Programmed synthesis of Hepta-differentiated b-Cyclodextrin: 1 out of 117655 arrangements

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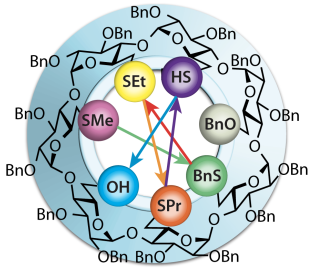


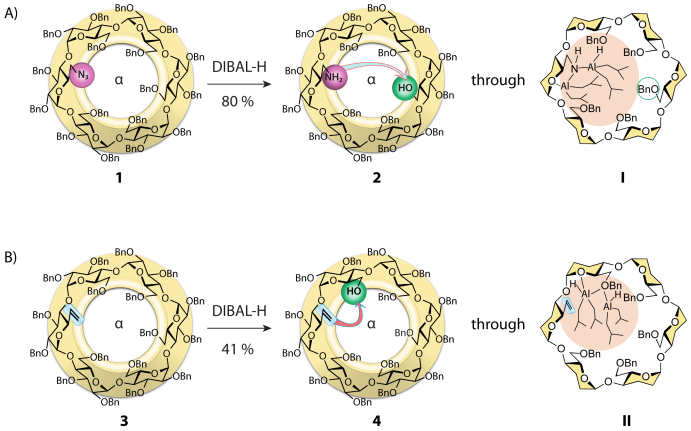
Abstract: Cyclodextrin poly-functionalization has fueled progress in their use in multiple applications such as enzyme mimicry, but also in the polymer sciences, luminescence, as sensors or for biomedical applications… However, the regioselective access to a given pattern of functions on β-cyclodextrin is still very limited. Here, we uncover a new orienting group, the thioacetate, expanding the toolbox available for cyclodextrin poly-hetero-functionalization using DIBAL-H promoted debenzylation. The usefulness of this group is illustrated in the first synthesis of a precisely hepta-hetero-functionalized β-cyclodextrin. By way of comparison, a random hepta-functionalization would give 117655 different molecules. This synthesis is not simply the vain quest for the Holy Grail of CD hetero-functionalization, but it illustrates the versatility of the DIBAL-H oriented hetero-functionalization strategy opening the way to a multitude of useful functionalization patterns for new practical applications.

Keywords: Cyclodextrin, site-selectivity, concave molecules, DIBAL-H

Cyclodextrins (CDs) are cyclic oligosaccharides that display a hydrophobic cavity while being water-soluble. This cavity can therefore host hydrophobic guests in aqueous solution, a property used in our daily lives in deodorants or in excipients for drugs for example. It has also been seen as a potential mimic of the active site of enzymes as early as the 1960's.[1] CD-based enzyme mimicry has thrived through the 1970-80's.[2] This development was correlated with the discovery of CD functionalization methods to add reactive residues to the active site mimic. First, only one function was added to the CD in order to combine a reactive center, for example a metal catalytic group, and a hydrophobic binding cavity.[3] But very soon the need to add two functions, to imitate the functioning of enzymes where reactive centers are precisely positioned in space for enantioselective or regioselective transformations in particular, was felt and the classical CD-bridging strategy was developed.[4,5] Tabushi and Breslow showed that by the use of bridging disulfonyl chlorides with an appropriate geometry it was possible to make disulfonate esters of β-CD with some regioselectivity[4,5] and synthesized beautiful bis-heterofunctional CDs with enzyme-like activities and some enantioselectivity.[6] However, this line of research slowly died out, most likely due to the difficult implementation of the poly-hetero-functionalization methods. Difficulty linked to the moderate regioselectivities and subsequent tedious chromatographic separations. Actually, even now, although a lot of applications of CDs rely on their multi-functionalization, random functionalization is commonly used[7,8,9] instead of a regioselective method which is apparently still seen as an arduous task. It is true that due to the presence of multiple equivalent OH groups random reaction of only the 7 primary hydroxyls of β-CD, constituted of 7 glucose units, with 7 different reagents of equal reactivity statistically leads to a mixture of **117655** different molecules, ranging from 7 molecules bearing 7 times the same substituent to 720 molecules with 7 different substituents.[10] This huge number illustrates the difficulty, but also the need, to achieve the hetero-multi-functionalization of the β-CD.

