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# Poly-hétéro-fonctionnalisation sélective des cyclodextrines : réalisation de l'hexadifférentiation de l'alfa-cyclodextrine et de la pentadifférentiation de la -béta-cyclodextrine

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# THÈSE DE DOCTORAT DE L'UNIVERSITÉ PIERRE ET MARIE CURIE

(École Doctorale de Chimie Moléculaire de Paris Centre –ED 406)

Spécialité  
**Chimie Organique**

Présentée par  
**M. Bo WANG**

Pour obtenir le grade de  
**DOCTEUR de l'UNIVERSITÉ PIERRE ET MARIE CURIE**

Sujet de la thèse :

**Poly-hétéro-fonctionnalisation sélective des cyclodextrines:  
réalisation de l'hexadifférentiation de l' $\alpha$ -cyclodextrine et de  
la pentadifférentiation de la  $\beta$ -cyclodextrine**

Soutenue le 07 Juillet 2015

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## ABBREVIATIONS

---

Ac	acetyl
BF <sub>3</sub> ·Et <sub>2</sub> O	boron trifluoride diethyl etherate
Bn	benzyl
BnBr	benzyl bromide
Boc <sub>2</sub> O	di-tert-butyl dicarbonate
Bu	butyl
Bz	benzoyl
Calcd.	calculated value
<i>cat.</i>	catalyst
CB	cucurbituril
CD	cyclodextrin
CGTase	cyclodextrin glycosyl transferase
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
CyH	cyclohexane
d	doublet
dd	doublet of doublet
$\delta$	chemical shift
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
DMP	Dess–Martin periodinane
DTMP	deoxythymidine monophosphate
eq.	equivalent
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
h	hour
HRMS	high-resolution mass spectrometry

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Hz	hertz
HOBt	hydroxybenzotriazole
$J_{i,j}$	coupling constant between $i$ and $j$ protons (in Hz)
KHMDS	potassium bis(trimethylsilyl)amide
<i>m</i> CPBA	<i>m</i> -chloroperbenzoic acid
Me	methyl
MeOTf	methyl triflate
min	minute
MsCl	methanesulfonyl chloride
MS	mass spectrometry
LDA	Lithium diisopropylamide
NBS	<i>N</i> -bromosuccinimide
nm	nanometer
NMR	nuclear magnetic resonance
nosyl	nitrobenzenesulfonyl
Pd/C	palladium on carbon
Ph	phenyl
ppm	parts per million
Pr	propyl
Py	pyridine
quant.	quantitative
r.t.	room temperature
s	singlet
t	triplet
TBSCl	tert-butyldimethylsilyl chloride
TBSOTf	tert-butyldimethylsilyl triflate
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPDSCl <sub>2</sub>	1,3-Dichloro-1,1,3,3-tetraisopropylidisiloxane
TLC	thin layer chromatography
Tr	triphenylmethyl
Ts	toluenesulfonyl

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**Selective poly-hetero-functionalization of cyclodextrins:  
realization of the hexadifferentiation of  $\alpha$ -cyclodextrin and  
the pentadifferentiation of  $\beta$ -cyclodextrin**

**ABSTRACT**

Functionalization of  $C_n$ -symmetric concave cycles, especially their *post-functionalization*, has an important impact on their nature and their applications. In the past few decades, plenty of work has been invested in the development of simple and efficient methods. Great progress has been made concerning functionalization of cyclodextrins particularly since the discovery of the DIBAL-H-mediated debenylation reaction. Based on this reaction and well-established site-directing rules, various cyclodextrin patterns are now accessible. However, the patterns with the higher level of complexity, i.e. hexadifferentiation of  $\alpha$ -cyclodextrin and heptadifferentiation of  $\beta$ -cyclodextrin, were still out of reach.

Firstly, we combined the previously delineated site-directing rules to synthesize, for the first time, the ultimate hexadifferentiated  $\alpha$ -cyclodextrin on which each glucose unit possesses a different function. It opens the way to the synthesis of all **7826** possible combinations of **6** functions on  $\alpha$ -cyclodextrin.

Then the reactivity of DIBAL-H was studied on sulfur- and selenium-derived  $\alpha$ -cyclodextrins, and two site-directing methods: tandem thioester-reduction/debenzylation and a new “frustration” strategy were disclosed, which enable the preparation of new patterns of cyclodextrins.

Much efforts were also paid to reach heptadifferentiated  $\beta$ -cyclodextrin. The initial amine strategy only gave the tetradifferentiated patterns probably due to the coordination between amine and aluminum reagents. Finally, utilization of the uncovered tandem thioester-reduction/debenzylation method allowed us to access pentadifferentiated patterns, which still need to undergo two successive debenylation reactions to reach the ultimate heptadifferentiated  $\beta$ -cyclodextrin with different thioethers on its primary rim.

**Keywords:** concave cycles, cyclodextrins, post-functionalization, diisobutylaluminum hydride, site-directing rules, hexadifferentiation, heptadifferentiation.



# Poly-hétéro-fonctionnalisation sélective des cyclodextrines: réalisation de l'hexadifférentiation de l' $\alpha$ -cyclodextrine et de la pentadifférentiation de la $\beta$ -cyclodextrine

## RÉSUMÉ

La fonctionnalisation des cycles concaves du symétrie  $C_n$ , en particulier leur *post-fonctionnalisation*, est importante pour leur nature et leurs applications. Au cours des dernières décennies, beaucoup de travail a été investi dans le développement de méthodes simples et efficaces pour ce fait. De grands progrès ont été réalisés concernant la fonctionnalisation des cyclodextrines, particulièrement depuis la découverte de la réaction de débenzylation utilisant DIBAL-H (l'hydrure de diisobutyl aluminium). Basés sur cette réaction et les méthodes de déprotection sélectives, divers motifs de l'hétéro-fonctionnalisation comportant de 2 à 3 fonctions différentes sont maintenant accessibles du façon sélective. Toutefois, les motifs plus complexes, comme l'hexadifférentiation de l' $\alpha$ -cyclodextrine et l'heptadifférentiation de la  $\beta$ -cyclodextrine, étaient encore inaccessibles. Tout d'abord, nous avons combiné les méthodes de déprotection sélectives établies précédemment, pour synthétiser, pour la première fois, l' $\alpha$ -cyclodextrine hexadifférenciée inédite sur laquelle chaque unité de glucose possède une fonction différente. Cette réalisation ouvre la voie d'accès à toutes les **7826** combinaisons possibles de **6** fonctions sur une  $\alpha$ -cyclodextrine.

Ensuite, la réactivité du DIBAL-H a été étudiée sur des  $\alpha$ -cyclodextrines fonctionnalisées avec des atomes de soufre et de sélénium, et deux méthodes sélectives: la réaction tandem de débenzylation/réduction de thioester et une nouvelle stratégie de "frustration" ont été mise à jour, ce qui permettent l'accès à de nouveaux motifs de fonctionnalisation de cyclodextrines.

Beaucoup d'efforts ont également été faits pour atteindre la  $\beta$ -cyclodextrine heptadifférenciée. La stratégie initiale utilisant les amines a seulement donné des motifs tétradifférenciés probablement à cause de la coordination entre les amines et les réactifs aluminium. Enfin, l'utilisation de la réaction tandem de débenzylation/réduction de thioester, nous a permis d'accéder à des cyclodextrines pentadifférenciées, qui doivent encore subir deux réactions de débenzylation successives pour atteindre la  $\beta$ -cyclodextrine heptadifférenciée avec des thioéthers différents sur sa couronne primaire.

**Mots-clés:** cycles concaves, cyclodextrines, post-fonctionnalisation, hydrure de diisobutylaluminium, régiosélective, hexadifférentiation, heptadifférentiation



# **CHAPTER I**

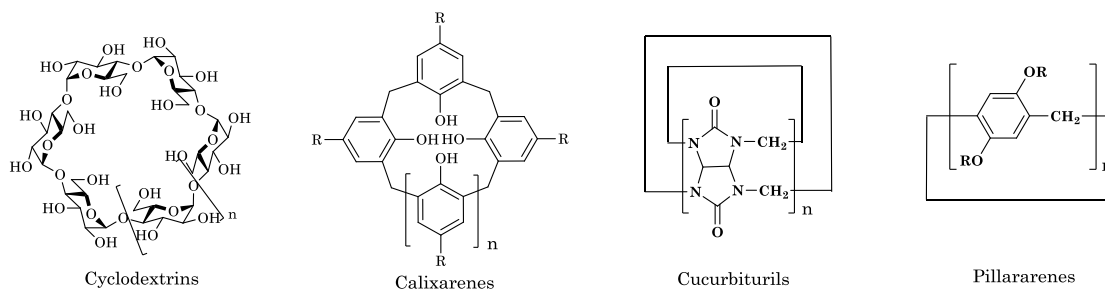
## **FUNCTIONALIZATION OF $C_n$ -SYMMETRIC CONCAVE CYCLES**





## 1. Introduction

Cyclic concave molecules are a family of macrocyclic molecules, composed of  $n$  identical monomers with  $C_n$ -symmetry. Some of the most studied molecules comprise natural cyclodextrins and synthetic calixarenes, cucurbiturils, and the most recent pillararenes (Figure I-1). They all possess unique tridimensional architecture with variable-sized cavities, allowing them to be used as molecular receptors<sup>1</sup> or catalysts<sup>2</sup>.



**Figure I-1:** Chemical structures of cyclic concave molecules

To adjust the properties and develop new applications, introduction of new functions on precise positions of these molecules is desired, which aims to: 1) alter their properties of complexation (such as changing the solubility in different media) or modulate the size of cavity; 2) import synthetic handle that can be further modified to meet specific applications, for instance, the introduction of terminal alkynes or azides for click reactions.

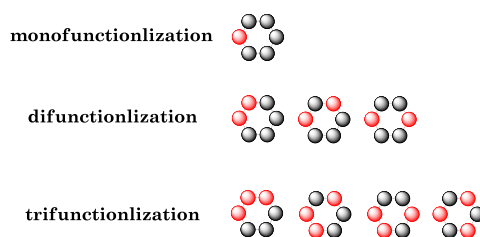
However, functionalization of these  $C_n$ -symmetric molecules is a challenging task to chemists. Intrinsically, the reason lies in the identical chemical reactivity of each unit which could give different regioisomeric products.

In this thesis, we use the following definitions:

**Functionalization** on a position means that this position has been modified. That is we can introduce the same group to substitute one or more hydroxyls. If only one position is modified, the molecule is monofunctionalized, difunctionalized if two positions are modified, trifunctionalized if three positions are modified and if all the hydroxyls are replaced by identical groups, it is called perfunctionalized (Figure I-2).

<sup>1</sup> (a) K. Hanaoka, K. Kikuchi, H. Kojima, Y. Urano, T. Nagano, *J. Am. Chem. Soc.*, **2004**, 126, 12470; (b) Y. Fang, X. Yuan, L. Wu, Z. Peng, W. Peng, N. Liu, D. Xu, S. Li, A. Sengupta, P. K. Mohapatra, L. Yuan, *Chem. Commun.*, **2015**, 51, 4263.

<sup>2</sup> J. Rebilly, B. Colasson, O. Bistri, D. Over, O. Reinaud, *Chem. Soc. Rev.*, **2015**, 44, 467.



**Figure I-2.** Examples of functionalization in  $C_6$ -cyclic concave

**Differentiation** of the positions means that different modifications have been made on more than one positions. Differentiation means that different groups are introduced (tridifferentiated if three groups are present, tetradifferentiated if four different groups are present, and so on). Each differentiation have different patterns. The number of arrangements can be calculated by combinatorics equations (Equation I-1).

$$R_k(n) = N_k(n) - \sum_{i=1}^{k-1} \binom{k}{i} R_i(n) \quad (\mathbf{a})$$

$$N_k(n) = \frac{1}{n} \sum_{i=1}^{v(n)} \varphi(d_i) k^{n/d_i} \quad (\mathbf{b})$$

**Equation I-1:** Calculation of arrangements for functionalization of  $C_n$ -symmetric concave cycles. (a) Equation for calculation of possible pattern arrangements; (b) Equation for calculation of cumulative arrangements ( $n$  means the number of monomer or functionalizable sites,  $k$  means the number of different functions)

According to combinatorics calculation (Equation I-1 and Table I-1): for a cycle of  $C_6$ -symmetry with six functionalizable sites, the number of cumulative arrangements  $N_k(n)$  includes the arrangements of the lower rank and that with **exactly**  $k$  colors. For example, there are 14 ways to arrange two functions, 130 ways to arrange three functions, 700 ways to arrange four functions, 2635 ways to arrange five functions and **7826** ways to arrange six functions, i.e. 6 arrangements of undifferentiated pattern, 180 arrangements of differentiated patterns, 1820 arrangements of tridifferentiated patterns, 3900 arrangements of tetradifferentiated patterns, 1800 arrangements of pentadifferentiated patterns and 120 arrangements of hexadifferentiated pattern (the detail calculation see Appendix 1). The arrangements of  $n$  beads of  $k$  colors can be generated on <http://www.jasondavies.com/necklaces/>, which corresponds to the well-known combinatorics problem of necklaces<sup>3</sup>. In practice, that means that reacting a  $C_6$ -functionalizable molecule

<sup>3</sup> Weisstein, E. W. "Necklace." FromMathWorld--A Wolfram Web Resource <http://mathworld.wolfram.com/Necklace.html>.

with six different reagents of equal reactivity statistically leads to a mixture of **7826** differently functionalized molecules, ranging from 6 molecules bearing six times the same substituent to 120 molecules with six different substituents.

As shown in Table I-1, many possibilities exist during the functionalization of a  $C_6$ -cyclic concave molecule because of intrinsically symmetrical nature, which makes the functionalization much more difficult. After searching the literature, it clearly appears that numerous functionalized patterns are now available either by laborious chromatographical purification or by specific regioselective methods.

In this chapter, the methodologies we will introduce based on the introduction of new functions to the parent concave cycles, namely *post-functionalization*. We will not exhaustively discuss all methodologies and functionalized derivatives, just some representative examples concerning calixarenes, cucurbiturils and pillararenes. A detailed introduction of cyclodextrins will be given in Chapter II.

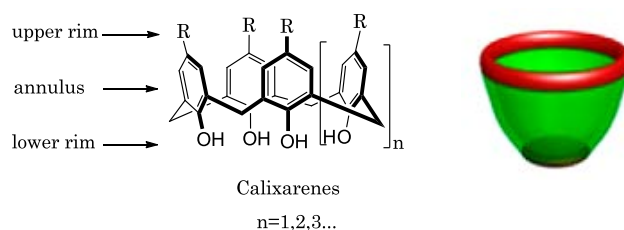
Functionalization of $C_6$ concave cycles						
Color of beads ( $k$ )	1	2	3	4	5	6
Sets of function $k \times n$ ( $n=6$ )						
Number of absolute patterns	1	7	18	13	3	1
Patterns						
Possible pattern arrangement	1	12	91	160	300	120
$R_k(n) = N_k(n) - \sum_{l=1}^{k-1} \binom{k}{l} R_l(n)$						
Cumulative arrangement	1	14	130	700	2635	7826
$N_k(n) = \frac{1}{n} \sum_{l=1}^{v(n)} \varphi(d_l) k^{n/d_l}$						

**Table I-1:** Functionalization of  $C_6$  concave cycles

Schematic representation of all the possible functionalization patterns for  $C_6$  concave cycles, each unit of the molecule is represented as a dot. Different colors ( $k$ ) means different functions.

## 2. Calixarenes

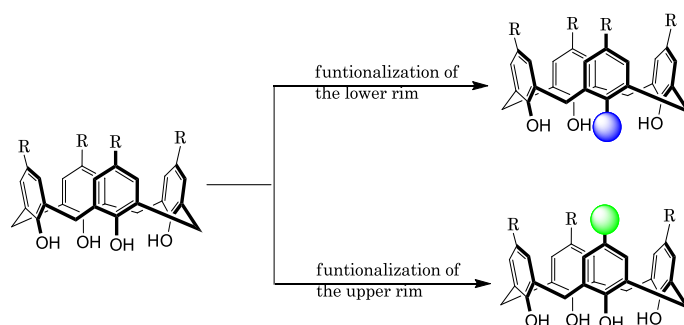
Calixarenes are a class of cyclic oligomers, synthesized via a hydroxyl alkylation/condensation between phenols and aldehydes<sup>4</sup>. Calix[ $n$ ]arenes are made of  $n$  phenol and methylene units. Representative members of calixarenes are calix[4]arene and calix[6]arene, composed of 4 and 6 units respectively. Calix[ $n$ ]arenes are flexible structures (4 conformations for calix[4]arene, 8 conformations for calix[6]arene) in a three-dimensional basket shape with a defined upper and lower rim and a central annulus (Figure I-3).



**Figure I-3:** Structure of calixarenes

Calixarenes possess remarkable conformational properties and hydrophobic cavities that are able to accommodate neutral or ionic species. Inspired by their unique geometries, calixarenes are attractive for applications in a variety of field, such as artificial enzymes<sup>5</sup>, ion sensitive electrodes or sensors<sup>6</sup> and supramolecular catalysts<sup>7</sup>. By functionally modifying either the upper and/or the lower rims, or by modulating their conformations, it is possible to prepare various derivatives with differing selectivities for various guest ions and small molecules.

Functionalization of calixarenes mainly focus on two parts (Figure I-4): functionalization of the lower rim and functionalization of the upper rim.



**Figure I-4:** Functionalization of calixarenes

<sup>4</sup> G. C. David, *Calixarenes (Royal Soc. Chem., Cambridge)* **1989**, 1.

<sup>5</sup> D. T. Schuhle, J. A. Peters, J. Schatz, *Coord. Chem. Rev.*, **2011**, 255, 2727.

<sup>6</sup> A. Mattiuzzi, I. Jabin, C. Mangeney, C. Roux, O. Renaud, L. Santos, J-F Bergamini, P. Hapiot, C. Lagrost, *Nat. Commun.*, **2012**, 3, doi:10.1038/ncomms2121.

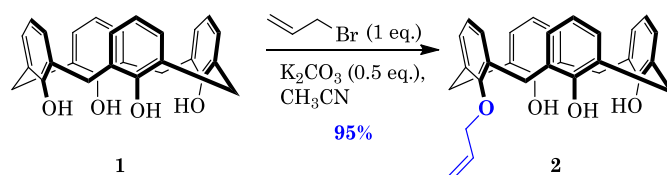
<sup>7</sup> (a) R. Cacciapaglia, S. Di Stefano, L. Mandolini, R. Salvio, *Supramol. Chem.* **2013**, 25, 537; (b) J. N. Rebilly, O. Renaud, *Supramol. Chem.*, **2014**, 26, 454.

## 2.1 Functionalization of the lower rim of calix[4]arene

The chemical modification of the lower rim of calixarenes, means introduction of functional groups to substitute the hydroxyl groups. According to the functional patterns, it can be divided into mono-, di- and perfunctionalization subparts. Obviously, perfunctionalization can be achieved easily. Hence, we just present the methodologies for mono- and difunctionalization.

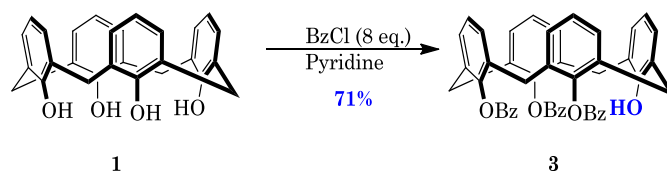
### 2.1.1 Monofunctionalization and trifunctionalization of calix[4]arene

In the case of calix[4]arene, monofunctionalization and trifunctionalization give the same pattern: one function differs from the three others. This kind of functionalization mainly fulfilled by two strategies: control the amount of reagents and utilization of tripodal groups. Monofunctionalized calix[4]arene **2** was synthesized with an excellent yield by reaction with 1 equivalent of allyl bromide in the presence of one-half molar equivalent of  $K_2CO_3$  in acetonitrile<sup>8</sup> (Scheme I-1). The obtained calix[4]arene **2** can then be transformed into an upper-rim functionalized calixarene by Claisen rearrangement (*vide infra*).



**Scheme I-1:** Monofunctionalization of the lower rim of calix[4]arene

Temporary tri-protection of calix[4]arene is another method to achieve monofunctionalized motif. Using 8 equivalents of benzoyl chloride in the presence of pyridine, three benzoyl groups were introduced on the lower rim to give calix[4]arene **3** in 71% yield<sup>9</sup> (Scheme I-2). After further functionalization of the free hydroxyl group, hydrolysis of benzoates gave the monofunctionalized calix[4]arene.

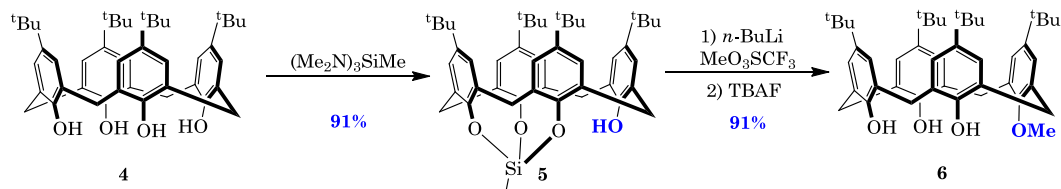


**Scheme I-2:** Trifunctionalization of the lower rim of calix[4]arene

<sup>8</sup> A. S. Abd-El-Aziz, P. O. Shipman, J. L. Piffold, P. R. Shipley, *Makromol. Chem. Phys.*, **2010**, 211, 996.

<sup>9</sup> C. D. Gutsche, L. G. Lin, *Tetrahedron*, **1986**, 42, 1633.

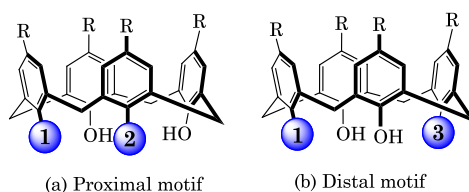
Alternatively, tripodal reagent  $(\text{Me}_2\text{N})_3\text{SiMe}$  was chosen to protect three phenols on the lower rim simultaneously<sup>10</sup> (Scheme I-3). The remaining phenol was then functionalized and it was followed by deprotection of silyl ether to give monofunctionalized calix[4]arene **6**.



**Scheme I-3:** Monofunctionalization of the lower rim of calix[4]arene by a tripod reagent

### 2.1.2 Difunctionalization of calix[4]arene

For difunctionalization of calix[4]arene, two possible regioisomers could be produced: proximal 1,2-motif and distal 1,3-motif (Figure I-5). Proximal 1,2-motif has two introduced functional groups on the adjacent hydroxyl groups, while distal 1,3-motif processes the functional groups on the diametrically opposed positions.



**Figure I-5:** Difunctionalization of calix[4]arene on the lower rim

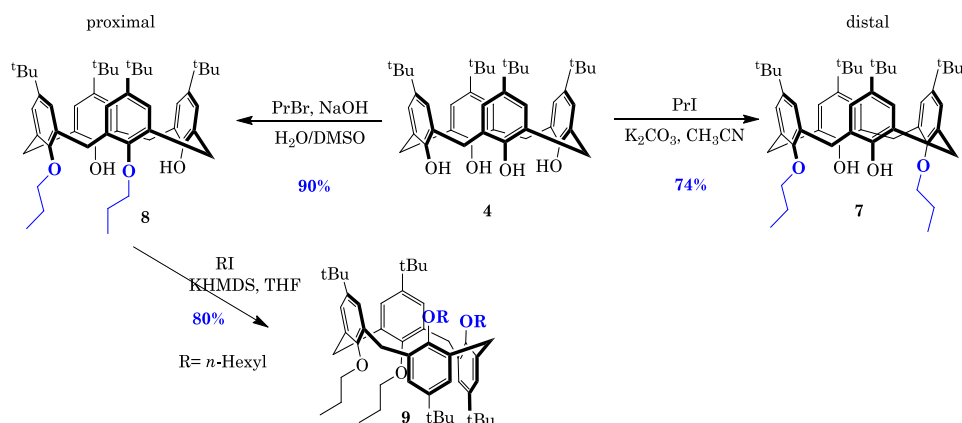
The selective synthesis of 1,3-difunctionalized calix[4]arene has been achieved in the presence of a weak base in acetonitrile. The alkylation of calix[4]arene **4** with propyl iodide in the presence of  $\text{K}_2\text{CO}_3$ , gave a distal propoxylated derivative **7** in 74% yield<sup>11</sup> (Scheme I-4). While using higher amount of  $\text{NaOH}$  in DMSO-water medium, 1,2-propylated calix[4]arene **8** was obtained preferentially in 90% yield<sup>12</sup>. The formed calix[4]arene **8** was then subjected to subsequent alkylation procedure with hexyl iodide in the presence of  $\text{KHMDs}$ , giving hetero-functionalized derivative **9** with 1,2-alternate conformation.

<sup>10</sup> S. Shang, D. V. Khasnis, J. M. Burton, C. J. Santini, M. Fan, A. C. Small, M. Lattman, *Organometallics*, **1994**, 13, 5157.

<sup>11</sup> K. Iwamoto, K. Araki, S. Shinkai, *J. Org. Chem.*, **1991**, 56, 4955.

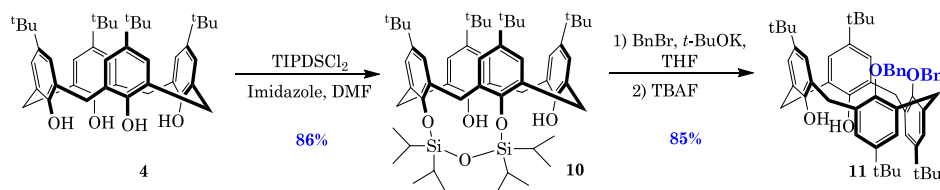
<sup>12</sup> (a) P. Lhotak, A. Bila, J. Budka, M. Pojarova, I. Stibor, *Chem. Commun.*, **2008**, 1662; (b) V. I. Boyko, A. A. Podoprigrorina, A. V. Yakovenko, V. V. Pirozhenko and V. I. Kalchenko, *J. Inclusion Phenom. Macrocyclic Chem.*, **2004**, 50, 193.





**Scheme I-4:** Difunctionalization of the lower rim of calix[4]arene

Narumi and Miyano<sup>13</sup> demonstrated another method to access easily 1,2-difunctionalized motif. Using a disiloxane bridge to protect two adjacent phenols, gave bridged calix[4]arene **10** (Scheme I-5), which was subsequently treated with benzyl bromide in the presence of *t*-BuOK to give dibenzylated product **11** in 1,2-alternate conformation. In contrast, switching to Cs<sub>2</sub>CO<sub>3</sub>, produced a partial-cone conformation derivative. Then through a quantitative fluoride-promoted desilylation, the selective proximal dibenzylation of calix[4]arene at the lower rim was reached.

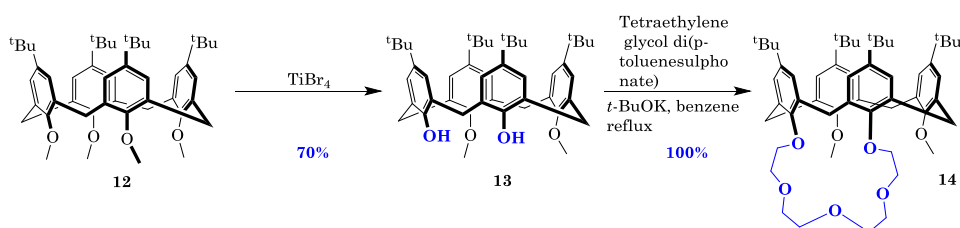


**Scheme I-5:** Difunctionalization of the lower rim of calix[4]arene by a disiloxane bridge

Selective deprotection of fully protected calix[4]arene is also an alternative strategy to obtain difunctionalized calixarene. Pochini<sup>14</sup> presented a method by treatment of calix[4]arene **12** with 2 equivalents of TiBr<sub>4</sub>, giving an 1,2-demethylated derivative **13** in good yield (Scheme I-6), which allowed the synthesis of a new type of calixarene-based crown ether **14**. The remaining two methyl groups could be removed using the same method, it was followed by introducing other functional groups to produce hetero-functionalized calix[4]arenes.

<sup>13</sup> F. Narumi, N. Morohashi, N. Matsumura, N. Iki, H. Kameyama, S. Miyano, *Tetrahedron Lett.*, **2002**, 43, 621.

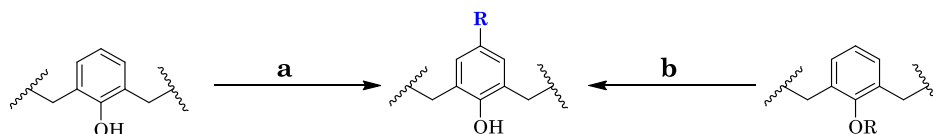
<sup>14</sup> A. Arduini, A. Casnati, L. Dodi, A. Pochini, R. Ungaro, *Chem. Commun.*, 1990, 1597.



**Scheme I-6:** Difunctionalization of the lower rim of calix[4]arene by a Ti(IV)-assisted method

## 2.2 Functionalization of the upper rim of calix[4]arene

Functionalization on the upper rim have obtained a lot of achievements<sup>15</sup>. However, it is generally accepted that functionalization on the upper rim is more complicated. It requires to protect the phenols with appropriate functions. As in the case of the lower rim functionalization, we will present the methodologies according to functionalization patterns (mono- and di-functionalization). They can be either directly functionalized on the aromatic cone (Figure I-6a), or by transferring from the functionalized lower rim to the aromatic cone using rearrangement reactions (Figure I-6b).



**Figure I-6:** Strategies for functionalization of the upper rim.

(a) Direct functionalization of the upper rim, (b) Transfer from the functionalized lower rim to aromatic cone

### 2.2.1 Monofunctionalization and trifunctionalization of calix[4]arene

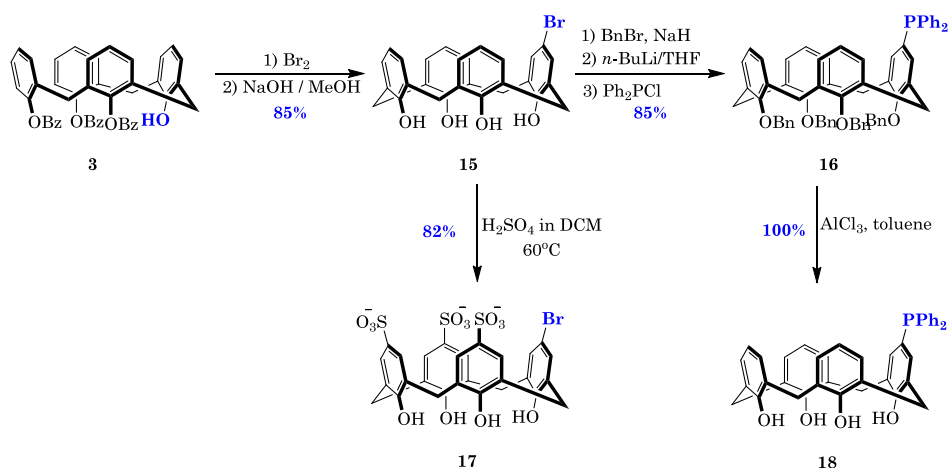
Monofunctionalization and trifunctionalization give the same pattern (*vide supra*). The tri-protected calix[4]arene **3** can be converted into bromo-calixarene **15** by direct bromination<sup>16</sup> and subsequent removal of benzoyl groups. Then it underwent sulfonation by neat sulfuric acid in dichloromethane, provided clean product **17**<sup>17</sup> (Scheme I-7). Aryl bromide **17** was intended to be a precursor for Suzuki couplings. In addition, calixarene **15** can also be transformed into monophosphine calixarene **16** by a sequence of benzylation, halogen-lithium exchange and reaction with  $\text{Ph}_2\text{PCl}$ . After debenylation by aluminum chloride, the obtained product **18** was used in the preparation of Suzuki-Miyaura cross-coupling catalysts.<sup>18</sup>

<sup>15</sup> W. Sliwa, M. Deska, *ARKIVOC*, **2011**, i, 496.

<sup>16</sup> M. Vezina, J. Gagnon, K. Villeneuve, M. Drouin, P. D. Harvey, *Organometallics*, **2001**, *20*, 273.

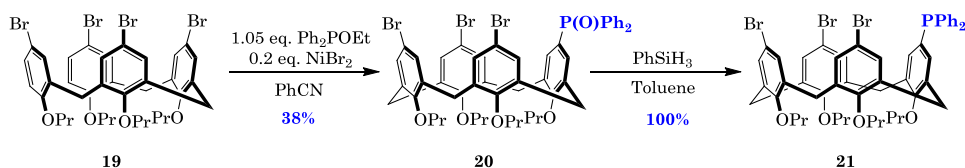
<sup>17</sup> K. D. Daze, M. C. F. Ma, F. Pineux, F. Hof, *Org. Lett.*, **2012**, *6*, 1512.

