Cyclodextrin Functionalization

DOI: 10.1002/anie.201204974

An "Against the Rules" Double Bank Shot with Diisobutylaluminum Hydride To Allow Triple Functionalization of α-Cyclodextrin**

*Elena Zaborova, Maxime Guitet, Giuseppe Prencipe, Yves Blériot, Mickaël Ménand, and Matthieu Sollogoub**

A dual characteristic of highly symmetrical concave molecules is that on the one hand they possess a cavity that confers them with a multitude of applications whilst on the other they are inherently difficult to regioselectively functionalize. Cyclodextrins (CDs) are typical in this respect. Native CDs are widely used in commercial formulations of drug molecules to increase their solubility, bioavailability, and stability,[1] and have also been widely used in combination with polymers to modulate their properties.[2] In the realm of catalysis, both native and uniformly modified CDs have very successfully served as mass-transfer additives.[3]

The simple addition of a single functionality to native CDs has tremendously increased their drug delivery potential by allowing the targeting of a specific receptor.[4] The installation of an additional functionality on the same scaffold, such as an imaging moiety, could deliver a theragnostic device, an emerging concept permitting simultaneous diagnostic and therapy.[5] Similarly the construction of beautiful supramolecular assemblies of CDs, such as photoswitchable hydrogels,[6] daisy-chains,[7] Cayley trees,[8] and macroscopic self-assemblies,[9] has been made possible by their monofunctionalization. It could be speculated that the addition of a supplementary functionality could pave the way to 3D structures and thus highly functional materials. With respect to applications in catalysis, the addition of a single functionality allowed the development of several catalysts incorporating CD-based metal ligands,[10] one of which proved to be particularly efficient in catalyzing a Suzuki coupling.[11] Installation of an additional functionality produced an enantioselective CD-ligand-based catalyst, the asymmetry of which is due to the arrangement of the substituents on the CD rim.[12] Further advances in applications of CDs will clearly rely on the ability to regioselectively and efficiently install more than one functionality on this concave scaffold.

A considerable amount of work has been invested in the search for selective methods to enable the poly-hetero-functionalization of CDs, but such studies have only resulted in access to a restricted number of functionality patterns. Regioselective opening, or formation of capped-CDs produced 6^A–6^B heterodifunctional CDs, in moderate yields (< 10% from native CDs),[13] until recent developments.[14] A selective direct sulfonation of an imidazolyl CD has been performed, and, among the 20 isomeric monosulfonates, the 6^A–6^D isomer was isolated in 13% yield.[15] The same method allowed tetrafunctionalization through a sequence that included the separation of two regioisomers. The discovery of a regioselective debenzylation of perbenzylated sugars,[16] coupled with the deciphering of its mechanism,[17] allowed the delineation of several strategies to access CDs with either two,[17–19] three,[20–22] or four[21] different functional groups that could be regioselectively introduced onto its primary or secondary[23] rim. Our strategy for the synthesis of tridifferentiated CDs relies on the control of the site of approach of the reagent either through steric hindrance or decompression. For example, a perbenzylated CD with one free hydroxy or an azide group on its primary rim underwent a selective deprotection of the primary alcohol on the diametrically opposed sugar during treatment with diisobutylaluminum hydride (DIBAL-H).[22] It has been proposed that this selectivity is due to steric crowding produced by a first molecule of aluminum reagent that reacts with the hydroxy or the azide group to form a covalent O–Al or N–Al bond. The second aluminum species then approaches the farthest possible site to effect the deprotection.[22] In a distinct strategy, deprotection occurs on the adjacent sugar unit clockwise to a glucose from which the benzyloxy group in position 6 has been removed. This defunctionalisation induces steric decompression only at the clockwise sugar owing to the cyclic directionality of the CD, and this accounts for the regioselectivity of the corresponding deprotection reaction (Figure 1).[20]

Considering the limited number of patterns of functionality that are currently accessible in a regioselective manner, combined with the potential benefits and inherent difficulties of developing such methods, we decided to challenge the system by combining both of these established orientating strategies. We hypothesized that removal of the benzyloxy group that is diametrically opposed to a hydroxy or azido group, a modification which frustrates the possibility of normal debenzylation, should then orientate deprotection clockwise by one unit relative to the deoxy position by a ricochet effect. (Figure 1) In the case of the 6^A-azido-6^D-deoxy CD, this should then give access to a novel and completely regioselective method of tetra-differentiation.