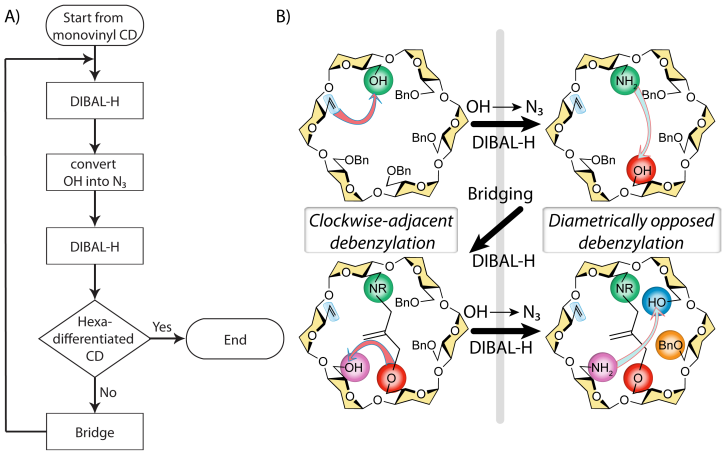
[†] These authors contributed equally to this work.

For some time now, we have been developing strategies to access poly-heterofunctionalized CDs in a practical manner,[11] building on a diisobutylaluminium-hydride (DIBAL-H)-induced debenzylation reaction.[12] We primarily focused our efforts on α-CD, made of 6 glucose units, for which we discovered a series of reactions involving orienting groups for site-directed debenzylation reactions.[13,14,15,1617,18,19] We observed that after a first debenzylation reaction it was possible to orient a second deprotection in two different directions: either on the diametrically opposed sugar or on the adjacent sugar in the clockwise direction when the CD is viewed from the primary rim. To operate these regioselective reactions, we established two main rules: steric hindrance induced by the reaction of DIBAL-H with an azide[17] orients a second reaction on the diametrically opposed sugar (Scheme 1A), while a sterically decompressed group such as a deoxy-,[13] a vinyl[15,16] or a bridging[14] orients the deprotection on the clockwise adjacent sugar (Scheme 1B). In both cases, the access of the DIBAL-H reagents to the debenzylation site is key, as it was postulated that at least two molecules of DIBAL-H were necessary for the reaction to occur.[12] The reaction is therefore highly sensitive to steric hindrance. In the first case, DIBAL-H initially reduces N_3 of CD **1** and forms a covalent N-Al bond creating a highly hindered species **I** that allows the second pair of aluminium reagents to access only the furthest OBn, i.e. the one carried by the diametrically opposite sugar to form **2**. (Scheme 1A).[17] When a vinyl group is replacing an OBn group as in CD **3**, a steric decompression around this group is produced. Due to the cyclic directionality of the CD this decompression is more sensitive on the adjacent clockwise sugar as illustrated on **II**. Therefore, it is easier for the DIBAL-H molecules to react with the OBn situated on this sugar and produce CD **4** (Scheme 1B).[13]



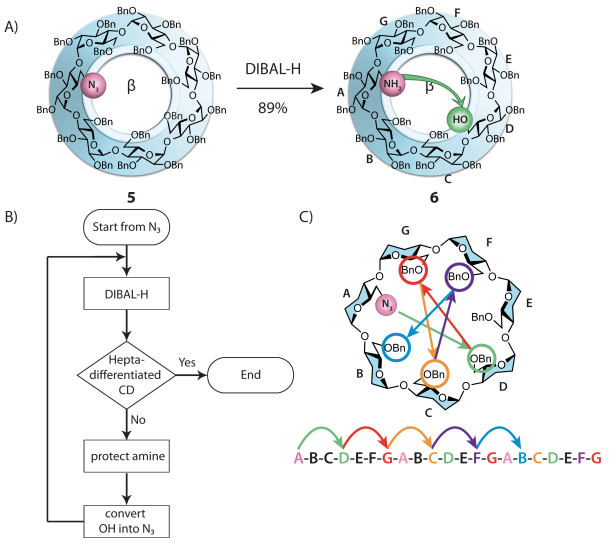
Scheme 1. Two different orienting groups for a DIBAL-H-mediated deprotection. A) An azide group promotes a distal diametrically opposed deprotection because of steric hindrance. B) A vinyl promotes a deprotection of the benzyl group on the adjacent clockwise sugar.

