Asymmetric Cyclodextrins

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Regiospecific Tandem Azide-Reduction/Deprotection To Afford Versatile Amino Alcohol-Functionalized α- and β-Cyclodextrins**

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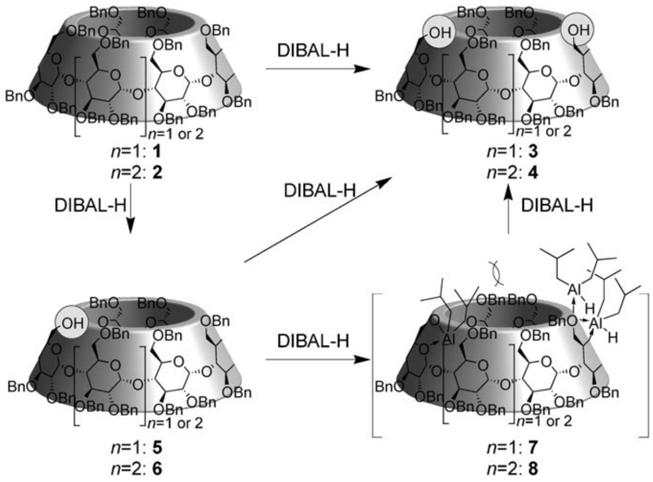
Dedicated to Michel Lopoukhine on the occasion of his 90th birthday

Regioselective functionalizations that confer chirality to large complex molecules, particularly those with a concave shape, are an important goal in the fields of molecular recognition and catalysis.[1] Cyclodextrins (CDs) qualify as interesting chiral hosts in this respect as they have shown excellent artificial enzymatic activity,[2] although they have found only limited applications in asymmetric catalysis.[3] Amino alcohols, or amino acids such as proline, have emerged as powerful chiral tools for enantioselective catalysis.[4,5] Therefore, the elaboration of a CD scaffold bearing an amino alcohol or an amino acid at a specific position is an attractive goal. However, the synthesis of such compounds requires a judicious functionalization (both regioselective and orthogonal) of two hydroxy groups of the CD. The regiospecific introduction of two different functionalities on the primary rim of CDs is a rapidly emerging area. Although the synthesis of monofunctionalized CDs is a relatively straightforward task,[6] the addition of a second function implies that a regioselective process must take place. Current methodologies rely on the regioselective opening[7] or formation[8] of capped CDs to afford 6^{A}-6^{B}-imidazolyl-sulfonyl-[7] or 6^{A}-6^{B}-thioether-ester substituted[8] CDs, respectively, albeit in moderate yields (less than 10% from unfunctionalized CDs). More recently, a selective direct sulfonation of an imidazolyl CD was performed and, among the 20 possible isomeric monosulfonates, the 6^{A}-6^{D} isomer was isolated in 13% yield.[9] However, these methods are inadequate for further conversion into amino alcohols because of the nature of the functional groups, which can also require difficult synthetic procedures.

We have developed a method that allows the introduction of one,[10] two,[11–15] or three[15,16] orthogonally protected alcohol groups on the primary rim of perbenzylated α- and β-CDs through successive sterically oriented deprotections induced in high yields by diisobutylaluminum hydride (DIBAL-H). The double deprotection of CDs **1** and **2** that afforded diols **3** and **4**, respectively, was shown to occur by a stepwise mechanism in which the two deprotection steps take place sequentially (Scheme 1). This was demonstrated by the deprotection of alcohol **5** to give diol **3**.[10,16] We proposed that protonolysis of the alcohol on **5** and **6** by DIBAL-H affords very hindered aluminum species, leading to CDs **7** and **8**, in which a pair of reactive aluminum centers are attached to the glucose units that are furthest apart to maximize their separation, thereby imposing the observed regioselectivity.[10]



Scheme 1. DIBAL-H-promoted double debenzylation reaction that occurs via the aluminum adduct of a monodeprotected product, thereby inducing regioselectivity. Bn = benzyl.

We reasoned that it should be possible to perform this reaction with an amine instead of an alcohol. Hence, monoalcohol-functionalized α-CD **5** was converted into azide **9** in 95% yield and the azido function reduced to give the amine **10** (Scheme 2). However, action of DIBAL-H on the amino-functionalized CD **10** resulted in a random debenzylation of the primary rim of the CD. In striking contrast, the action of DIBAL-H on azido-functionalized α-CD **9** under the same conditions afforded solely 6^{A}-amino-6^{D}-hydroxy-substituted CD **11** in 74% yield (45% from unfunctionalized α-CD) on a multigram scale. Amine-functionalized **10** can be obtained without debenzylation under more moderate conditions. Protonolysis of an amine by DIBAL-H is a rather slow process[17] that can therefore compete with