<sup>18</sup> L. Monnereau, D. Sémeril, D. Matt, L. Toupet, *Chem. Eur. J.*, **2010**, *16*, 9237.



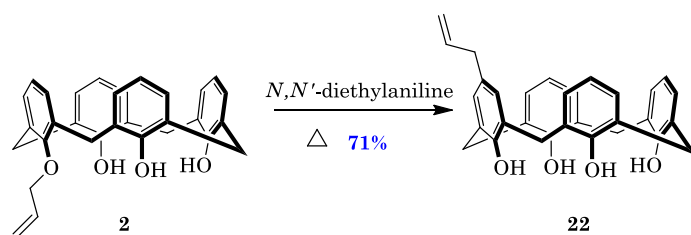
**Scheme I-7:** Monofunctionalization of the upper rim of calix[4]arene

Besides calixarene **16**, tribromo-monophosphine calixarene **21** was synthesized<sup>19</sup> starting from tetrabromo-calixarene **19**. Calixarene **19** was submitted to nickel-catalyzed monophosphorylation to give phosphine oxide **20** in 38% yield (Scheme I-8). Subsequent reduction with  $\text{PhSiH}_3$  produced phosphine **21** quantitatively.



**Scheme I-8:** Synthesis of monophosphine calix[4]arene

Another method for monofunctionalization of the upper rim was explored by Claisen rearrangement<sup>8</sup>. Monosubstituted calixarene **2** was refluxed in *N,N'*-diethylaniline for 2 h, giving the upper rim functionalized calixarene **22** in 71% yield (Scheme I-9).



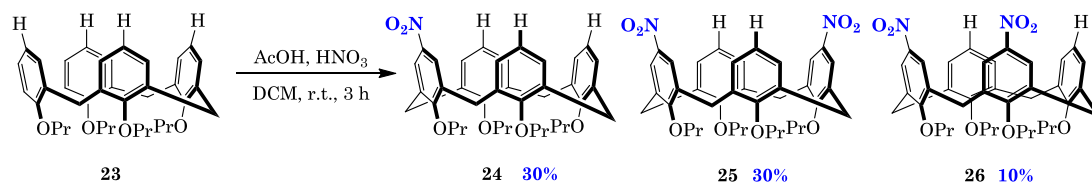
**Scheme I-9:** Monofunctionalization of calix[4]arene by Claisen rearrangement

## 2.2.2 Difunctionalization of calix[4]arene

Electrophilic aromatic substitution represents straightforward strategy for functionalization of the upper rim of calixarenes, such as nitration or acylation. For instance, nitration of calix[4]arene is a well-established method which can be performed directly, or via

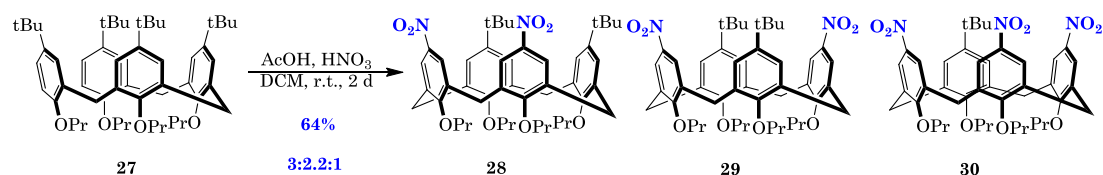
<sup>19</sup> S. Sameni, M. Lejeune, C. Jeuness, D. Matt., R. Welter, *Dalton Trans.*, **2009**, 7912.

*ipso*-substitution. Reinhoudt<sup>20</sup> showed that tetrapropoxycalix[4]arene **23** can react directly with nitric acid in DCM to give mononitro-calix[4]arene **24**, dinitrocalix[4]arenes **25** and **26** in 30%, 30% and 10% yields, respectively (Scheme I-10).



**Scheme I-10:** Direct nitration of aromatic positions of calix[4]arene

Meanwhile, Reinhoudt introduced another nitration method by *ipso*-aromatic nitration<sup>21</sup>. Calix[4]arene **27** was reacted with concentrated nitric acid in a mixture of dichloromethane and acetic acid for 2 days, affording an inseparable mixture of dinitrocalix[4]arene **28**, dinitrocalix[4]arene **29** and trinitrocalix[4]arene **30** with a ratio of 3:2.2:1 in a total yield of 64% (Scheme I-11).



**Scheme I-11:** Nitration of aromatic positions of calix[4]arene via *ipso*-aromatic nitration

To be regioselective, McGinley<sup>22</sup> disclosed a method that performed regioselective substitution of the upper rim through partial alkylation of the lower rim. The distal dibutylated derivative **31a** was prepared using butyl bromide in the presence of  $K_2CO_3$ . It was subsequently submitted to *ipso*-nitration to give calix[4]arene **32** with both the nitro groups on the para-positions of nonsubstituted phenolic units (Scheme I-12). Introduction of two alkyl groups into distal positions makes these two aromatic rings less reactive than those bearing free hydroxyl groups.

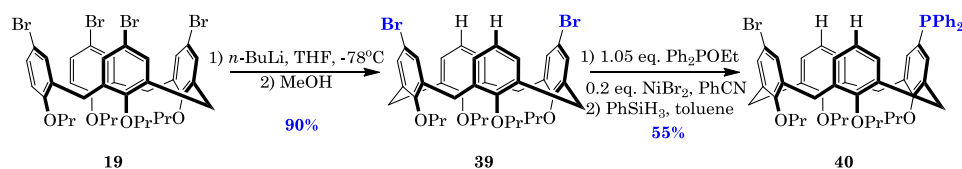
<sup>20</sup> E. Kelderman, L. Derhaeg, G. Heesink, W. Verboom, J. Engbersen, N. Hulst, A. Persoons, D. Reinhoudt, *Angew. Chem. Int. Ed.*, **1992**, 31, 1075.

<sup>21</sup> W. Verboom, A. Durie, R. Egberink, Z. Asfari, D. Reinhoudt, *J. Org. Chem.*, **1992**, 57, 1313.

<sup>22</sup> B. S. Creaven, T. L. Gernon, J. McGinley, A. Moore, H. Toftlund, *Tetrahedron*, **2006**, 62, 9066.



Moreover, deprotection of fully functionalized *para*-positions of aromatic rings was employed to functionalize the upper rim of calix[4]arene regioselectively. The preparation of calixarene **40** is similar to that of **21** (Scheme I-8). Firstly, distal 1,3-bromo-calixarene **39** was synthesized in 90% yield by reaction of **19** with 2 equivalents of *n*-BuLi and subsequent quenching with methanol (Scheme I-14). Then using the same procedures as in the case of calix[4]arene **21** (Scheme I-8), gave 1,3-differentiated calixarene **40** in 55% yield<sup>19</sup>.

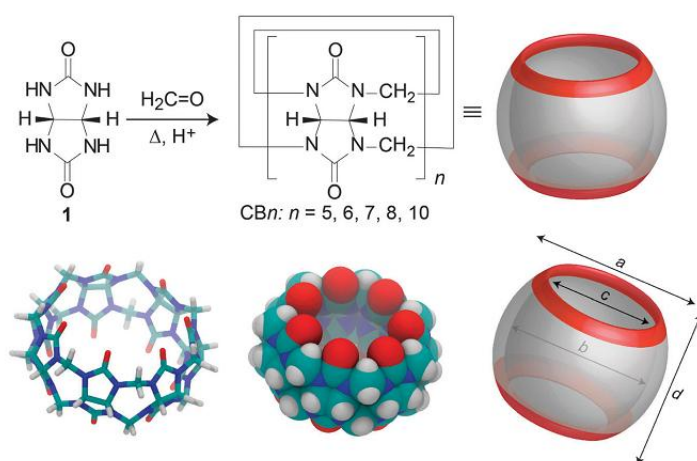


**Scheme I-14:** Synthesis of 1,3-differentiated calixarene

In this part, some selective methodologies were introduced for functionalization of calix[4]arene, which have been used for preparation of useful synthetic building blocks. Undoubtedly, there are a large amount of strategies developed to perform the modification of calix[4]arene efficiently. However, there are few strategies for the polydifferentiation of calixarenes, especially calix[6]arene or higher homologues. This problem is ubiquitous in the field of functionalization of such cyclic concave molecules.

### 3. Cucurbiturils

Cucurbiturils (CBs) are a family of synthetic compounds obtained from the acid-induced condensation reaction with urea, glyoxal and formaldehyde. In 1905, they were firstly reported by Behrend and co-workers<sup>26</sup>, and until 1981, the chemical nature and structure were elucidated by Mock and Freeman *et al.*<sup>27</sup> It turned out to be a cyclic oligomer of glycoluril units linked by methylene bridges. In the early 2000s, different size of cucurbit[*n*]urils (CB[*n*], *n*=5, 6, 7, 8, 10) homologues have been synthesized and isolated<sup>28</sup> (Figure I-7). Cucurbit[*n*]urils have the pumpkin-like shape with two identical hydrophilic carbonyl-laced portals and a hydrophobic cavity, which can form stable host-guest complexes with organic or inorganic cations, and neutral organic guests in aqueous media.<sup>29</sup>



**Figure I-7:** (Top) Synthesis of CB[*n*] homologues by condensation of glycoluril and formaldehyde under acidic conditions. (Bottom) Different representations of the CB[7] structure<sup>29c</sup>

Although the scope of the CB chemistry have been amplified by the discovery of new CB homologues, their applications were still restricted mainly because of the poor solubility in organic solvents, and difficulty for the introduction of functional groups on their surfaces, which is in contrast to other host families including calixarenes and cyclodextrins. Particularly, introduction of reactive functional groups at the periphery was a long-standing problem. In principle, there are two main strategies to introduce functional groups (Scheme

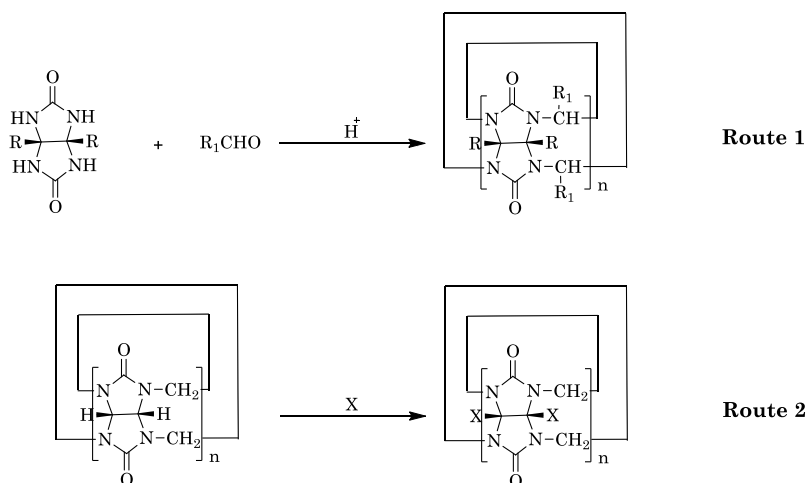
<sup>26</sup> R. Behrend, E. Meyer, F. I. Rusche, *Liebigs Ann. Chem.*, **1905**, 339, 1.

<sup>27</sup> W. A. Freeman, W. L. Mock, N. Y. Shih, *J. Am. Chem. Soc.*, **1981**, 103, 7367.

<sup>28</sup> (a) J. Kim, I. S. Jung, S. Y. Kim, E. Lee, J. K. Kang, S. Sakamoto, K. Yamaguchi, K. Kim, *J. Am. Chem. Soc.*, **2000**, 122, 540; (b) A. Day, A. P. Arnold, R. J. Blanch, B. Snushall, *J. Org. Chem.*, **2001**, 66, 8094; (c) A. I. Day, R. J. Blanch, A. P. Arnold, S. Lorenzo, G. R. Lewis, I. Dance, *Angew. Chem. Int. Ed.*, **2002**, 41, 275.

<sup>29</sup> (a) J. W. Lee, S. Samal, N. Selvapalam, H. J. Kim, K. Kim, *Acc. Chem. Res.*, **2003**, 36, 621; (b) J. Lagona, P. Mukhopadhyay, S. Chakrabarti, L. Isaacs, *Angew. Chem. Int. Ed.*, **2005**, 44, 4844; (c) K. I. Assaf, W. M. Nau, *Chem. Soc. Rev.*, **2015**, 44, 394.

I-15): 1) Functionalization by cucurbituril-forming reaction<sup>30</sup> (Route 1), condensation of glycouril derivatives with various aldehydes, would give CB[*n*] derivatives bearing the substituents on the “equator” positions or at the methylene bridges of CB[*n*]. A lot of derivatives have been synthesized using this strategy. However, our interests focus on the *post-functionalization* of the macrocyclic molecules, thus we will discuss the second strategy. 2) Direct functionalization of the “equator” positions gives the corresponding CB[*n*] derivatives (Route 2).



**Scheme I-15:** Synthetic strategies for the functionalization of cucurbit[*n*]urils

### Direct functionalization on the “equator” positions

Direct introduction of functionalities on the surface of CB[*n*] was thought to be impossible for a long time. The first direct functionalization method was uncovered by Kim group, giving hydroxyl derivatives of CB[*n*]. By treatment of excess CB[*n*] (*n*=5-8) with K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> in water at 85°C, it was followed by crystallization to give perhydroxylated CB[*n*] as potassium complexes (Scheme I-16).<sup>31</sup> While a typical yield of the reaction is 40-45% for CB[5] and CB[6], the higher homologues give a lower yield, presumably due to the instability of the perhydroxylated products. The obtained perhydroxylated derivatives can undergo further modification, such as acylation or alkylation, which were used in a range of supramolecular systems.<sup>32</sup>

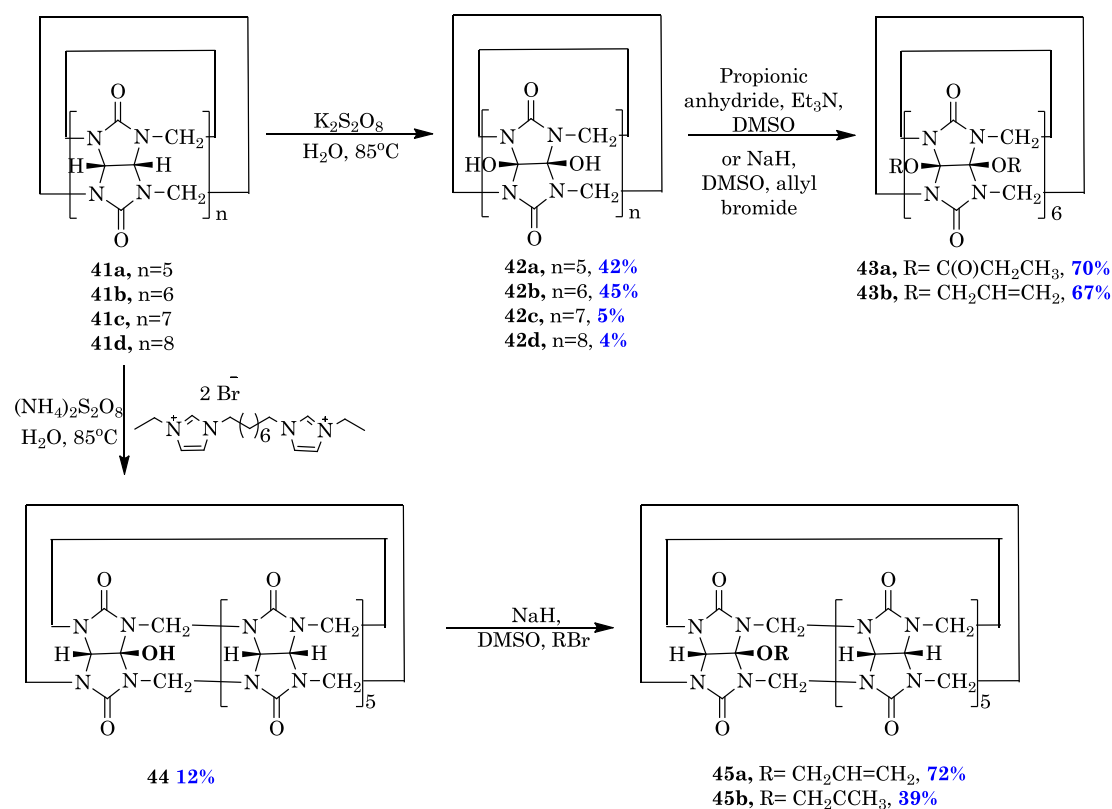
<sup>30</sup> (a) A. Flinn, G. C. Hough, J. F. Stoddart, D. J. Williams, *Angew. Chem. Int. Ed.*, **1992**, 31, 1475; (b) S. Sasmal, M. K. Sinha, E. Keinan, *Org. Lett.*, **2004**, 6, 1225; (c) J. Z. Zhao, H. J. Kim, J. Oh, S. Y. Kim, J. W. Lee, S. Sakamoto, K. Yamaguchi, K. Kim, *Angew. Chem. Int. Ed.*, **2001**, 40, 4233; (d) B. Vinciguerra, L. Gao, J. Cannon, P. Zavalij, C. Fenselau, L. Isaacs, *J. Am. Chem. Soc.*, **2012**, 134, 13133; (e) D. Lucas, T. Minami, G. Iannuzzi, L. Gao, J. Wittenberg, P. Anzenbacher, L. Isaacs, *J. Am. Chem. Soc.*, **2011**, 133, 17966.

<sup>31</sup> S. Jon, N. Selvapalam, D. Oh, J. Kang, S. Kim, Y. Jeon, J. Lee, K. Kim, *J. Am. Chem. Soc.*, **2003**, 125, 10186.

<sup>32</sup> (a) Y. Jeon, H. Kim, S. Jon, N. Selvapalam, D. Oh, I. Seo, C. Park, S. Jung, D. Koh, K. Kim, *J. Am. Chem. Soc.*, **2004**, 126, 15944; (b) H. Lee, K. Park, Y. Jeon, D. Kim, D. Oh, H. Kim, C. Park, K. Kim, *J. Am. Chem. Soc.*, **2005**, 127, 5006.



After optimization of reaction conditions, Scherman *et.al.* showed a method to prepare monohydroxylated CB[6] directly from the parent CB[6] in aqueous solution by virtue of host-guest interactions to control the oxidation mechanism and product ratio.<sup>33</sup> During this process, a tailor-made bisimidazolium guest was used to form a host-guest complex, which was able to enhance the solubility of the parent CB[6] prior to controlled oxidation, thus influenced the product ratios. Thereafter the obtained pure monohydroxylated product underwent the alkylations, notably the propargylation yielding an alkyne, which could be submitted to click reactions.



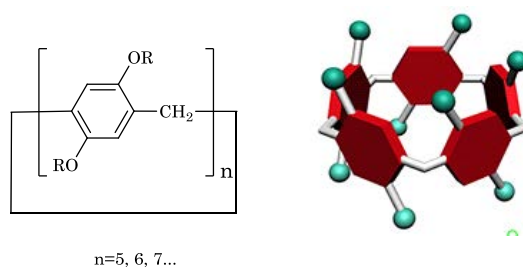
**Scheme I-16:** Direct functionalization of CB[*n*] on “equator” positions

Much progress has been made for the functionalization of cucurbit[*n*]urils and give a myriad of CB derivatives nowadays, particularly by cucurbituril-forming reactions. However, the direct functionalization has not yet been sufficiently explored, and development of efficient methods for such functionalization would be highly desired because it would have an important impact on the host-guest chemistry.

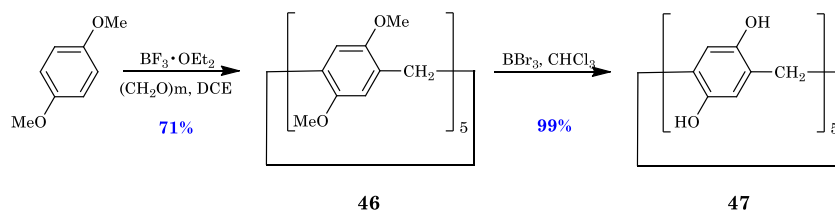
<sup>33</sup> N. Zhao, G. Lloyd, O. Scherman, *Chem. Commun.*, **2012**, 48, 3070.

## 4. Pillararenes

Pillararenes<sup>34</sup> (Figure I-8), a recent class of macrocyclic hosts discovered by Ogoshi and co-workers<sup>35</sup> in 2008, are increasingly important in host-guest chemistry. Pillar[*n*]arenes are made up of *n* identical hydroquinone units held together on *para*-positions by methylene bridges through a Lewis acid-catalyzed Friedel-Craft cyclization (Scheme I-17). Compared with calix[*n*]arenes with a basket-shaped structure, Pillar[*n*]arenes have a unique rigid pillar architecture, but a similar  $\pi$ -electron-rich cavity which can interact strongly with electron-poor species.



**Figure I-8:** Different representations of the pillar[*n*]arene structure

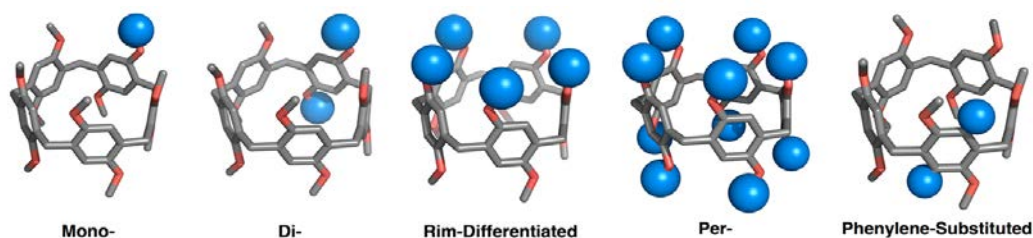


**Scheme I-17:** Synthesis of pillar[5]arene by Lewis acid-catalyzed Friedel-Craft cyclization

Like other concave cycles, in order to meet the requirement of various applications in different areas, functionalization of pillar[*n*]arenes with synthetic handles was necessary. In this section, functionalization of pillar[*n*]arenes will be presented according to the substitution patterns (Figure I-9), namely monofunctionalization, difunctionalization, rim-differentiation, perfunctionalization and phenylene substitution.

<sup>34</sup> (a) M. Xue, Y. Yang, X. Chi, Z. Zhang, F. Huang, *Acc. Chem. Res.*, **2012**, 45, 1294; (b) N. L. Strutt, H. Zheng, S. T. Schneebeli, J. F. Stoddart, *Acc. Chem. Res.*, **2014**, 47, 2631; (c) G. Yu, K. Jie, F. Huang, *Chem. Rev.*, **2015**, doi: 10.1021/cr5005315.

<sup>35</sup> T. Ogoshi, S. Kanai, S. Fujinami, T. Yamagishi, Y. Nakamoto, *J. Am. Chem. Soc.*, **2008**, 130, 5022.

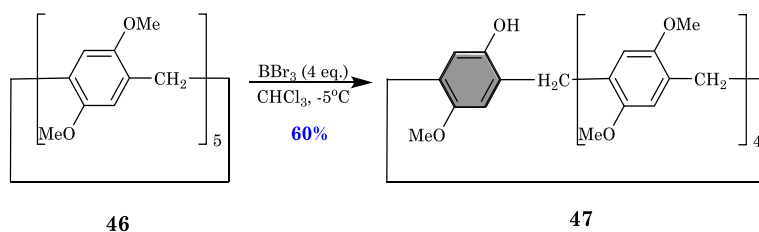


**Figure I-9:** Five distinct patterns of pillar[5]arene functionalization<sup>34b</sup>, wherein the blue spheres represent generic functional groups

#### 4.1 Monofunctionalization of pillararenes

Monofunctionalization means that only one reactive position is substituted, which allows for the addition of novel features without altering significantly essential ability. Apart from direct co-cyclization method<sup>36</sup>, the commonly used strategy is deprotection of one alkyl group from fully protected pillar[*n*]arenes.

The synthetic strategy employed to produce monofunctionalized pillar[5]arene **47** was introduced by Ogoshi group.<sup>37</sup> Using less than one equivalent of  $\text{BBr}_3$  at room temperature gave mono-demethylated pillar[5]arene, albeit with a lower yield (22%). Cao and coworkers<sup>38</sup> optimized the reaction conditions to give pillar[5]areneol **47** in 60% yield (Scheme I-18)



**Scheme I-18:** Monofunctionalization of pillar[5]arene by deprotection method

Subsequently, the unmasked hydroxyl group of **47** was used to introduce further functionalities using a Williamson ether-type synthesis. A single alkylammonium tether<sup>37</sup> was appended onto pillar[5]arene **47** to form product **48**, allowing it to undergo self-complexation (Scheme I-19). A dimer **49** of pillar[5]arene<sup>39</sup> was also connected through a *para*-xylenyl linker by the similar method. Cao and co-workers<sup>38</sup> have synthesized monophosphoryl pillar[5]arene from pillar[5]areneol **47**, which can act as a hydrogen-bond

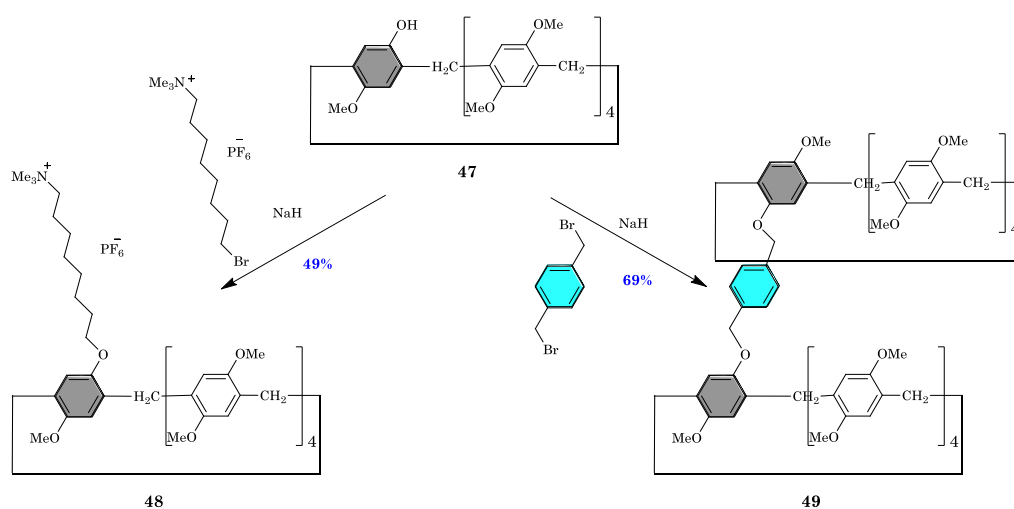
<sup>36</sup> (a) N. L. Strutt, R. S. Forgan, J. M. Spruell, Y. Y. Botros, J. F. Stoddart, *J. Am. Chem. Soc.*, **2011**, 133, 5668; (b) N. L. Strutt, H. Zhang, M. A. Giesener, J. Lei, J. F. Stoddart, *Chem. Commun.*, **2012**, 48, 1647; (c) H. Zhang, N. L. Strutt, R. S. Stoll, H. Li, Z. Zhu, J. F. Stoddart, *Chem. Commun.*, **2011**, 47, 11420; (d) H. Zhang, X. Ma, J. Guo, K. T. Nguyen, Q. Zhang, X. J. Wang, H. Yan, L. Zhu, Y. Zhao, *RSC Adv.*, **2013**, 3, 368.

<sup>37</sup> T. Ogoshi, K. Demachi, K. Kitajima, T. Yamagishi, *Chem. Commun.*, **2011**, 47, 7164.

<sup>38</sup> Y. Chen, M. He, B. Li, L. Wang, H. Meier, D. Cao, *RSC Adv.*, **2013**, 3, 21405.

<sup>39</sup> T. Ogoshi, K. Demachi, K. Kitajima, T. Yamagishi, *Chem. Commun.*, **2011**, 47, 10290.

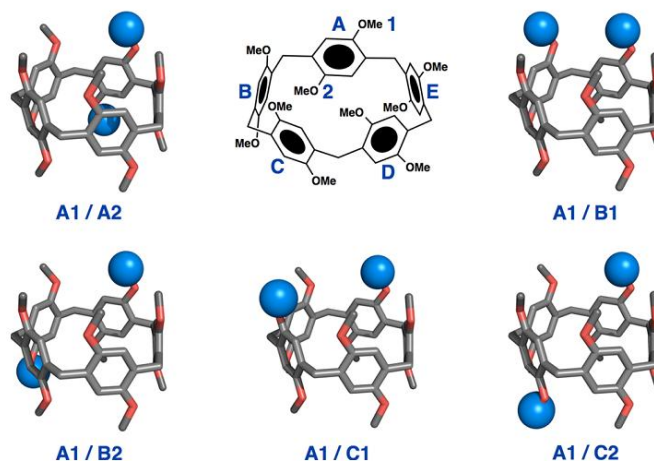
acceptor for aliphatic alcohols.



**Scheme I-19:** Further functionalization of pillar[5]arene

## 4.2 Difunctionalization of pillararenes

Introduction of two functional groups onto pillar[*n*]arenes, is more complicated than the monofunctionalization, because of more constitutional isomeric patterns (Figure I-10)<sup>40</sup>. Among these patterns, A1/A2 pattern with new functional groups at both ends of one hydroquinone unit is straightforward to be obtained, while the regioselective formation of other constitutional isomers is still an unsolved challenge.



**Figure I-10:** Constitutional isomers of difunctionalized pillar[5]arene

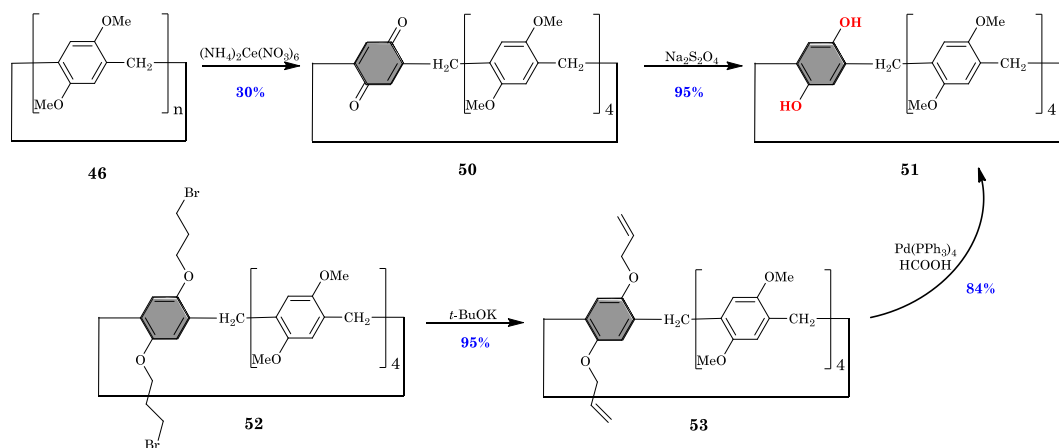
In separate reports, Huang<sup>41</sup> and Ogoshi<sup>42</sup> have prepared pillar[5]arene **50** with one benzoquinone unit by the partial oxidation of **46**, which was then reduced to

<sup>40</sup> T. Ogoshi, K. Kitajima, S. Fujinami, T. Yamagishi, *Chem. Commun.*, **2011**, 47, 10106.

<sup>41</sup> C. Han, Z. Zhang, G. Yu, F. Huang, *Chem. Commun.*, **2012**, 48, 9876.

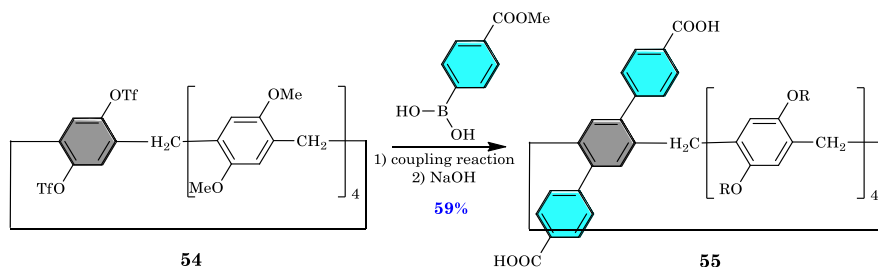
<sup>42</sup> T. Ogoshi, D. Yamafuji, D. Kotera, T. Aoki; S. Fujinami, T. Yamagishi, *J. Org. Chem.*, **2012**, 77, 11146.

A1/A2-pillar[5]arenediol **51** in 95% yield (Scheme I-20, top). Alternatively, Stoddart<sup>43</sup> introduced another synthetic route (Scheme I-20, bottom) to form **51**, involving the formation of pillar[5]arene **52**, which subsequently underwent elimination reaction and a deprotection.