While we established a set of tools to add two or three different functions on CDs, others also defined methods to do so based on this reaction[20,21] or using other strategies that have been parallelly uncovered. [22,23,24,25] As in the early days of CD chemistry, these processes fueled a rebirth of the CD-based enzyme mimicry,[26,27] but also CD-metal complex association[28,29,30,31] or metal encapsulation,[32] supramolecular self-assemblies[33] or variation of host-guest complexes,[34,35] applications in the polymer sciences[36,37,38] luminescence[39], as sensors,[40] for bioimaging,[41]… Given the progress made possible by the addition of one or two functions on the CD, we logically wondered whether we could add more, still in a regioselective manner. We next combined the different strategies and obtained α-CDs with 4,[18] 5 and even 6[19] different functions on the primary rim. To accomplish the ultimate hexafunctionalisation of α-CD, we followed a simple algorithm depicted in scheme 2A: from a starting mono-vinyl-CD, we first operate a DIBAL-H-induced clockwise adjacent debenzylation, convert the formed OH into an azide, operate a DIBAL-H-induced tandem azide-reduction/ diametrically opposed debenzylation, bridge the CD, and repeat once.[19] (Scheme 2)



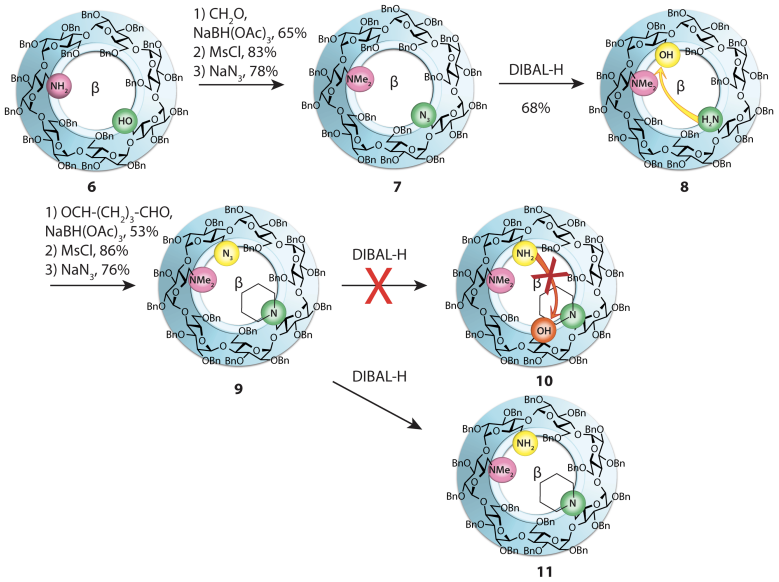
Scheme 2. Synthesis of the first hexadifferentiated α-CD A) Algorithm of the synthesis. B) Key steps to hexadifferentiated α-CD.

