CHPh), 4.49 (d, ^2J = 13.5 Hz, 1H; 1×CHPh), 4.55 (d, ^2J = 12.9 Hz, 1H; 1×CHPh), 4.69 (d, $^3J_{1,2}$ = 3.3 Hz, 1H; 1-H), 4.77–4.90 (m, 5H; 1×1-H, 4×CHPh), 5.01 (d, ^2J = 10.6 Hz, 1H; 1×CHPh), 5.11 (s, 1H; 1×OCH$_2$C(CH$_2$O)=CH_2), 5.12 (br d, $^3J_{cis}$ = 11.4 Hz, 1H; CH=CH_2), 5.28 (d, ^2J = 10.6 Hz, 1H; 1×CHPh), 5.38 (dd, $^3J_{trans}$ = 17.3 Hz, ^2J = 1.5 Hz, 1H; CH=CH_2), 5.54 (d, $^3J_{1,2}$ = 4.3 Hz, 1H; 1-H), 5.56 (d, ^2J = 10.9 Hz, 1H; 1×CHPh), 6.60 (ddd, ^3J = 4.3 Hz, $^3J_{cis}$ = 10.9 Hz, $^3J_{trans}$ = 17.1 Hz, 1H; CH=CH$_2$), 7.06–7.31 ppm (m, 30H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.0 (C-6), 69.3, 70.8 (2×C-5), 71.5 (C-6), 72.1 (OCH_2C(CH$_2$O)=CH$_2$), 72.3 (C-5), 72.35, 72.8, 73.4, 73.8, 75.9, 76.4 (6×CH_2Ph), 77.8 (C-2), 78.6 (C-2), 79.2 (C-4), 80.3 (C-2), 80.4 (C-3), 80.8 (C-3), 81.2 (C-3), 81.8 (C-4), 87.6 (C-4), 97.6, 99.4, 99.6 (3×C-1), 115.1 (OCH$_2$C(CH$_2$O)=CH$_2$), 115.8 (CH=CH_2), 126.0–128.4 (CH arom.), 135.5 (CH=CH$_2$), 137.7, 138.2, 138.5, 139.2, 139.3, 139.5 (6×C arom. quat.), 142.3 ppm (OCH$_2$C(CH$_2$O)=CH$_2$); MS (FAB): m/z: 2120.9 $[M+Na]^+$; HRMS (ESI) calcd for $C_{126}H_{136}O_{28}Na$: 2119.91159, found: 2119.9169 (2 ppm).