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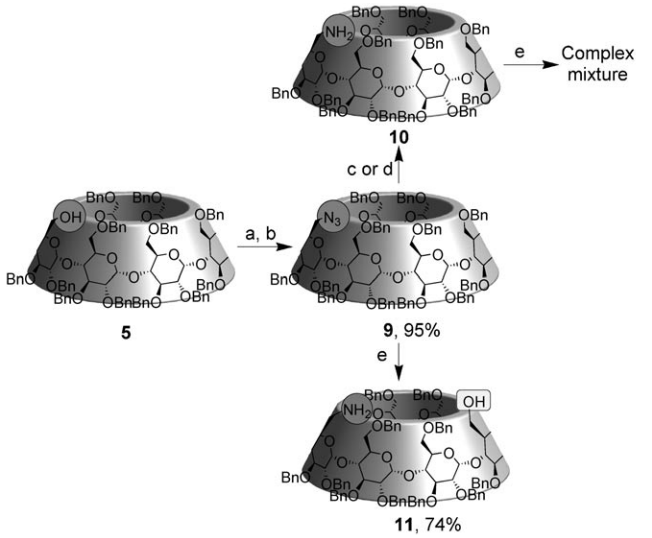
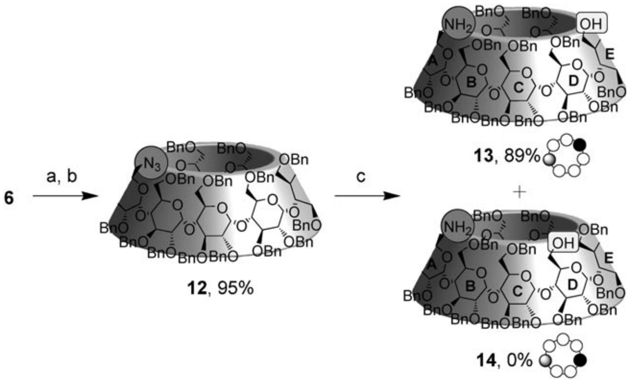


Scheme 2. Synthesis of amino alcohol functionalized α-CD **11**. Reagents and conditions: a) MsCl, Et_3N, CH_2Cl_2, 0°C→RT, 12 h; b) NaN_3, DMF, 80°C, 18 h; c) PBu_3, THF, RT, 1 h, then H_2O, RT, 12 h, 80%; d) DIBAL-H (1 equiv every 24 h, for 5 days), toluene, RT, 72%; e) DIBAL-H (30 equiv, 1 M), toluene, 50°C, 1 h. Ms = methanesulfonyl.

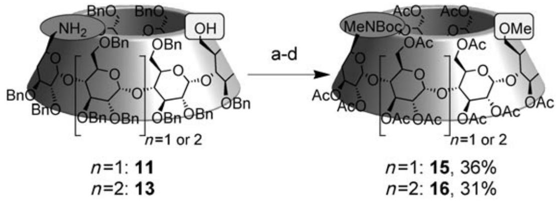
the debenzylation reaction in the case of amino-functionalized CD **10**. The deprotection reaction is not directed by an aluminum center that is attached to the molecule and results in the observed mixture. On the other hand, the tandem azide reduction and deprotection of CD **9** starts with a previously unreported azide reduction by DIBAL-H. The resulting aluminum species that is covalently attached to the nitrogen atom directs the debenzylation to the most distant site, as in the case of CD **5**.

Azido-functionalized β-CD **12** was obtained in 95% yield from CD **6** following a conventional route. The action of DIBAL-H on **12** afforded a single compound, 6^{A}-amino-6^{E}-hydroxy-substituted CD **13** (89% yield, and 50% from unfunctionalized β-CD; Scheme 3), resulting from the same tandem reduction–deprotection reaction. Surprisingly, regionisomeric 6^{A}-amino-6^{D}-hydroxy-substituted CD **14** was not detected.

The regiochemical outcome of the tandem reaction was unambiguously determined by NMR spectroscopic analysis of modified compounds **15** and **16**. These were obtained through protection of the amine with a Boc protecting group (Boc = *tert*-butoxycarbonyl), dimethylation, debenzylation, and peracetylation of CDs **11** and **13** (Scheme 4). All the protons of each glucose moiety were identified using COSY, TOCSY, and HMQC experiments. The assignments of glucose units A and D for α-CD **15** and the A and E units for β-CD **16** (Figure 1) were derived from NOESY cross-peaks between methyl groups and H-6 atoms. The substitution pattern was deduced by following the sequence of NOESY cross-peaks between H-1 and H-4 of adjacent glucose units around the CD ring.