**Scheme I-20:** Preparation of A1/A2-pillar[5]arenediol

Pillar[5]arenediol **51** with two hydroxyl groups on the same unit can be transformed into the ditriflate **54** (Scheme I-21), which underwent Suzuki coupling reaction and ester hydrolysis to give pillar[5]arene-containing organic strut **55** in 59% yield<sup>43</sup>.



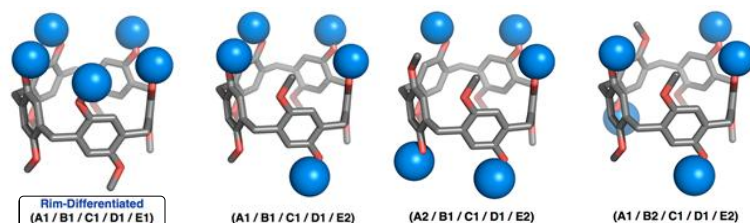
**Scheme I-21:** Preparation of A1/A2-functionalized pillar[5]arene by Suzuki reaction

### 4.3 Rim-differentiation of pillararenes

Pillar[*n*]arenes have two identical rims (upper rim and lower rim), that is entirely different to cyclodextrins or calix[*n*]arenes. Rim-differentiation of pillar[*n*]arenes means that the substituents on the upper rim are different from those on the lower rim. Huang and co-workers<sup>44</sup> demonstrated that four regioisomers (Figure I-11) are formed when 1-butoxy-4-methoxybenzene is used as the aromatic repeating unit of pillar[5]arene.

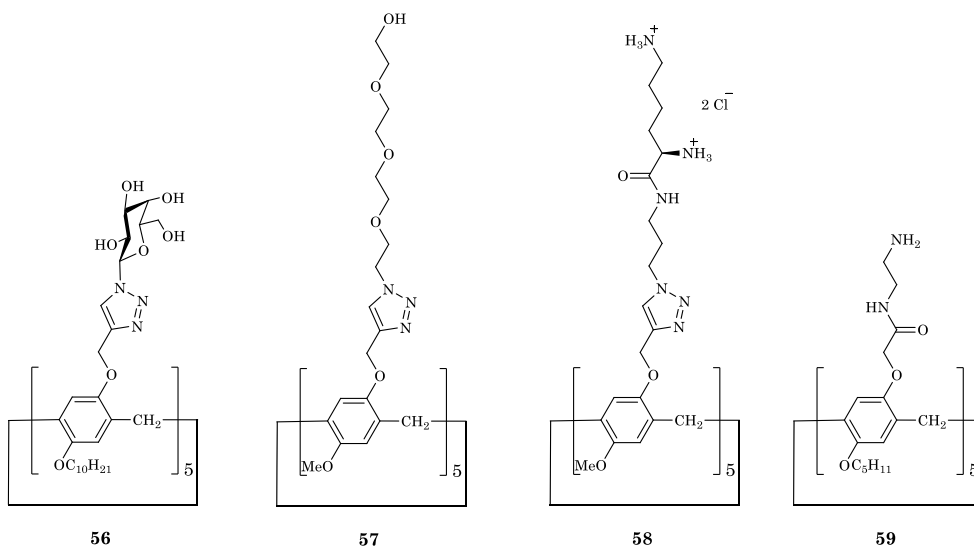
<sup>43</sup> N. L. Strutt, D. Fairen-Jimenez, J. Iehl, M. B. Lalonde, R. Snurr, Q.; O. K. Farha, J. T. Hupp, J. F. Stoddart, *J. Am. Chem. Soc.*, **2012**, 134, 17436.

<sup>44</sup> Z. Zhang, Y. Luo, B. Xia, C. Han, Y. Yu, X. Chen, F. Huang, *Chem. Commun.*, **2011**, 47, 2417.



**Figure I-11:** Four constitutional isomers of rim-differentiated pillar[5]arenes

Because of identical properties of the two rims, to date, it is still impossible to differentiate the two rims of pillar[ $n$ ]arenes by post-functionalization of parent pillar[ $n$ ]arenes. Rim-differentiation of pillar[ $n$ ]arenes are mainly fulfilled through cyclization reaction of unsymmetrical hydroquinone derivatives. Albeit in low yield, many research groups have developed them for specific applications. Rim-differentiated pillar[5]arene derivatives have been employed to design the amphiphiles with hydrophilic groups and hydrophobic groups on the two rims. A sugar-functionalized amphiphilic pillar[5]arene **56** (Figure I-12) was synthesized and used for the bacterial cell agglutination<sup>45</sup>. Other amphiphilic pillar[5]arene **57**, **58** and **59** (Figure I-12) have also been employed to create micelles<sup>46</sup>, nanotubes<sup>47</sup> and vesicles<sup>48</sup>, respectively.



**Figure I-12:** Examples of rim-differentiated pillar[5]arenes

<sup>45</sup> G. Yu, Y. Ma, C. Han, Y. Yao, G. Tang, Z. Mao, C. Gao, F. Huang, *J. Am. Chem. Soc.*, **2013**, 135, 10310.

<sup>46</sup> H. Zhang, X. Ma, K. T. Nguyen, Y. Zhao, *ACS Nano*, **2013**, 7, 7853.

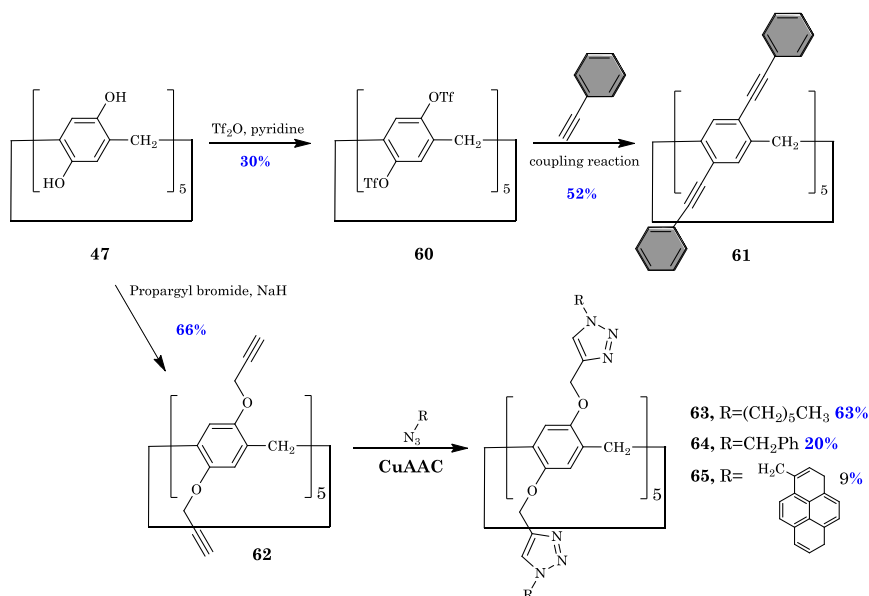
<sup>47</sup> T. Nishimura, Y. Sanada, T. Matsuo, T. Okobira, E. Mylonas, N. Yagi, K. Sakurai, *Chem. Commun.*, **2013**, 49, 3052.

<sup>48</sup> Y. Yao, M. Xue, J. Chen, M. Zhang, F. Huang, *J. Am. Chem. Soc.*, **2012**, 134, 15712.

#### 4.4 Perfunctionalization of pillararenes

Pillar[*n*]arenes have two identical rims, which bear  $2n$  hydroxyl groups. Perfunctionalization of these macrocycles means introduction of identical functional groups to all the hydroxyls.

Ogoshi and co-workers<sup>49</sup> demonstrated the preparation of perfunctionalization of pillar[5]arene **60** (Scheme I-22) by direct full triflation of perhydroxylated pillar[5]arene. Pillar[5]arene **60** can undergo Sonogoshira Pd-catalyzed cross coupling reaction to afford a highly conjugated pillar[5]arene **61** which results in the efficient through-space  $\pi$ -delocalization. They also prepared a “clickable” pillar[5]arene **62**, bearing 10 terminal alkynes using Williamson-type ether reaction<sup>50</sup> (Scheme I-22). Peralkylated pillar[5]arene **62** is a key starting material, which can be submitted to Copper-catalyzed Azide Alkyne Cycloaddition (CuAAC) reaction, affording different perfunctionalized hosts.



**Scheme I-22:** Perfunctionalization of pillar[5]arenes by direct substitution

#### 4.5 Phenylene-substituted pillararenes

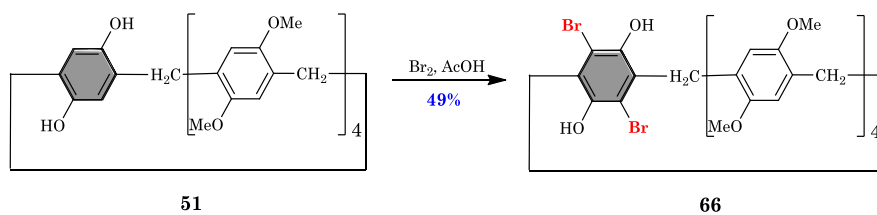
The functionalization of pillar[*n*]arenes is mostly achieved on the hydroxyl groups. Certainly, it can also be expanded to the aromatic positions, which are *ortho* to both the methylene bridges and oxygen substituents. This mode of functionalization can be used to substitute the parent pillar[*n*]arenes.

Stoddart and co-workers<sup>51</sup> have reported an example of phenylene-substituted pillar[5]arene **66** (Scheme I-23) by direct bromination of A1/A2-pillar[5]arenediol **51**. The formed pillar[5]arene **66** can be used as a precursor to perform further functionalization.

<sup>49</sup> T. Ogoshi, K. Umeda, T. Yamagishi, Y. Nakamoto, *Chem. Commun.*, **2009**, 45, 4874.

<sup>50</sup> T. Ogoshi, R. Shira, M. Hashizume, T. Yamagishi, *Chem. Commun.*, **2011**, 47, 6927.

<sup>51</sup> N. L. Strutt, S. T. Schneebeli, J. F. Stoddart, *Supramol. Chem.*, **2013**, 25, 596.



**Scheme I-23:** Synthesis of phenylene-substituted pillar[5]arene.

As above mentioned, numerous methods have been developed for the functionalization of pillar[ $n$ ]arenes, but there are still some challenge in this field, such as substitution at the methylene bridges, the selective synthesis of unsymmetrical difunctionalized pillar[ $n$ ]arenes, and rim-differentiated pillar[ $n$ ]arenes. The development of simple, efficient functionalization methodologies will expand the applications of this molecule.



## 5. Conclusion

In this chapter, we described the post-functionalization of  $C_n$ -symmetric concave cyclic molecules: calixarenes, cucurbiturils and pillararenes. A lot of achievements have been obtained for calix[4]arene on both the upper and lower rims. However, the efficient methodologies for polyfunctionalization of calix[6]arene or higher homologues are still needed to be explored. Although using cucurbituril-forming reactions numerous cucurbituril derivatives are prepared, the direct functionalization on parent cycle (post-functionalization) is reported rarely. For burgeoning pillararenes, numerous methods have been developed, but there are still some challenges, such as substitution on methylene bridges, rim-differentiation.

Owing to these methodologies, many functionalized derivatives have been applied in a wide diversity of areas. It is clear that functionalization of such molecules is of crucial importance to their applications. Therefore, the development of simple and efficient functionalization methods are still desired.

**CHAPTER II**

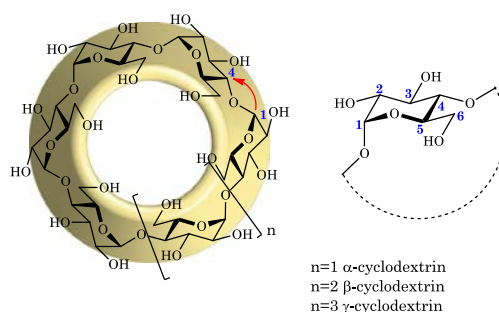
**REGIOSELECTIVE  
FUNCTIONALIZATION OF CONCAVE  
CYCLES, THE CASE OF  
CYCLODEXTRINS**



## 1. Definition and properties

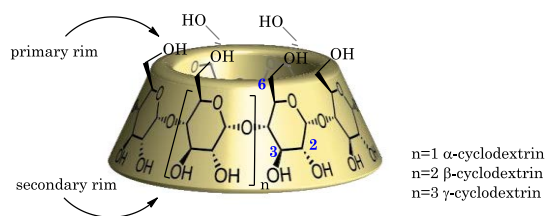
Cyclodextrins (CDs) are a series of cyclic oligomers composed of  $\alpha$ -1,4 linked D-(+)-glucopyranose units with a  ${}^4C_1$  chair conformation. They were isolated firstly from starch by Villiers in 1891,<sup>52, 53</sup> but the structure was not elucidated until 1936 by Freudenberg<sup>54</sup>.

Today, cyclodextrins are industrial products, obtained from starch by means of enzymatic degradation with an enzyme called Cyclodextrin Glycosyl Transferase (CGTase)<sup>55</sup>. They are separated by selective precipitation with yields ranging from 40 to 60%. The most common cyclodextrins are  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin, and  $\gamma$ -cyclodextrin, bearing 6, 7, and 8 glucose units, respectively (Figure II-1).



**Figure II-1.** Structure of cyclodextrins

Cyclodextrins are formed with glucopyranoside units in a ring that assumes a special tridimensional shape, resembling a truncated funnel with a  $C_n$  symmetry ( $n$  here is the number of glucose units)<sup>56</sup>. Cyclodextrin possesses a hydrophobic cavity and an external hydrophilic shell. The cavity has two rims (Figure II-2) formed by the primary alcohols (OH-6, primary rim) and secondary alcohols (OH-2, 3, secondary rim). The hydroxyls on position 2 are directed towards the interior of the cavity and those on position 3 are oriented towards the exterior.



**Figure II-2.** Tridimensional structure of cyclodextrins

<sup>52</sup> A. Villiers, *Compt. Rend. Acad. Sci.*, **1891**, 112, 435.

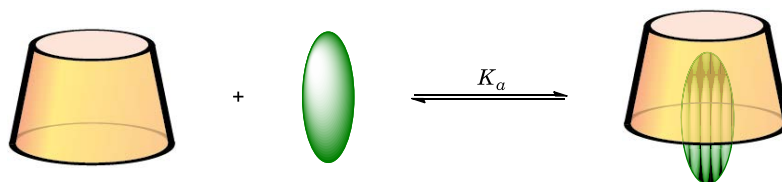
<sup>53</sup> A. Villiers, *Compt. Rend. Acad. Sci.*, **1891**, 112, 536.

<sup>54</sup> K. Freudenberg, G. Blomqvist, L. Ewald, K. Soff, *Ber. Dtsch. Chem. Ges.*, **1936**, 69, 1258.

<sup>55</sup> Q. Qi, W. Zimmermann, *Appl. Microbiol. Biotechnol.*, **2005**, 66, 475.

<sup>56</sup> K. Freudenberg, F. Cramer, H. Plieninger, *Ger Patent*, **1953**, 895.

With a lot of hydroxyls and a truncated funnel-shaped cavity, cyclodextrins are endowed with remarkable complexation capability (Figure II-3) to accommodate apolar molecular guests in aqueous solution, mainly through hydrophobic interaction, and/or other interactions<sup>57</sup>.



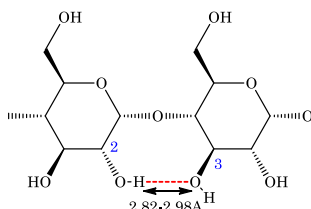
**Figure II-3.** Inclusion complex formation

The size of guest molecules matching the dimensions of cavity, increases with the diameter of cyclodextrin because of the constant height (0.78 nm) of torus. The parameters of cyclodextrins depend on the number of glucose units as shown in Table II-1<sup>57</sup>.

Property	$\alpha$ -CD	$\beta$ -CD	$\gamma$ -CD
No. of glucose units	6	7	8
Min diameters of cavity (nm)	0.44	0.58	0.74
Max diameters of cavity (nm)	0.57	0.78	0.95
Height of CDs (nm)	0.78	0.78	0.78
Cavity volume ( $\text{\AA}^3$ )	174	262	427

**Table II-1.** The dimensions of cyclodextrins

Native cyclodextrins have relatively rigid structures. Although the primary hydroxyls can rotate somewhat freely, the secondary hydroxyls fix the structure of CDs by intramolecular hydrogen bonding (Figure II-4) between OH-2s and OH-3s of two adjacent glucose units. Because of this, the solubility of cyclodextrins in water varies from 231 g/L in  $\gamma$ -CD to 18.5 g/L in  $\beta$ -CD<sup>58</sup>. The intramolecular hydrogen bonds are favored in  $\beta$ -CD, which explains its poor solubility in water. For  $\gamma$ -CD, hydrogen bonds are less favored, due to its bigger size.



**Figure II-4.** Hydrogen bonds on the secondary rim of cyclodextrins

<sup>57</sup> G. Wenz, *Angew. Chem. Int. Ed.*, **1994**, 33, 803.

<sup>58</sup> J. Szejtli, *Chem. Rev.*, **1998**, 98, 1743.

## 2. Nomenclature and reactivity of cyclodextrins

### 2.1 Nomenclature of cyclodextrins

Although according to IUPAC rules, roman numerals (I, II, III...) are utilized for the numeration of cyclodextrins, the predominant nomenclature used in the literature is the numbering of the glucopyranose units by majuscule letters (A, B, C...) <sup>59</sup>. Each glucose unit is attributed a capital letter following the direction of the  $\alpha$ -1,4 linked glycosidic bond (Figure II-5). If more than one glucose unit is modified, numbering should follow the shortest way.

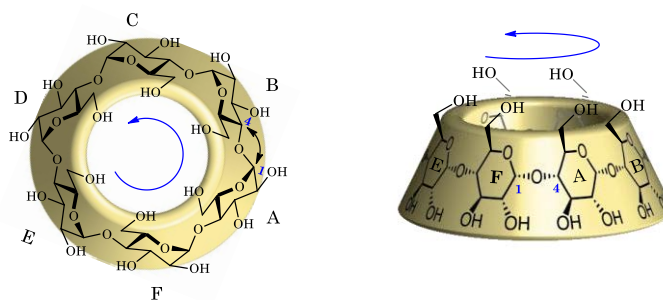


Figure II-5. Nomenclature of cyclodextrins

### 2.2 Reactivity of cyclodextrins

Cyclodextrins bear abundant hydroxyls, which makes selective chemical modifications rather difficult, moreover, the hydrophobic cavity often has a tendency to form inclusion complexes with reagents, which also influences the reactivity <sup>60</sup>.

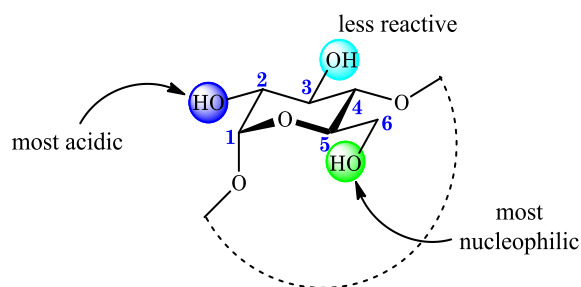
The hydroxyls on the primary rim (OH-6) are the less hindered, the most basic and often the most nucleophilic ones, which enables them to react with steric hindered electrophiles under less basic conditions (Figure II-6).

The secondary hydroxyl groups on position 2 (OH-2) are the most acidic ( $pK_a=12.2$ ) <sup>61</sup> because of the proximity to the anomeric carbon. So these hydroxyls can be deprotonated selectively under basic conditions. Finally, OH-3s are the least reactive, they could be modified only after the pre-protection of the positions 2 and 6.

<sup>59</sup> R. Breslow, J. B. Doherty, G. Guillot, C. Lipsey, *J. Am. Chem. Soc.*, **1978**, 100, 3227.

<sup>60</sup> K. Takahashi, *Chem. Rev.*, **1998**, 98, 2013.

<sup>61</sup> R. I. Gelb, L. M. Schwartz, J. J. Bradshaw, D. A. Laufer, *Bioorg. Chem.*, **1980**, 9, 299



**Figure II-6.** Reactivity of hydroxyls of cyclodextrins

In spite of the differences in reactivity that exist among these hydroxyls, more reactive reagents will react with a poor selectivity.

### 3. Functionalization of the primary rim of cyclodextrins

The intrinsic structure of cyclodextrins, makes them suitable and fascinating hosts. This distinctive feature appealed to many scientists. Owing to this property, cyclodextrins have been seen as versatile molecules, applied in a broad range of fields, such as in drug-delivery system<sup>62</sup>, artificial enzymes<sup>63</sup>, and supramolecular chemistry<sup>64</sup>. However, this rigid structure restricts their applications to some degree. So given this, introduction of some other functions to alter their properties and amplify their scope is of great interest.

#### 3.1 Selective functionalization

##### 3.1.1 Chemoselective functionalization

Cyclodextrins bear three types of hydroxyls (position 2, 3 and 6) with different reactivities. In light of the nucleophilicity of the primary hydroxyl groups, they are functionalized more selectively than their secondary counterparts.

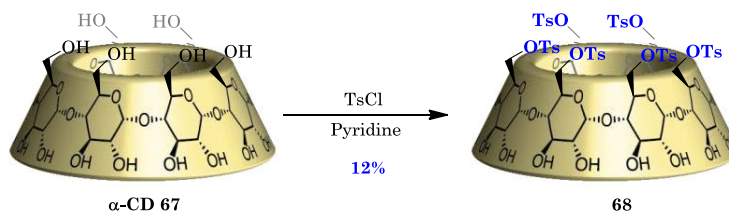
The persubstitution of the position 6 hydroxyls can be carried out under weak basic conditions. Using pyridine as the solvent and weak base, the primary hydroxyl groups of native  $\alpha$ -cyclodextrin **67** were tosylated, albeit with a poor yield ( $\sim 12\%$ )<sup>65</sup>. Here the steric crowding might account for the unsatisfying yield (Scheme II-1).

<sup>62</sup> (a) K. Hayashida, T. Higashi, D. Kono, K. Motoyama, K. Wada, H. Arima, *Beilstein J. Org. Chem.*, **2014**, 10, 2756; (b) Q. Hu, G. Tang, P. K. Chu, *Acc. Chem. Res.*, **2014**, 47, 7, 2017.

<sup>63</sup> (a) F. O. Caballero, C. Rousseau, B. Christensen, T. E. Petersen, M. Bols, *J. Am. Chem. Soc.*, **2005**, 127, 3238; (b) L. Marinescu, M. Mølbach, C. Rousseau, M. Bols, *J. Am. Chem. Soc.*, **2005**, 127, 17578; (c) L. G. Marinescu, M. Bols, *Angew. Chem. Int. Ed.*, **2006**, 45, 4590.

<sup>64</sup> (a) L. Wang, L. Li, Y. Fan, H. Wang, *Adv. Mater.*, **2013**, 25, 3888; (b) Y. Zhao, F. Sakai, L. Su, Y. Liu, K. Wei, G. Chen, M. Jiang, *Adv. Mater.*, **2013**, 25, 5215; (c) A. Harada, A. Hashidzume, H. Yamaguchi, Y. Takashima, *Chem. Rev.*, **2009**, 109, 5974

<sup>65</sup> S. Umezawa, K. Tatsuta, *Bull. Chem. Soc. Jpn.*, **1968**, 41, 464.



**Scheme II-1:** Pertosylation on the primary rim of native  $\alpha$ -cyclodextrin

Reagent *tert*-butyldimethylsilyl chloride (TBSCl) is chosen commonly for the preparation of silyl ethers on the primary rim of cyclodextrins. After treating native cyclodextrins in pyridine at room temperature, 6-substituted derivatives **70** and **71** were obtained with excellent yields, 75% for  $\alpha$ -cyclodextrin and 83% for  $\beta$ -cyclodextrin (Scheme II-2).<sup>66</sup>



**Scheme II-2:** Persilylation on the primary rim of native cyclodextrins

In the course of tosylation or silylation on the primary rim of cyclodextrins, the mono-substituted products could be reached by reducing the number of equivalents of reagents or minimizing the reaction time<sup>67</sup>, although compromising with low yields and extensive purification (**Path A**, Scheme II-3). The yields of the final products are often reduced because the tosylate can undergo an exchange by chloride ion or an elimination process to give either 3, 6-anhydro compounds or alkene<sup>68</sup>.

The most popular method for monofunctionalization on the position-6 of cyclodextrins is a nucleophilic attack to replace the mono-6-sulfonyl group in the cyclodextrins. So with the mono-tosylated cyclodextrins in hand, a number of corresponding derivatives can be synthesized. For example, using sodium azide in DMF at a higher temperature, the azido-derivatives were prepared with outstanding yields of around 95% (**Path B**, Scheme II-3)<sup>69</sup>.

The monoazido-cyclodextrins could also be synthesized directly from native cyclodextrins (**Path C**, Scheme II-3) by using triphenylphosphine, tetrabromide and sodium azide and in

<sup>66</sup> (a). K. Takeo, K. Uemura, H. Mitoh, *J. Carbohydr. Chem.*, **1988**, 7, 292; (b). K. Takeo, H. Mitoh, K. Uemura, *Carbohydr. Res.*, **1989**, 187, 203.

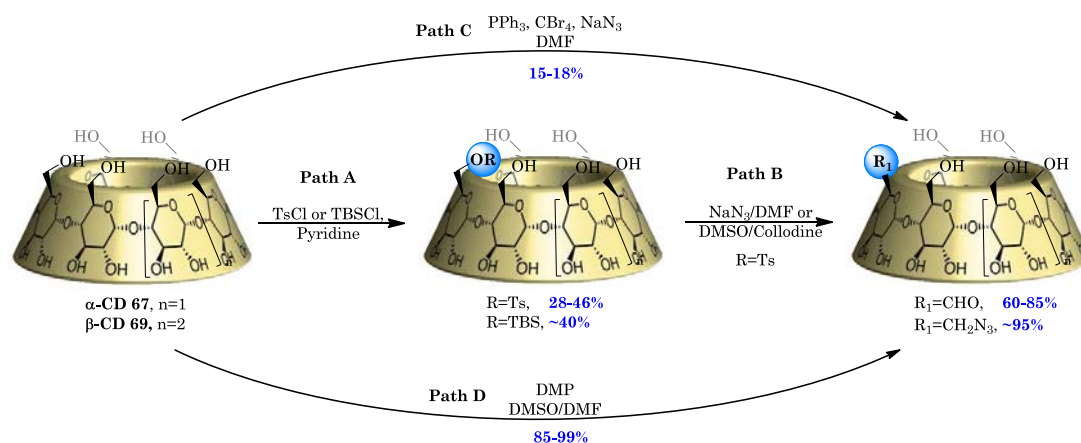
<sup>67</sup> (a). L. D. Melton, K. N. Slessor, *Carbohydr. Res.*, **1971**, 18, 29; (b). Y. Matsui, T. Yokoi, K. Mochida, *Chem. Lett.*, **1976**, 1037; (c). I. Tabushi, N. Shimizu, T. Sugimoto, M. Shiozuka, K. Yamamura, *J. Am. Chem. Soc.*, **1977**, 99, 7100.

<sup>68</sup> A. R. Khan, P. Forgo, K. J. Stine, V. T. D'Souza, *Chem. Rev.*, **1998**, 98, 1977.

<sup>69</sup> L. D. Melton, K. N. Slessor, *Carbohydr. Res.*, **1971**, 18, 29.



DMF<sup>70</sup>, albeit with a lower yield.

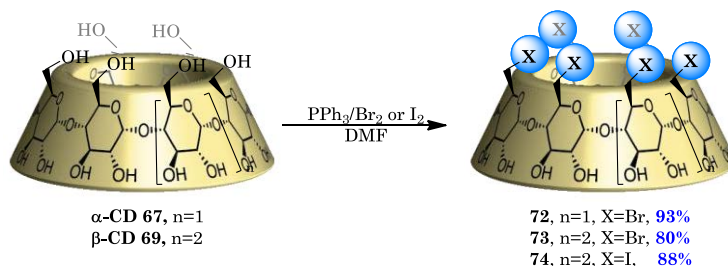


**Scheme II-3:** Monofunctionalization on the primary rim of cyclodextrins.

The monooxidation of cyclodextrins is another highly efficient method for monofunctionalization. By means of direct Dess-Martin oxidation, native cyclodextrins were transformed into monoaldehyde products with yields of 85% to 99% (**Path D**, Scheme II-3)<sup>71</sup>.

It is also possible to access the monoaldehyde cyclodextrins by the oxidation of monotosylated cyclodextrins, utilizing dimethyl sulfoxide in the presence of a non nucleophilic base (such as collidine or diisopropylethylamine) (**Path B**, Scheme II-3)<sup>72</sup>.

In addition to pertosylation and silylation, another frequently used method to functionalize the primary rim of cyclodextrins is perhalogenation (Scheme II-4). Native cyclodextrins were converted into per-bromo/iodo-cyclodextrins **72**, **73** and **74** with good yields. These reactions were carried out in the presence of triphenylphosphine and bromine or iodine in DMF under heating<sup>73</sup>. The substitution on the secondary rim was avoided by the utilization of crowded reagents. 6-halogenated cyclodextrins are a class of important precursors, because appropriate nucleophiles can attack the electrophilic carbon atoms on position 6 to produce the corresponding functionalities.



**Scheme II-4:** Perhalogenation on the primary rim of native cyclodextrins

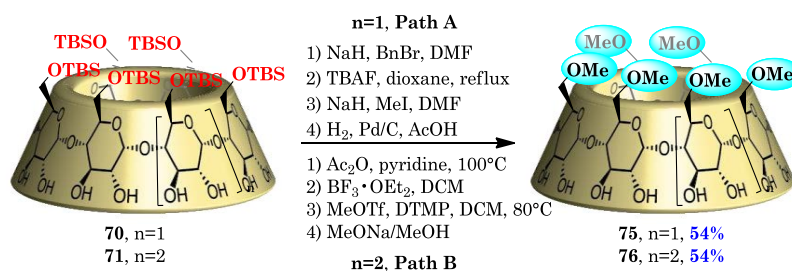
<sup>70</sup> S. Hanessian, A. Bnealil, C. Laferrikre, *J. Org. Chem.*, **1995**, 60, 4786.

<sup>71</sup> M. J. Cornwell, J. B. Huff, C. Bieniarz, *Tetrahedron Lett.*, **1995**, 36, 8371.

<sup>72</sup> (a) K. A. Marrin, A. W. Czarnik, *Tetrahedron Lett.*, **1994**, 35, 6781; (b) J. B. Huff, C. Bieniarz, *J. Org. Chem.*, **1994**, 59, 7511; (c) J. Yoon, S. Hong, K. A. Marrin, A. W. Czarnik, *J. Org. Chem.*, **1995**, 60, 2792.

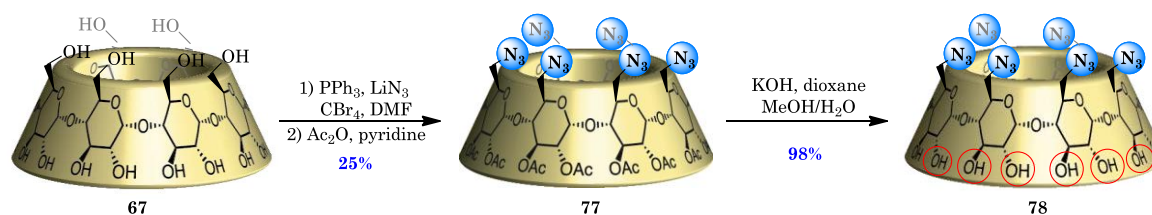
<sup>73</sup> A. Gadelle, J. Defaye, *Angew. Chem. Int. Ed.*, **1991**, 30, 78.

Methylation of the primary rim of cyclodextrins posed a problem to the chemists. Due to the difference in acidity, the per-6-methylation of cyclodextrins cannot be obtained without touching the secondary alcohols by a direct strategy (using sodium hydride and methyl iodide for methylation). Given this, Takeo<sup>74</sup> proposed indirect protection-deprotection strategy. From persilylated cyclodextrins **70** and **71**, through a sequence of protection-deprotection reactions, the methylated primary rim of cyclodextrins **75** and **76** were synthesized with moderate yields (Scheme II-5).



**Scheme II-5:** Permethylation on the primary rim of cyclodextrins by protection-deprotection strategies

The perazidation of the primary rim of cyclodextrin can also be fulfilled through a three steps strategy from native cyclodextrin **67** (Scheme II-6)<sup>75</sup>. After the bromination of the primary rim, a nucleophilic substitution by lithium azide *in situ* to give azidated cyclodextrin which could be isolated after acetylation (**77**, Scheme II-6). Then cyclodextrin **78** was generated after removal of the acetates through saponification. The acetylation here was implemented to facilitate the separation of the product.