[*] Dr. E. Zaborova, M. Guitet, Dr. G. Prencipe, Prof. Y. Blériot, Dr. M. Ménand, Prof. M. Sollogoub
UPMC Univ Paris 06, Institut Universitaire de France
Institut Parisien de Chimie Moléculaire, UMR-CNRS 7201
C. 181, 4 place Jussieu, 75005 Paris (France)
E-mail: matthieu.sollogoub@upmc.fr
Homepage: http://www.ipcm.fr/Presentation,293

[**] We thank Cyclolab (Hungary) for generous supply of α-CD, Philippe Pelupessy and Elsa Caytan for their precious assistance in recording the NMR spectra, and Professor Antony Fairbanks for appreciated help.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201204974.

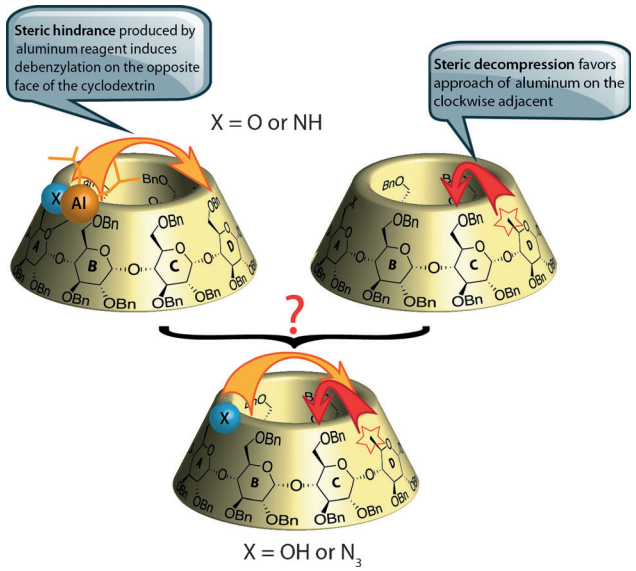
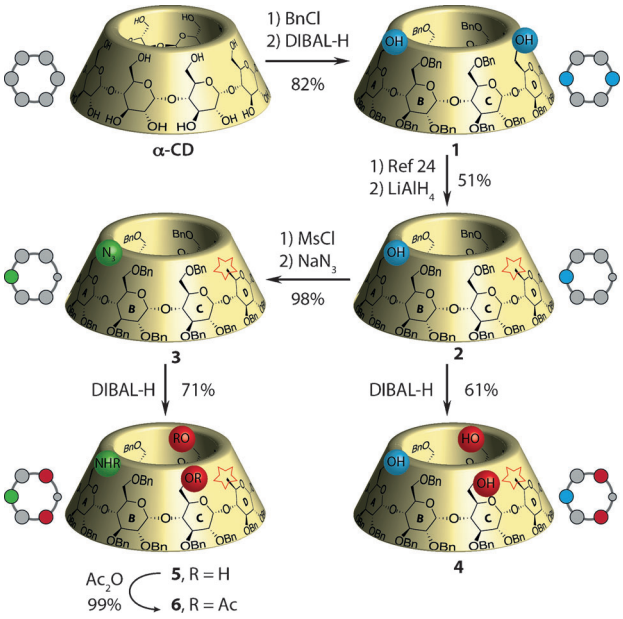


Figure 1. Combination of both directing strategies.



Scheme 1. Double-bank shot-like double deprotection of CD **2** and **5**. Bn = benzyl, DIBAL-H = diisobutylaluminum hydride, Ms = mesyl.

An in-house perbenzylation/double debenzylation sequence afforded diol **1**,[17] which was capped with a sulfate bridge according to the method of Bols et al.[24] Opening of the cyclic sulfate with lithium aluminum hydride provided, after hydrolysis, 6^A hydroxy-6^D-deoxy-CD **2** in 51 % yield. The alcohol on CD **2** was substituted by an azido group to give CD **3** in 98 % yield (34 % overall yield from native α-CD). When CD **2** was treated with 30 equivalents of a 1 M solution of DIBAL-H, triol **4** was formed in 61 % yield rather than the expected diol. Furthermore, when azido-CD **3** was reacted with DIBAL-H under similar conditions, an aminodiol **5** was isolated in 71 % yield (Scheme 1).