It is therefore now possible to access all the 7826 patterns of poly-heterofunctionalization on the primary rim of α-CD in a regioselective manner. However, all this effort concerns α-CD but the Holy Grail in this chemistry would be the access to all patterns of functionality on β-CD. This larger CD can accommodate a much wider range of guests with a better affinity and therefore has many applications. This is a much more challenging task, as a single additional sugar exponentially increases the number of combinations of functionalization patterns from 7826 for 6 functions on α-CD to 117655 for 7 functions on β-CD.[10] To date, only a tetra-hetero-functional β-CD was synthesized using a beautiful orientated acylation on a trifunctional CD,[42] but this later could only obtained through rather low yielding reactions[43] with sometimes low regioselectivities,[44] and in all cases lengthy chromatographic purifications of polar molecules. Recently, an interesting desymetrisation of a perfunctionalized β-CD by a metal induced interesting recognition properties, illustrating the benefits of a well-controlled polyheterofunctionalization strategy.[45] DIBAL-H deprotection methodology allowed the access to tri-hetero-functional β-CDs using the same tandem azide reduction/debenzylation[17] and bridging strategies[15] as for α-CD, albeit with slightly lower regioselectivities, probably due to the bigger size of β-CD and therefore a different sensitivity to the steric hindrance imposed by the DIBAL-H. However, very interestingly due to the odd number of sugars there is no diametrically opposed sugar to the azido group in β-CD **5**, nevertheless the debenzylation reaction remains regioselective and occurs on the third sugar, from the one bearing the N_3, in the counterclockwise direction, hence mono-azido β-CD **5** is converted into the amino-alcohol **6** (Scheme 3A).[17,46] This simple fact made us realize that we could reach the Holy Grail, heptadifferentiated β-CD, through a very simple algorithm: begin with a monoazido-CD **5**, react with DIBAL-H, protect amine, convert OH into azide, repeat process until hepta-differentiation is reached (Scheme 3B). Indeed, as illustrated on scheme 3C, 5 successive rounds of this algorithm should lead to the formation of a β-CD with 5 different amines, a benzyl ether and a hydroxyl group.



Scheme 3. Heptadifferentiation strategy, based on tandem azide reduction/distant debenzylation. A) Distal deprotection promoted by an azide on β-CD. B) Algorithm for the synthesis of a heptadifferentiated β-CD. C) Successive azide-oriented distal debenzylation reactions lead to heptadifferentiation.

So we embarked on this quest: the synthesis of heptadifferentiated β-CD. To follow the algorithm, we started from CD **6** and protected its amine using a double reductive amination with formaldehyde, mesylation of the alcohol, and displacement of the afforded mesylate by an azide gave amino-azide **7**. DIBAL-H tandem azide-reduction/debenzylation on **7** afforded amino-alcohol **8** according to plan. This sequence of reactions was repeated using glutaraldehyde in the reductive amination step, however, when we performed the DIBAL-H reaction on **9**, we could not form the desired amino-alcohol **10**, we only detected the azide-reduced amine **11** by mass-spectrometry (Scheme 4). It was a very disappointing result, fatal to our synthetic strategy… We tried very hard to get around this obstacle by varying the protecting groups on the amines, we tried two other sets of alkyl chains on the amines, without any improvement (see SI). The presence of three amines on the CD seems to inhibit the deprotection reaction and we are stuck at the azide-reduction step.