**Scheme II-6:** Perazidation on the primary rim of native cyclodextrins

### 3.1.2 Capping reagents

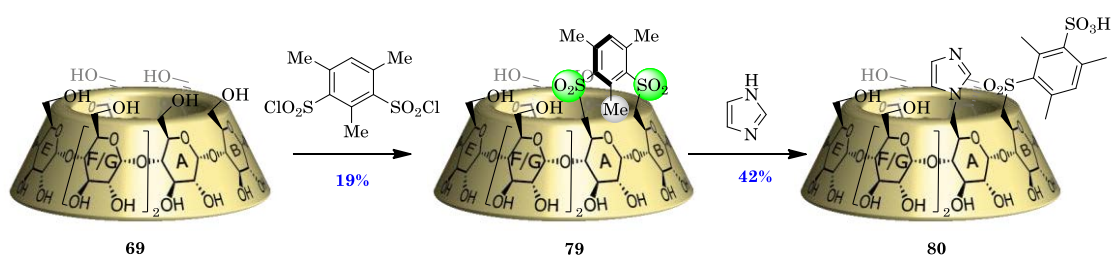
A large amount of capping reagents have been employed to difunctionalize both rims of cyclodextrins. The rigid structure of  $\beta$ -cyclodextrin offers a precise distance between different hydroxyls, enabling the design of reagents that react regioselectively. Nonetheless, a few capping reagents also have good results on  $\alpha$ - and  $\gamma$ -cyclodextrins.

<sup>74</sup> (a). K. Takeo, K. Uemura, H. Mitoh, *J. Carbohydr. Chem.*, **1988**, 7, 292; (b). K. Takeo, H. Mitoh, K. Uemura, *Carbohydr. Res.*, **1989**, 187, 203.

<sup>75</sup> J. Boger, R. J. Corcoran, J.-M. Lehn, *Helv. Chim. Acta.*, **1978**, 61, 2190.

## a. Symmetrical caps

Various disulfonyl chloride reagents have been applied to the difunctionalization of cyclodextrins. Initially, *meta*-benzenedisulfonyl dichloride was reacted with  $\beta$ -cyclodextrin to give an instable 6A, 6B-capped  $\beta$ -cyclodextrin in 40% yield<sup>76</sup>. Fujita<sup>77</sup> optimized the reagent by introduction of stabilizing methyl group on the phenyl ring, yielding a stable difunctionalized cyclodextrin **79** on positions 6A and 6B in 19% yield (Scheme II-7). It was followed by a regioselective displacement with imidazole, which preferentially took place on position 6A, giving cyclodextrin **80** in 42% yield. The steric hindrance created by methyl group between the sulfonyls explains the observed regioselectivity.



**Scheme II-7:** 6A, 6B-difunctionalization on the primary rim of  $\beta$ -cyclodextrin by a capping reagent and the selective opening

Another useful capping reagent is 4,4'-methylenebis(benzene-1-sulfonyl chloride)<sup>78</sup>. Tabushi firstly showed its versatility and applications for the introduction of different chemical groups<sup>79</sup>. The hydroxyls were activated by the sulfonyl esters which enabled the grafting of new groups such as thiol or amine through nucleophilic attack<sup>80</sup> (Scheme II-8).

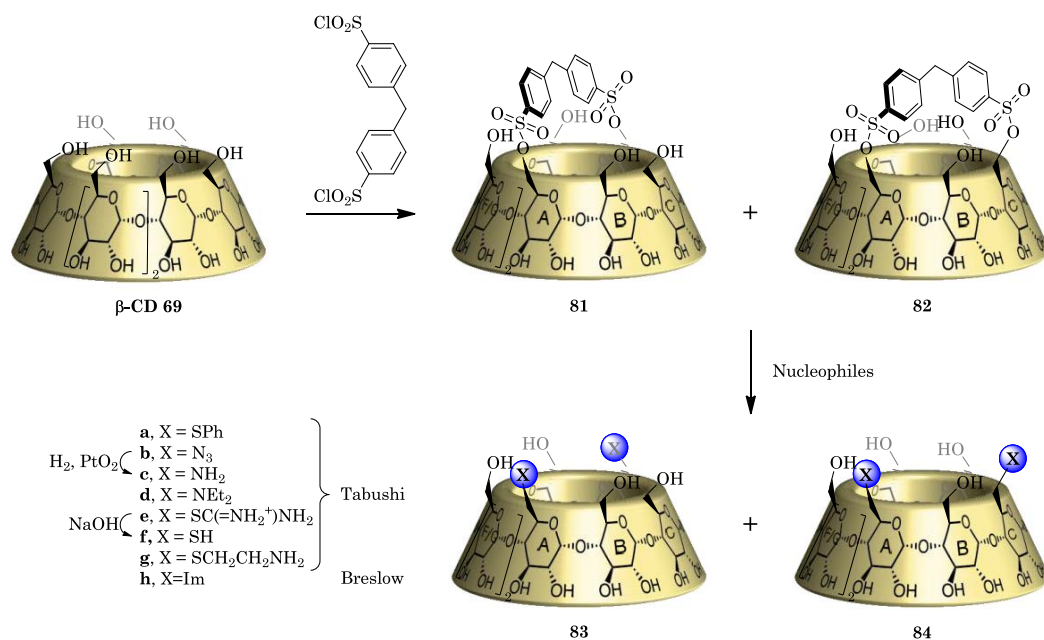
<sup>76</sup> (a) I. Tabushi, T. Nabeshima, K. Fujita, A. Matsunaga, T. Imoto, *J. Org. Chem.*, **1985**, 50, 2638; (b) R. Breslow, J. W. Canary, M. Varney, S. T. Waddell, D. Yang, *J. Am. Chem. Soc.*, **1990**, 112, 5212.

<sup>77</sup> D. Q. Yuan, T. Yamada, K. Fujita, *Chem. Comm.*, **2001**, 2706.

<sup>78</sup> I. Tabushi, K. Shimokawa, N. Shimizu, H. Shirakata, K. Fujita, *J. Am. Chem. Soc.*, **1976**, 98, 7855.

<sup>79</sup> I. Tabushi, K. Shimokawa, K. Fujita, *Tetrahedron Lett.*, **1977**, 1527.

<sup>80</sup> R. Breslow, J. B. Doherty, G. Guillot, C. Lipsey, *J. Am. Chem. Soc.*, **1978**, 100, 3227.



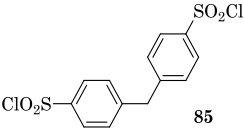
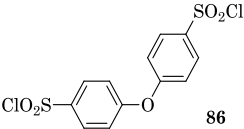
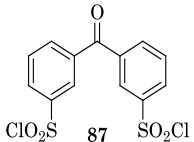
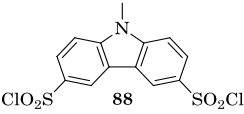
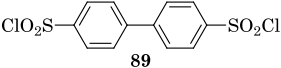
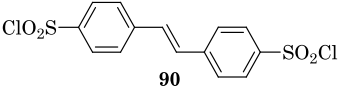
**Scheme II-8:** Capping reagent and the nucleophilic attack

Given the practicability of this kind of method, many capping reagents have been put into use with moderate regioselectivity (Table II-2).<sup>81</sup> According to Table II-2, reagents **85** and **86** showed less regioselectivity because of their flexibilities (Entry 1 and 2).<sup>78,79,82</sup> To solve this problem, other capping reagents with more rigid structures were designed (Entry 3-6). The distance between the two reactive centers were controlled subtly. In virtue of this, the capping reactions favored the substitution of AC (Entry 3 and 4)<sup>81,83</sup> or AD (Entry 5 and 6).<sup>82,83</sup>

<sup>81</sup> I. Tabushi, K. Yamamura, T. Nabeshima, *J. Am. Chem. Soc.*, **1984**, 106, 5267.

<sup>82</sup> R. Breslow, P. Bovy, C. Lipsey Hersh, *J. Am. Chem. Soc.*, **1980**, 102, 2115.

<sup>83</sup> I. Tabushi, Y. Kuroda, K. Yokota, L. C. Yuan, *J. Am. Chem. Soc.*, **1981**, 103, 711.

Entry	Capping reagent	Yield (%)	A,C : A,D <sup>a</sup>
1	 85	40	56 : 34
2	 86	39	51 : 38
3	 87	53	75 : 8
4	 88	41	61 : 35
5	 89	54	10 : 84
6	 90	33 30	24 : 57 11 : 81 <sup>b</sup>

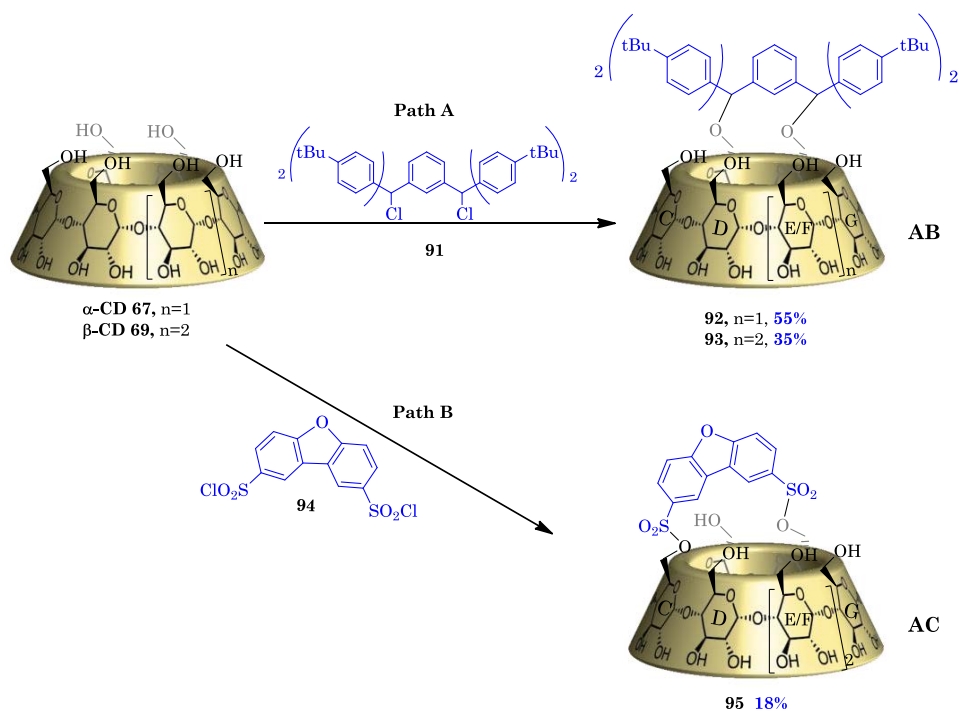
**Table II-2:** Selectivity of different reagents of disulfonyl chlorideConditions: [ $\beta$ -CD] =17.6 mM, [reagent] =15.0 mM, 25°C.<sup>a</sup>Sum A,B+A,C+A,D=100. <sup>b</sup>[ $\beta$ -CD] =2.6 mM, [reagent] = 2.2 mM

Besides the abovementioned capping reagents, bulky reagent **91** was another alternative, which gave the AB-difunctionalized  $\beta$ -cyclodextrin **93** selectively in 35% yield<sup>84</sup> (**Path A**, Scheme II-9).

In regard to  $\alpha$ -cyclodextrin, the capping reaction was less studied, nevertheless, some interesting results have been obtained for the selective difunctionalization of the primary rim. Using the same capping reagent **91**, AB-difunctionalized  $\alpha$ -cyclodextrin **92** was also generated (**Path A**, Scheme II-9). The AC-difunctionalized derivative **95** was achieved using a dibenzofuran derivative **94** in 18% yield<sup>85</sup> (**Path B**, Scheme II-9).

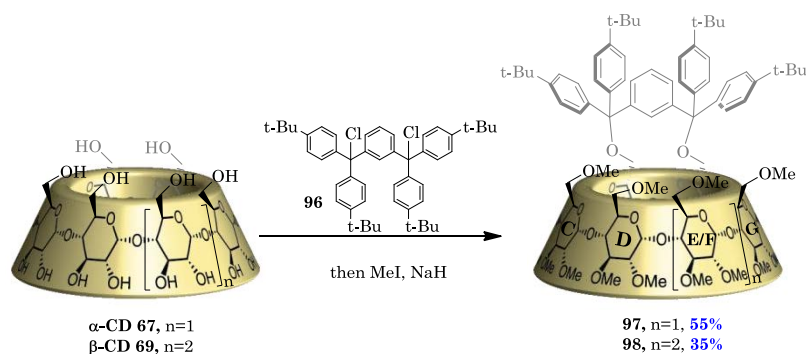
<sup>84</sup> D. Armspach, L. Poorters, D. Matt, B. Benmerad, F. Balegroune, L. Toupet, *Org. Biomol. Chem.*, **2005**, 3, 2588.

<sup>85</sup> K. Koga, D.-Q. Yuan, K. Fujita, *Tetrahedron Lett.*, **2000**, 41, 7855.



**Scheme II-9:** Difunctionalization on the primary rim of  $\alpha/\beta$ -cyclodextrin by capping reagents

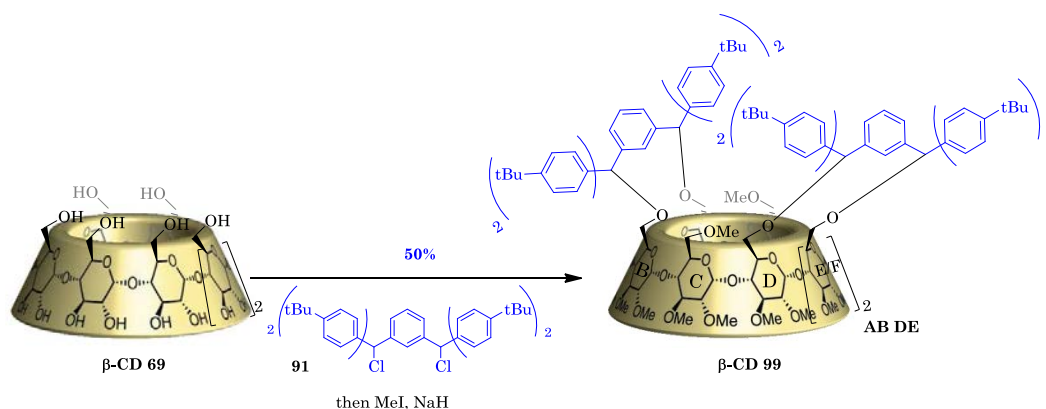
Another example was the use of a synthesized capping reagent **96** (Bis-trityl) to selectively AB-difunctionalize  $\alpha$ -cyclodextrin **67**. This process was carried out in DMF using DMAP/1,8-bis(dimethylamino)naphthalene (as proton sponge) with an equal amount of cyclodextrin and dichloride, after methylation of the remaining hydroxyls, the AB-difunctionalized  $\alpha$ -cyclodextrin **97** was obtained in 55% yield (Scheme II-10)<sup>84</sup>. This reaction was also suitable for  $\beta$ -cyclodextrin to give AB-difunctionalized cyclodextrin **98** in 35% yield.



**Scheme II-10:** 6A, 6B-difunctionalization on the primary rim of  $\alpha/\beta$ -cyclodextrin by Bis-trityl

The above mentioned examples all used a single capping reagent. Actually, a second capping reagent can also be attached to cyclodextrin to form tetrafunctionalized derivative. Without doubt, it is more difficult than the first capping reaction because of the increasing steric

crowding. Nevertheless, it is more selective. Matt and Armspach have shown that, reacting  $\beta$ -cyclodextrin with 2 eq. of capping reagent **91**, a tetrafunctionalized cyclodextrin derivative was prepared. After permethylation of all remaining hydroxyls and purification, cyclodextrin **99** was obtained with installation of two capping groups on position 6A, 6B and 6D, 6E in 50% yield (Scheme II-11)<sup>86</sup>. Using reagent **87** (showed in Table II-2), another 6A, 6C, 6D, 6F- $\beta$ -cyclodextrin was achieved with two capping groups grafted on the primary rim in 35% yield<sup>87</sup>. The same strategy was applied on  $\alpha$ -cyclodextrin as well, but unfortunately, with no success, that might be due to its smaller size, too small to accommodate two such crowded groups.



**Scheme II-11:** Tetrafunctionalization on the primary rim of  $\beta$ -cyclodextrin

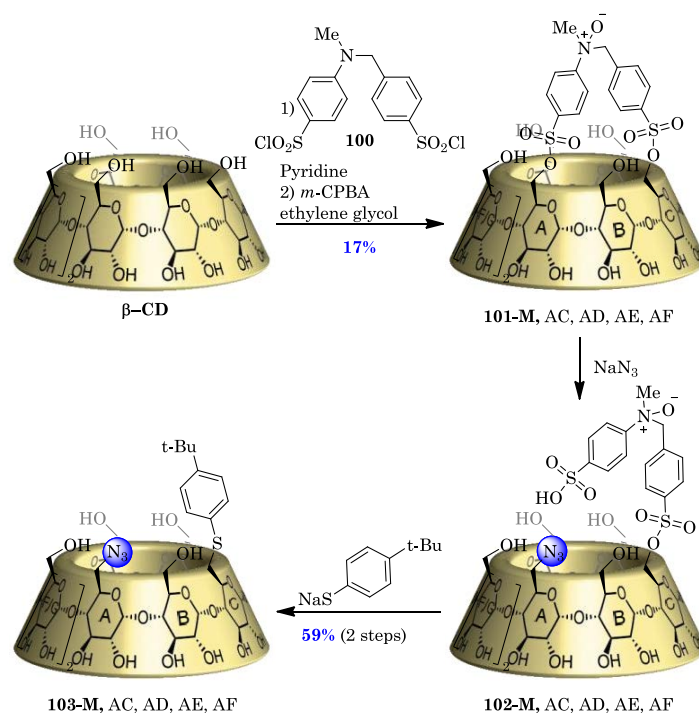
### b. Unsymmetrical caps

Employing a symmetrical capping reagent in a single step leads to a differentiated pattern (either single capping or double capping). However, tridifferentiated cyclodextrins might be achieved using unsymmetrical reagents. This kind of reagents have been reported with a visual name: “Flamingo cap”. Tabushi and co-workers have proposed the first unsymmetrical capping reagent **100**, *N*-benzyl-*N*-methylanilin-*p,p'*-disulfonyl chloride. A mixture of AC, AD, AE, AF- $\beta$ -cyclodextrins were prepared by treatment of reagent **100** with  $\beta$ -cyclodextrin in dry pyridine, then *m*CPBA oxidation gave *N*-oxide derivatives **101-M** in 17% overall yield (Scheme II-12)<sup>88</sup>. Subsequent selective nucleophilic sodium azide attack on the more electrophilic position, i.e. the *para* position of *N*-oxide, followed by another nucleophilic displacement by thiophenol gave tridifferentiated derivatives **103-M**.

<sup>86</sup> R. Gramage-Doria, D. Rodriguez-Lucena, D. Armspach, C. Egloff, C. Jouffroy, D. Matt, L. Toupet, *Chem. Eur. J.*, **2011**, 17, 3911.

<sup>87</sup> I. Tabushi, L. C. Yuan, K. Shimokawa, K. Yokota, T. Mizutani, Y. Kurota, *Tetrahedron Lett.*, **1977**, 1527.

<sup>88</sup> I. Tabushi, T. Nabeshima, H. Kitaguchi, K. Yamamura, *J. Am. Chem. Soc.*, **1982**, 104, 2017.

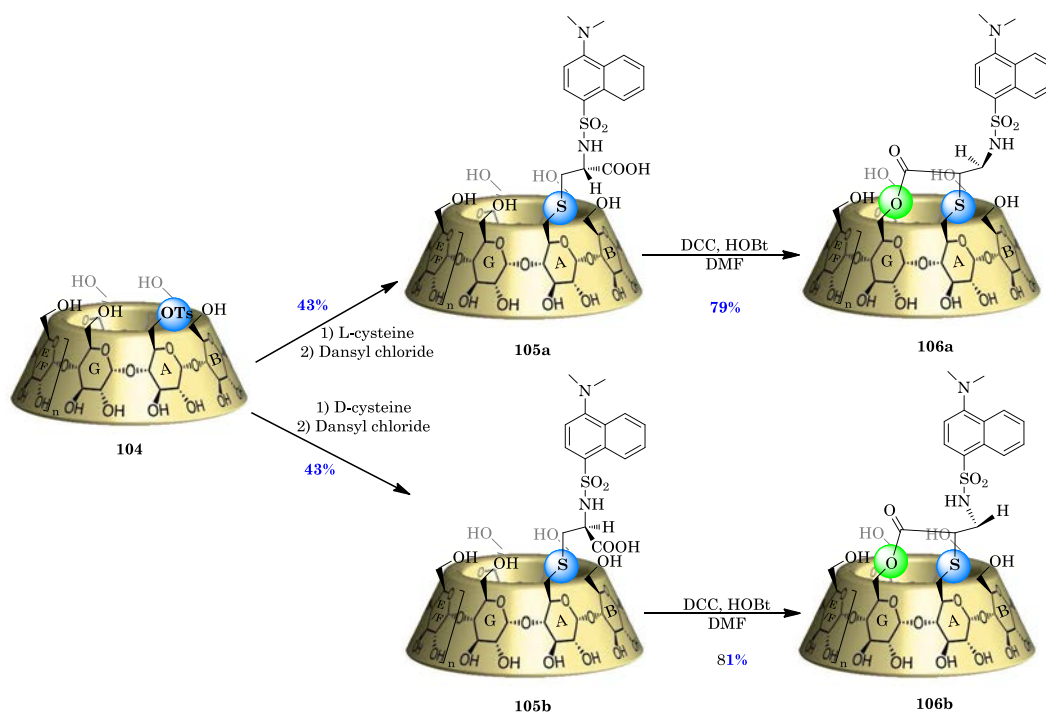


**Scheme II-12:** “Flamingo” cap used on  $\beta$ -cyclodextrin

Poor selectivity is still a troublesome problem during the capping reactions, so the capping reactions should be carefully controlled on both distance and direction. Fujita introduced a two-steps strategy to meet this demand on  $\beta$ -cyclodextrin. Monotosylated  $\beta$ -cyclodextrin **104** was treated with either L-cysteine or D-cysteine, which reacted through its thiol group to give monofunctionalized cyclodextrins. Then by treatment of the amino groups with dansyl chloride, the obtained acids **105a** and **105b** underwent esterification to give isomers **106a** and **106b** selectively with yields of about 80%<sup>89</sup> (Scheme II-13).

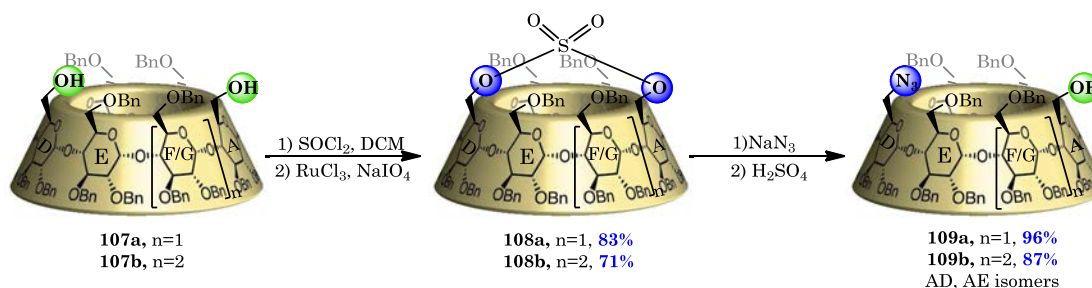
<sup>89</sup> D. Q. Yuan, Y. Kitagawa, M. Fukudome, K. Fujita, *Org. Lett.*, **2007**, 9, 4591.





**Scheme II-13:** Regioselective hetero-capping on the primary rim of  $\beta$ -cyclodextrin

Bols and co-workers<sup>90</sup> proposed another method for differentiation of positions 6A and 6D that could be realized through regioselective opening of a symmetrical sulfonate bridge. The reaction was implemented on  $\alpha$ - and  $\beta$ -cyclodextrins, which bear two hydroxyl groups on the positions 6A and 6D with the remaining positions being protected by benzyl ethers. By treatment with thionyl chloride, the two free hydroxyls reacted to form a sulfite bridge, which underwent the oxidation to give cyclodextrins **108a** and **108b** carrying a sulfate bridge. Then opening of bridge was executed on one side by a sodium azide nucleophilic attack, it is followed by the sulfate removal under acidic conditions, giving tridifferentiated  $\alpha$ - and  $\beta$ -cyclodextrins **109a** and **109b** in about 90% yields (Scheme II-14).



**Scheme II-14:** Selective opening of a cyclic sulfate bridge on cyclodextrins

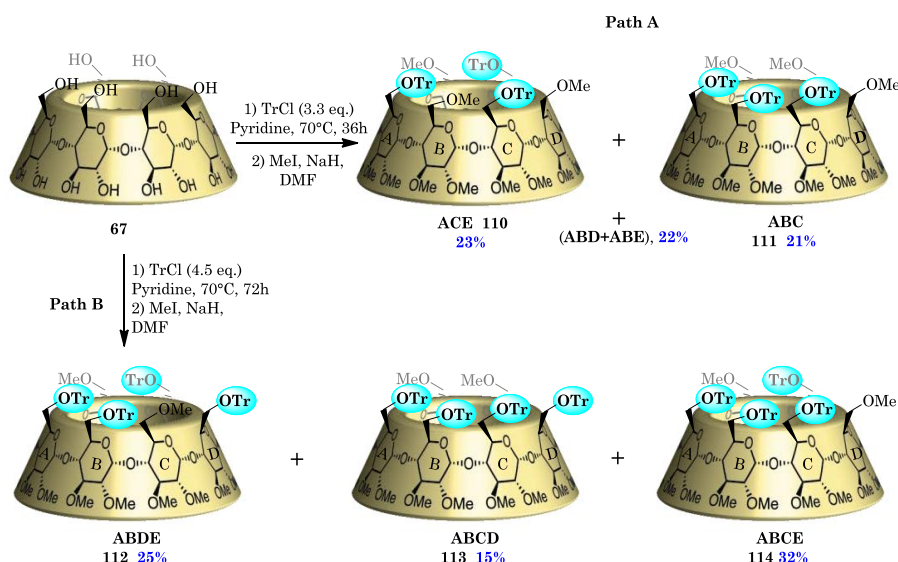
<sup>90</sup> M. Petrillo, L. Marinescu, C. Rousseau, M. Bols, *Org. Lett.*, **2009**, 11, 1983.

For  $\alpha$ -cyclodextrin **108a**, both positions 6A and 6D are equivalent, and the cyclic sulfate opened on one or the other side leads to the unique regioisomer **109a** with the azide nucleophilic attack on position 6D. As regards to  $\beta$ -cyclodextrin **108b**, the two positions 6A and 6D are unequivalent due to  $C_7$  symmetry. So opening of cyclic sulfate in **108b** gave two regioisomers in 87% yield. Some other nucleophiles such as ammonia, piperidine or sodium allylate, have been used displaying the same regioselectivity, even though lower yields are obtained.

### 3.1.3 Sterically crowded reagents

Using sterically hindered reagents, occasionally could yield unpredictable results in the multifunctionalization on the primary rim of cyclodextrins. So far, two kinds of sterically crowded reagents were exploited to functionalize cyclodextrins directly. One of them is trityl and their derivatives, and another is triphenylphosphine.

Native cyclodextrin **67** can be modified to multifunctionalized derivatives using trityl chloride in pyridine at 55°C. This method afforded 6A, 6C, 6E-cyclodextrin **110** selectively in 23% yield<sup>91</sup>. Through a longer reaction time (36 h) and higher temperature (70°C), a mixture of trifunctionalized cyclodextrins were obtained. Methylation of the remaining hydroxyls, flash chromatography then gave ACE-isomer **110** (23%), ABC-isomer **111** (21%), and a mixture (22%) of ABD- and ABE-isomers (**Path A**, Scheme II-15)<sup>92</sup>. When more trityl chloride (4.5 eq.) was added and stirred for 72 h, three possible tetrasubstituted products ABDE (25%), ABCD (15%) and ABCE (32%) were generated (**Path B**, Scheme II-15).

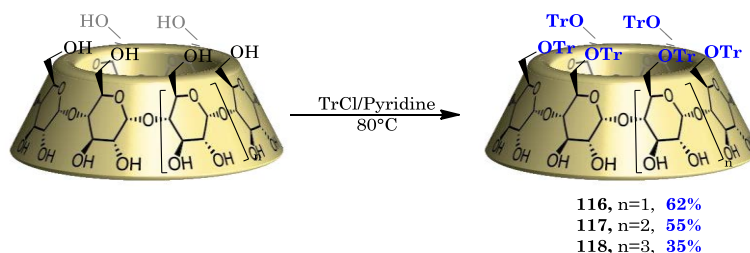


**Scheme II-15:** Direct tri- or tetrafunctionalization on the primary rim of  $\alpha$ -cyclodextrin

<sup>91</sup> J. Boger, D. G. Brenner, J. R. Knowles, *J. Am. Chem. Soc.*, **1979**, 101, 7630.

<sup>92</sup> C.-C. Ling, A. W. Coleman, M. Miocque, *Carbohydr. Res.*, **1992**, 223, 287.

Because of the large physical dimension of the trityl group, per-6-*O*-tritylation on the primary rim of cyclodextrins seems to be difficult. Ling and co-workers<sup>93</sup> reached this kind of products under harsh conditions. Native cyclodextrins were firstly reacted with 6 equivalents of trityl chloride at 80°C for 24 h, and during the subsequent 5 days, an additional 1 eq. of the reagent was added each day, i.e. total 11 eq. of trityl chloride. After purification, per-6-*O*-tritylated  $\alpha$ -,  $\beta$ - and  $\gamma$ -cyclodextrins **116**, **117** and **118** were afforded in 62%, 55% and 35% yields, respectively (Scheme II-16).



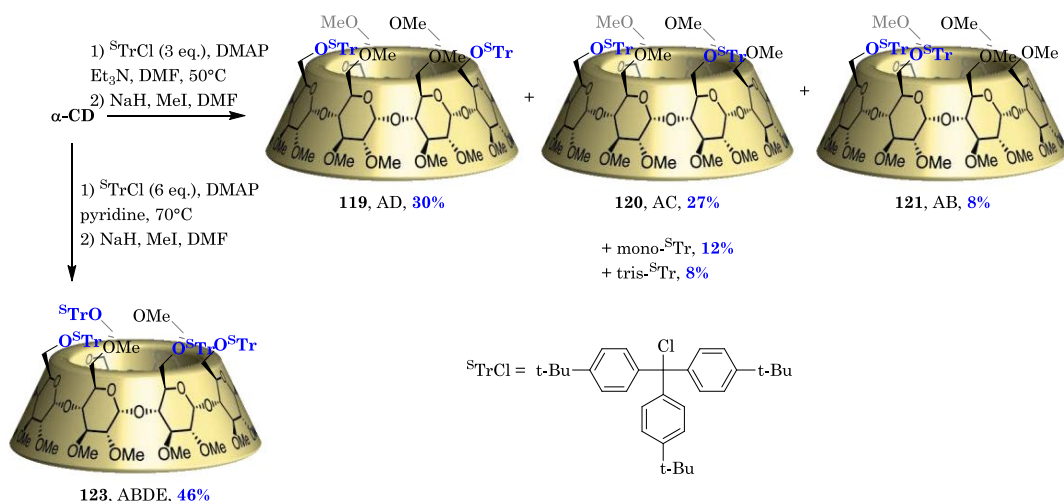
**Scheme II-16:** Pertritylation on the primary rim of cyclodextrins

Normally the tri- or tetrafunctionalized cyclodextrins were formed when trityl groups were exploited. For the sake of difunctionalization of the primary rim of cyclodextrin, another bulkier group remains desirable. Gratifyingly, Matt and Armspach showed that tris-(4-*tert*-butylphenyl)methyl (super-trityl) proved to be successful in the synthesis of new patterns of functionalization<sup>94</sup>. Super-trityl (3 eq.) was employed to react with  $\alpha$ -cyclodextrin **67** in DMF to give different difunctionalized regioisomers. After permethylation, purification by chromatography gave AD-isomer **119** (30%), AC-isomer **120** (27%), AB-isomer **121** (8%), as well as small amounts of trisubstituted (8%) and monosubstituted (12%) species (Scheme II-17). Through the enhancement of the temperature and of the amount of the reagent, the tetrafunctionalized pattern **123** was also reached in 46% yield<sup>95</sup>.

<sup>93</sup> P. Zhang, A. Wang, L. Cui, C. C. Ling, *Org. Lett.*, **2012**, 6, 1612.