The regiochemical outcome of both reactions was unambiguously determined by NMR analysis of compounds **4** and **6**, the latter being obtained by acetylation of **5** to facilitate NMR analysis. COSY, TOCSY, and HMQC/HSQC experiments allowed the identification of all protons borne by the same glucose moiety. The 6-deoxy positions were easily attributed ($\delta = 1.30$ ppm, doublet in **4**, and $\delta =$ 1.27 ppm, doublet in **6**), allowing the identification of sugar unit D in both compounds (Figure 2 a; Supporting Information, Figure S9a). In the case of compound **4** TOCSY cross-correlations with the three 6-OH groups allowed the identification of sugar units A, C, and E (Figure 2 a). For compound **6**, HMBC cross-coupling peaks between the quaternary carbons of the acetate groups and the corresponding H-6 atoms (Supporting Information, Figure S9c) confirmed the presence of three acetylated units. Ring A was also identified through NHAc/H-6 COSY cross coupling (Supporting Information, Figure S9b). HMBC cross-coupling peaks observed between C-6 and the benzylic protons confirmed the presence of two 6-OBn groups on sugar rings B and F (Figure 2 b; Supporting Information, Figure S9d). Finally, the order of

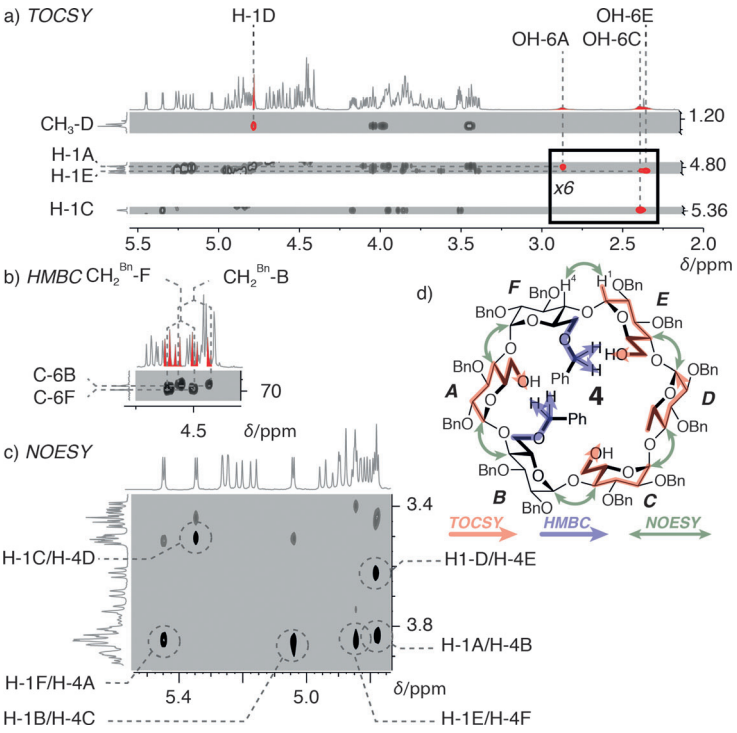


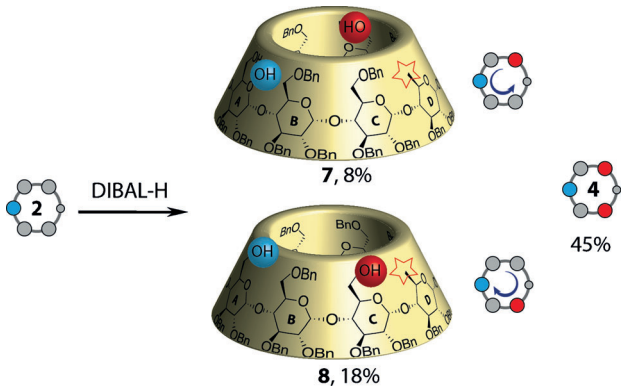
Figure 2. NMR analysis of CD **4**.

connection of the sugar units was deduced from the inter-residue H-1/H-4 NOESY-cross couplings (Figure 2 c; Supporting Information, Figure S9e).

In all respects, the outcome of both reactions is surprising considering our previous results. First, it is unprecedented that a double deprotection with DIBAL-H does not operate on either the diametrically opposed or adjacent sugar units, but instead affords an ACE pattern.[25] Furthermore, we have

never observed the formation of a triol on the primary rim of an α-CD with such a high rate and efficiency. It should be noted that longer reaction times and higher amounts of DIBAL-H did allow Ling to isolate triols and even tetrols in low to moderate yields though free hydroxy groups were either on adjacent sugars or on different rims.[26] In this case, it seems that steric decompression fails to direct deprotection selectively onto the clockwise sugar, as the counterclockwise adjacent sugar is also simultaneously deprotected.