Diol 30: A solution of **29** (260 mg, 124 μmol), pyridine (60 μL, 744 μmol) and *tert*-butyldimethylsilyltrifluoromethanesulfonate (171 μL, 744 μmol) in dichloromethane (5 mL) was stirred at room temperature for 2 h, diluted with dichloromethane (10 mL), washed with aq. sat. NH_4Cl (2×15 mL), dried over $MgSO_4$, filtered and concentrated. Silica gel flash chromatography (cyclohexane/EtOAc, 6:1) gave the disilylated compound (290 mg, 100 %). [Pd(PPh$_3$)$_4$] (6 mg, 5.5 μmol) was added to a solution of disilylated compound (128 mg, 55 μmol) in degassed THF (2.3 mL). The reaction mixture was stirred at room temperature under argon for 10 min, then a degassed 1 M solution of $ZnCl_2$ in THF (825 μL, 825 μmol) was added, followed by a slow addition of Et_3SiH (133 μL, 825 μmol). The reaction mixture was refluxed under argon for 2 h, then diluted with EtOAc (5 mL). Water (5 mL) was added, and layers were separated. The aqueous layer was extracted with EtOAc (3×5 mL). The organic layers were combined, dried over $MgSO_4$, filtered and evaporated. The crude was dissolved in toluene and purified by silica gel flash chromatography (cyclohexane/EtOAc, 6:1, then 3:1) to give diol **30** (100 mg, 80 %) as a white foam. $[\alpha]_D^{20}$ = +33 (c = 0.4 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3H; CH_3Si), 0.06 (s, 3H; CH_3Si), 0.91 (s, 9H; (CH$_3$)$_3$Si), 2.12 (dd, J = 5.1 Hz, J = 7.7 Hz, 1H; OH), 3.45–3.53 (m, 3H; 3×2-H), 3.57 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.1 Hz, 1H; 4-H), 3.77–3.81 (m, 3H; 1×5-H, 2×6-H), 3.84 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.0 Hz, 1H; 4-H), 3.86 (t, $^3J_{4,3}$ = $^3J_{4,5}$ = 9.0 Hz, 1H; 4-H), 3.90–4.03 (m, 2H; 1×5-H, 1×6-H), 4.04–4.20 (m, 4H; 3×3-H, 1×6-H), 4.38–4.46 (m, 3H; 1×5-H, 2×CHPh), 4.50 (d, ^2J = 12.7 Hz, 1H; 1×CHPh), 4.57 (d, ^2J = 12.3 Hz, 1H; 1×CHPh), 4.67 (d, ^2J = 12.3 Hz, 1H; 1×CHPh), 4.68 (d, ^2J = 12.2 Hz, 1H; 1×CHPh), 4.82–5.00 (m, 5H; 1×1-H, 4×CHPh), 5.10 (d, $^3J_{1,2}$ = 3.4 Hz, 1H; 1-H), 5.20 (br d, $^3J_{cis}$ = 11.3 Hz, 1H; CH=CH_2), 5.28 (d, ^2J = 10.8 Hz, 1H; 1×CHPh), 5.30 (d, ^2J = 10.6 Hz, 1H; 1×CHPh), 5.33 (d, $^3J_{1,2}$ = 3.8 Hz, 1H; 1-H), 5.41 (br d, $^3J_{trans}$ = 17.2 Hz, 1H; CH=CH_2), 6.07 (ddd, ^3J = 6.2 Hz, $^3J_{cis}$ = 10.4 Hz, $^3J_{trans}$ = 16.9 Hz, 1H; CH=CH$_2$), 7.13–7.30 ppm (m, 30H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.4 (CH_3Si), −5.1 (CH_3Si), 17.5 ((H$_3$C)$_3$CSi), 25.9 ((H$_3$C)$_3$CSi), 61.9, 62.7 (2×C-6), 70.9, 71.3 (2×C-5), 72.1 (CH_2Ph), 72.9 (C-5), 73.0, 73.1, 74.6, 75.4, 76.2 (5×CH_2Ph), 78.6 (C-2), 78.9 (C-2, C-4), 79.5 (C-2), 80.4 (C-3), 80.9 (C-3), 81.0 (C-4), 81.1 (C-3), 82.4 (C-4), 98.0, 98.1, 98.3 (3×C-1), 118.6 (CH=CH_2), 126.6–128.2 (CH arom.), 136.2 (CH=CH$_2$), 137.7, 138.2, 138.5, 139.2, 139.3, 139.5 ppm (6×C arom. quat.); MS (FAB): m/z: 2298.3 $[M+Na]^+$; elemental analysis calcd (%) for $C_{134}H_{160}O_{28}Si_2$: C 70.75, H 7.09; found: C 70.95, H 7.21.

Tetradifferenciated α-CD 31: Compound **30** (70 mg, 31 μmol) was dissolved in pyridine (2 mL) and was treated with acetic anhydride (1 mL) and DMAP (1 mg). The reaction mixture was stirred at room temperature for 1 h, then concentrated. After purification by silica gel flash chromatography (cyclohexane/EtOAc, 4:1), the acetylated compound (75 mg,