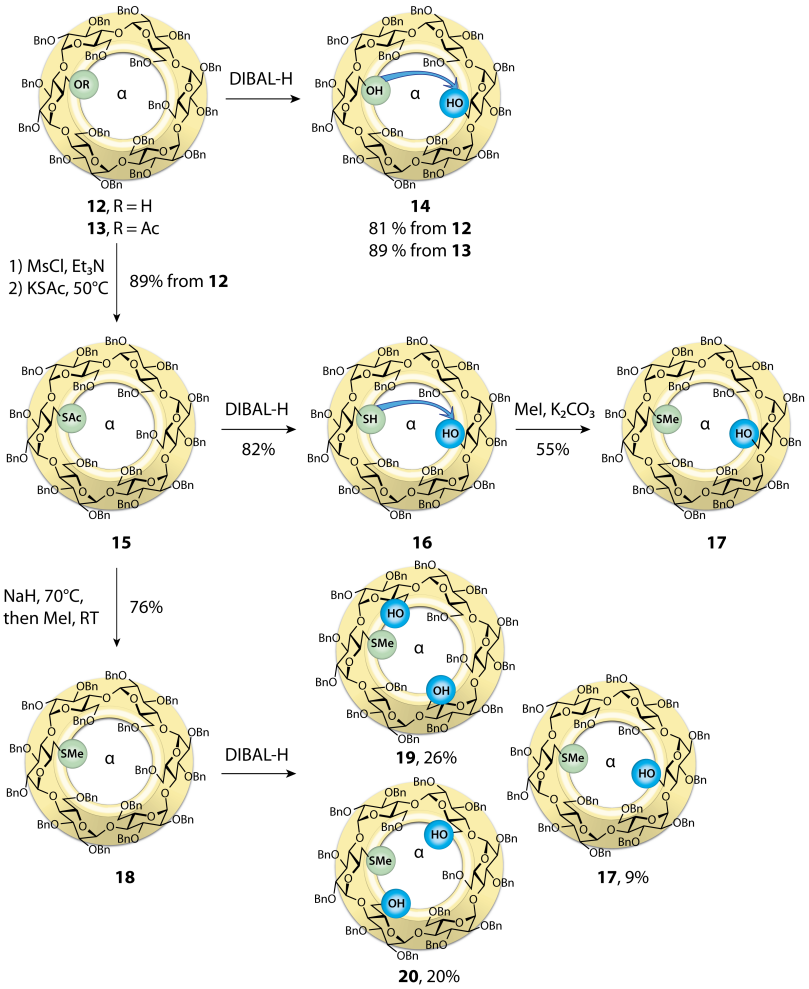


Scheme 4. Successive tandem azide reduction/debenzylation reactions can only deliver tetra-differentiated β-CD.

We reasoned that as the reaction mechanism involves critical Lewis acid and base interactions, the presence of three amines, notoriously good Lewis bases, probably captures aluminium reagents and prevents further reaction by the steric hindrance it induces. We therefore thought that to carry on we needed a function that could orient a second deprotection without forming a strong Lewis acid/base interaction. Nitrogen being a rather hard Lewis base, it interacts with the hard aluminium-based Lewis acid. Logically, we decided to use a soft Lewis base to prevent its interaction with aluminium. Our first thought was to turn to sulfur. Thus, we now have to develop a sulfur based orientating group. In the azide strategy, the first step is a reduction of the azide, this reaction is not transposable to sulfur, so we kept the reduction and looked for a simple group to introduce that would be reducible and that would result in the formation of an aluminium-sulfur covalent bond. A simple reduction of ester should do the trick.

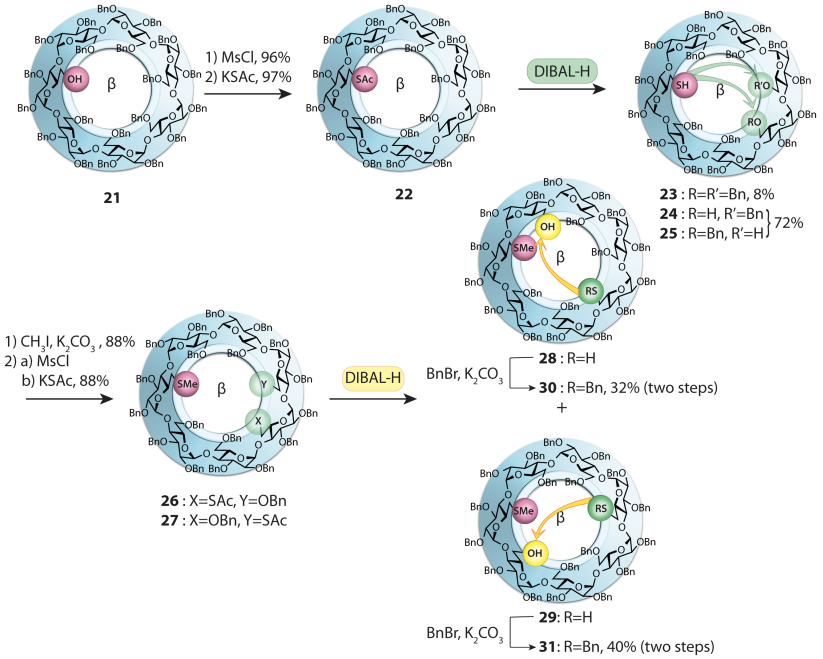
We first probed the idea with a simple ester **13** and obtained the diol **14** in 89% yield and total regioselectivity. The reaction obviously starts with the reduction of the ester to give the aluminoxide that orients the debenzylation on the farthest position as demonstrated previously, on alcohol **12**. Monol **12** was therefore converted into a mesylate which was displaced by a thioacetate using KSAc at 50°C to afford thioacetate α-CD **15** in 89% yield over the two steps. Upon action of DIBAL-H, **15** gave the thio-alcohol **16** that we hoped in 82% yield, validating the first condition to be a good orienting group for the multidifferentiation of CDs. The second condition is the possibility to chemoselectively protect the thiol with a group inert to the action of DIBAL-H. To probe this property, we first operated a regioselective thio-etherification of thio-alcohol **16**, in the presence of a weak base, and obtained the S-methylated derivative **17** with its alcohol remaining free. The inertness of the thioether was next probed. To do so we converted the thioester of CD **15** into a thioether in one step using Krief's method[47] to give methyl-thio-CD **18**. When CD **18** was reacted with DIBAL-H three products were formed: diols