Scheme 3. Regiospecific synthesis of amino alcohol functionalized β-CD **13**. Reagents and conditions: a) MsCl, Et_3N, CH_2Cl_2, 0°C→RT, 3 h; b) NaN_3, DMF, 80°C, 12 h; c) DIBAL-H (30 equiv, 1 M), toluene, 50°C, 1 h.



Scheme 4. Synthesis of CDs **15** and **16** for NMR analysis. Reagents and conditions: a) Boc_2O, $EtOH/CH_2Cl_2$, RT; b) MeI, NaH, DMF, RT; c) H_2, Pd/C, THF/H_2O, RT; d) Ac_2O, pyridine, RT. Boc = *tert*-butyloxycarbonyl.

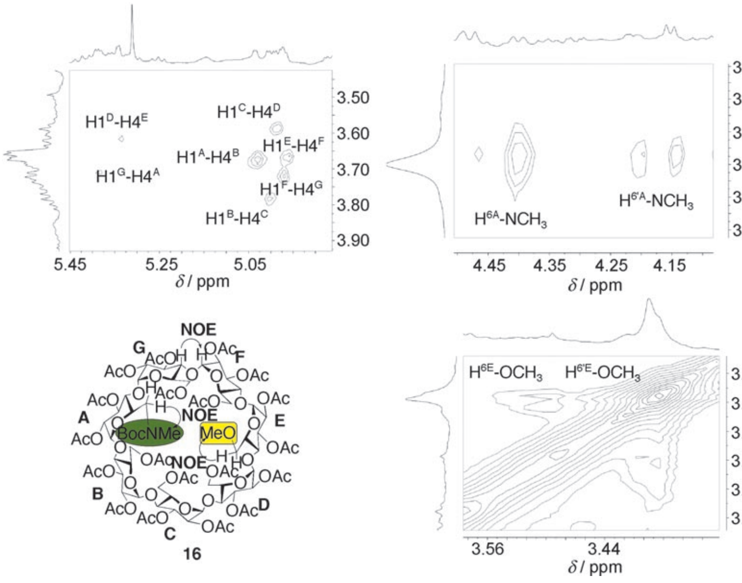
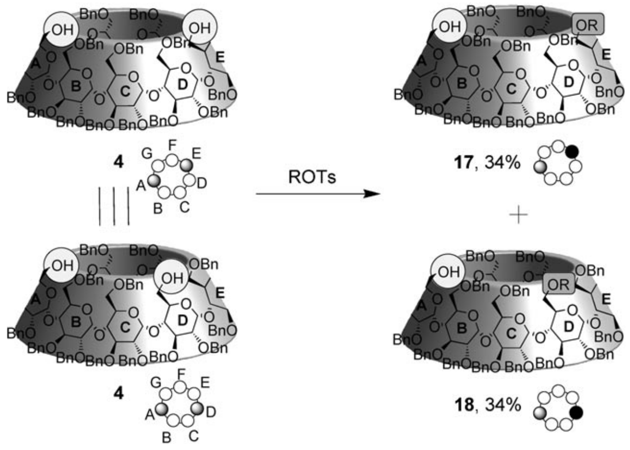


Figure 1. Key NOESY cross-peaks for the structural elucidation of β-CD **16**.[18]

The amine group of CDs **13** and **14** is separated from the newly formed alcohol by two glucopyranoside units, in either a clockwise (**13**) or counterclockwise (**14**) direction. The tandem reaction affords only a single product **13** despite the strict equidistance between rings A and D, and E and A. This selectivity cannot be detected in the double debenzylation reaction of CD **2** to give diol **4**, because **2** can be regarded as either a 6^{A}-6^{E} or a 6^{A}-6^{D} diol, which results in the equivalence of the two hydroxy groups. Indeed, when β-CD-diol **4** was monoalkylated in a previous study,[19] we obtained, as expected, an inseparable 1:1 mixture of 6^{A}-hydroxy-6^{E}-alkyl **17** and 6^{A}-hydroxy-6^{D}-alkyl **18**, resulting from the statistical alkylation of the two undistinguishable alcohols (Scheme 5). Therefore, this pathway is ineffective for the formation of a single β-CD compound,[20] whereas the regiospecific tandem reaction clearly reveals all its interest, particularly if we aim to use those compounds for asymmetric induction.



Scheme 5. Monoalkylation of diol **4** that results in a random mixture of AE (**17**) and AD (**18**) regioisomers. [19] Ts = toluene-4-sulfonyl.