quant.) was isolated as a white foam and dissolved in CH_2Cl_2 (3 mL). The solution was cooled to −78 °C and ozone was bubbled through it for 1 min, until the solution turned slightly blue. Me_2S (0.1 mL, excess) was added. The reaction mixture was stirred at room temperature for 10 min and then evaporated; the residue was dissolved in CH_2Cl_2/MeOH (1:1, 2 mL) and treated at 0 °C by $NaBH_4$ (8 mg, 186 μmol). After 2 h stirring at room temperature, the reaction mixture was concentrated and purified by silica gel flash chromatography (cyclohexane/EtOAc, 3:1). Compound **31** (40 mg, 55 % over three steps) was obtained as a white foam. $[\alpha]_D^{20}=+33$ ($c=0.8$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.06$ (s, 3H; CH_3Si), 0.09 (s, 3H; CH_3Si), 0.91 (s, 9H; $(CH_3)_3Si$), 2.09 (s, 3H; $CH_3C=O$), 3.158 (brs, 1H; OH), 3.43 (dd, $^3J_{2,1}=3.3$ Hz, $^3J_{2,3}=9.9$ Hz, 1H; 2-H), 3.53 (dd, $^3J_{2,1}=3.4$ Hz, $^3J_{2,3}=9.7$ Hz, 1H; 2-H), 3.58 (dd, $^3J_{2,1}=3.9$ Hz, $^3J_{2,3}=9.7$ Hz, 1H; 2-H), 3.72–3.92 (m, 7H; 3×4-H, 1×5-H, 3×6-H), 4.08–4.19 (m, 5H; 2×3-H, 1×5-H, 1×6-H), 4.23 (dd, $^3J_{3,2}=9.5$ Hz, $^3J_{3,4}=8.0$ Hz, 1H; 3-H), 4.41–4.55 (m, 6H; 4×CHPh, 2×6-H), 4.61 (d, $^2J=12.5$ Hz, 1H; CHPh), 4.75 (d, $^2J=12.1$ Hz, 1H; CHPh), 4.78 (d, $^3J_{1,2}=3.4$ Hz, 1H; 1-H), 4.81 (d, $^2J=10.7$ Hz, 1H; CHPh), 4.85 (d, $^2J=11.8$ Hz, 1H; CHPh), 4.92 (d, $^2J=10.7$ Hz, 1H; CHPh), 4.93 (d, $^2J=11.9$ Hz, 1H; CHPh), 4.96 (d, $^3J_{1,2}=3.5$ Hz, 1H; 1-H), 5.24 (d, $^2J=10.6$ Hz, 1H; CHPh), 5.37 (d, $^2J=10.7$ Hz, 1H; CHPh), 5.58 (d, $^3J_{1,2}=3.9$ Hz, 1H; 1-H), 7.12–7.30 ppm (m, 30H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.4$ (CH_3Si), −5.3 (CH_3Si), 18.4 ($CH_3C=O$), 20.8 ($(H_3C)_3CSi$), 26.0 ($(H_3C)_3CSi$), 62.7 , 63.3, 64.4 (3×C-6), 69.8 (C-5), 71.6 (C-5), 72. (CH_2Ph), 73.15 (CH_2Ph), 73.2 (C-5), 73.3, 74.2, 75.7, 76.3 (4×CH_2Ph), 76.8 (C-4), 77.9 (C-2), 78.9 (C-2), 79.8 (C-2), 80.6 (C-3), 80.9 (2×C-4), 81.2 (C-3), 97.4, 98.2, 98.9 (3×C-1), 126.4–128.3 (CH arom.), 137.9, 138.1, 138.6, 139.15, 139.2, 139.3 (6×C arom. quat.), 170.6 ppm ($CH_3C=O$); MS (FAB): m/z: 2389.1 $[M+Na]^+$; HRMS (ESI) calcd for $C_{136}H_{164}O_{32}Si_2Na$: 2388.06420, found: 2388.0640 (0 ppm).

Capped β-CD 38: nBu$_4$NI (16 mg, 44 μmol), NaH 60 % w/w (67 mg, 1.69 mmol) and allyl bromide (146 μL, 1.69 mmol) were added to a solution of diol **4** (1.2 g, 442 μmol) in THF (25 mL). The reaction mixture was stirred for 6 h at room temperature. MeOH was added and the reaction mixture was concentrated, diluted with CH_2Cl_2 (80 mL) and washed with a saturated aqueous solution of NH_4Cl (2×40 mL) and with brine (40 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel flash chromatography (cyclohexane/EtOAc, 6:1). Compound **37** (1.15 g, 89 %) was obtained as a white foam. $[\alpha]_D^{20}=+34$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=3.56$–3.73 (m, 14H; 7×2-H, 7×6-H), 3.92–4.18 (m, 32H; 7×3-H, 7×4-H, 7×5-H, 7×6-H, 4×OCH_2CH=CH_2), 4.50–4.65 (m, 24H; 24×CHPh), 4.86–4.91 (m, 7H; 7×CHPh), 5.11–5.32 (m, 17H; 6×1-H, 4×OCH$_2$CH=CH_2, 7×CHPh), 5.35 (d, $^3J_{1,2}=3.4$ Hz, 1H; 1-H), 5.80–5.90 (m, 2H; 2×OCH$_2$CH=CH$_2$), 7.20–7.36 ppm (m, 95H; H-arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=69.0$–69.1 (7×C-6), 71.1 (2×C-5), 71.3 (2×C-5), 71.4 (2×C-5), 71.5 (C-5), 72.0, 72.1 (2×OCH_2CH=CH$_2$), 72.5 (OCH_2Ph), 72.55 (2×OCH_2Ph), 72.6, 72.65, 72.7, 72.8 (4×OCH_2Ph), 73.1 (OCH_2Ph), 73.15 (2×OCH_2Ph), 73.2, 73.3 (2×OCH_2Ph), 75.1, 75.2, 75.3, 75.4 (4×OCH_2Ph), 75.45 (2×OCH_2Ph), 75.5 (OCH_2Ph), 77.7, 78.2, 78.5 (3×CH), 78.6–78.7 (8×CH), 78.9 (CH), 79.0 (2×CH), 80.8–80.9 (7×C-3), 98.3, 98.35 (2×C-1), 98.4 (2×C-1), 98.5 (3×C-1), 116.75, 116.8 (2×OCH$_2$CH=CH$_2$), 126.8–128.2 (CH-arom.), 134.6 (2×OCH$_2$CH=CH$_2$), 138.05 (3×C-arom. quat.), 138.1, 138.15, 138.2, 138.25 (4×C-arom. quat.), 138.3 (3×C-arom. quat.), 138.35, 138.40 (2×C-arom. quat.), 139.1 (2×C-arom. quat.), 139.2 ppm (5×C-arom. quat.); MS (FAB): m/z: 2948.5 $[M+Na]$; elemental analysis calcd (%) for $C_{181}H_{192}O_{35}$: C 74.26, H 6.61; found: C 70.16, H 6.40.