19, **20**, and monol **17** in 26, 20 and 9% yields respectively. This result corresponds approximately to the statistical deprotection of each Bn group and proves the inertness of SMe, in contrast to OMe which is reacting,[12] towards the action of DIBAL-H. So, while SAc is an orienting group for further DIBAL-H-assisted debenzylation, SR groups are unreactive. We therefore have the required properties for a sulfur-based strategy towards the heptadifferentiation of β-CD using the same algorithm as for the amine-strategy (Scheme 5).



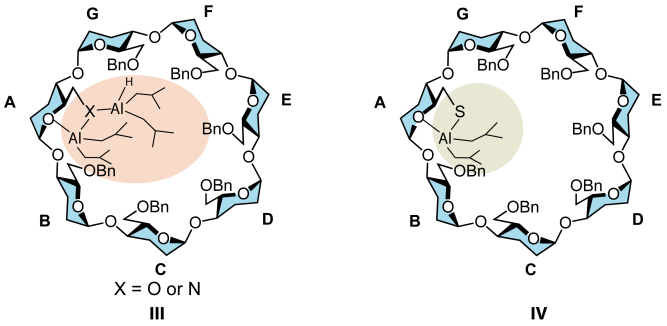
Scheme 5. Thioester can be used to orient a DIBAL-H-induced debenzylation on the distal sugar, and thioethers are inert to the action of DIBAL-H.

The algorithm of scheme 3B can be adapted to a strategy involving thioesters instead of azides (Scheme S4). Accordingly, monol β-CD **21**[48] was converted into thioester CD **22**, which underwent thioester reduction and debenzylation upon action of DIBAL-H. This time, however, an inseparable mixture of thiol-alcohol CDs (72%), that we assumed to be **24** and **25**, was obtained together with a small quantity of simple thiol **23** (8%). We proceeded nonetheless on the mixture with a chemoselective S-methylation of the thiol of **24** and **25** using methyl iodide and potassium carbonate, followed by a mesylation/thioester formation sequence to form a mixture of regioisomers **26** and **27**. This mixture was again submitted to the action of DIBAL-H and gave a mixture of two thio-alcohols **28** and **29**, which could only be fully separated after their chemoselective S-benzylation in **30** and **31** in 32 and 40% yield respectively after two steps (Scheme 6).