However, the selectivities observed in previous work are all based on steric hindrance and hence on distance.[11–16] We constructed a simple molecular model (Figure 2) of a β-CD containing the first aluminum center covalently attached to N-6^{A} and complexed to O-5^{A},[10,21] as well as two pairs of aluminum centers on rings D and E involved in the dealkylation process, to measure distances between them.[22] Not surprisingly, Al^{A} is the same distance from Al-1^{D} and Al-1^{E} because they are attached to the sugar moieties in the same relative positions. The only significant difference in distance that we determined is between the isobutyl groups borne by Al^{A} and Al-2 on rings D and E. We therefore assume that it is more difficult for a second aluminum center to approach O-6^{D} than O-6^{E}. This observation probably accounts for the regiospecificity of this reaction and adds further support to our mechanistic hypothesis that two aluminum centers, each with a different role, participate in the reaction.[10]

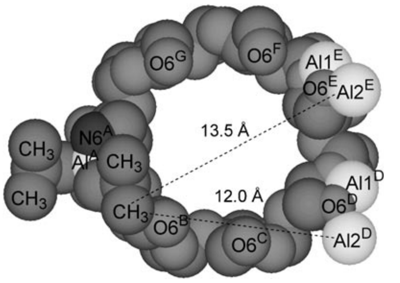
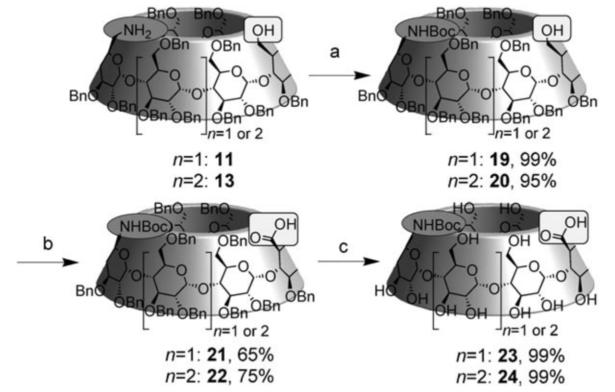


Figure 2. Molecular model of a simplified amino-functionalized β-CD bearing one Al center on the nitrogen atom and two on O-6^{D} and O-6^{E}.

The utility of this tandem reaction has been illustrated by the efficient synthesis of regioisomerically pure NH-Boc-protected amino acids derived from α- and β-CDs (Scheme 6).[23] These CDs can then be incorporated into peptide sequences through solid-phase synthesis to afford peptides bearing a hydrophobic funnel at a specific position. The amine groups of amino alcohols **11** and **13** were chemoselectively protected by a Boc group,[24] and the resulting alcohols **19** and **20** were then oxidized to the corresponding acid. The resulting CDs **21** and **22** were debenzylated to quantitatively afford CD-derived amino acids **23** and **24** (in 46 % and 55 % yield, respectively, from alcohols **5** and **6**, and 30 % and 33 % from unfunctionalized α- and β-CDs by using our methodology).



Scheme 6. Efficient conversion of amino alcohols **11** and **13** into amino acid functionalized CDs **23** and **24**. Reagents and conditions: a) Boc_2O, EtOH/CH_2Cl_2, RT; b) Dess–Martin periodinane, CH_2Cl_2, RT then $NaClO_2$, *t*BuOH, H_2O, NaH_2PO_4, RT; c) H_2, Pd/C, THF/H_2O, RT.

In conclusion, we have delineated a regiospecific tandem azide reduction/debenzylation reaction as a practical solution to a classical problem in β-CD chemistry, namely the selective introduction of two different diametrically opposed functionalities. We have efficiently synthesized highly versatile cyclodextrins bearing diametrically opposed amino alcohol units, which can pave the way to many applications such as asymmetric catalysis or the synthesis of CD-bearing peptides. As in our previous work, but this time following a different route, we have demonstrated the remarkable ability of DIBAL-H to decipher the cyclic directionality of the CD in order to differentiate a single position out of the possible five or six.

Experimental Section

General experimental procedure for tandem azide reduction/debenzylation: DIBAL-H (1.5 M in toluene, 30 equiv) was slowly added to a solution of azido-functionalized CD (1 equiv) in toluene (so that the concentration of DIBAL-H was 1 $mol\,L^{-1}$) under argon at RT. The reaction mixture was stirred at 50 °C for 1 h, then poured onto ice. HCl (1 $mol\,L^{-1}$ in water) and EtOAc were added and the solution was stirred for 1 h. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo, and the residue was purified by flash chromatography on silica gel eluting with cyclohexane/EtOAc.

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[22] Molecular mechanics calculations were performed using the OPLS-2005 force field in the MACROMODEL 7.0 package. Aluminum centers were added to an X-ray structure of β-CD to model the desired compound using the BUILDER option of MAESTRO before transfer to MACROMODEL. Energy optimization was then carried out using standard conjugate gradient minimizations until convergence was reached.

[23] For α-CD and nonregioselective synthesis of related β-CD compounds, see Ref. [20].

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