A first-generation Grubbs catalyst (11 mg, 13 μmol) was added to a solution of **37** (800 mg, 273 μmol) in CH_2Cl_2 (35 mL). The reaction mixture was refluxed for 5 h. The solution was allowed to cool down to room temperature, $Pb(OAc)_4$ (9 mg, 1.5 equiv/Ru) was added and the reaction mixture was stirred at room temperature for 3 h and then concentrated. The residue was purified by silica gel flash chromatography (cyclohexane/EtOAc, 5:1) to afford bridged β-CD **38** (1.15 g, 89 %) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): disappearance of the ethylenic proton (CH=CH$_2$); MS (FAB): m/z: 2922.2 $[M+Na]^+$; elemental analysis calcd (%) for $C_{179}H_{188}O_{35}$: C 74.15, H 6.54; found: C 73.84, H 6.76.

Diols 39 and 40: DIBAL-H (1.5 M in toluene, 24 mL, 36 mmol) was added To a solution of bridged β-cyclodextrin **38** (3 g, 1.0 mmol) in toluene (12 mL) at room temperature under argon. The reaction mixture was stirred at 50 °C for 2 h, cooled to room temperature and poured on ice. The aqueous layer was extracted with EtOAc (100 mL) then treated with HCl (1 M, 35 mL) and extracted again with EtOAc (2×70 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Silica gel flash chromatography of the residue (cyclohexane/EtOAc, 2:1) afforded an unseparable mixture of two regioisomers **39** and **40** (2.1 g, 74 %) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.33$ (brs, 1H; OH), 2.55 (brs, 1H; OH), 3.41–3.54 (m, 4H; 4×2-H), 3.55–4.25 (m, 42H; 3×2-H, 7×3-H, 7×4-H, 7×5-H, 16×6-H, 4×OCH_2CH=CHCH_2O), 4.38–4.68 (m, 20H; 20×CHPh), 4.70–4.90 (m, 10H; 1×1-H, 9×CHPh), 4.92 (d, $^3J_{1,2}=3.3$ Hz, 1H; 1-H), 5.05 (d, $^2J=10.9$ Hz, 1H; CHPh), 5.06 (d, $^3J_{1,2}=3.7$ Hz, 1H; 1-H), 5.10 (d, $^2J=10.9$ Hz, 1H; CHPh), 5.17 (d, $^3J_{1,2}=3.8$ Hz, 1H; 1-H), 5.18 (d, $^3J_{1,2}=3.8$ Hz, 1H; 1-H), 5.22 (d, $^2J=10.8$ Hz, 1H; CHPh), 5.30 (d, $^2J=10.3$ Hz, 1H; CHPh), 5.32 (d, $^2J=10.7$ Hz, 1H; CHPh), 5.47 (d, $^3J_{1,2}=3.8$ Hz, 1H; 1-H), 5.57 (d, $^3J_{1,2}=3.9$ Hz, 1H; 1-H), 5.75 (s, 2H; OCH$_2$CH=CHCH$_2$O), 7.00–7.31 ppm (m, 85H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=61.3$, 61.4 (2×C-6), 68.85, 68.9, 69.0 (3×C-6), 70.4 (2×C-6), 71.05 (1×C-5), 71.1 (OCH_2CH=CHCH_2O), 71.2, 71.4, 71.45 (3×C-5), 71.7 (OCH_2CH=CHCH_2O), 71.9 (C-5), 71.95 (2×C-5), 72.2, 72.3, 72.6, 72.8 (4×CH_2Ph), 73.0 (2×CH_2Ph), 73.2 (2×CH_2Ph), 73.3 (2×CH_2Ph), 74.0, 74.3, 75.15, 75.2, 75.4, 75.5, 76.2 (7×CH_2Ph), 77.7, 77.9 (2×C-2), 78.3 (2×C-4), 78.5 (2×C-2), 79.2 (C-4), 79.3 (C-2), 79.4 (C-4), 79.85 (2×C-2), 79.9 (2×C-4), 80.1 (C-4), 80.55, 80.6, 80.65, 80.85, 80.9, 81.2 ,81.4 (7×C-3), 97.3, 97.6, 97.8, 98.3, 99.1, 99.3, 99.4 (7×C-1), 127.0–138.2 (85×CH arom.), 128.5, 129.3 (OCH$_2$CH=CHCH$_2$O), 137.8, 137.9, 138.0 (3×C arom.quat.), 138.05 (2×C arom.quat.), 138.15, 138.25, 138.3, 138.35, 138.5, 138.9, 138.95, 139.1, 139.2, 139.25, 139.3, 139.4 ppm (12× C arom.quat.); MS(FAB): m/z: 2741.5 $[M+Na]^+$; elemental analysis calcd (%) for $C_{165}H_{176}O_{35}$: C 72.88, H 6.51; found: C 72.46, H 6.51.