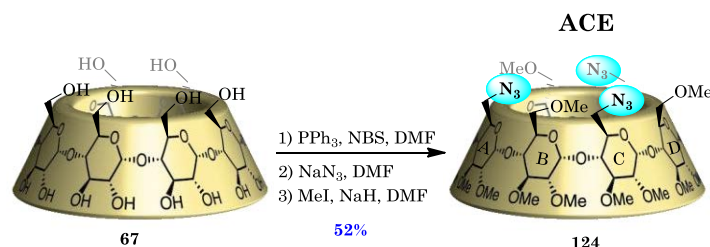
<sup>94</sup> D. Armspach, D. Matt, *Carbohydr. Res.*, **1998**, 310, 129.

<sup>95</sup> L. Poorters, D. Armspach, D. Matt, *Eur. J. Org. Chem.*, **2003**, 1377.



**Scheme II-17:** Direct difunctionalization of the primary rim of  $\alpha$ -cyclodextrin by super-trityl

Triphenylphosphine mediated Mitsunobu reaction has been applied in the perhalogenation of the primary rim of cyclodextrins (Scheme II-4). To be selective, optimizing the reaction conditions led to a trifunctionalized cyclodextrin on positions 6A, 6C, 6E (Scheme II-18)<sup>96</sup>. Native cyclodextrin was treated with triphenylphosphine and *N*-bromosuccinimide in DMF, giving ACE-tribromo-cyclodextrin. It was followed by one-pot azidation and permethylation, the final product **124** was obtained after extraction of the solid residue by ether and a simple crystallization in acetonitrile.



**Scheme II-18:** Triphenylphosphine mediated ACE trifunctionalization of the primary rim of  $\alpha$ -cyclodextrin

### 3.2 DIBAL-H-mediated selective functionalization

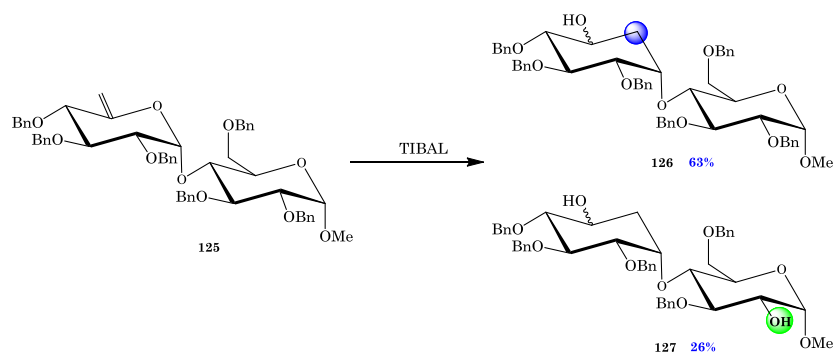
As we have mentioned before, much more progress has been made in recent years for the functionalization of the primary rim of cyclodextrins. Those methods are mainly based on the reactivity of hydroxyls, capping reagents or the steric crowding reagents. Nevertheless, time-consuming chromatographical isolation is needed with relatively poor yield and regioselectivity. To overcome these limitations, a method of higher efficiency remains greatly desirable. One possibility is to work on protected cyclodextrins, which, on the one hand, could be modified selectively and on the other hand could be removed readily. The regioselective

<sup>96</sup> R. Heck, L. Jicsinszky, A. Marsura, *Tetrahedron Lett.*, **2003**, 44, 5411.

de-*O*-benzylation of polybenzylated sugars by aluminum reagents meet these criterions. Using this method, polydifferentiated cyclodextrins have been already accessed. In the following of this chapter, a detailed introduction on this method and its applications for polydifferentiations of cyclodextrins will be presented.

### 3.2.1 The discovery and mechanistic study of the selective debenzylation method

Aluminum reagents are not conventional reagents for de-*O*-benzylation reactions. However, it was found serendipitously in our laboratory during the course of tributylaluminum (TIBAL)-mediated rearrangement, which induced the conversion of sugars into carbasugars by means of [1,3]-oxygen-to-carbon rearrangement<sup>97</sup> (Scheme II-19). After treating disaccharide **125** with TIBAL, in addition to the rearrangement product **126**, another product **127** (debenzylated product) was also generated<sup>98</sup>.



**Scheme II-19:** Discovery of the debenzylation reaction

This finding became a useful method for sugar chemistry. After optimization, diisobutylaluminum hydride (DIBAL-H) was chosen to react with perbenzylated  $\alpha$ - and  $\beta$ -cyclodextrins **128** and **129**, generating the corresponding diols<sup>99,100</sup> **107a** and **107b** regioselectively with excellent yields of about 80% (Scheme II-20). Interestingly, it is also possible to obtain monol-cyclodextrin **130** and **131** with good yields by controlling carefully the reaction conditions, either by using dilute conditions or by reducing reaction time<sup>100</sup>. The monol can also be converted into diol under the action of DIBAL-H, indicating that the reaction proceeded in a stepwise manner. It is reported that these reactions can be accelerated under the help of micro-wave with less equivalent of DIBAL-H and short reaction time.<sup>101</sup>

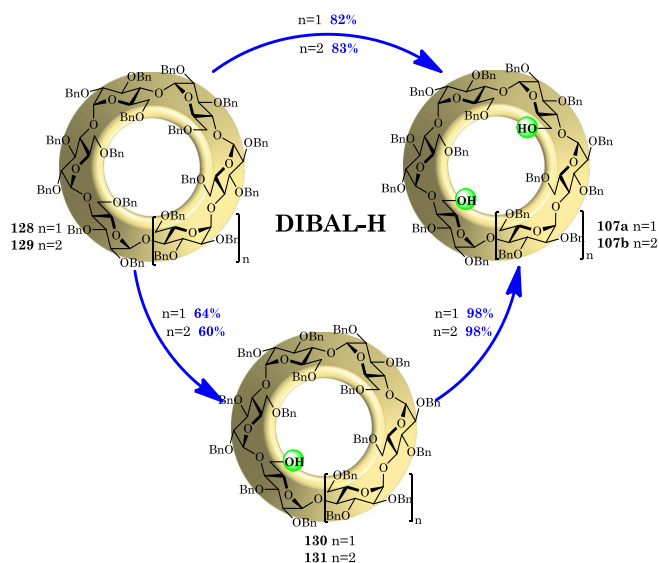
<sup>97</sup> C. G. Nasveschuk, T. Rovis, *Org. Biomol. Chem.*, **2008**, 6, 240.

<sup>98</sup> A. J. Pearce, M. Sollogoub, J. Mallet, P. Sinaÿ *Eur. J. Org. Chem.*, **1999**, 2103.

<sup>99</sup> A. J. Pearce, P. Sinaÿ *Angew. Chem. Int. Ed.*, **2000**, 39, 3610.

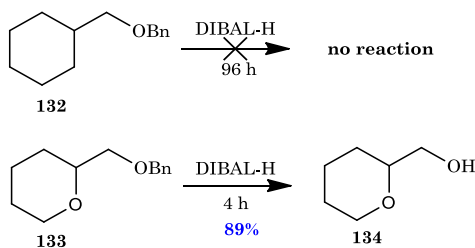
<sup>100</sup> T. Lecourt, A. Herault, A. J. Pearce, M. Sollogoub, P. Sinaÿ *Chem. Eur. J.*, **2004**, 10, 2960.

<sup>101</sup> E. zaborova, Y. Bleriot, M. Sollogoub, *Tetrahedron Lett.*, **2010**, 51, 1254.



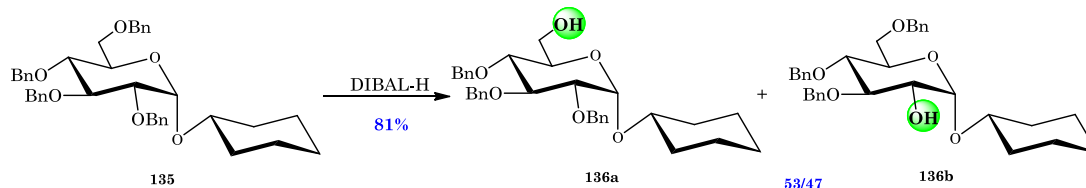
**Scheme II-20:** Regioselective debenzoylation of perbenzoylated  $\alpha/\beta$ -cyclodextrin by DIBAL-H

Since a number of encouraging results have been obtained, the following work was to clarify the mechanism of this reaction. Hence, different substrates were submitted to the action of DIBAL-H, among which, an alkyl ether **132** did not give the corresponding debenzoylated product even after 4 days. In sharp contrast, benzyl group was removed favorably from a furan ether **133** with an excellent yield in 4 h (Scheme II-21). In view of these preliminary results, it was assumed that, a second oxygen on the molecular fragment is important to chelate the aluminum atom.



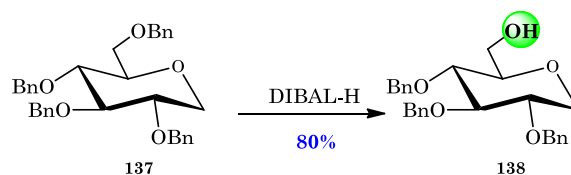
**Scheme II-21:** Deprotection of alkyl ether by DIBAL-H

Another two examples were studied to give an insight into the mechanism. In the case of carbohydrate derivative, substrate **135** afforded debenzoylated product **136a** and **136b** under the action of DIBAL-H. This result was explained by the chelation of aluminum species between the position 6 oxygen and the endocyclic oxygen, or the chelation between position 2 oxygen and the anomeric oxygen (Scheme II-22).



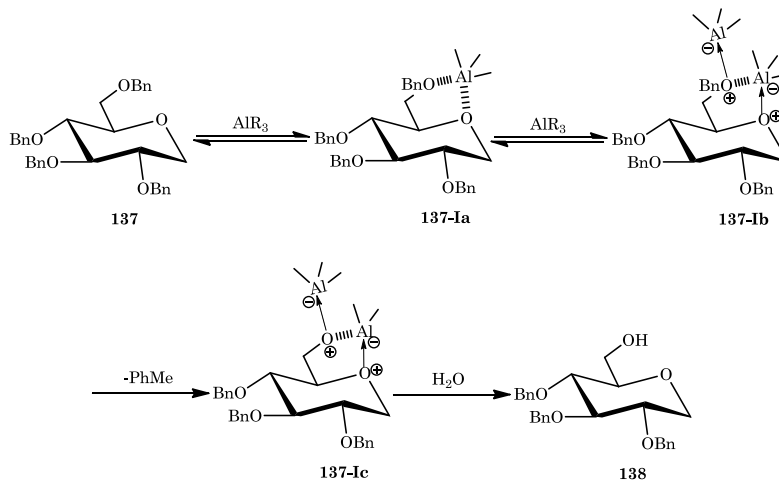
**Scheme II-22:** Deprotection on sugar derivative by DIBAL-H

In the case of sugar **137**, a compound missing anomeric oxygen, the only site available for aluminum chelation resides between endocyclic oxygen and oxygen on position 6, consequently, only product **138** is obtained selectively (Scheme II-23).



**Scheme II-23:** DIBAL-H deprotection on 1-deoxy sugar

On account of the above systematic study, it was concluded that the two oxygens chelating the aluminum derivative were necessary. Here a reasonable mechanism was proposed considering the case of 1-deoxy sugar **137** (Scheme II-24).

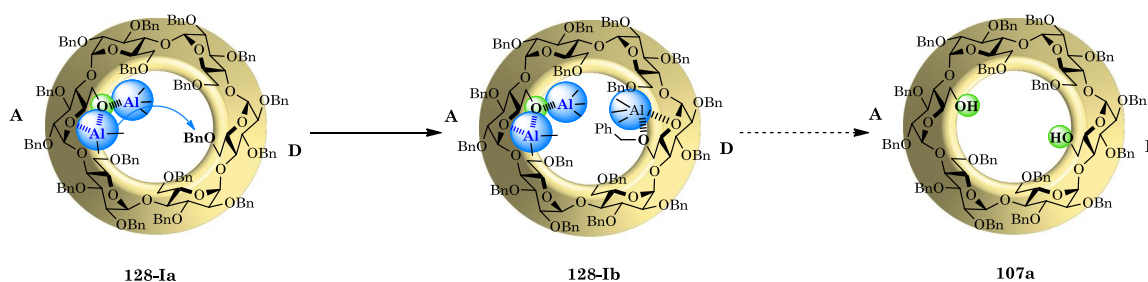


**Scheme II-24:** Mechanism of DIBAL-H induced debenzilylation on sugar

During the course of the debenzilylation reaction, it was proposed that at least two molecules of DIBAL-H were involved. The first aluminum reagent was chelated between the two oxygens of sugar **137** to give the cyclic complex **137-Ia**. Then complex **137-Ib** was formed by a second aluminum coordination to the less hindered oxygen (oxygen on the position 6). The two aluminum derivatives, one as Lewis acid, which activated the C-O bond of the benzyl ether, and the other played a role in the hydride transfer for the dealkylation to give the complex **137-Ic**. The following hydrolysis afforded the selective mono-debenzylated product **138**.

In the case of perbenzylated  $\alpha$ -cyclodextrin **128**, DIBAL-H-mediated debenzilylation only

happened on the primary rim because of the surrounding congestion on the secondary rim. The mechanism is the same as the one proposed for the monosaccharide (Scheme II-24). Once the first debenzoylation took place on sugar unit **A**, the following second debenzoylation occurred on sugar **D**, diametrically opposed position to sugar **A**. This regioselective debenzoylation is rationalized by the steric crowding created by the formed aluminum complexes **128-1a** (Scheme II-25).

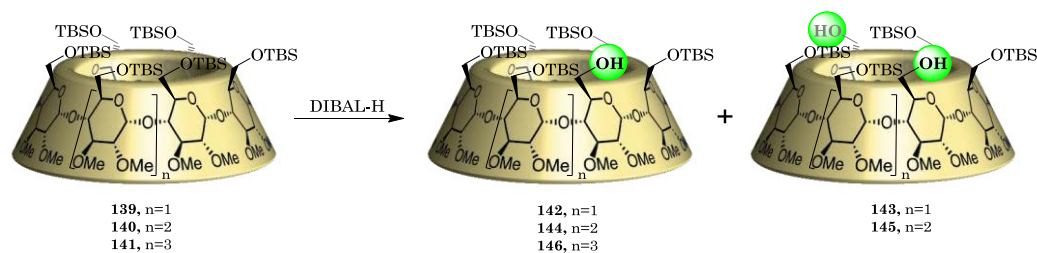


**Scheme II-25:** Mechanism of DIBAL-H on perbenzylated cyclodextrin



**DIBAL-H applied to persilylated primary rim of cyclodextrins**

Recently, Ling and co-workers carried out a series of research concerning persilylated primary rim of cyclodextrins. As demonstrated in the case of perbenzylated cyclodextrins, when cyclodextrins bearing tert-butyldimethylsilyl ether on the primary rim, were submitted to the action of DIBAL-H, de-*O*-silylation proceeded selectively to give the 6A, 6D-dihydroxyl cyclodextrins (Scheme II-26, Table II-3)<sup>102</sup>. Due to the big size and flexibility of  $\gamma$ -cyclodextrin, a mixture of inseparable regioisomers were yielded.



**Scheme II-26:** DIBAL-H mediated de-*O*-silylation on the primary rim of cyclodextrins

Entry	Substrate	Condition	Yield (%) <sup>a</sup>				
			142	143	144	145	146
1	$\alpha$ -CD 139	3.5 eq., 0.10 M, 0°C, 3h	71	16	-	-	-
2	$\alpha$ -CD 139	7.0 eq., 0.30 M, 0°C, 4h	10	68	-	-	-
3	$\beta$ -CD 140	3.0 eq., 0.15 M, 0°C, 3h	-	-	62	22	-
4	$\beta$ -CD 140	6.0 eq., 0.30 M, 0°C, 4h	-	-	12	71	-
5	$\gamma$ -CD 141	3.0 eq., 0.10 M, 0°C, 4h	-	-	-	-	58 <sup>b</sup>
6	$\gamma$ -CD 141	6.0 eq., 0.10 M, 0°C, 4h	-	-	-	-	16 <sup>b</sup>

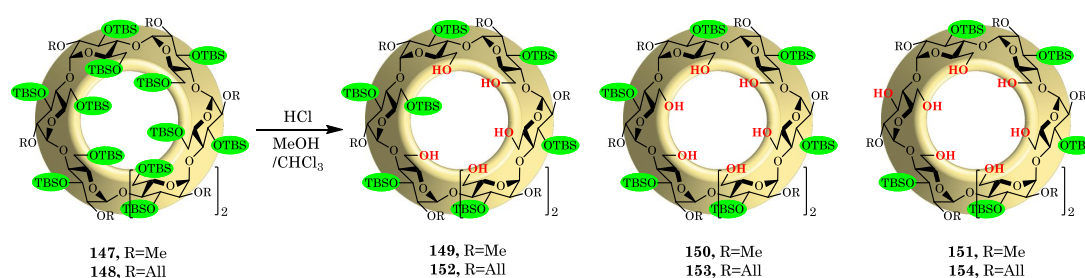
**Table II-3:** DIBAL-H mediated de-*O*-silylation

(a) Yield of isolated product. (b) The reaction also afforded a mixture of inseparable di-desilylated compounds (26% for entry 5 and 53% for entry 6)

<sup>102</sup> R. Ghosh, P., Zhang, A. Wang, C. C. Ling, *Angew. Chem. Int. Ed.*, **2012**, 51, 1548.

**Acid-mediated regioselective desilylation of cyclodextrins**

Besides the de-*O*-silylation mediated by the action of DIBAL-H, very recently Ling and co-workers proposed another new method of acid-mediated regioselective de-*O*-silylation for multifunctionalization of cyclodextrins<sup>103</sup>. Based on the acid-sensitivity of the *O*-silyl group, HCl solution with various pH values (pH 2-3) were used to operate selective removal of silyl groups from cyclodextrins, not only on the primary rim, but also on the secondary rim, giving tri- and tetrafunctionalized cyclodextrins in a short reaction sequence (Table II-4, Scheme II-27). Most importantly, the developed method has been found applicable to all  $\alpha$ -,  $\beta$ - and  $\gamma$ -cyclodextrins on multigram scales.



**Scheme II-27:** Controlled acid-mediated regioselective de-*O*-silylation of cyclodextrins

Entry	Substrate	Condition	Yield (%)					
			149	150	151	152	153	154
1	$\beta$ -CD 147	pH=2-3, 3h	13	44	-	-	-	-
2	$\beta$ -CD 147	pH=2-3, 18h	-	37	32	-	-	-
3	$\beta$ -CD 148	pH=2-3, 3h	-	-	-	11	58	-
4	$\beta$ -CD 148	pH=2-3, 18h	-	-	-	-	40	30

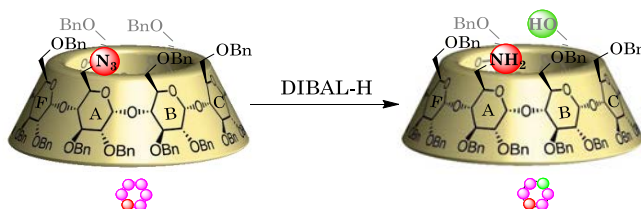
**Table II-4:** Controlled acid-mediated de-*O*-silylation of cyclodextrins

<sup>103</sup> J. M. Gu, T. Chen, P. Zhang, C. C. Ling, *Eur. J. Org. Chem.*, 2014, 5793.

### 3.2.2 DIBAL-H-mediated debenzoylation method applied on cyclodextrins to access polydifferentiated cyclodextrins

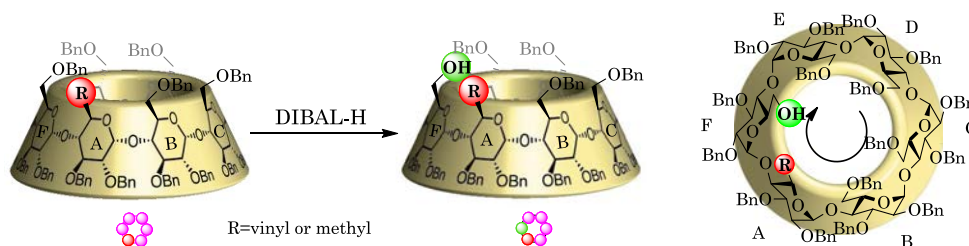
Since the debenzoylation method by DIBAL-H on cyclodextrins was developed, a large number of differentiated cyclodextrin motifs have been obtained. Some of them have been used in varied fields, such as organic catalysis, supramolecular chemistry and artificial enzymes. To sum up all the obtained results, four principal site-directing rules were disclosed by our group:

- a. Tandem azide-reduction/debenzoylation** (Scheme II-28), that means an azido group, existed on the primary rim of cyclodextrin directs the diametrically opposed debenzoylation reaction selectively to give the amino-alcohol cyclodextrin motif<sup>104</sup>.



**Scheme II-28:** Tandem azide-reduction/debenzoylation of monoazido-cyclodextrin

- b. Steric decompression effect** (Scheme II-29), that facilitates the debenzoylation reaction only on the clockwise adjacent position (viewed from the primary rim), when less crowded groups (vinyl or methyl) which are inert to the action of DIBAL-H, are grafted onto the primary rim of cyclodextrins<sup>105</sup>.



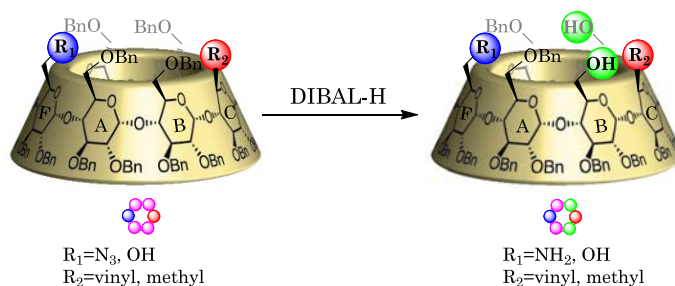
**Scheme II-29:** steric decompression effect

- c. “Frustration strategy”** (Scheme II-30) is a method which combines strategies **a** and **b**, giving tetradifferentiated cyclodextrins in a short reaction sequence. By substituting benzyl group on the diametrically opposed position with a deoxy or a vinyl function, the directing effect of a hydroxyl or an azido group was depressed to give rise to a double-debenzoylation on

<sup>104</sup> S. Guieu, M. Sollogoub, *Angew. Chem. Int. Ed.*, **2008**, 47, 7060.

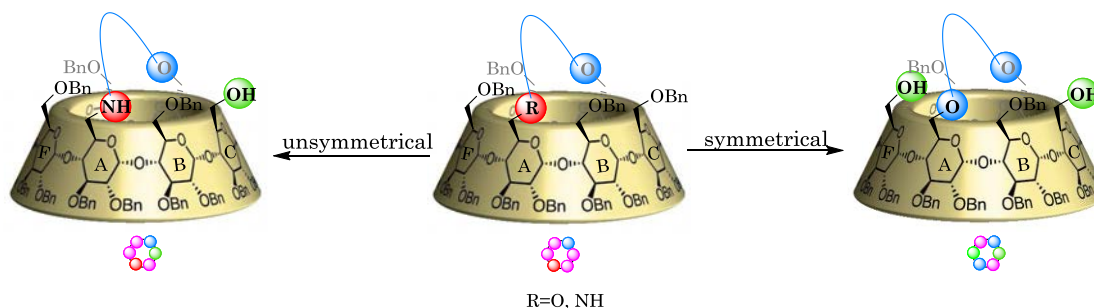
<sup>105</sup> S. Guieu, M. Sollogoub, *J. Org. Chem.*, **2008**, 73, 2819.

both the sterically decompressed sides<sup>106</sup>.



**Scheme II-30:** “Frustration” strategy induced double-deprotection

**d. Bridging strategy** (Scheme II-31) comprises symmetrical bridge and unsymmetrical bridge. The bridges are formed either via ring-closing metathesis, or by direct alkylation under basic conditions. For an ether protected symmetrical bridged cyclodextrin, DIBAL-H debenzylation processed in a double-deprotection manner, releasing two free alcohols on both clockwise adjacent positions of the bridging ether. This kind of phenomenon can also be deemed as steric decompression. In contrast to the symmetrical bridge, a tetradifferentiated cyclodextrin pattern was afforded when an unsymmetrical bridged cyclodextrin bearing a secondary amine and an ether on the diametrically opposed positions, underwent the action of DIBAL-H. This outcome was ascribed to the complexation of the secondary amine with aluminum reagents<sup>107</sup>.



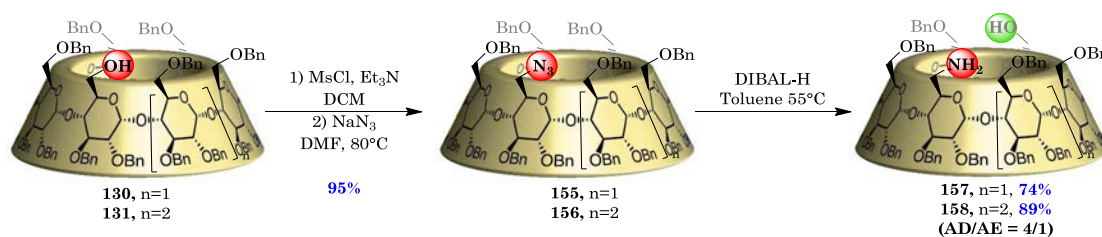
**Scheme II-31:** Symmetrical/unsymmetrical bridges induced debenzylation

<sup>106</sup> E. Zaborova, M. Guitet, G. Prencipe, Y. Bleriot, M. Menand, M. Sollogoub, *Angew. Chem. Int. Ed.*, **2013**, 52, 639.

<sup>107</sup> (a) E. Zaborova, Polydifférenciation sélective des cyclodextrines: Illustration de leur pseudo-chiralité intrinsèque, synthèse de nouveaux motifs et de catalyseurs, *Thèse de Doctorat de l'Université Pierre et Marie Curie*, **2010**; (b) B. Wang, E. Zaborova, S. Guieu, M. Petrillo, M. Guitet, Y. Blériot, M. Ménand, Y. Zhang, M. Sollogoub, *Nat. Commun.*, **2014**, 5, 5354, doi: 10.1038/ncomms6354.

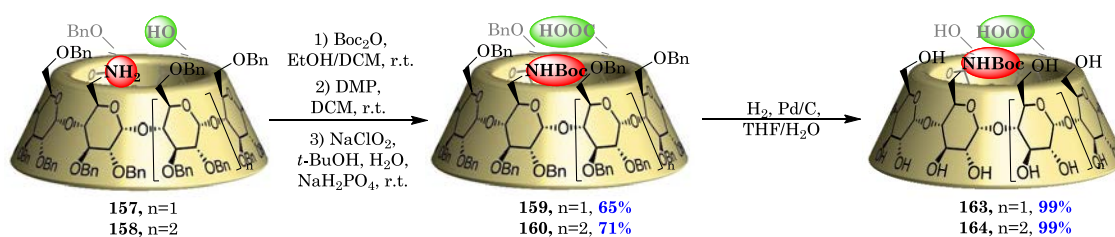
**Tandem azide-reduction/debenzylation**

The selective introduction of two different functions on diametrically opposed positions of cyclodextrins in a straight way with high yield was always a problem. Thanks to the highly regioselective DIBAL-H-mediated debenylation method, diol-cyclodextrins were obtained with excellent yields in a stepwise manner (Scheme II-25). By means of conventional procedures, monoazido-cyclodextrins **155** and **156** were synthesized with ease from monol-cyclodextrins **130** and **131** in high yields. When  $\alpha$ -cyclodextrin **155** was submitted to the action of DIBAL-H, a unique regioisomer **157** was afforded in 74% yield with amino and hydroxyl groups on diametrically opposed positions<sup>104</sup> (Scheme II-32). The regioselectivity was attributed to the steric hindrance caused by the complexation of aluminum reagent to the nitrogen in the course of azide reduction. Being a little different with the case of  $\alpha$ -cyclodextrin, DIBAL-H reacted with  $\beta$ -cyclodextrin **156** under the same conditions, giving a mixture of AD, AE isomers (ratio 4:1) in 89% yield because of its asymmetry.



**Scheme II-32:** Tandem azide-reduction/debenzylation on  $\alpha/\beta$ -cyclodextrins

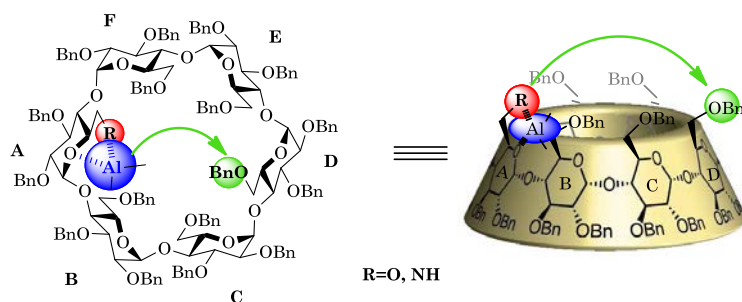
This tandem azide reduction/debenzylation strategy paved the way to multifunctionalization of cyclodextrins and regioselective synthesis of NH-Boc-protected amino acids derived from cyclodextrins. The amine on cyclodextrin was protected by a Boc group, it was followed by the alcohol oxidation and palladium-mediated hydrogenolysis of benzyl groups to give the cyclodextrin-derived amino acids (Scheme II-33).



**Scheme II-33:** Synthesis of cyclodextrin-derived amino acids

DIBAL-H mediated de-*O*-benzylation reactions are controlled by steric hindrance, which is caused either by deprotonation of alcohol, or by reduction of azide forming a hindered aluminum adduct. In these two cases, the debenylation reactions took place on the farthest

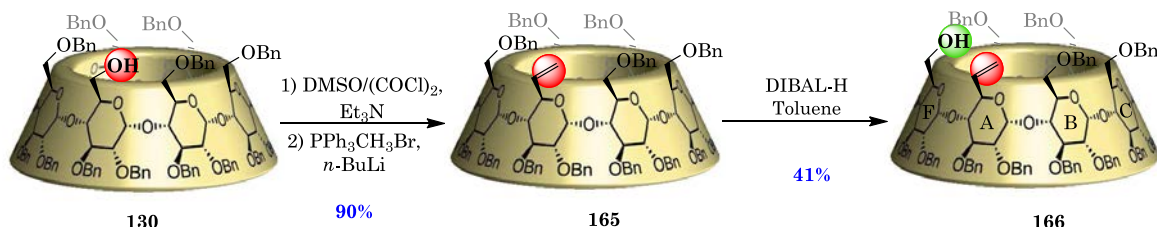
position to the previously existing functions (OH or N<sub>3</sub>) (Figure II-7).



**Figure II-7:** Steric hindrance orients the farthest debenzoylation

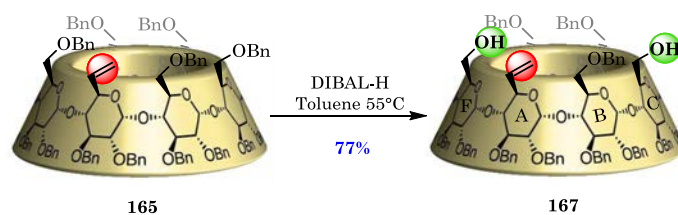
### Steric decompression effect

In contrast to hydroxyl or azido, there are some other functions such as vinyl and methyl, which have smaller steric hindrance and are immune to the action of DIBAL-H. In those cases, the previously existing functions directed the DIBAL-H debenzoylation reactions on the clockwise adjacent positions by virtue of steric decompression. As shown in Scheme II-34, alkene cyclodextrin **165** was prepared from monol-cyclodextrin **130** in 90% yield by Swern oxidation and followed Wittig reaction. Then the formed cyclodextrin **165** underwent the action of DIBAL-H, affording a unique mono-debenzoylated isomer **166** in moderate yield, with a free alcohol released on sugar unit **F**, clockwise adjacent position to sugar unit **A**<sup>105</sup>.



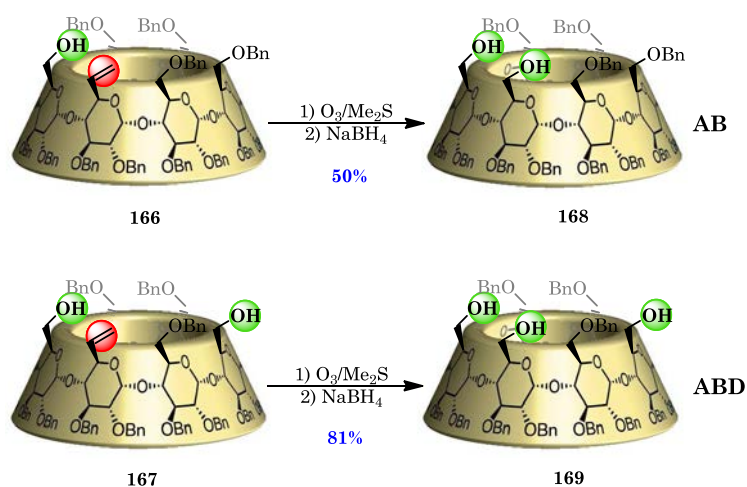
**Scheme II-34:** Regioselective mono-debenzoylation of vinyl- $\alpha$ -cyclodextrin

Diol-cyclodextrin **167** can also be obtained under stronger conditions. Much longer reaction time, higher concentration and equivalents of DIBAL-H were adopted (Scheme II-35). Concerning this reaction, it proceeded also in a stepwise manner as in the case of the formation of diol-cyclodextrin **107b** (Scheme II-20). The first debenzoylation gave a sterically hindered aluminum derivative, which forced the removal of one more benzyl group on the farthest position.