In an effort to understand the mechanism of this surprising reaction, we first wondered if the triol was actually a product from over-debenzylation of the expected diol **8**. We therefore stopped the reaction of CD **2** with DIBAL-H before it had gone to completion, and isolated a mixture of triol **4** (45%) and diols **7** and **8** (26% yield of a 3:7 mixture). These two diols were separated by chromatography, and a pure sample of each compound was obtained and characterized by NMR using the same method employed for triol **4**. Compounds **7** and **8** clearly result from a single debenzylation of alcohol **2** on either the counterclockwise or the clockwise sugar adjacent to the deoxy sugar D, respectively (Scheme 2).



Scheme 2. Structure of isolated transient diols **7** and **8**.

This seems to indicate that the reaction first gives a mixture of regioisomeric diols **7** and **8**, and that the reaction pathways then converge to give the same triol **4**. To gain further insight into this reaction, we studied the relative concentrations of the four CDs involved in this process over time. CD **2** was reacted with DIBAL-H under typical reaction conditions, and a 5 μL aliquot was taken from the reaction mixture every 2 minutes and immediately quenched with 1M aqueous HCl, extracted with AcOEt, and the organic layer analysed by HPLC. A stack of HPLC traces and the time-dependent concentration profiles are shown in Figure 3. On the assumption that the reaction is pseudo first order for all of the CD derivatives and that the concentration of DIBAL-H is constant, resolution of the differential equations and global curve fitting allowed extraction of the relative rate constants. Such an analysis reveals that both diols **7** and **8** are formed at similar rates, the expected clockwise derivative **8** having a slightly higher rate constant. The rate constant for the clockwise deprotection in the second step was even higher (Figure 3).

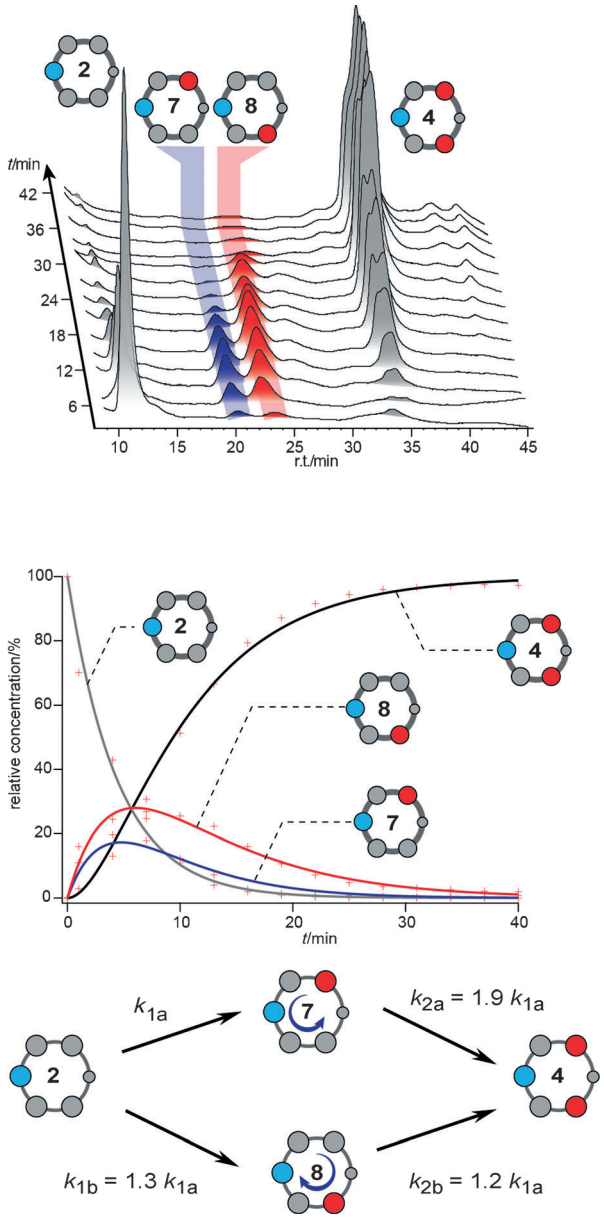
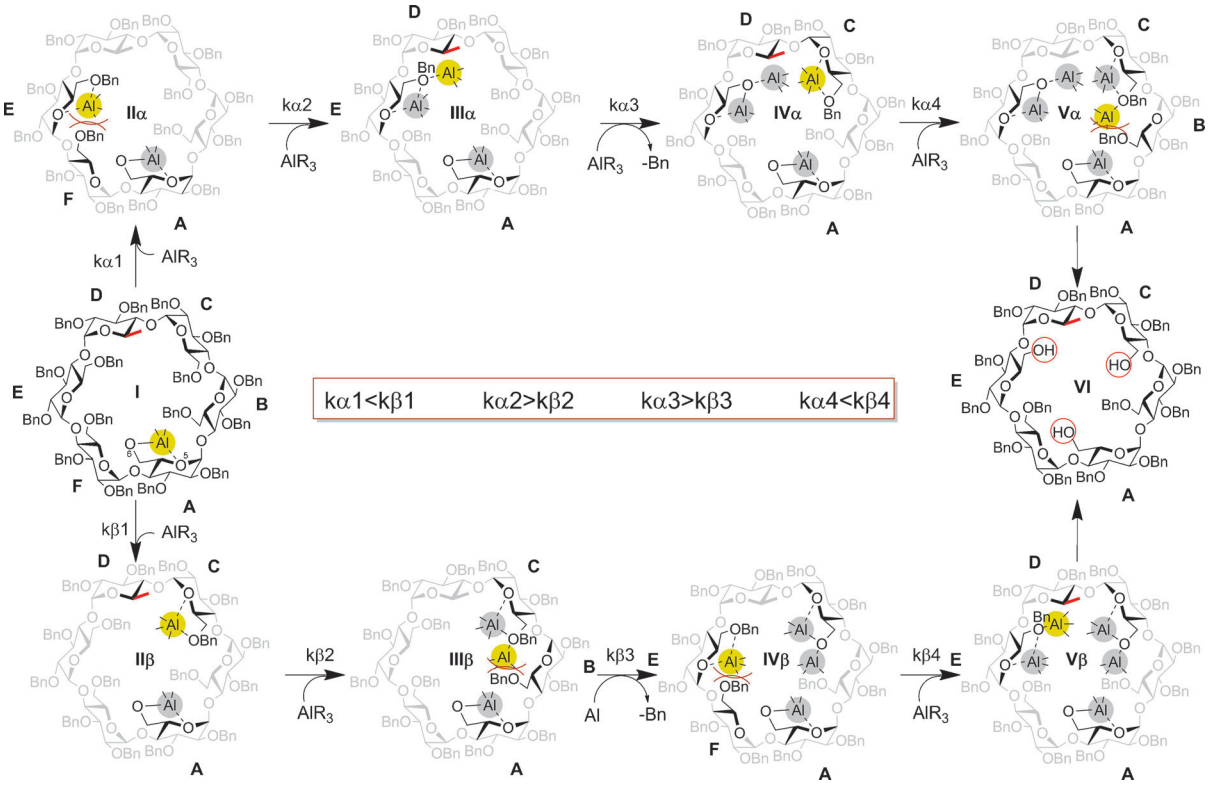