Tridifferenciated β-CDs 41 and 42: A solution containing the mixture of **39** and **40** (2 g, 754 μmol), pyridine (370 μL, 4.5 mmol) and *tert*-butyldimethylsilyltrifluoromethanesulfonate (1 mL, 4.5 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature 2 h under argon, diluted with CH_2Cl_2 (10 mL), washed with a saturated solution of NH_4Cl (2×30 mL), dried over $MgSO_4$, filtered and concentrated. Silica gel flash chromatography of the residue (cyclohexane/EtOAc, 6:1) afforded an unseparable mixture of the two silyl-protected regioisomers (2.2 g, 100 %). [Pd(PPh_3)$_4$] (314 mg, 271 μmol) was added to a solution containing these two regioisomers (2 g, 679 μmol) dissolved in THF (18 mL). A degassed 0.5 M solution of $ZnCl_2$ in THF (20 mL, 10.2 mmol) was added dropwise under argon. The reaction mixture was stirred at room temperature for 10 min. Bu_3SnH (2.74 mL, 10.2 mmol) was slowly added. The reaction mixture was refluxed for 20 h under argon, concentrated, dissolved in toluene, and purified by silica gel flash chromatography (cyclohexane/EtOAc, 4:1) to afford **41** (1.2 g, 60 %) and **42** (290 mg, 15 %) as white foams.[25]

Tridifferenciated β-CD 41:[25] $[\alpha]_D^{20}=+40$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.06$ (s, 3H; CH_3Si), 0.08 (s, 3H; CH_3Si), 0.12 (s, 3H; CH_3Si), 0.15 (s, 3H; CH_3Si), 0.91 (s, 9H; $(CH_3)_3Si$), 0.98 (s, 9H; $(CH_3)_3Si$), 3.40 (dd, $^3J_{2,1}=3.0$ Hz, $^3J_{2,3}=9.6$ Hz, 2H; 2×2-H), 3.45 (dd, $^3J_{2,1}=3.4$ Hz, $^3J_{2,3}=9.2$ Hz, 1H; 2-H), 3.50 (dd, $^3J_{2,1}=3.6$ Hz, $^3J_{2,3}=8.9$ Hz, 1H; 2-H), 3.59 (dd, $^3J_{2,1}=3.7$ Hz, $^3J_{2,3}=8.6$ Hz, 3H; 3×2-H), 3.65–4.12 (m, 35H; 7×3-H, 7×4-H, 7×5-H, 14×6-H), 4.45–4.79 (m, 28H; 28×CHPh), 4.81 (d, $^2J=11.2$ Hz, 1H; 1×CHPh), 4.86 (d, $^2J=10.4$ Hz, 1H; 1×CHPh), 4.87 (d, $^3J_{1,2}=3.4$ Hz, 1H; 1-H), 4.97 (d, $^3J_{1,2}=3.4$ Hz, 1H; 1-H), 5.06 (d, $^3J_{1,2}=3.4$ Hz, 1H; 1-H), 5.11 (d, $^2J=11.2$ Hz, 1H; 1×CHPh), 5.12–5.25 (m, 4H; 2×1-H, 2×CHPh), 5.28 (d, $^2J=10.1$ Hz, 1H; 1×CHPh), 5.49 (d, $^3J_{1,2}=3.5$ Hz, 1H; 1-H), 5.56 (d, $^3J_{1,2}=3.9$ Hz, 1H; 1-H), 7.18–7.30 ppm (m, 85H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.2$ (2×CH_3Si), −5.0 (2×CH_3Si), 18.3, 18.4 (2×$(H_3C)_3CSi$), 25.9, 26.0 (6×$(H_3C)_3CSi$), 61.7, 61.75, 62.35, 62.5 (4×C-6), 68.8, 68.9, 69.5 (3×C-6), 71.4, 71.5, 71.6, 71.7, 71.9, 72.7, 72.9 (7×C-5), 72.2, 72.35, 72.4, 72.6, 72.65, 72.8, 72.9 (7×CH_2Ph), 73.3, 73.4, 73.5 (3× CH_2Ph), 74.4, 74.5, 74.9 (3×CH_2Ph), 75.6, 75.8, 76.0, 76.1 (4×CH_2Ph), 77.3, 77.4 (2×C-2), 78.8, 78.9, 78.95, 79.1 (3×C-2, C-4), 79.4, 79.45, 79.6, 79.9 (6×C-4), 81.25, 81.2, 81.1, 80.9, 80.8, 80.6, 80.4 (7×C-3), 97.0, 97.6, 97.7, 98.2, 98.3, 98.35, 99.1 (7×C-1), 127.3–128.25 (85×CH arom.), 137.95, 137.9, 138.0, 138.15,