**Scheme II-35:** Regioselective di-debenzylation of vinyl- $\alpha$ -cyclodextrin

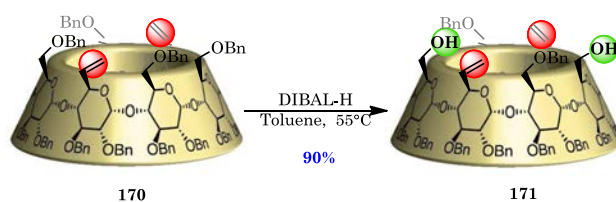
The vinyl groups on cyclodextrin **166** and **167** were then converted into free alcohols by reductive ozonolysis giving AB-diol **168** and ABD-triol **169** in 50% and 81% yields, respectively (Scheme II-36).



**Scheme II-36:** Deprotection of monovinyl- $\alpha$ -cyclodextrins

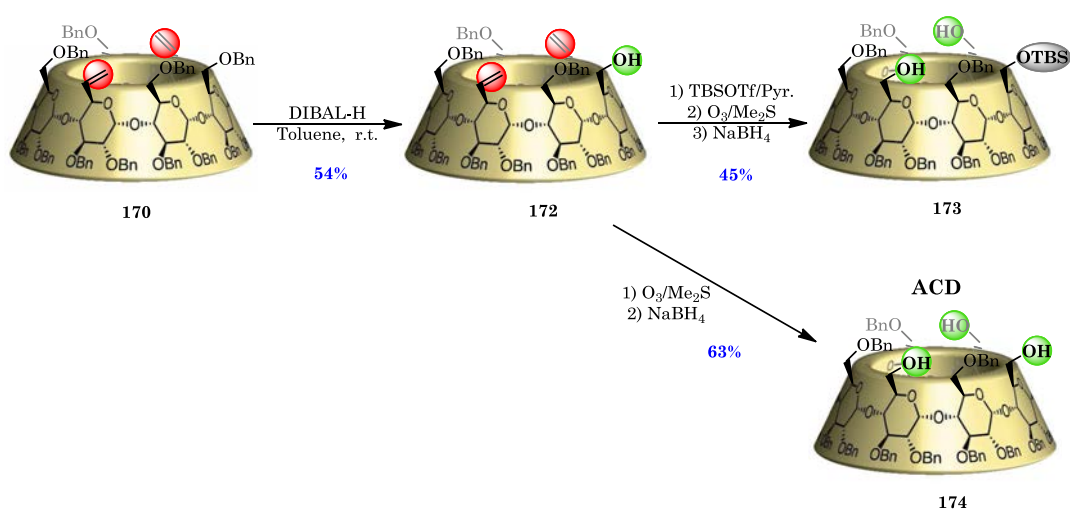
In the case of monovinyl cyclodextrin **165** (Scheme II-35), the steric decompression effect mediated the debenzylation following the clockwise orientation. When a  $C_2$ -symmetrical cyclodextrin derivative with two sterically decompressed vinyl functions, was submitted to the action of DIBAL-H, a double-deprotection derivative might be obtained. Based on this deduction, a divinyl-cyclodextrin **170** was prepared using the same procedures as in the case of monovinyl-cyclodextrin **165**. Then DIBAL-H reaction under the usual conditions gave a sole regioisomer **171** (Scheme II-37), bearing two free alcohols on the clockwise adjacent positions to the existing vinyl functions in excellent yield<sup>108</sup>.

<sup>108</sup> O. Bistri, P. Sinaÿ, J. Jiménez-Barbero, M. Sollogoub, *Chem. Eur. J.*, **2007**, 13, 9757.



**Scheme II-37:** Regioselective di-debenzylation of divinyl- $\alpha$ -cyclodextrin

After optimizing the reaction conditions by reducing DIBAL-H concentration and the reaction temperature, mono-debenzylated cyclodextrin **172** was obtained as a major product. More precisely, using 0.1 M of DIBAL-H and reacting at room temperature, cyclodextrin **172** was afforded in 54% yield with a free alcohol on its primary rim (Scheme II-38). The regioselectivity of the mono-debenzylation was in favor of the sterically decompressed position, consistent with the case of di-debenzylation (Scheme II-37). Then protection of the free alcohol by a silyl group and reduction ozonolysis of alkenes, a tridifferentiated cyclodextrin **173** was synthesized in 45% yield. Alternatively, the direct regeneration of hydroxyls of cyclodextrin **172** gave another triol-cyclodextrin isomer **174** with three alcohols on sugar units **A**, **C**, **D** in 63% yield.

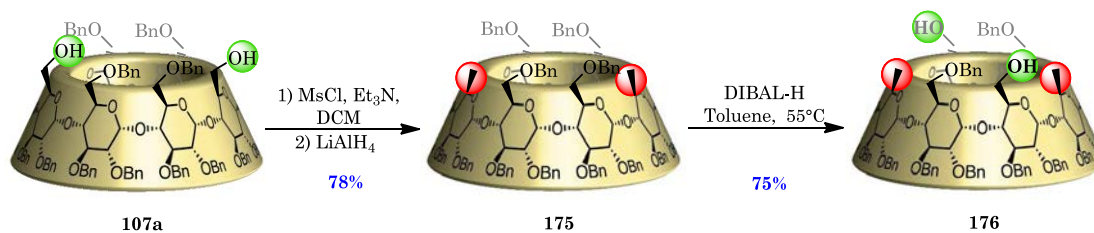


**Scheme II-38:** Regioselective mono-debenzylation of  $\alpha$ -cyclodextrin

Likewise, dideoxy-cyclodextrin **175** also possesses a similar property, which can induce a double-deprotection (Scheme II-39). Cyclodextrin **175** was prepared through mesylation and subsequent reduction in 78% yield. Upon reaction with DIBAL-H, diol-cyclodextrin **176** was given in 75% yield<sup>109</sup>. In this case, the only drawback was the difficulty for the further functionalization of the methyl groups.

<sup>109</sup> O. Bistri, P. Sinaÿ, M. Sollogoub, *Tetrahedron Lett.*, **2005**, 46, 7757.

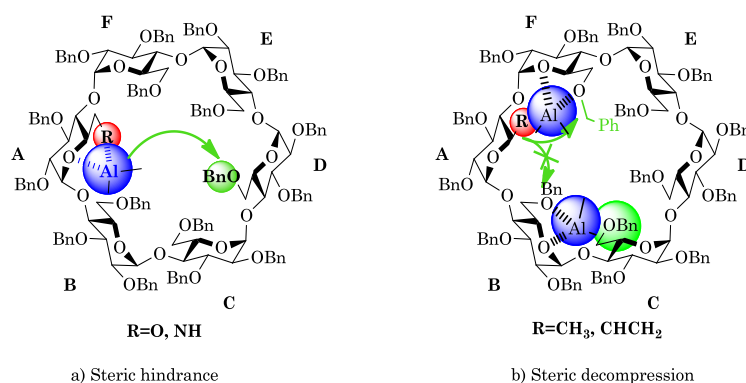




**Scheme II-39:** Regioselective di-debenzylation of dideoxy- $\alpha$ -cyclodextrin

### “Frustration” strategy

Cyclodextrin derivatives bearing a hydroxyl or an azido group, facilitated the de-*O*-benzylation on the diametrically opposed positions because of steric hindrance (a, Figure II-8); in sharp contrast, vinyl- or deoxy-cyclodextrins were inclined to form cyclodextrin derivatives with free alcohols on the clockwise adjacent sugar units taking advantage of steric decompression effect (b, Figure II-8).



**Figure II-8:** Two site-directing rules for a second deprotection

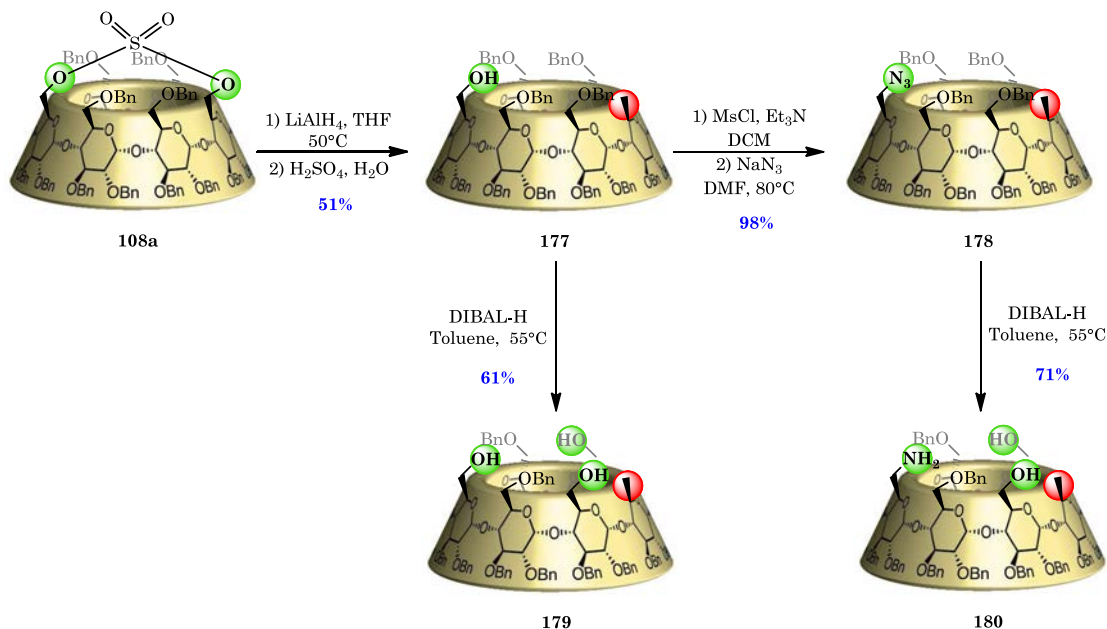
Given that, if the benzyloxy group on the diametrically opposed positions of a hydroxyl or an azido was replaced by a deoxy or a vinyl group, which frustrates the normal debenzylation, presumably should orient the deprotection on the clockwise units to give a tetradifferentiated pattern.

Sulfate-bridged cyclodextrin **108a** was prepared using Bol's method<sup>110</sup>. After opening the sulfate bridge with lithium aluminum hydride and the subsequent hydrolysis, deoxy-cyclodextrin **177** was synthesized in 51% yield bearing a deoxy and a hydroxyl groups on the diametrically opposed positions. The alcohol on cyclodextrin **177** was converted into an azido group using conventional procedures to give cyclodextrin **178** in an excellent yield. When cyclodextrin **177** underwent the action of DIBAL-H (30 eq. 1 M), surprisingly, a tridifferentiated triol-cyclodextrin **179** was obtained, rather than the expected diol. Using

<sup>110</sup> M. Petrillo, L. Marinescu, C. Rousseau, M. Bols, *Org. Lett.*, **2009**, 11, 1983.

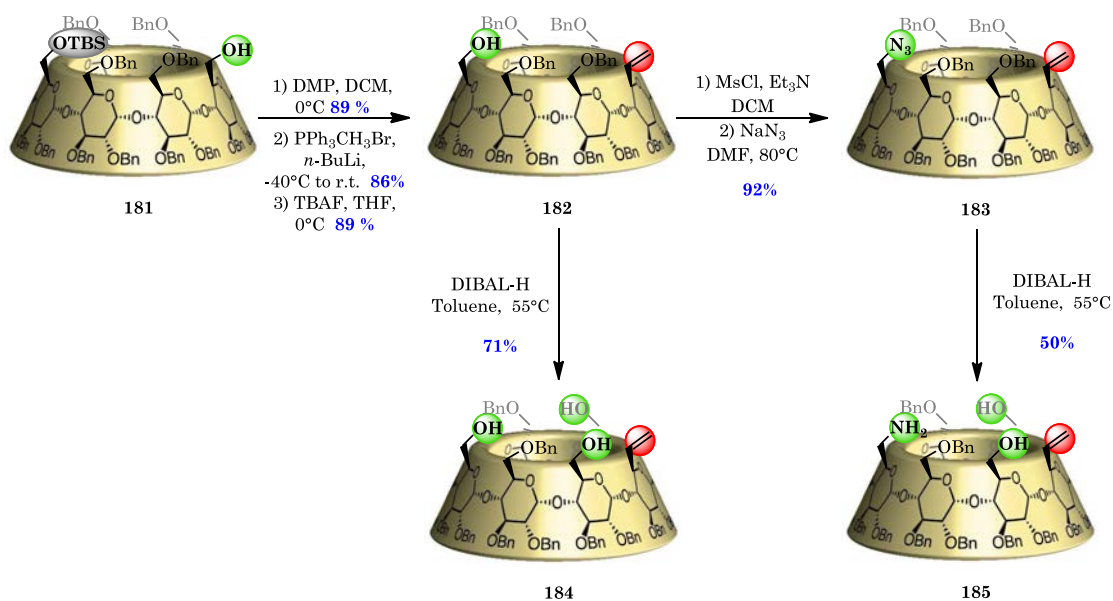
similar conditions, the reaction on cyclodextrin **178** gave a consistent result, with debenzoylation on both sides of the sterically decompressed position<sup>106</sup> (Scheme II-40).

An unambiguous NMR study and a kinetic study deciphered that both sides of the decompression site undergo the first mono-debenzoylation to give a mixture of monol-isomers. Then each isomer leads to the same final product.



**Scheme II-40:** Regioselective debenzoylation of monol/azido-deoxy- $\alpha$ -cyclodextrins

The same reaction sequence was also applied on vinyl-functionalized cyclodextrins **182** and **183**, without surprise, triol-cyclodextrin **184** and amino-diol-cyclodextrin **185** were afforded with yields of 71% and 50%, respectively (Scheme II-41).



**Scheme II-41:** Regioselective debenzoylation of monol/azido-vinyl- $\alpha$ -cyclodextrins

Therefore, this frustration strategy, combining two delineated deprotection methods could be used to access tridifferentiated cyclodextrins, and also can give new tetradifferentiated cyclodextrin motifs in a highly selective fashion.

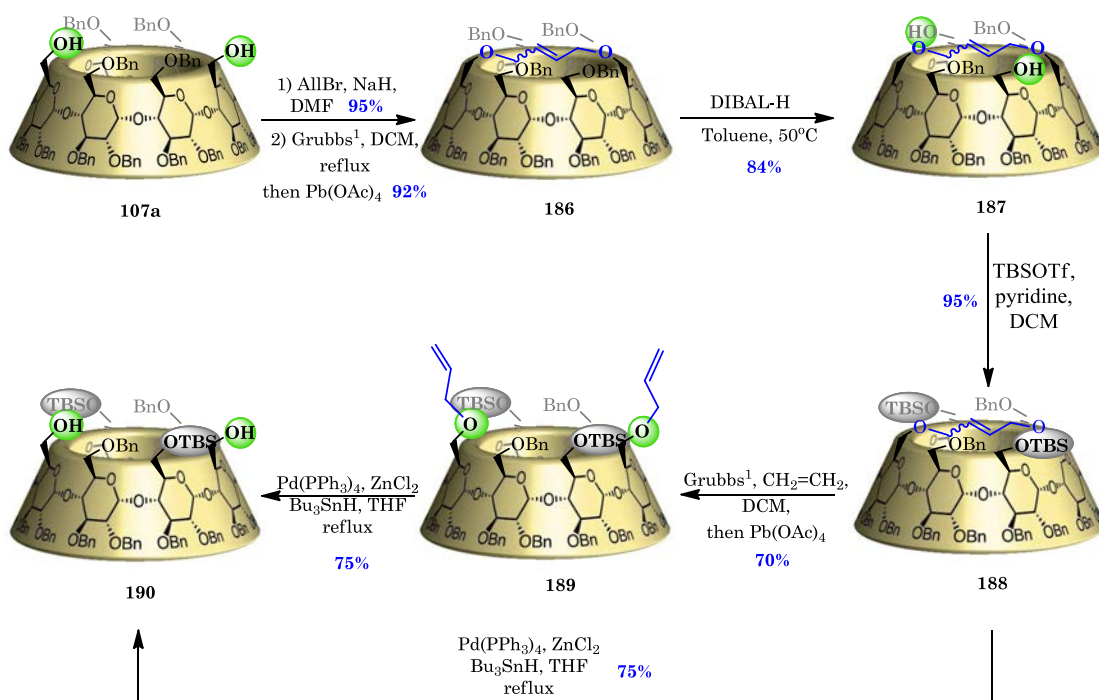
### **Bridging strategy**

The methods using capping reagents have been employed to get functionalized cyclodextrins, albeit normally through extensive chromatographical purification and with low yields. Based on DIBAL-H debenzylation, a new method of functionalization of cyclodextrins called “bridging strategy” was developed. Herein this strategy will be detailed in two parts, i.e. symmetrical bridge strategy and unsymmetrical bridge strategy.

The symmetrical bridge was synthesized from  $C_2$ -symmetrical diol- $\alpha$ -cyclodextrin **107a**, which was obtained by the in-house debenzylation. The two free alcohols were functionalized by allyl groups with allyl bromide in the presence of sodium hydride in 95% yield. Ring-closing metathesis gave bridged cyclodextrin **186** employing the Grubbs<sup>1</sup> catalyst with an excellent yield. DIBAL-H reacted with cyclodextrin **186** under usual conditions, giving a unique di-debenzylated cyclodextrin **187** in regioselective manner<sup>108,111</sup> (Scheme II-42), as in the case of divinyl or dideoxy cyclodextrins **170** and **175**. In this case, the clockwise adjacent deprotection can also be explained by steric decompression effect. The released diametrically opposed alcohols were then protected by TBS group, it was followed by a ring-opening metathesis to restore allyl groups in 70% yield. The allyl protected cyclodextrin **189** was submitted to the action of Pd<sup>0</sup> in the presence of zinc chloride and tributyltin hydride to afford tridifferentiated cyclodextrin **190** with three pairs of orthogonal functions, or performing the same method on cyclodextrin **188** gave cyclodextrin **190** in a single step. Because of the toxicity of tin derivative, triethylsilane was another alternative.

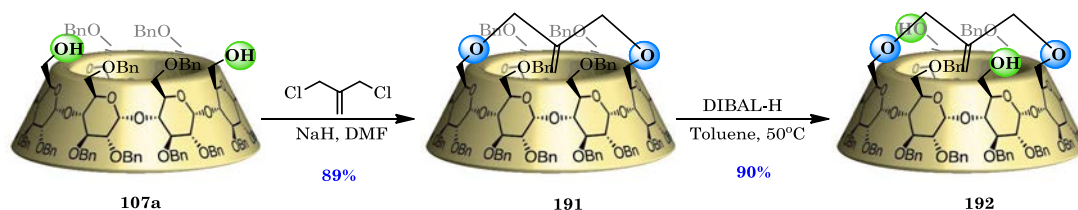
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<sup>111</sup> O. Bistri, P. Sinaÿ, M. Sollogoub, *Chem. Commun.*, **2006**, 1112.



**Scheme II-42:** Regioselective debenzoylation of metathesis bridged cyclodextrin

The bridged cyclodextrin can also be formed in a single step. Using 3-chloro-2-(chloromethyl) prop-1-ene in the presence of sodium hydride, methallyl bridged cyclodextrin **191** was reached in 89% yield<sup>112</sup>. The following DIBAL-H-mediated debenzoylation gave diol-cyclodextrin **192** in the clockwise manner<sup>113</sup> (Scheme II-43).

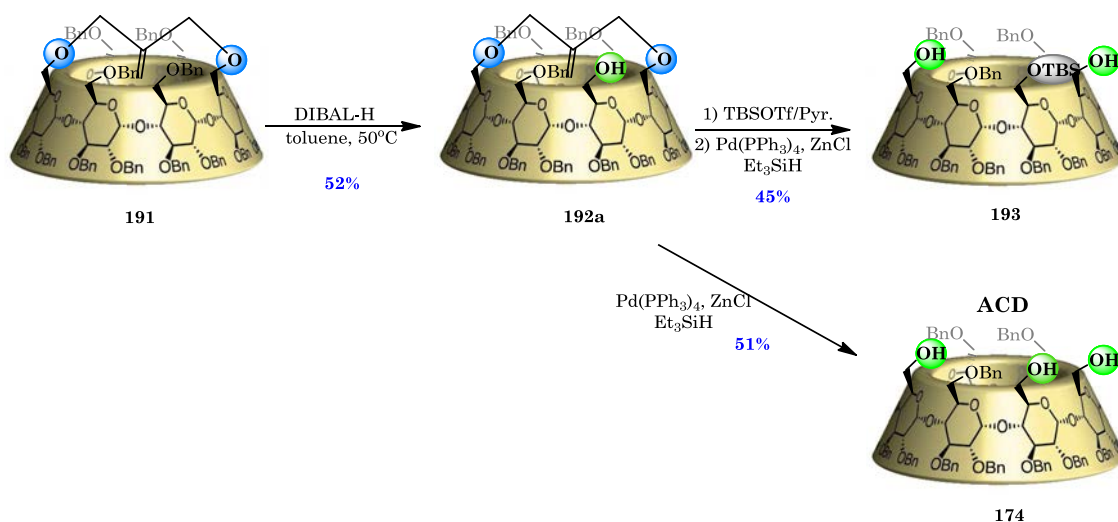


**Scheme II-43:** Regioselective di-debenzoylation of methallyl bridged cyclodextrin

Under milder conditions, the debenzoylation can be stopped at the monol stage, albeit at the cost of reducing the yield slightly. As shown in Scheme II-44, bridged-monol-cyclodextrin **192a** was obtained in 52% yield. Then, further functionalization gave tridifferentiated cyclodextrin **193** through a sequence of TBS protection and Pd<sup>0</sup>-mediated bridge opening. The direct bridge opening afforded ACD triol-cyclodextrin **174** which has been prepared from cyclodextrin **172** by the reductive ozonolysis (Scheme II-38).

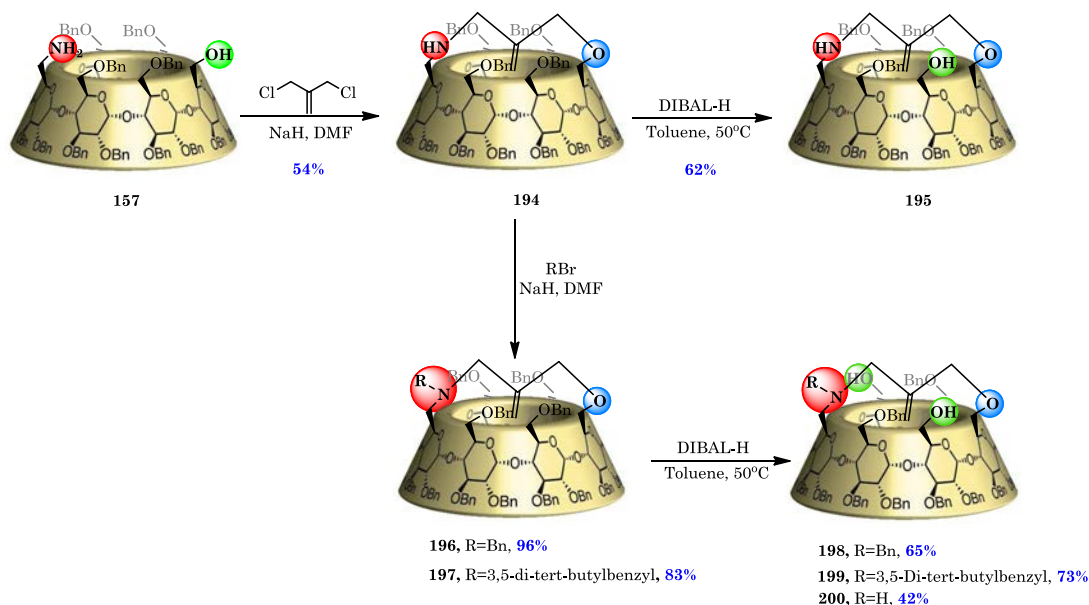
<sup>112</sup> C. Rousseau, B. Christensen, T. E. Petersen, M. Bols, *Org. Biomol. Chem.*, **2004**, *2*, 3476.

<sup>113</sup> O. Bistri, P. Sinaÿ, M. Sollogoub, *Tetrahedron Lett.*, **2006**, *47*, 4137.



**Scheme II-44:** Regioselective monol-debenzylation of methallyl bridged cyclodextrin

The symmetrically bridged cyclodextrins, synthesized from diol-cyclodextrin **107a**, which underwent DIBAL-H debenylation, giving the tridifferentiated cyclodextrin motif. Since amino-alcohol cyclodextrin **157** can be prepared easily by means of tandem azide-reduction/debenzylation, unsymmetrically bridged cyclodextrin **194** (Scheme II-45) was then obtained in 54% yield by the direct alkylation of amine and alcohol<sup>107</sup> as in the case of cyclodextrin **191** (Scheme II-43).



**Scheme II-45:** Mono/di-debenzylation of unsymmetrical bridged cyclodextrins

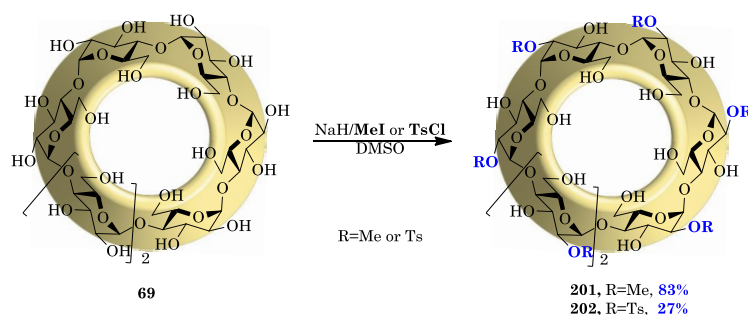
If comparing the results obtained with the symmetrically bridged cyclodextrin **191**, cyclodextrin **194** under the action of DIBAL-H should give C, F-diol-cyclodextrin **200**. In order to discriminate between these two positions, a bulky group was utilized for the

protection of the amine side to prevent debenzoylation on sugar **F**. To reach this goal, the amine on sugar **A** was benzylated to give cyclodextrin **196** in 96% yield. Disappointingly, after the action of DIBAL-H, diol-cyclodextrin **198** was obtained in 65% yield corresponding to a bis clockwise debenzoylation (Scheme II-45). Then, another bulkier protection group: 3, 5-di-tert-butylbenzyl, was used, but frustratingly, it did not induce the mono-deprotection, preferentially giving diol-cyclodextrin **199** in 73% yield. On the contrary, the mono-debenzoylation was carried out mostly on sugar **C**, giving cyclodextrin **195** in 62% yield, when unprotected cyclodextrin **194** was submitted to the action of DIBAL-H. The corresponding diol cyclodextrin **200** could also be obtained only under stronger reaction conditions with a moderate yield. On account of this phenomenon, a hypothesis was proposed that, DIBAL-H reacted with secondary amine to generate a sterically hindered complex, which prevented the clockwise deprotection.

#### 4. Functionalization of the secondary rim of cyclodextrins

Selective functionalization of the secondary rim of cyclodextrins seems challenging to chemists due to its steric crowding caused by the very high density of hydroxyl groups (twice as much as on the primary rim) on the secondary rim. In addition, hydrogen bondings between hydroxyl groups of position 2 and 3 make the secondary rim rigid and less flexible compared to primary alcohols. Nevertheless, some methods or strategies have been uncovered in the literature for selective functionalization of the secondary alcohols, either on position 2 or on position 3.

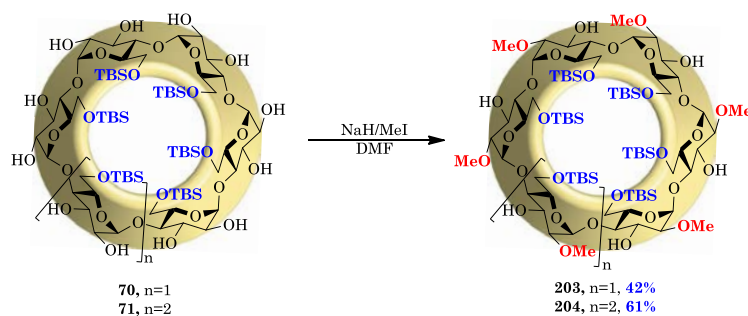
As mentioned above, hydroxyls on position 2 are more acidic than the others, so a straightforward method to functionalize OH-2 can be fulfilled by employing a strong base to form 2-alkoxide ions which react with alkyl or sulfonyl chlorides. Using sodium hydride in anhydrous DMSO, native cyclodextrins were deprotonated on positions 2, giving much more nucleophilic alkoxides, which then reacted with methyl iodide or tosyl chloride to afford per-2-methylated or tosylated cyclodextrins<sup>114</sup> (Scheme II-46).



**Scheme II-46:** Selective per-2-methylation and tosylation of cyclodextrins

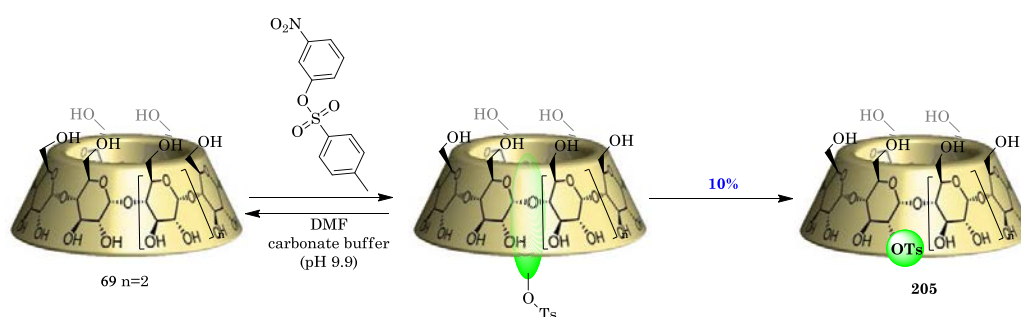
<sup>114</sup> (a) A. P. Croft, R. A. Bartsch, *Tetrahedron*, **1983**, 39, 1417; (b) D. Rong, V. T. D'Souza, *Tetrahedron Lett.*, **1990**, 31, 4275.

However, with the increase of functionalized positions, this selectivity becomes weaker because of the steric hindrance of the secondary rim. The electrophiles can then react with the primary alcohols. In order to solve this problem, the primary alcohols were masked in advance. In the presence of weak base, such as imidazole, the primary rim can be protected with TBS groups, the hydroxyls on position 2 were thereafter methylated using a strong base, giving cyclodextrins **203** and **204** in acceptable yields<sup>74</sup> (Scheme II-47).



**Scheme II-47:** Per-2-methylation and per-6-silylation of cyclodextrins

A group transfer strategy based on supramolecular inclusion was applied to the functionalization of secondary alcohols at times. Cyclodextrin **69** reacts with *meta*-nitrophenyl tosylate in DMF/water buffer to form an inclusion complex owing to the hydrophobic interaction. Then the orientation of the reagent inside the cavity enables only the position 2 to be functionalized<sup>115</sup> (Scheme II-48). This compound was then used to prepare 3-functionalized cyclodextrin. It was fulfilled by intramolecular  $S_N2$  epoxidation and the following nucleophilic attack on position 3. In the course of these sequential reactions, the inversion of configuration<sup>68,116</sup> happened on the both of positions 2 and 3.



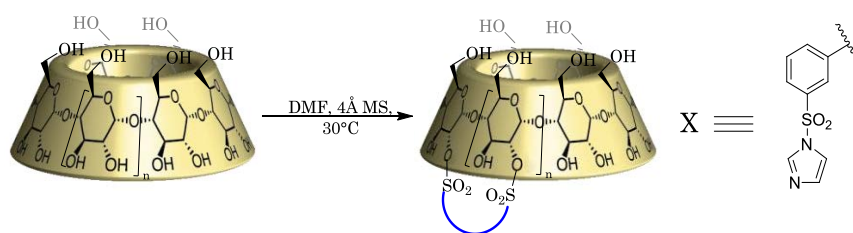
**Scheme II-48:** Monofunctionalization of the secondary alcohol on position 2

Capping reagents such as disulfonate chloride have been broadly employed for the functionalization of the primary rim of cyclodextrins, they can also be utilized on the

<sup>115</sup> A. Ueno, R. Breslow, *Tetrahedron Lett.*, **1982**, 23, 3451.