Figure 3. Kinetics study.

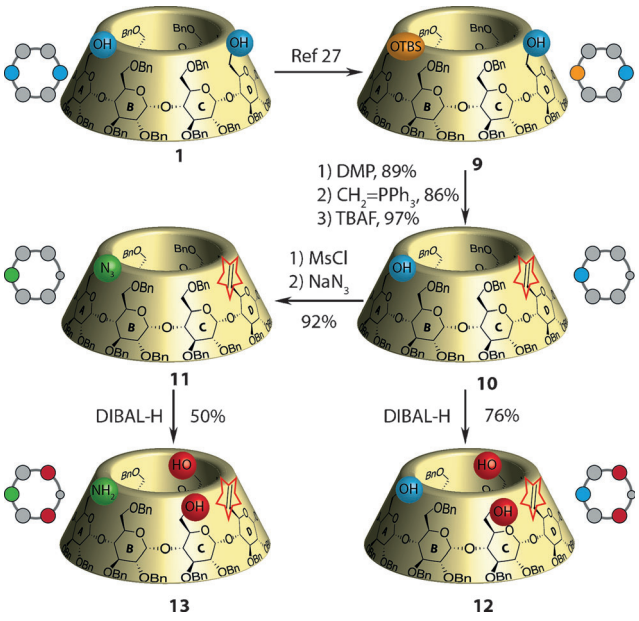
These data, combined with our previous observations and mechanistic proposals, support the following explanation for the double deprotection observed in this case. Each debenzylation reaction involves the approach of two distinct aluminum reagents, each of which is sensitive to steric hindrance. We have shown that steric decompression facilitates chelation between O-5 and O-6 on the clockwise sugar.[20] We have also shown that steric hindrance directs the approach of Al to O-6.[22] We now propose that steric decompression on a specific sugar unit can facilitate the approach of the Al reagent to O-6 of its counterclockwise sugar. Thus, in a first step DIBAL-H reacts with the free alcohol of CD **2** to form a covalent bond (**I**, Scheme 3), then a second aluminum reagent is chelated by O-5 and O-6 of either sugar ring E (**IIα**) or ring C (**IIβ**). According to our previous studies on deoxy-CD derivatives, approach to ring C