138.1, 138.2, 138.3, 138.4, 138.45, 138.5 (10×C arom.quat.), 138.9, 138.95, 139.0, 139.1, 139.3, 139.4, 139.45 ppm (7×C arom.quat.); MS (FAB): *m/z*: 2917.6 $[M+Na]^+$; elemental analysis calcd (%) for $C_{173}H_{200}O_{35}Si_2$: C 71.76, H 6.96; found: C 71.51, H 6.88.

Tridifferenciated β-CD 42:[25] $[\alpha]_D^{20}=+49$ ($c=0.8$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.05$ (s, 3H; CH_3Si), 0.06 (s, 3H; CH_3Si), 0.07 (s, 3H; CH_3Si), 0.085 (s, 3H; CH_3Si), 0.90 (s, 9H; $(CH_3)_3Si$), 0.93 (s, 9H; $(CH_3)_3Si$), 2.32 (brs, 1H; OH), 2.40 (brs, 1H; OH), 3.36 (dd, $^3J_{2,1}=3.5$ Hz, $^3J_{2,3}=9.6$ Hz, 1H; 2-H), 3.41 (dd, $^3J_{2,1}=3.5$ Hz, $^3J_{2,3}=9.5$ Hz, 1H; 2-H), 3.43–3.60 (m, 5H; 5×2-H), 3.62–3.72 (m, 4H; 4×6-H), 3.78–4.15 (m, 30H; 7×3-H, 7×4-H, 7×5-H, 9×6-H), 4.17 (dd, $^3J_{6,5}=4$ Hz, $^2J=11.9$ Hz, 1H; 6-H), 4.37–4.57 (m, 16H; 16×CHPh), 4.62–4.77 (m, 14H; 14×CHPh), 4.86 (d, $^3J_{1,2}=3.3$ Hz, 1H; 1-H), 5.00 (d, $^3J_{1,2}=3.4$ Hz, 1H; 1-H), 5.03(d, $^3J_{1,2}$=3.5 Hz, 1H; 1-H), 5.06 (d, $^2J=11.2$ Hz, 1H; 1×CHPh), 5.13 (d, $^2J=11.5$ Hz, 1H; 1×CHPh), 5.14 (d, $^2J=10.9$ Hz, 1H; 1×CHPh), 5.15 (d, $^3J_{1,2}=3.5$ Hz, 1H; 1-H), 5.17 (d, $^3J_{1,2}=3.5$ Hz, 1H; 1-H), 5.18 (d, $^2J=10.7$ Hz, 1H; 1×CHPh), 5.22 (d, $^2J=10.8$ Hz, 1H; 1×CHPh), 5.40 (d, $^3J_{1,2}=3.6$ Hz, 1H; 1-H), 5.44 (d, $^3J_{1,2}=3.6$ Hz, 1H; 1-H), 7.00–7.40 ppm (m, 85H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.2$ (2×CH_3Si), −5.15 (2×CH_3Si), 18.3, 18.4 (2×$(H_3C)_3CSi$), 26.0 (6×$(H_3C)_3CSi$), 61.7 (4×C-6), 69.2, 68.8, 68.9 (3×C-6), 71.4–71.65 (7×C-5), 72.4 (CH_2Ph), 72.6 (3× CH_2Ph), 72.7–72.9 (3×CH_2Ph), 73.3 (CH_2Ph), 73.4 (2×CH_2Ph), 74.6 (3× CH_2Ph), 75.8 (2× CH_2Ph), 76.0 (2× CH_2Ph), 77.7, 77.8 (2×C-2), 78.8 (2×C-2), 78.9 (2×C-2), 79.5 (C-2), 79.7 (C-4), 79.8 (2×C-4), 80.3 (2×C-4), 80.4 (2×C-4), 80.7 (C-3), 80.8 (2×C-3), 80.9 (2×C-3), 81.2, 81.3 (2×C-3), 97.3, 97.4, 97.8, 98.2, 98.3, 98.5, 99.0 (7×C-1), 137.0–129.0 (85× CH arom.), 137.7, 137.9 (2×C arom.quat.), 138.1 (2×C arom.quat.), 138.2 (2×C arom.quat.), 138.3, 138.4, 138.5, 138.6, 138.7 (5×C arom.-quat.), 139.0, 139.05, 139.1, 139.3, 139.4, 139.5 ppm (6×C arom.quat.); $[\alpha]_D^{20}=+49$ ($c=0.8$ in $CHCl_3$); MS (FAB): *m/z*: 2917.6 $[M+Na]^+$; elemental analysis calcd (%) for $C_{173}H_{200}O_{35}Si_2$: C 71.76, H 6.96; found: C 71.51, H 6.88.