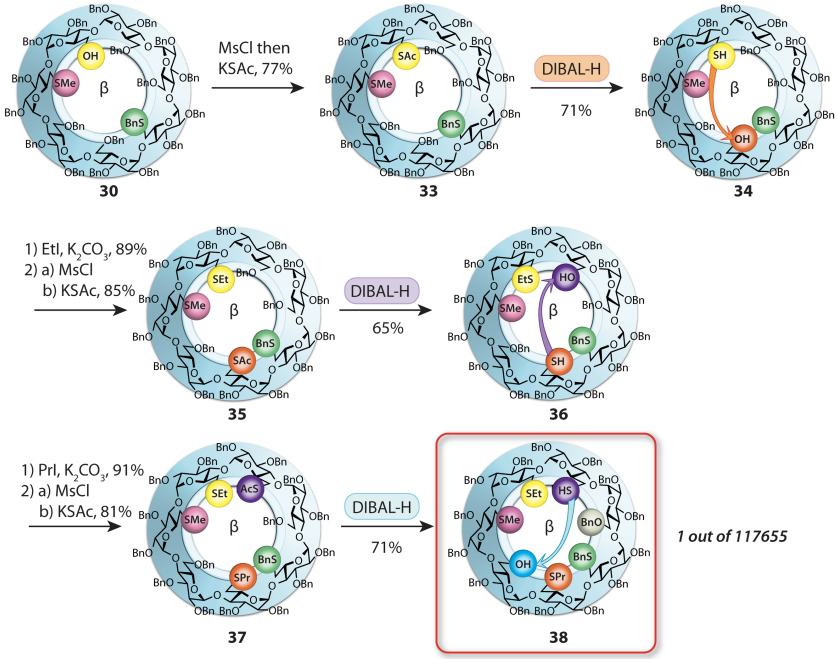
Scheme 6. Tandem thioester reduction/debenzylation on β-CD performed twice in a row gives two regioisomers.

The lack of selectivity in the first tandem thioester reduction/debenzylation reaction compared to that of the azide is probably linked to the lack of affinity of the sulfur for aluminium. While nitrogen and oxygen would coordinate to aluminium to form very hindered species **III** orienting the deprotection as far as possible,[12,17] the sulfur might not form a complex with a second Al (**IV**) reducing the hindrance and therefore the selectivity. However, this degree of selectivity is enough for the second round of deprotection which gives only one regioisomer **28** and **29** per thioacetate **26** or **27** respectively (Scheme 7).



Scheme 7. Difference in coordination of Al with O, N and S.

We therefore took the regioisomer that we had in greater quantity (**31**) and carried on the synthesis. After introduction of the thioester to give **32**, we attempted the third DIBAL-H reaction and were particularly discouraged to obtain a mixture of isomers (Scheme S5). Nevertheless, we also used the other isomer **30** to form thioester **33** that underwent the DIBAL-H tandem thioester reduction/debenzylation smoothly in a regioselective manner to give **34** in 71 % yield. The rest of the synthesis was a lot easier and the sequence mesylation, thioacetylation, DIBAL-H reduction/debenzylation followed by S-alkylation was performed twice more according to the algorithm scheme S4. In this sequence, DIBAL-H reaction was performed on CDs **35** and **37** to give CDs **36** and **38** in 65 and 71% yield respectively and with complete regioselectivity (Scheme 8). The structure of heptadifferentiated CD **38**, the Holy Grail, was confirmed independently by NMR spectroscopy and MS^n experiences (see SI). Heptadifferentiated CD **38** was finally obtained in 21 linear steps with a 0.6% overall yield starting from native β-CD (Scheme S6). In one run, we started from 21 g of native β-CD and obtained 400 mg of heptadifferentiated CD **38** demonstrating the robustness of this synthesis.



Scheme 8. End of the synthesis of heptadifferentiated β-CD **38**.

Our Grail Quest was finally successful! The ultimate heptadifferentiated β-CD could be reached using the initially designed algorithm, but not the previously reported tandem azide reduction/distal debenzylation because we observed that three amines on the CD inhibits further debenzylation reactions. Instead, we had to delineate a new orienting group that does not prevent further debenzylations. The use of thioesters as orienting groups together with the inertness of thioethers allowed to solve that problem. As much as we know that heptadifferentiated CD **38** might not bring new applications of CDs right now, we are confident that the synthetic strategies and practical solutions that we present here offer a wide range of possibilities to the community. In this work alone, we synthesized 18 different tetra-differentiated β-CDs, 3 pentadifferentiated CDs and 3 hexadifferentiated CDs. We can now also think of the many combinations that are offered by the two tandem reactions azide reduction/debenzylation[17] and thioester reduction/debenzylation coupled with a bridging strategy[15] and one can envisage many many different useful patterns of functionalization of CDs.

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