Scheme 3. Mechanistic proposal.

should be easier for the Al reagent because of the steric decompression induced by the 6-deoxy position on ring D. However, here it seems that owing to the proximity of the first Al (only one sugar away), this approach is slowed down, which correspondingly allows competitive approach to ring E, albeit at a slower rate due to the steric hindrance of the BnO-6^F ($k\alpha1 < k\beta1$). In the third step, approach of Al to ring E is favored (**IIIα**) over approach to ring C (**IIIβ**) for the same reasons: steric decompression of deoxy-6^D and hindrance of BnO-6^B ($k\alpha2 > k\beta2$). Overall, the first debenzylation occurs at a similar rate for both pathways. A fourth Al then approaches to operate the second deprotection. Again DIBAL-H approach is easier to ring C (**IVα**) than to ring E (**IVβ**) ($k\alpha3 > k\beta3$) and in the next step it is the opposite ($k\alpha4 < k\beta4$). Overall, both pathways seem to be almost equivalent, and can both be followed to obtain the final triol (Scheme 3).

This process therefore gives efficient access to a new pattern of tetradifferentiated CDs. However, as the deoxy position cannot itself be further functionalized, we decided to apply the same reaction sequence to vinyl-functionalized CDs. Their synthesis started with the known monosilylation[27] of diol **1** affording CD **9**, which was oxidized, olefinated, and desilylated to give CD **10**. The free alcohol of **10** can easily be converted into an azide giving CD **11** in two steps and 92% yield. When CDs **10** and **11** were submitted to an excess of DIBAL-H, both underwent the expected double debenzylation to give CDs **12** and **13** in 76% and 50% yield, respectively (Scheme 4). NMR analysis using the same methods outlined above allowed the unambiguous structure

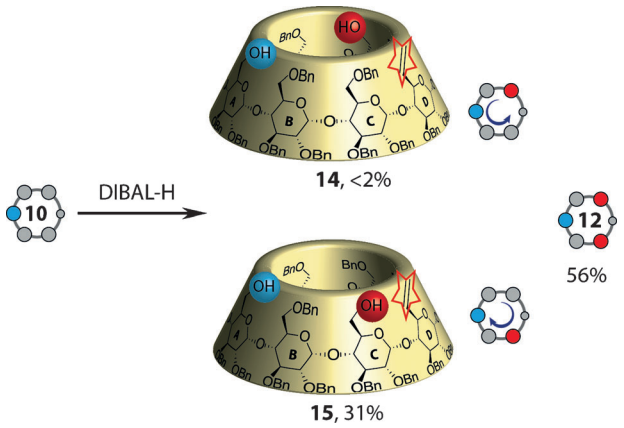


Scheme 4. Double-bank shot on a vinyl CD.

determination of both compounds (See the Supporting Information).

As in the case of CD **2**, we also stopped the reaction of CD **10** at various times before completion, and in this case observed the simultaneous presence of triol **12**, and diols **14** and **15**, albeit in different proportions as compared to the deprotection of CD **2**. In fact, counterclockwise diol **14** was

only observed as in trace amounts in the NMR spectra of the clockwise diol **15** (Scheme 5). The absence of significant quantities of diol **14** prevented us from performing kinetic



Scheme 5. Structure of isolated transient diols **14** and **15**.

studies as in the case of the deoxy-CD **2**. However, this result supports our mechanistic proposal. Indeed, according to this proposal the clockwise debenzylation should be favored by the sterically decompressed chelation of Al between O-5^{C} and O-6^{C} owing to the absence of a substituent at position 6^{D}. In the case of the counterclockwise debenzylation it is the approach of the second Al to O-6^{E} that is facilitated by the absence of a substituent at C-6^{D}. As a consequence, both diols **7** and **8** are observed because the relative rates of their formation and consumption are similar. When a vinyl group is introduced at C-6 instead of a methyl group, the approach of DIBAL-H between O-5^{C} and O-6^{C} is unchanged, unlike the approach of the second Al to O-6^{E}, which is slightly more difficult than in the case of the deoxy sugar CD because of the presence of an additional methylene group. (Figure 4) Therefore, both kα2 and kβ4 in Scheme 3 are decreased, resulting in the observed accumulation of **15** and the consumption of **14** (Scheme 5).