Bis-olefinic β-CD 43: A solution of DMSO (202 μL, 2.8 mmol) in CH_2Cl_2 (1.6 mL) was added dropwise to a solution of oxalyl chloride (123 μL, 1.4 mmol) in CH_2Cl_2 (1.6 mL) cooled to −78 °C under argon. The reaction mixture was stirred at −78 °C for 30 min, then a solution of diol **4** (405 mg, 142 μmol) in CH_2Cl_2 (4.1 mL) was added to it. After 2 h at −78 °C, Et_3N (400 μL, 2.8 mmol) was added, the reaction mixture was warmed to room temperature and treated with water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give a bis-aldehyde. Ph_3PCH_3Br (1.15 g, 3.2 mmol) was suspended in THF (2 mL), cooled to −40 °C and treated dropwise with *n*BuLi (2.5 M in hexane, 1.1 mL, 2.8 mmol). The reaction mixture was stirred at −40 °C for 15 min, then at 0 °C for 5 min, and a solution of the bis-aldehyde diluted in THF (2 mL) was added. The reaction mixture was stirred at room temperature for 4 h under argon, diluted with Et_2O (10 mL), and poured on a saturated solution of NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. After purification by silica gel chromatography (cyclohexane, 100%, then cyclohexane/EtOAc, 10:1, then 8:1), the bis-olefinic CD **43** (257 mg, 65% over two steps) was obtained as a white foam. $[\alpha]_D^{20}=+49$ ($c=0.8$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=3.40$–3.55 (m, 6H; 5×2-H, 1×6-H), 3.58–3.70 (m, 7H; 2×2-H, 2×4-H, 3×6-H), 3.72–4.18 (m, 22H; 7×3-H, 5×4-H, 5×5-H, 5×6-H), 4.23 (brd, $^2J=9.8$ Hz, 1H; 6-H), 4.30–4.63 (m, 24H; 2×5-H, 22×CHPh), 4.65–4.84 (m, 6H; 6×CHPh), 4.88–4.94 (m, 9H; 4×1-H, 5×CHPh), 5.00 (d, $^3J_{1,2}=3.4$ Hz, 1H; 1-H), 5.04 (dd, $^3J_{cis}=10.6$ Hz, $^2J=1.7$ Hz, 1H; CH=CH_2), 5.07 (dd, $^3J_{cis}=10.4$ Hz, $^2J=1.3$ Hz, 1H; CH=CH_2), 5.25 (d, $^2J=10.6$ Hz, 1H; CHPh), 5.30 (d, $^2J=10.9$ Hz, 1H; CHPh), 5.34 (d, $^2J=10.4$ Hz, 1H; CHPh), 5.36 (d, $^3J_{trans}=17.1$ Hz, 2H; 2×CH=CH_2), 5.46 (d, $^2J=11.0$ Hz, 1H; CHPh), 5.50 (d, $^2J=10.5$ Hz, 1H; CHPh), 5.68 (d, $^3J_{1,2}=4.3$ Hz, 1H; 1-H), 5.69 (d, $^3J_{1,2}=4.5$ Hz, 1H; 1-H), 5.75 (ddd, $^3J=7.6$ Hz, $^3J_{cis}=10.2$ Hz, $^3J_{trans}=17.4$ Hz, 1H; CH=CH$_2$), 5.86 (ddd, $^3J=7.6$ Hz, $^3J_{cis}=10.1$ Hz, $^3J_{trans}=17.4$ Hz, 1H; CH=CH$_2$), 7.14–7.38 ppm (m, 95H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 68.6, 68.8, 69.9, 69.2, 69.6 (5×C-6), 70.6, 70.8, 71.4, 71.5, 71.7 (6×C-5), 72.0 (CH_2Ph), 72.3 (C-5), 72.5–73.3 (CH_2Ph), 74.1–74.2 (CH_2Ph), 75.7–76.5 (CH_2Ph), 77.4, 77.5 (2×C-4), 78.05, 78.1, 78.6, 78.9, 78.95, 79.4, 79.7 (7×C-2), 79.9–81.5 (7×C-3, 3×C-4), 81.7, 81.9 (2×C-4), 97.4, 97.5, 97.6, 97.9 (4×C-1), 99.1 (2×C-1), 99.8 (C-1), 119.0, 119.4 (2×CH=CH_2), 126.4–128.3 (CH arom.), 136.9, 137.0 (2× *C*H=CH_2), 137.8, 137.9 (2×C arom. quat.), 137.95 (2×C arom. quat.), 138.0, 138.1 (2×C arom. quat.), 138.2 (2×C arom. quat.), 138.3 (C arom. quat.), 138.5 (2×C arom. quat.), 138.6 (C arom. quat.), 139.0, 139.1, 139.2, 139.4, 139.5 (5×C arom. quat.), 139.6 ppm (2×C arom. quat.); MS (FAB): *m/z*: 2862.1 $[M+Na]^+$; elemental analysis calcd (%) for $C_{177}H_{184}O_{33}$: C 74.87, H 6.53; found: C 74.93, H 6.59.