<sup>116</sup> R. Breslow, S. D. Dong, *Chem. Rev.*, **1998**, 98, 1997.

secondary rim. Imidazole was an alternative for chloride as a leaving group<sup>117</sup>. By optimization of linker in capping reagents, Teranishi demonstrated that 2<sup>A</sup>, 2<sup>B</sup>; 2<sup>A</sup>, 2<sup>C</sup> or 2<sup>A</sup>, 2<sup>D</sup> disulfonates were obtained selectively (Table II-5). Using 1 equivalent of reagent **206** in DMF, AB-isomers were synthesized in approximately 30% yield without other isomers<sup>117</sup> (Entry 1, Table II-5). To access AC-isomers<sup>118</sup>, capping reagent **207** was utilized with a longer linker, giving the desired products with yields of 40%-50% (Entry 2, Table II-5). Apart from the AB- and AC-isomers, AD-isomers<sup>119</sup> were also obtained in approximately 30% yield under the action of reagent **208** (Entry 3, Table II-5).



Entry	Capping reagent	Yield	Isomer
1	 <b>206</b>	α-CD: 30%	AB
		β-CD: 32%	
		γ-CD: 30%	
2	 <b>207</b>	α-CD: 40%	AC
		β-CD: 49%	
		γ-CD: 39%	
3	 <b>208</b>	α-CD: 30%	AD
		β-CD: 32%	
		γ-CD: 21%	

**Table II-5:** Disulfonation of the secondary rim of cyclodextrins

Besides disulfonate caps, another reagent *a,a'*-dibromo-*o*-xylene was used. The difference was that it can be installed selectively on the secondary alcohols of the same sugar unit (Scheme II-49). Treatment of native cyclodextrins with the above reagent in DMSO with the assistance of lithium diisopropylamide (LDA) afforded 2A, 3A-*O*-(*o*-xylene) cyclodextrins **209** and **211** in about 30% yields<sup>120</sup>. Then methylation and Pd-mediated catalytic hydrogenolysis provided cyclodextrins having two vicinal free secondary alcohols for further functionalization.

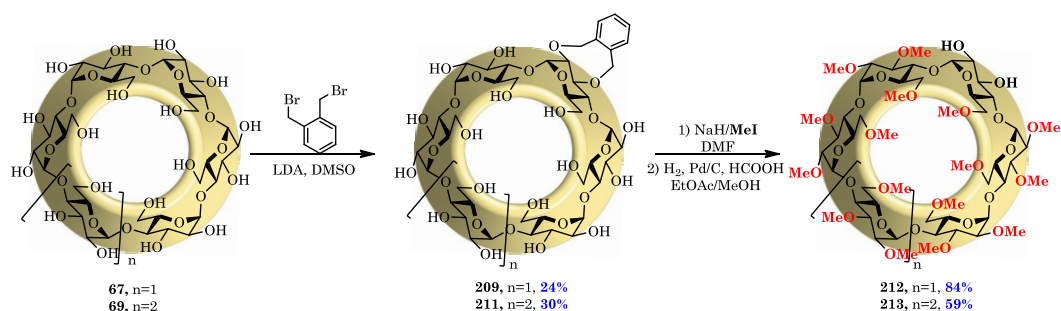
<sup>117</sup> K. Teranishi, *Chem. Commun.*, **2000**, 1255.

<sup>118</sup> (a) K. Teranishi, *Tetrahedron Lett.*, **2000**, 41, 7085; (b) K. Teranishi, *Tetrahedron*, **2003**, 59, 2519.

<sup>119</sup> (a) K. Teranishi, *Tetrahedron Lett.*, **2001**, 42, 5477; (b) K. Teranishi, *J. Incl. Phenom. Macrocycl. Chem.*, **2002**, 44, 313.

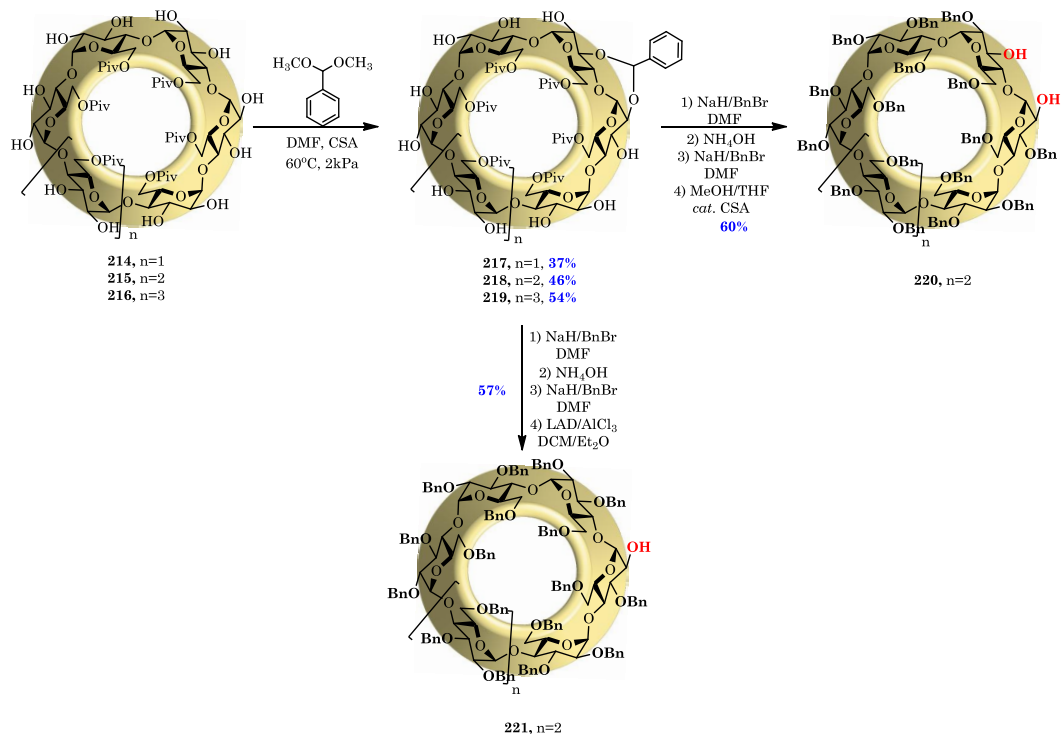
<sup>120</sup> (a) P. Balbuena, D. Lesur, J. M. Gonzalez Alvarez, F. Mendicuti, C. Ortiz Mellet, J. M. García Fernández, *Chem. Commun.*, **2007**, 3270; (b) P. Balbuena, R. Goncalves-Pereira, J. L. Jiménez Blanco, M. I. García-Moreno, D. Lesur, Ortiz Mellet, J. M. García Fernández, *J. Org. Chem.*, **2013**, 1390.





Scheme II-49: Benzylic alkylation of secondary alcohols

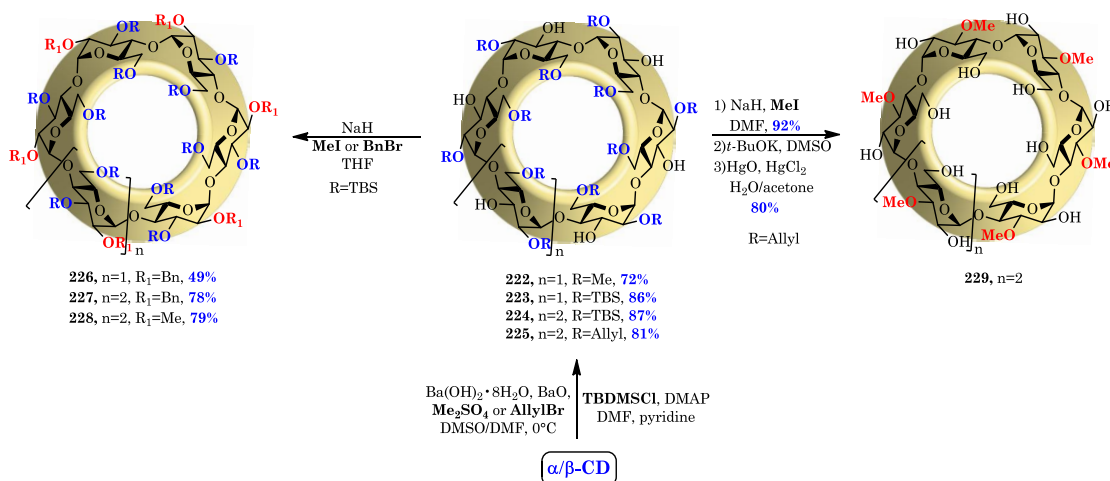
Alternatively, benzylidene group can be used in the functionalization of the secondary rim of cyclodextrins by bridging between two contiguous position 2 and 3 hydroxyls. The per-6-pivaloylated cyclodextrins were treated with 2 molar equivalents of benzaldehyde dimethylacetal in DMF at 60°C under reduced pressure (2 kPa) in the presence of CSA as the catalyst, giving cyclic mono-benzylidene acetal cyclodextrins in 37-54% yields<sup>121</sup>. It is noteworthy that the yields of the interglycosidic benzylidene acetals are dependent on the ring size of the native cyclodextrins (Scheme II-50). It was followed by a sequence of chemical transformations to give diol-cyclodextrin **220** in 60% yield. The reductive cleavage of the interglycosidic benzylidene group with lithium aluminum hydride/aluminum chloride in DCM-Et<sub>2</sub>O, afforded cyclodextrin **221** with only one unprotected position 2.



Scheme II-50: Benzylidenation of secondary alcohols and further functionalization

<sup>121</sup> N. Sakairi, N. Nishi, S. Tokura, H. Kuzuhara, *Carbohydr. Res.*, **1996**, 291, 53.

The hydroxyls on position 3 are the least reactive probably due to the participation in hydrogen bonding. Normally, functionalization on position 3 was achieved only when the other hydroxyls have been protected. Under the treatment of dimethylsulfate or allyl bromide in the presence of BaO/Ba(OH)<sub>2</sub>, native cyclodextrins were permethylated or perallylation on positions 2 and 6.<sup>122</sup> At a higher temperature, TBS protected cyclodextrins **223** and **224** were afforded in the presence of pyridine and DMAP<sup>123</sup> (Scheme II-51). The obtained TBS protected cyclodextrins were then transformed to per-(2-benzyl-3,6-di-O-TBS)-cyclodextrins **226** and **227** by treatment of sodium hydride and benzyl bromide in dry THF<sup>124</sup>. The migration of TBS group from position 2 to position 3 is an intramolecular process and involves a five-membered ring intermediate containing a pentacoordinate silicon atom. The allylated cyclodextrin **225** can be converted into per-3-methylated cyclodextrin **229** in 3 steps. The remaining free OH-3s were methylated firstly by the conventional procedure, then the labile enol ether was obtained by the isomerization mediated with *t*BuOK. It was followed by the mild acid hydrolysis to remove the allyl groups, giving cyclodextrin **229** with a yield of 72% in 3 steps<sup>125</sup>.



**Scheme II-51:** Functionalization of secondary alcohols on position 3

Direct selective functionalization of position 3 of cyclodextrins is a difficult task, because of the existing more reactive 2- or 6-hydroxyl groups. A method initially used for *O*-3-debenzylation of poly-*O*-benzylated mono- and disaccharide<sup>126</sup>, was employed for the selective functionalization of position 3 of cyclodextrins. Combining of triethylsilane and iodine at low temperature (-60 to -35°C), perbenzylated  $\alpha$ -cyclodextrin **128** underwent the

<sup>122</sup> Borger, R. J. Corcoran, J. M. Lehn, *Helv. Chim. Acta.*, **1978**, 61, 2190.

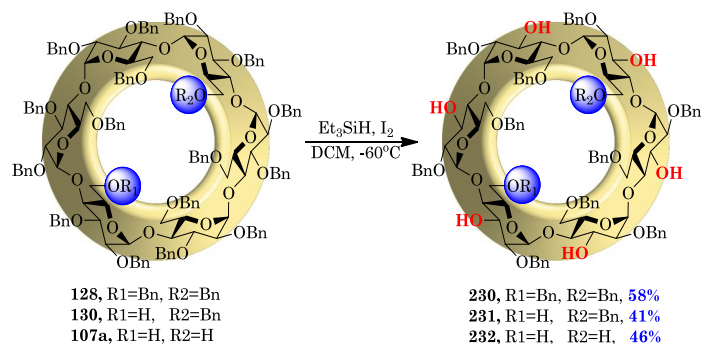
<sup>123</sup> A. W. Coleman, P. Zhang, C. C. Ling, H. Parrot-Lopez, H. Galon, *Carbohydr. Res.*, **1992**, 224, 307.

<sup>124</sup> P. R. Ashton, S. E. Boyd, G. Gattuso, E. Y. Hartwell, R. Koniger, N. Spencer, J. F. Stoddart, *J. Org. Chem.*, **1995**, 60, 3898.

<sup>125</sup> R. J. Bergeron, M. P. Meeley, Y. Machida, *Bioorganic chemistry*, **1976**, 5, 121.

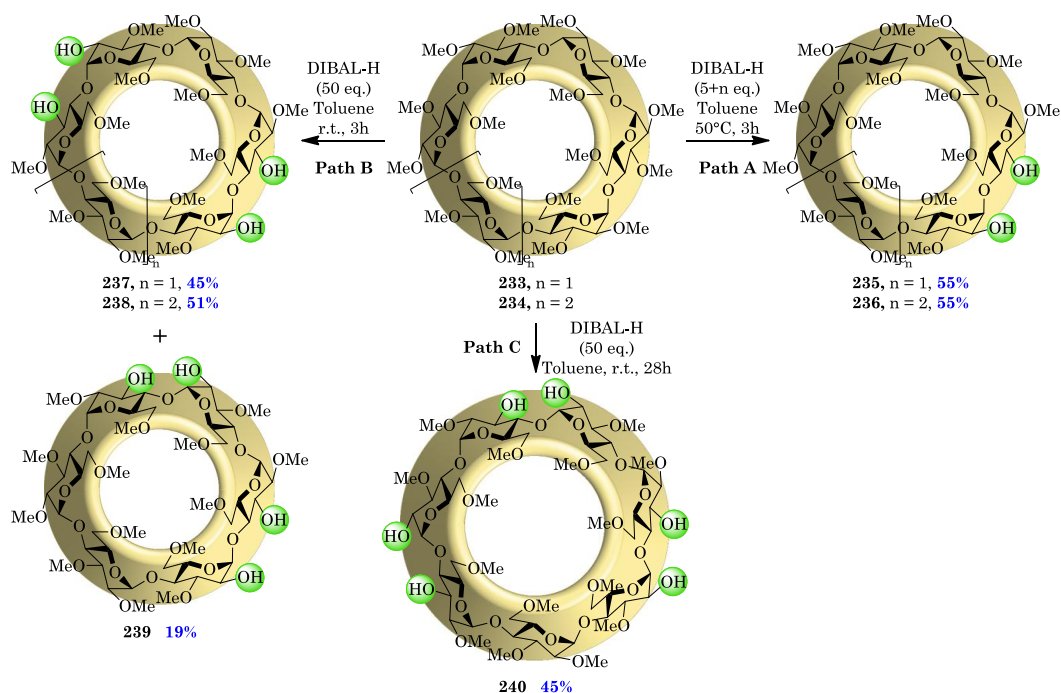
<sup>126</sup> A. Pastore, S. Valerio, M. Adinolfi, A. Iadonisi, *Chem. Eur. J.*, **2011**, 17, 5881.

*O*-3-debenzylation reaction to give per-2,6-benzylated cyclodextrin **230** in 58% yield<sup>127</sup> (Scheme II-52). This method was also applied to monol and diol-cyclodextrins **130** and **107a**, giving the same results in about 45% yield.



**Scheme II-52:** Et<sub>3</sub>SiH-I<sub>2</sub> mediated *O*-3-debenzylation of cyclodextrins

DIBAL-H mediated de-*O*-benzylation has proved to be a method of choice for the functionalization of cyclodextrins. Similar method was used as well in the selective deprotection of methyl ethers, giving gratifying results (Scheme II-53).



**Scheme II-53:** DIBAL-H mediated de-*O*-methylation on the secondary rim of cyclodextrins

Unlike perbenzylated cyclodextrins, the lower steric hindrance of methyl groups enables de-*O*-methylation to proceed on the secondary rim of cyclodextrins, although with a minor of

<sup>127</sup> M. Guitet, S. Adam de Beaumais, Y. Bleriot, B. Vauzeilles, Y. Zhang, M. Menand, M. Sollogoub, *Carbohydr. Res.*, **2012**, 35, 278.

6A-monohydroxy cyclodextrin<sup>128</sup>. When permethylated  $\alpha$ - or  $\beta$ -cyclodextrin **233** and **234** were subjected to the action of DIBAL-H (6 or 7 equivalents) at 50°C, de-*O*-methylation took place on positions 2 and 3 of two adjacent sugar units, giving 2A,3B-diol cyclodextrins **235** and **236** in 55% yields (**Path A**, Scheme II-53). As the quantity of DIBAL-H increased to 50 equivalents, regioselective tetra-de-*O*-methylation was observed at room temperature, affording 2A, 3B, 2D, 3E-tetrahydroxy-cyclodextrins **237** and **238** in approximately 50% yield (**Path B**, Scheme II-53)<sup>129</sup>. In this case, another tetrol isomer **239** was also formed in 19% yield<sup>130</sup>. Upon prolongation of reaction time to 28 h, 2A, 3B, 2C, 3D, 2E, 3F-hexahydroxy cyclodextrin **240** was formed in 45% yield (**Path C**, Scheme II-53)<sup>129</sup>.

In order to clarify the above results, a mechanism was proposed<sup>131</sup>. As in the debenzylation reaction, two molecules of aluminum reagents were proposed to participate. The first one was chelated on the oxygens of position 2 and adjacent position 3, the second aluminum species was thereafter coordinated on the less hindered position 3 oxygen, where the dealkylation happened. Sequentially, the anomeric oxygen then got involved the aluminum coordination to leave more space for DIBAL-H to approach the position 2 oxygen, which leads to the demethylation occurred on this position. The following formation of tetrol and hexol was directed by the steric crowding of aluminum adducts just as happened in the case of perbenzylated cyclodextrins.

<sup>128</sup> B. Roizel, J. P. Baltaze, P. Sinaÿ, *Tetrahedron Lett.*, **2002**, 43, 2371.

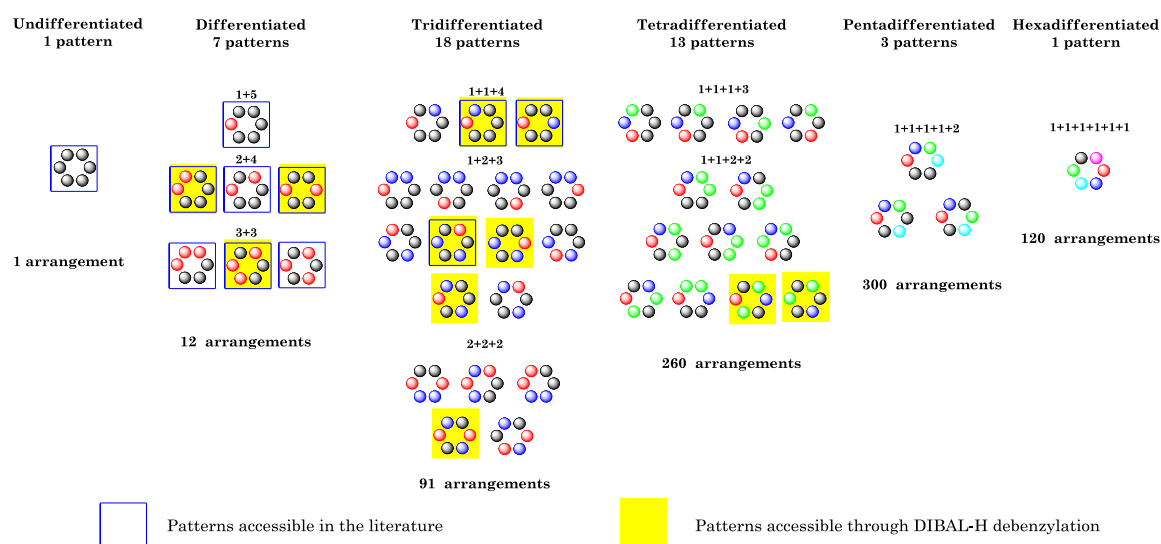
<sup>129</sup> (a) X. Luo, Y. Chen, J. G. Huber, Y. Zhang, P. Sinaÿ *C. R. Chimie*, **2004**, 7, 25; (b) Y. Chen, J. G. Huber, Y. Zhang, P. Sinaÿ *C. R. Chimie*, **2005**, 8, 27.

<sup>130</sup> S. Xiao, D. Zhou, M. Yang, P. Sinaÿ, M. Sollogoub, Y. Zhang, *Tetrahedron Lett.*, **2011**, 52, 5273.

<sup>131</sup> S. Xiao, M. Yang, P. Sinaÿ, Y. Blerit, M. Sollogoub, Y. Zhang, *Eur. J. Org. Chem.*, **2010**, 1510.

## 5. Conclusion

In summary, the methods reviewed in this chapter pave the way to diversify cyclodextrin polyfunctionalization, which thereafter can be applied to various areas. By means of the traditional methods, taking advantages of different reactivities of alcohols, reagents, intrinsic structure of cyclodextrins or others new emerged method<sup>132</sup>, a limited amount of cyclodextrin motifs were achieved with the compromise of yield, regioselectivity or time-consuming chromatography. Nevertheless, DIBAL-H mediated debenylation seems to be an attractive and promising approach. To highlight the versatility of this method, a number of cyclodextrin patterns of much higher complexity, such as tri- or tetradifferentiated cyclodextrins have been accessed with high efficiency (Figure II-9). Although much progress has been made in recent years, the higher level of complexity in cyclodextrin functionalization have not yet been obtained. Accordingly, in the next chapter we envisaged the possibility to access the penta-, or even hexadifferentiated  $\alpha$ -cyclodextrins.



**Figure II-9:** Functionalization patterns

<sup>132</sup> D. Alvarez-Dorta, E. Leon, A. R. Kennedy, A. Martin, I. Perez-Martin, E. Suarez, *Angew. Chem. Int. Ed.*, **2015**, *54*, 3674.

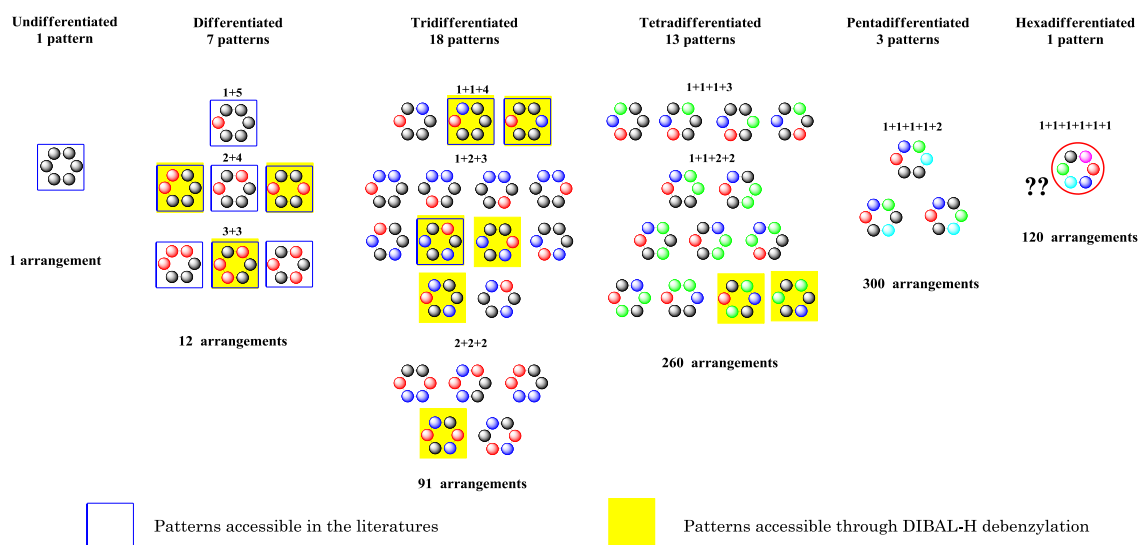
## **CHAPTER III**

# **SITE-SELECTIVE HEXA-HETERO- FUNCTIONALIZATION OF $\alpha$ -CYCLODEXTRIN**



## 1. Introduction

In Chapter II, we have shown a myriad of cyclodextrin derivative patterns synthesized either by the traditional methods, or by DIBAL-H-mediated strategies. The following Figure III-1 gives us an explicit demonstration of which kind of patterns are already reached.



**Figure III-1:** Functionalization patterns

According to Figure III-1, several cyclodextrin derivatives<sup>100-113</sup> have been achieved by means of DIBAL-H-mediated debenzoylation strategies. However, the patterns with higher level of complexity such as penta- or hexadifferentiated patterns, are still out of reach, which need a synthetic strategy that should meet some requirements: 1) during a single debenzoylation reaction, only one benzyl group should be removed in a regioselective manner; 2) the new functional group introduced should be capable of orienting the following debenzoylation reaction regioselectively. Consequently, to meet this challenge, it is necessary to delineate a set of site-directing methods introduced in Chapter II.

## 2. Strategy of the synthesis

DIBAL-H mediated de-*O*-benzoylation of cyclodextrins<sup>100</sup> is a well-defined reaction and the mechanism has been clarified unambiguously. The steric hindrance of the aluminum species plays an important role on the regioselectivity of the reactions.

Based on this attractive approach, an ensemble of site-directing rules (Figure III-2) have been established and well applied to polyfunctionalization of cyclodextrins.

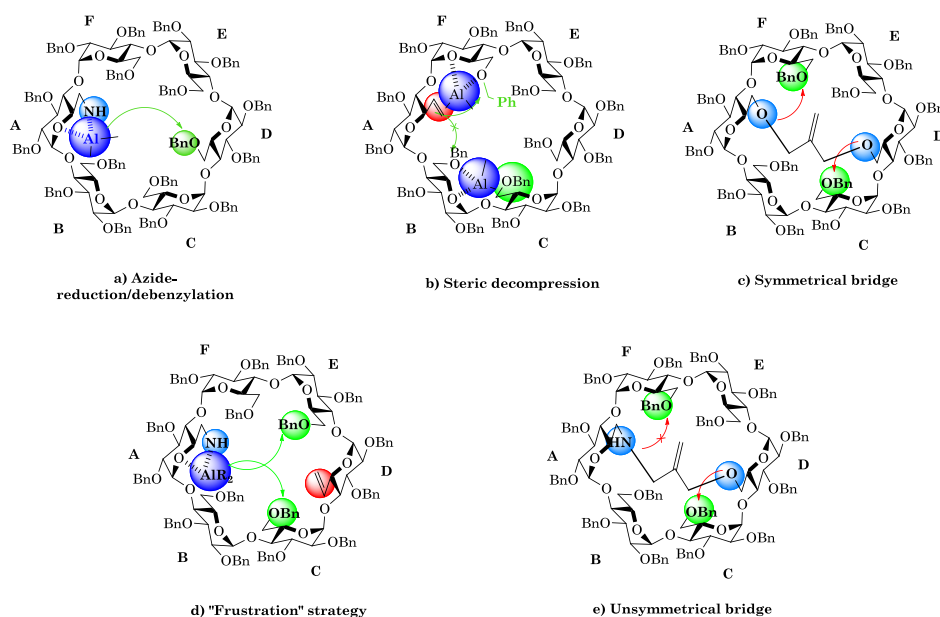
**1) Coupled azide-reduction/debenzoylation reaction (Figure III-2a):** DIBAL-H reduces the azide firstly, and then orients the debenzoylation on the diametrically opposed position due to the steric hindrance of the aluminum complex<sup>104</sup>;



**2)** Steric decompression on the primary rim of cyclodextrins (Figure III-2b): introduction of a deoxy or a vinyl group on sugar unit **A**, induces an adjacent clockwise deprotection on sugar unit **F**<sup>105</sup>. This site-directing decompression can also be realized by bridging the diametrically opposed sugar units **A** and **D** (Figure III-2c) to proceed a double-deprotection on both the sterically decompressed ether sides<sup>108</sup>;

**3)** “Frustration” strategy devised by a combination of both methods **1** and **2** (Figure III-2d). Changing the benzyloxy group on sugar unit **D** by a less crowded vinyl group, the azide-derived sugar unit **A** direct the debenzoylation to give an unexpected tetradifferentiated cyclodextrin with free alcohols on both sides of sterically decompressed position<sup>106</sup>. Although this method displays a very good regioselectivity, it is a dead-end towards hexadifferentiation of  $\alpha$ -cyclodextrin, which need a mono-debenzylation during a single debenzoylation reaction.

**4)** Unsymmetrical bridge strategy (Figure III-2e): introduction of a methallyl bridge on an amino-alcohol cyclodextrin orients the debenzoylation just on the sterically decompressed ether side, affording a tetradifferentiated cyclodextrin derivative.

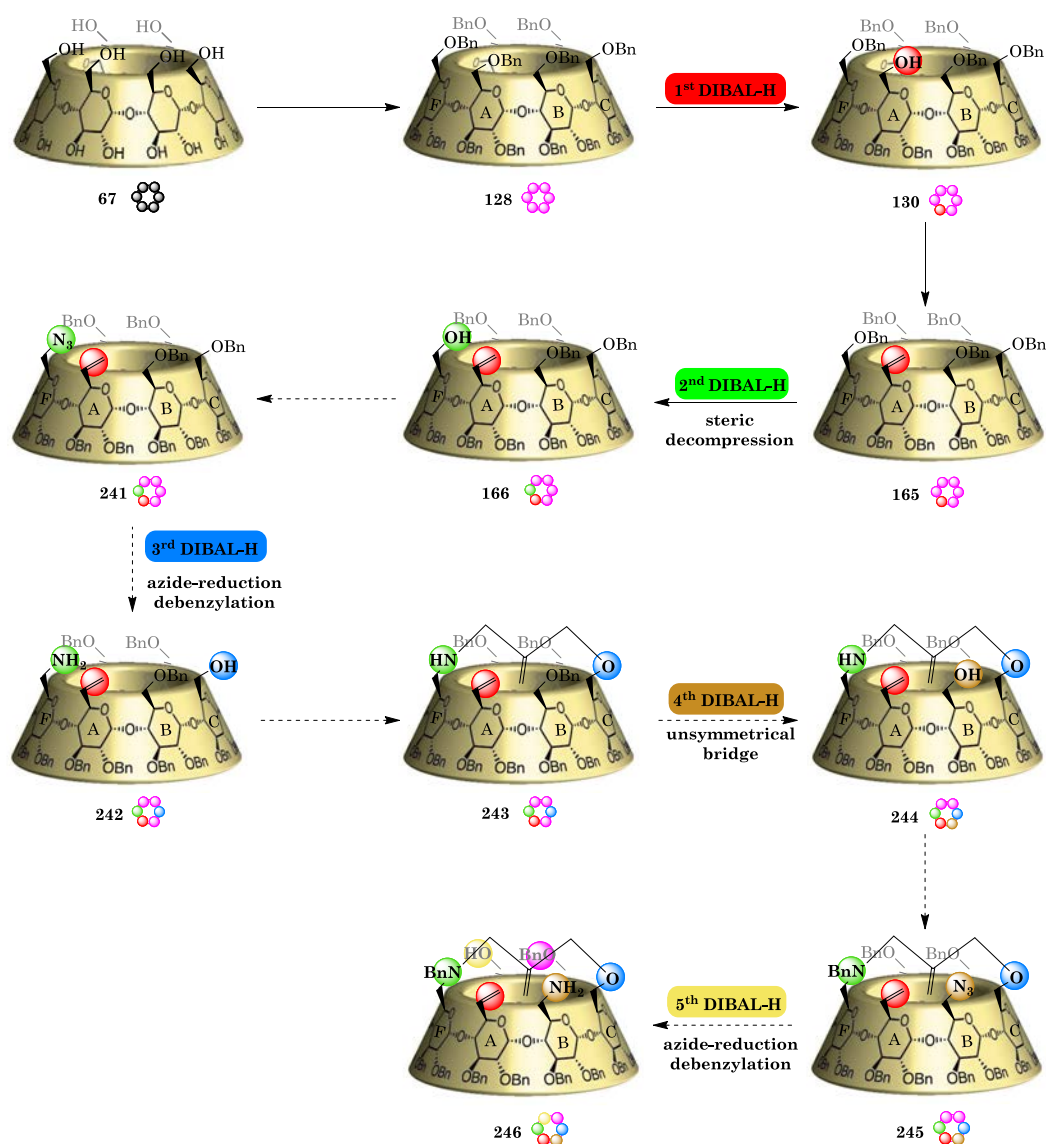


**Figure III-2:** Site-directing rules for functionalization of cyclodextrins

The understanding of the site-directing effects and mechanisms on cyclodextrins enables the access to diverse cyclodextrin derivatives. Thus combining the existing rules, we devised a synthetic route to reach hexadifferentiated cyclodextrin **246**, possessing six different functions on the primary rim of  $\alpha$ -cyclodextrin. It is an important challenge in the functionalization of  $C_n$ -symmetric concave cycles.