In conclusion, the combination of two deprotection methods previously used to produce tridifferentiated CDs unexpectedly gave a new tetrafunctional CD in a highly

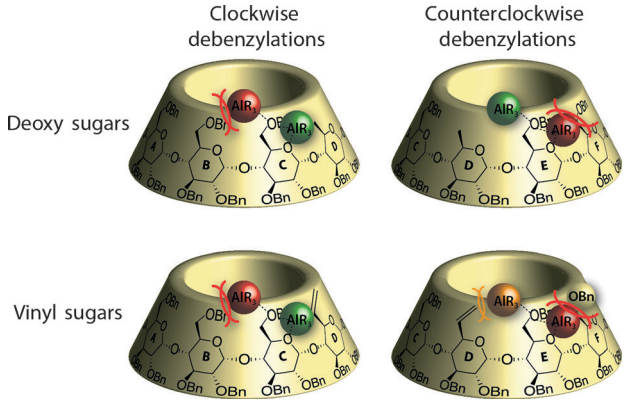


Figure 4. Different approaches of Al reagents on deoxy CD and vinyl CD.

selective fashion. Furthermore, an understanding of the mechanism of its formation allowed the modulation of the reactivity of the CD. This is an example of a regioselective reaction that produces a single product by two pathways: the initially divergent deprotection steps reconverge in a second step to give a single product in high yield.[28]

Received: June 25, 2012
Published online: November 22, 2012

Keywords: concave cycles · cyclodextrin · heterofunctionalization · mechanistic studies · selectivity

[1] R. Arun, C. K. Ashok Kumar, V. V. N. S. S. Sravanthi, *Sci. Pharm.* **2008**, *76*, 567 – 598.
[2] For example see : a) C. Koopmans, H. Ritter, *J. Am. Chem. Soc.* **2007**, *129*, 3502 – 3503; b) O. Kretschmann, C. Steffens, H. Ritter, *Angew. Chem.* **2007**, *119*, 2764 – 2767; *Angew. Chem. Int. Ed.* **2007**, *46*, 2708 – 2711.
[3] a) H. A. Zahalka, K. Januszkiewicz, H. Alper, *J. Mol. Catal.* **1986**, *35*, 249 – 253; b) E. Monflier, E. Blouet, Y. Barbaux, A. Mortreux, *Angew. Chem.* **1994**, *106*, 2183 – 2185; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2100 – 2102.
[4] J. M. Benito, M. Gómez-García, C. Ortiz Mellet, I. Baussanne, J. Defaye, J. M. García Fernández, *J. Am. Chem. Soc.* **2004**, *126*, 10355 – 10363.
[5] D.-E. Lee, H. Koo, I.-C. Sun, J. H. Ryu, K. Kim, I. C. Kwon, *Chem. Soc. Rev.* **2012**, *41*, 2656 – 2672.
[6] S. Tamesue, Y. Takashima, H. Yamagushi, S. Shinkai, A. Harada, *Angew. Chem.* **2010**, *122*, 7623 – 7626; *Angew. Chem. Int. Ed.* **2010**, *49*, 7461 – 7464.
[7] M. Miyauchi, Y. Takashima, H. Yamagushi, A. Harada, *J. Am. Chem. Soc.* **2005**, *127*, 2984 – 2989.
[8] E. Alvarez-Parrilla, P. R. Cabrer, W. Al-Soufi, F. Meijide, E. R. Nunez, J. Vazquez Tato, *Angew. Chem.* **2000**, *112*, 2978 – 2980; *Angew. Chem. Int. Ed.* **2000**, *39*, 2856 – 2858.
[9] A. Harada, R. Kobayashi, Y. Takashima, A. Hashidzume, H. Yamagushi, *Nat. Chem.* **2011**, *3*, 34 – 37.
[10] M. T. Reetz, S. R. Waldvogel, *Angew. Chem.* **1997**, *109*, 870 – 873; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 865 – 867; D. Armspach, D. Matt, *Chem. Commun.* **1999**, 1073 – 1074; E. Engeldinger, D. Armspach, D. Matt, *Angew. Chem.* **2001**, *113*, 2594 – 2597; *Angew. Chem. Int. Ed.* **2001**, *40*, 2526 – 2529.
[11] E. Zaborova, J. Deschamp, S. Guieu, Y. Blériot, G. Poli, M. Ménand, D. Madec, G. Prestat, M. Sollogoub, *Chem. Commun.* **2011**, *47*, 9206 – 9208.
[12] S. Guieu, E. Zaborova, Y. Blériot, G. Poli, A. Jutand, D. Madec, G. Prestat, M. Sollogoub, *Angew. Chem.* **2010**, *122*, 2364 – 2368; *Angew. Chem. Int. Ed.* **2010**, *49*, 2314 – 2318.
[13] a) D. Q. Yuan, T. Yamada, K. Fujita, *Chem. Commun.* **2001**, 2706 – 2707; b) H. Yu, D.-Q. Yuan, Y. Makino, M. Fukudome, R.-G. Xie, K. Fujita, *Chem. Commun.* **2006**, 5057 – 5059; c) H. Yu, Y. Makino, M. Fukudome, R.-G. Xie, D.-Q. Yuan, K. Fujita, *Tetrahedron Lett.* **2007**, *48*, 3267 – 3271; d) D.-Q. Yuan, Y. Kitagawa, M. Fukudome, K. Fujita, *Org. Lett.* **2007**, *9*, 4591 – 4594.
[14] M. Jouffroy, R. Gramage-Doria, D. Armspach, D. Matt, L. Toupet, *Chem. Commun.* **2012**, *48*, 6028 – 6030.
[15] D.-Q. Yuan, Y. Kitagawa, K. Aoyama, T. Douke, M. Fukudome, K. Fujita, *Angew. Chem.* **2007**, *119*, 5112 – 5115; *Angew. Chem. Int. Ed.* **2007**, *46*, 5024 – 5027.
[16] M. Sollogoub, S. K. Das, J.-M. Mallet, P. Sinaÿ, *C. R. Acad. Sci. Ser. IIc* **1999**, 441 – 448.
[17] T. Lecourt, A. J. Pearce, A. Herault, M. Sollogoub, P. Sinaÿ, *Chem. Eur. J.* **2004**, *10*, 2960 – 2971.