Diols 44 and 45: DIBAL-H (1.5 M in toluene, 1.56 mL, 2.34 mmol) was slowly added to a solution of **43** (189 mg, 67 μmol) in toluene (780 μL) under argon at room temperature. The reaction mixture was heated at 50 °C for 1 h, then cooled to room temperature and poured on ice. The aqueous layer was extracted with EtOAc (10 mL) then treated with HCl (1 M, 5 mL) and extracted again with EtOAc (2×10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Silica gel flash chromatography of the residue (cyclohexane/EtOAc, 2:1) afforded an unseparable mixture of the two regioisomeric diols **44** and **45** (99 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.11$ (brs, 1H; OH), 2.51 (brs, 1H; OH), 3.30–4.14 (m, 36H; 7×2-H, 7×3-H, 7×4-H, 5×5-H, 10×6-H), 4.29–4.62 (m, 22H; 2×5-H, 20×CHPh), 4.64–5.55 ppm (m, 25H; 7×1-H, 14×CHPh, 4×CH=CH_2), 5.98 (ddd, $^3J=7.0$ Hz, $^3J_{cis}=10.3$ Hz, $^3J_{trans}=17.2$ Hz, 1H; CH=CH$_2$), 6.08 (ddd, $^3J=6.4$ Hz, $^3J_{cis}=10.4$ Hz, $^3J_{trans}=16.9$ Hz, 1H; CH=CH$_2$), 7.17–7.32 ppm (m, 85H; CH arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=61.0$, 61.8, 63.0 (CH_2), 68.9–69.3 (CH_2), 71.2–71.9 (CH), 72.1–73.3 (CH_2), 74.5–76.1 (CH_2), 76.4 (CH), 77.8, 78.1 (CH), 78.3–81.2 (CH), 97.5, 97.9, 98.05, 98.3, 98.5, 98.7, 98.75 (7×C-1), 118.2, 118.8 (2×CH=CH_2), 126.6–128.3 (CH arom.), 135.9, 136.7 (2×*C*H=CH_2), 137.7–138.5 (C arom. quat.), 138.9–139.4 ppm (C arom. quat.); MS (FAB): *m/z*: 2681.2 $[M+Na]^+$; HRMS (ESI) calcd for $C_{163}H_{172}O_{33}Na$: 2680.16786; found: 2680.1704 (1 ppm).

Tridifferenciated β-CD 41 and 42: A solution of **44** and **45** (260 mg, 124 μmol), pyridine (14 μL, 176 μmol) and *tert*-butyldimethylsilyltrifluoromethanesulfonate (40 μL, 176 μmol) in dichloromethane (1.2 mL) was stirred at room temperature for 1 h, diluted with dichloromethane (10 mL), washed with aq. sat. NH_4Cl (2×10 mL), dried over $MgSO_4$, filtered and concentrated. Silica gel flash chromatography (cyclohexane/EtOAc, 5:1) afforded the silylated compounds, which were dissolved in CH_2Cl_2 (10 mL). The solution was cooled to −78 °C and ozone was bubbled through it for 1 min, until the solution turned slightly blue. Me_2S (0.5 mL, excess) was added. The reaction mixture was stirred at room temperature for 10 min and then evaporated; the resulting residue was dissolved in CH_2Cl_2/MeOH (1:1, 2 mL) and treated at 0 °C with $NaBH_4$ (10 mg, excess). After 2 h stirring at room temperature, the reaction mixture was concentrated and purified by silica gel flash chromatography (cyclohexane/EtOAc, 6:1, then 4:1). Compound **42** (30 mg) and compound **41** (8 mg) were obtained as white foams (79:21, 60% global yield over 3 steps).[25]

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[25] Detailed structural elucidation can be found as Supporting Information.

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