[18] E. Zaborova, Y. Blériot, M. Sollogoub, *Tetrahedron Lett.* **2010**, *51*, 1254 – 1256.
[19] This debenzylation reaction has been recently extended to silyl groups: R. Ghosh, P. Zhang, A. Wang, C.-C. Ling, *Angew. Chem.* **2012**, *124*, 1580 – 1584; *Angew. Chem. Int. Ed.* **2012**, *51*, 1548 – 1552.
[20] a) O. Bistri, P. Sinaÿ, M. Sollogoub, *Tetrahedron Lett.* **2005**, *46*, 7757 – 7760; b) O. Bistri, P. Sinaÿ, M. Sollogoub, *Chem. Commun.* **2006**, 1112 – 1114; c) O. Bistri, P. Sinaÿ, M. Sollogoub, *Chem. Lett.* **2006**, *35*, 534 – 535; d) O. Bistri, P. Sinaÿ, M. Sollogoub, *Tetrahedron Lett.* **2006**, *47*, 4137 – 4139; e) O. Bistri, P. Sinaÿ, J. Jiménez Barbero, M. Sollogoub, *Chem. Eur. J.* **2007**, *13*, 9757 – 9774; f) M. Sollogoub, *Eur. J. Org. Chem.* **2009**, 1295 – 1303.
[21] S. Guieu, M. Sollogoub, *J. Org. Chem.* **2008**, *73*, 2819 – 2828.
[22] S. Guieu, M. Sollogoub, *Angew. Chem.* **2008**, *120*, 7168 – 7171; *Angew. Chem. Int. Ed.* **2008**, *47*, 7060 – 7063.
[23] S. Xiao, M. Yang, P. Sinaÿ, Y. Blériot, M. Sollogoub, Y. Zhang, *Eur. J. Org. Chem.* **2010**, 1510 – 1516.
[24] M. Petrillo, L. Marinescu, C. Rousseau, M. Bols, *Org. Lett.* **2009**, *11*, 1983 – 1985.
[25] R. Heck, L. Jicsinszky, A. Marsura, *Tetrahedron Lett.* **2003**, *44*, 5411 – 5413.
[26] a) G. K. Rawal, S. Rani, S. Ward, C.-C. Ling, *Org. Biomol. Chem.* **2010**, *8*, 171 – 180; b) G. K. Rawal, S. Rani, C.-C. Ling, *Tetrahedron Lett.* **2009**, *50*, 4633 – 4636.
[27] S. Hanessian, C. Hocquelet, C. K. Jankowski, *Synlett* **2008**, 715 – 719.
[28] See, for example, in radical chemistry: A. Bruch, R. Fröhlich, S. Grimme, A. Studer, D. P. Curran, *J. Am. Chem. Soc.* **2011**, *133*, 16270 – 16276.