Perbenzylated  $\alpha$ -cyclodextrin **128** is submitted to the action of DIBAL-H to form monol-cyclodextrin **130**, which is converted into vinyl-cyclodextrin **165**. Cyclodextrin **165**

undergoes the action of DIBAL-H to give vinyl-monol-cyclodextrin **166** by the virtue of steric decompression. Then the alcohol **166** can be transformed into azido-cyclodextrin **241** which mediates azide-reduction/debenzylation to form amino-alcohol cyclodextrin **242**. After introduction of the bridge group (**243**), the unsymmetrical bridge will orient DIBAL-H debenzoylation to give cyclodextrin **244**. Finally duplication of azide-reduction/debenzylation will produce the ultimate hexadifferentiated cyclodextrin **246** (Scheme III-1). Therefore, hexadifferentiation of  $\alpha$ -cyclodextrin will be accessed through five successive DIBAL-H mediated debenzoylation by using appropriate chemical groups. In the following part of this chapter, the detailed description will be presented for this kind of total synthesis.



**Scheme III-1:** Synthetic route towards hexadifferentiated cyclodextrin **246**.

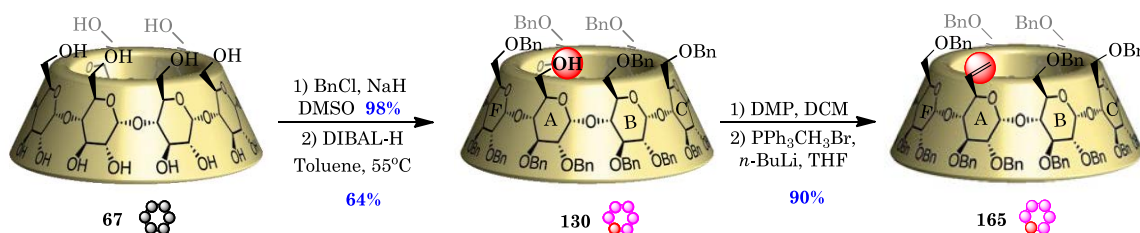
Plain arrows mean the previous reactions; dash arrows mean the new reactions presented in this work.

### 3. Successive debenzylations towards hexadifferentiated $\alpha$ -cyclodextrin

#### 3.1 First debenzylation by DIBAL-H

Native  $\alpha$ -cyclodextrin **67** was converted into cyclodextrin **128** in quantitative yield<sup>133</sup>. The first debenzylation offered monol- $\alpha$ -cyclodextrin **130** in 64% yield (Scheme III-2)<sup>100</sup>. Because of the steric hindrance on the secondary rim, debenzylation only occurred on the primary rim. Careful attention should be paid to this reaction, since with more equivalents of DIBAL-H, higher concentration and temperature would lead to a second debenzylation on the diametrically opposed sugar unit **D**.

Then the hydroxyl of  $\alpha$ -cyclodextrin **130** was converted into a vinyl group in 90% yield by Dess-Martin oxidation and followed Wittig olefination. Using Dess-Martin periodinane, the free alcohol was oxidized to the corresponding aldehyde at room temperature in DCM. Vinyl-cyclodextrin **165** was obtained in the following olefination by using methylphosphonium salt in the presence of *n*-butyllithium at -40°C.

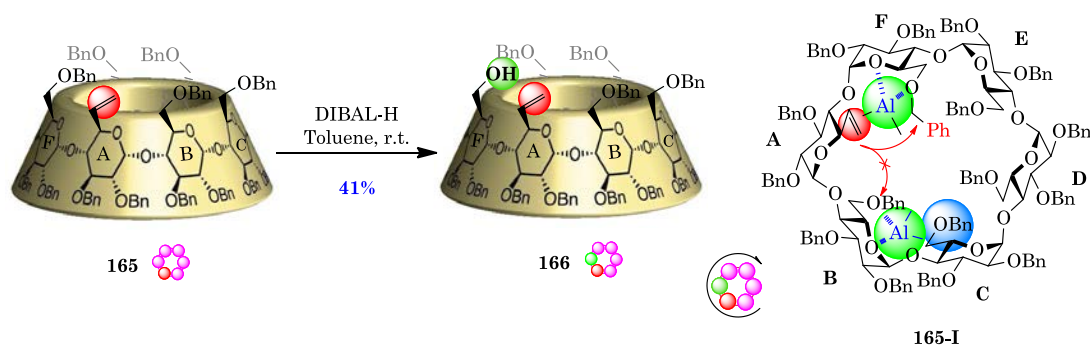


**Scheme III-2:** First debenzylation by DIBAL-H to give monol-cyclodextrin

#### 3.2 Second debenzylation by steric decompression effect

With A-vinyl- $\alpha$ -cyclodextrin **165** in hand, the second DIBAL-H-mediated debenzylation gave A-vinyl-F-alcohol- $\alpha$ -cyclodextrin **166** as the major product in 41% yield, as well as 22% of starting material **165** and 20% of diol-cyclodextrin<sup>105</sup> (Scheme III-3). In the course of this reaction, the steric decompression caused by a vinyl group on unit **A** favored the debenzylation on unit **F**, clockwise adjacent to sugar **A** (**165-I**). Similarly to the first debenzylation (Scheme III-2), the equivalent of DIBAL-H, the concentration and the temperature should be carefully controlled to avoid the formation of diol-cyclodextrin. Through two successive DIBAL-H debenzylations, tridifferentiated  $\alpha$ -cyclodextrin **166** was obtained with a free alcohol on sugar unit **F**.

<sup>133</sup> Native cyclodextrin must be dried through lyophilization.

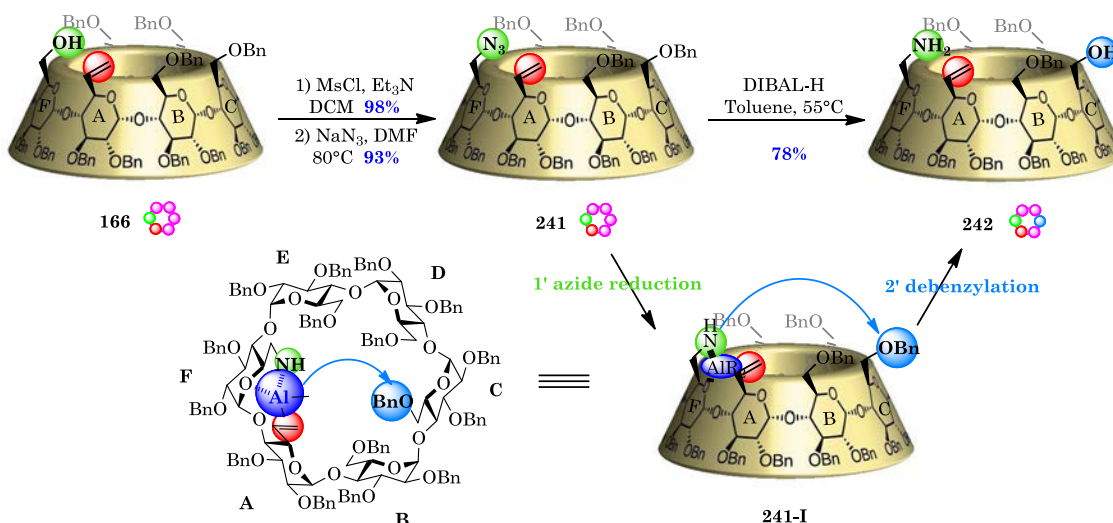


**Scheme III-3:** Second debenzylation induced by steric decompression effect

### 3.3 Third debenzylation by azide-reduction/debenzylation

As we know, introduction of an azide can induce a regioselective debenzylation and release of only one hydroxyl, so the free hydroxyl on cyclodextrin **166** was then converted into an azido group using MsCl in the presence of Et<sub>3</sub>N, followed substitution by azide sodium in DMF at 80°C.

The F-azido-A-vinyl-cyclodextrin **241** underwent a tandem azide-reduction/debenzylation reaction to give tetradifferentiated cyclodextrin **242** in 78% yield, bearing a free hydroxyl located on sugar unit **C**, diametrically opposed to sugar unit **F**<sup>104</sup> (Scheme III-4). This reaction proceeded through two sequential steps: firstly, the reduction of azide by DIBAL-H generated a sterically crowded aluminum derivative (**241-I**), which then forced the de-*O*-benzylation on the farthest position, i.e. sugar unit **C** in this case.



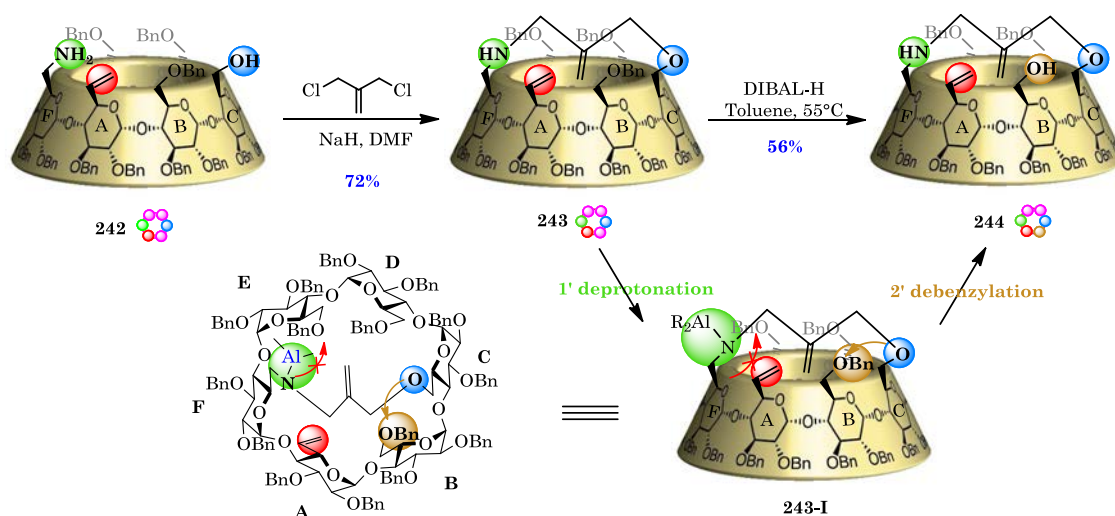
**Scheme III-4:** Third debenzylation by tandem azide-reduction/debenzylation

Since tetradifferentiated cyclodextrin **242** with C-alcohol, F-amine was prepared, the following work is functionalization of these two functions and removal of another benzyl group selectively.

### 3.4 Fourth debenzylation by unsymmetrical bridge strategy

According to our previously established site-directing rules, a symmetrical methallyl capped cyclodextrin can undergo a double-debenzylation reaction (Figure III-2c), in contrast, an unsymmetrical bridge (Figure III-2e) induced a mono-debenzylated reaction on the sterically decompressed side.

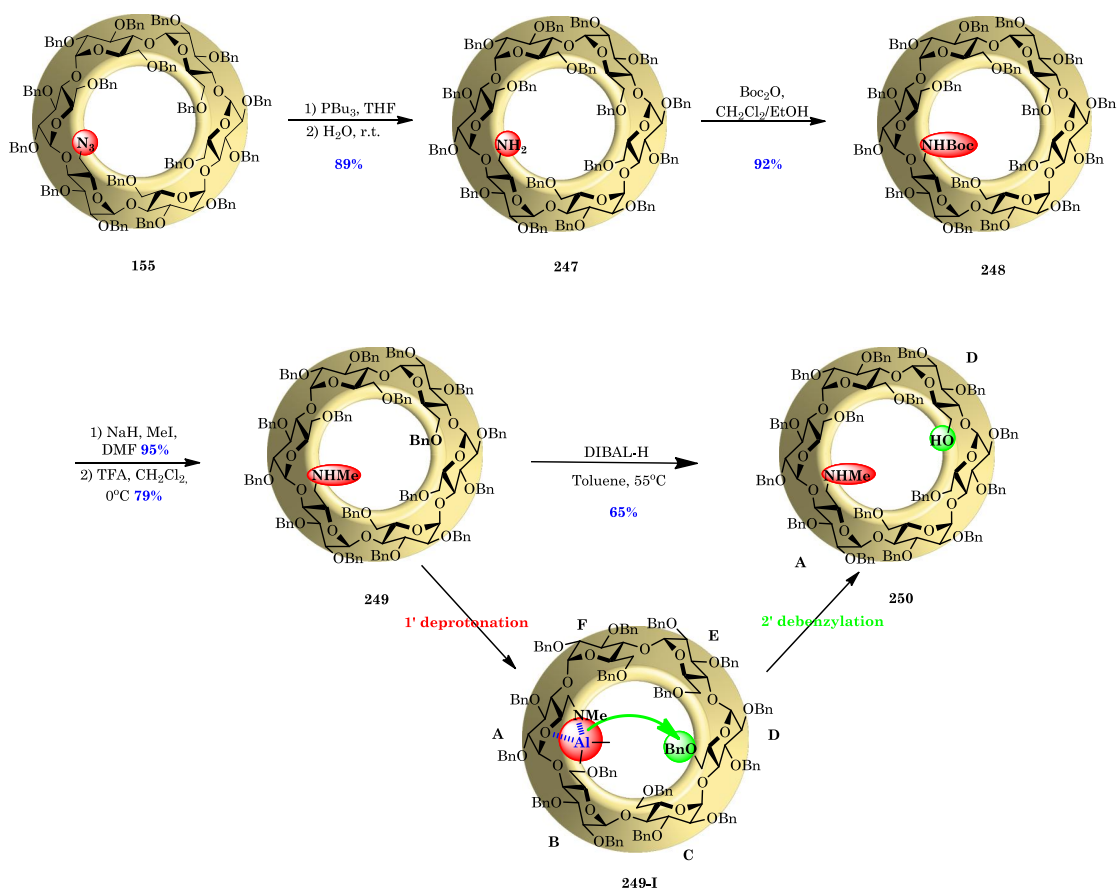
Thus, the two functions amine and alcohol underwent direct alkylations to afford bridged cyclodextrin **243** in 72% yield by using 3-chloro-2-(chloromethyl) prop-1-ene in the presence of sodium hydride. Then the following DIBAL-H debenzylation reaction gave an inedited pentadifferentiated  $\alpha$ -cyclodextrin **244** with an acceptable yield<sup>107</sup> (56%, Scheme III-5). In this reaction, mono-debenzylation occurred only on sugar unit **B**, clockwise adjacent to the ether moiety of unit **C**. To explain this result, it was assumed that the secondary amine on unit **F** can chelated with DIBAL-H crowding the region surrounding the amine (**243-I**). The clockwise deprotection was then prevented on the amine side, while favored on the ether side.



**Scheme III-5:** Fourth debenzylation mediated by an unsymmetrical bridge strategy

To confirm this proposal, a secondary amino-cyclodextrin **249** was synthesized from monoazido-cyclodextrin **155**. Using Staudinger reaction, amino-cyclodextrin **247** was obtained, it was followed by the Boc protection, methylation and acid-mediated Boc deprotection to give secondary amino-cyclodextrin **249** with a yield of 60% in four steps. It was then submitted to the action of DIBAL-H, affording an expected mono-debenzylated cyclodextrin **250** bearing a free alcohol on the diametrically opposed sugar unit **D** (Scheme

III-6). This regioselectivity confirmed our assumption that DIBAL-H reacted with the secondary amine on sugar **A** to form an aluminum complex (**249-I**), which induced the usual steric orientation of DIBAL-H on the diametrically opposed sugar unit **D**.



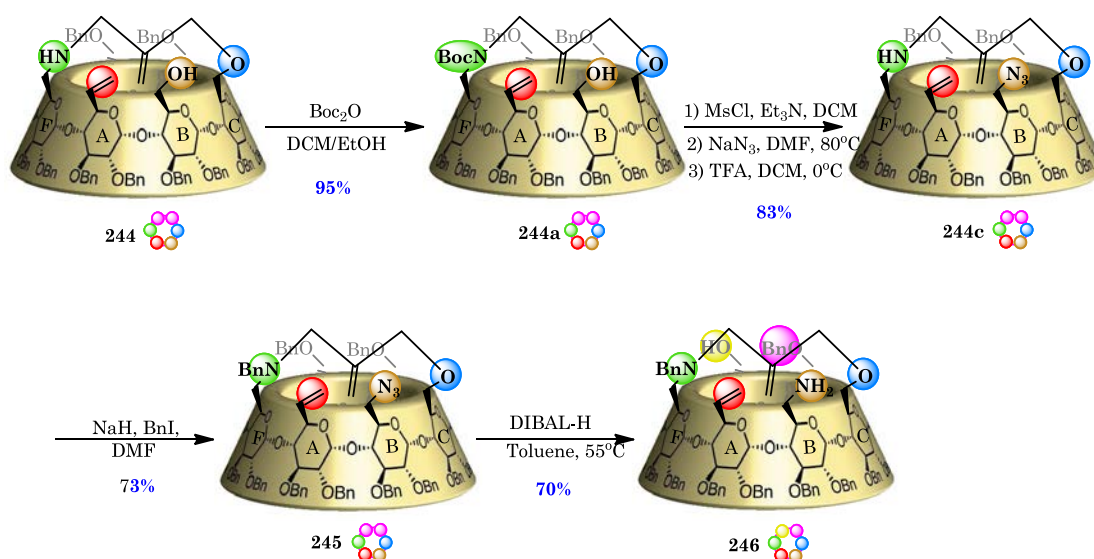
**Scheme III-6:** Secondary amine site-directing effect through attachment of an aluminum reagent.

Now we have accessed pentadifferentiated  $\alpha$ -cyclodextrin **244** unreached before, through sequential four DIBAL-H-mediated debenzoylation reactions. The last debenzoylation, i.e. the fifth debenzoylation can be preceded by another tandem azide-reduction/debenzoylation to give cyclodextrin **246**.

### 3.5 The fifth debenzoylation by azide-reduction/debenzoylation

As shown previously (Scheme III-4), the free alcohol was firstly transformed into an azide. To avoid the interaction of F-amine with mesyl group, the amine was protected temporarily with a Boc group. A sequence of mesylation, azidation and the followed acid-mediated deprotection of Boc group, gave cyclodextrin **244c** bearing an azido group on sugar unit **B** with a yield of 83% in three steps (Scheme III-7). To avoid the association of F-amine with aluminum, it should

be protected by an appropriate group which is immune to the action of DIBAL-H and is not so bulky to prevent the clockwise adjacent debenzylation. Herein benzyl group was chosen according to the above mentioned rules<sup>107</sup>. Firstly, the benzyl bromide was tried, but disappointedly, the benzylation didn't work. Therefore, the more reactive benzyl iodide<sup>134</sup> was used in the benzylation reaction, giving cyclodextrin **245** in 73% yield. It was followed by the tandem reaction to afford exclusively the diametrically opposed B-amino-E-hydroxyl cyclodextrin **246** in 70% yield (a total yield of 2.2% from native  $\alpha$ -cyclodextrin, Scheme III-7), which was the first hexadifferentiated cyclodextrin bearing six different chemical groups on position 6 of each unit.

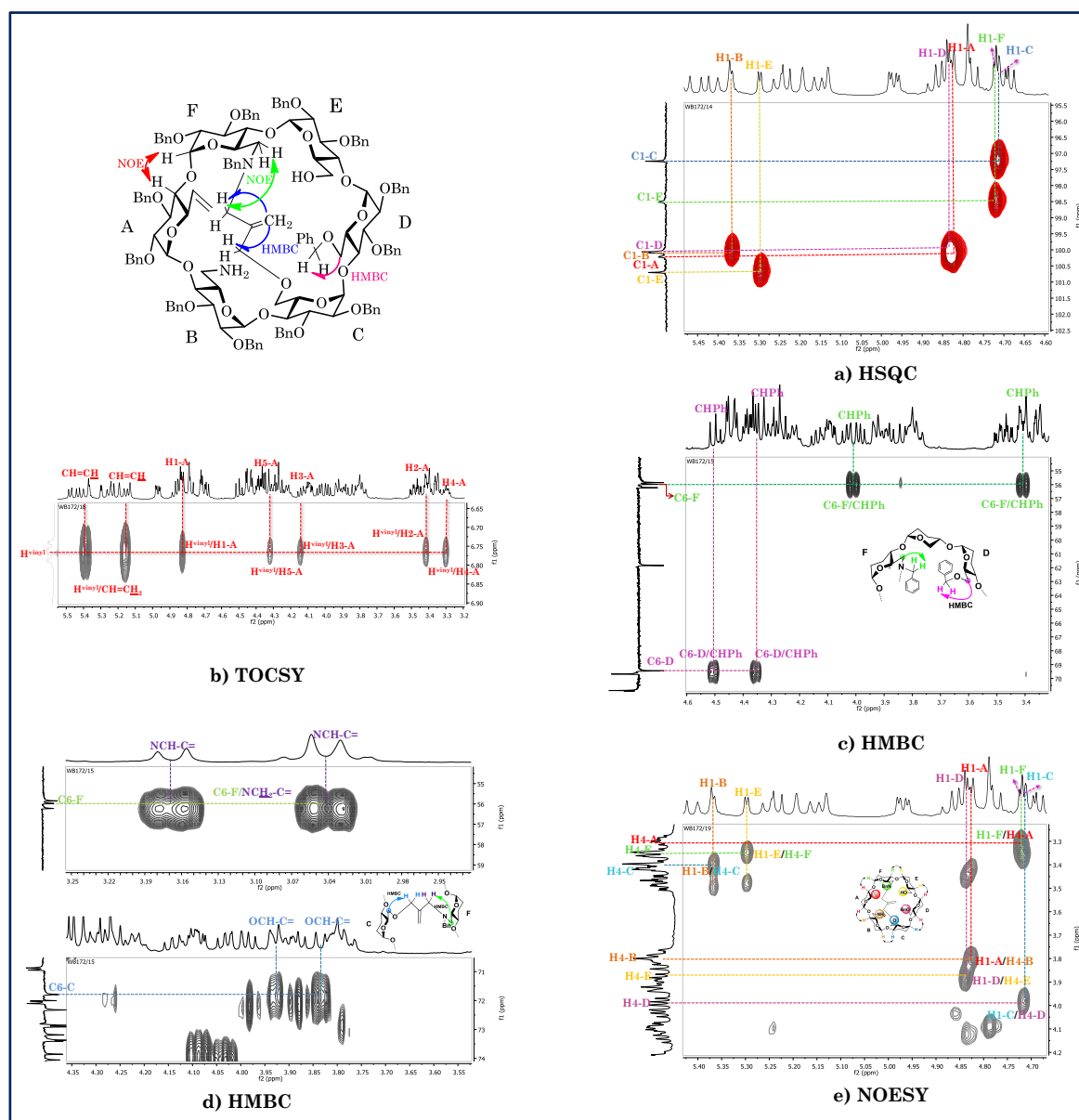


**Scheme III-7:** The fifth debenzylation accesses to hexadifferentiated cyclodextrin

The structure of hexadifferentiated cyclodextrin **246** was characterized thoroughly using NMR spectroscopy. As shown in Figure III-3, the C-1s and H-1s were identified through HSQC with characteristic chemical shifts of the acetal carbons around 100 ppm (Figure III-3a). Combining COSY and TOCSY 2D experiments, all the other protons of each unit were attributed since we identified all the H-1s. For example, Figure III-3b showed the protons of sugar A. The different functions installed on the primary rim can be identified individually. For instance, cycle A was identified through the correlation of H-5 with a vinylic proton in TOCSY and COSY (Figure III-3b). In cycle C, HMBC indicated a cross-correlation between C-6 and allylic protons of the bridge (Figure III-3d). A similar correlation was found in cycle F, but an additional correlation was observed with the benzylic protons (Figure III-3d and III-3c). Another correlation with benzylic protons was observed in cycle D (Figure III-3c). Finally, cycles B and E were identified because they do not cross-correlate with any substituent, C-6B and C-6E were differentiated through their characteristically different

<sup>134</sup> Benzyl iodide was prepared according to literature:  
C. T. Hoang, V. Alezra, R. Guillot, C. Kouklovsky, *Org. Lett.*, **2007**, 9, 2521.

chemical shifts (42 and 62 ppm respectively). Finally the order of all sugar cycles was determined through NOE cross coupling between H-4s and H-1s of adjacent sugars, confirmed by cross-correlation in HMBC between H-4s and C-1s (Figure III-3e).



**Figure III-3:** NMR (600 MHz, 300 K, CDCl<sub>3</sub>) analysis of cyclodextrin **246**

(a) Correlations of C-1s and H-1s in HSQC; (b) Protons of sugar unit A in TOCSY; (c) Correlations of C-6s and benzylic protons in HMBC; (d) Correlations of C-6C, C-6F and allylic protons in HMBC; (e) Correlations of H-1s and vicinal H-4s in NOESY

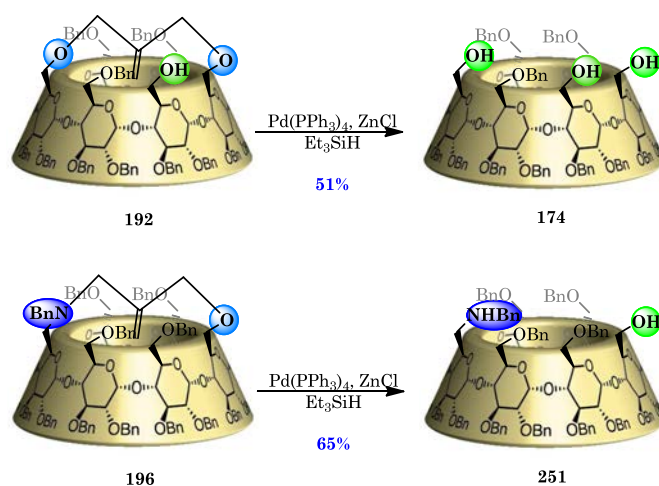
#### 4. Post-functionalization of penta- and hexadifferentiated cyclodextrins

Through five successive DIBAL-H mediated debenzylations, the ultimate hexadifferentiated cyclodextrin **246** was accessed. In addition, we also synthesized another pentadifferentiated



cyclodextrin **245** unreached before and obtained two new tetradifferentiated patterns. But it is not a dead-end. Consequently, we envisage the possibility to synthesize the corresponding derivatives, bearing six orthogonal functions: amine, alkene, azide, alcohol, ether and chloride from the penta- and hexadifferentiated cyclodextrins through further chemical transformations.

To achieve this goal, a set of reactions were tested. During this process, the key point is to open the methallyl bridge smoothly using a reliable method. To adjust this problem, palladium-mediated bridge opening<sup>113</sup> was applied. This method has been used on ether bridged cyclodextrin **192** (Scheme III-8). So it was optimized on unsymmetrically bridged cyclodextrin analogue **196**. Using Pd(PPh<sub>3</sub>)<sub>4</sub> in the presence of zinc chloride and triethylsilane, the benzyl protected amino-alcohol cyclodextrin **251** was obtained in 65 % yield (Scheme III-8).



**Scheme III-8:** Bridge opening by palladium-mediated method

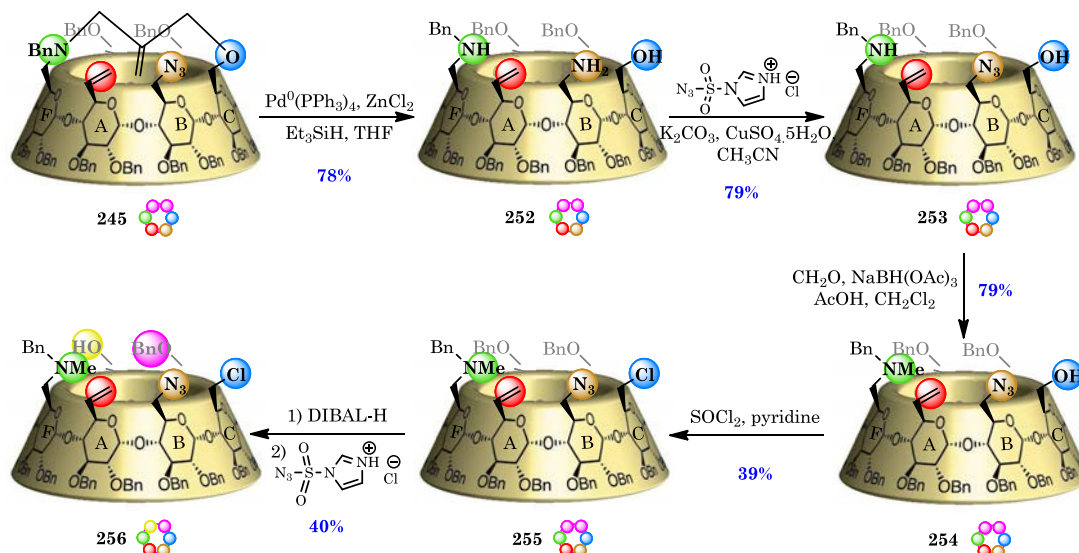
We also submitted chloride-cyclodextrin and vinyl-cyclodextrin to this reaction, demonstrated that these two functions are tolerate during the process of bridge opening. Based on the above results, a series of chemical transformations were combined to carry out the post-functionalization.

#### 4.1 Post-functionalization of pentadifferentiated cyclodextrin **245**

For the post-funtionalization of cyclodextrin **245** to another hexadifferentiated motif, six sequential chemical transformations were included (Scheme III-9). The first step was to remove the methallyl group. Using depicted method, the functionalizable secondary amine and alcohol were formed in 78% yield. But surprisingly, the azide on sugar unit **B** was also reduced to an amine. Therefore, the next step was to restore the azide function. This reaction was executed by a lab-made reagent, Imidazole-1-sulfonyl azide hydrochloride (ImSO<sub>2</sub>N<sub>3</sub>)<sup>135</sup>.

<sup>135</sup> E. D. Goddard-Borger, R. V. Stick, *Org. Lett.*, **2007**, 9, 3797.

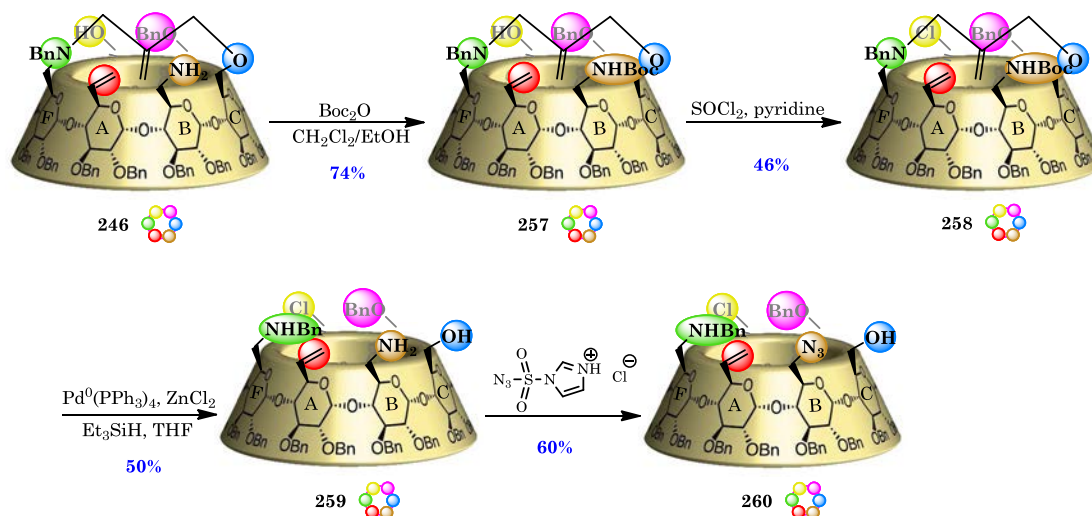
With the copper catalyst, the primary amine was reconverted into azide in 79% yield. Then after the protection of secondary amine via reductive amination and chlorination of hydroxyl on unit C, the azide-reduction/debenzylation and the following azidation gave hexadifferentiated cyclodextrin **256**, bearing six orthogonal functions: amine, alkene, azide, chloride, ether and alcohol.



**Scheme III-9:** Further chemical transformations of pentadifferentiated cyclodextrin **245**

#### 4.2 Post-functionalization of hexadifferentiated cyclodextrin **246**

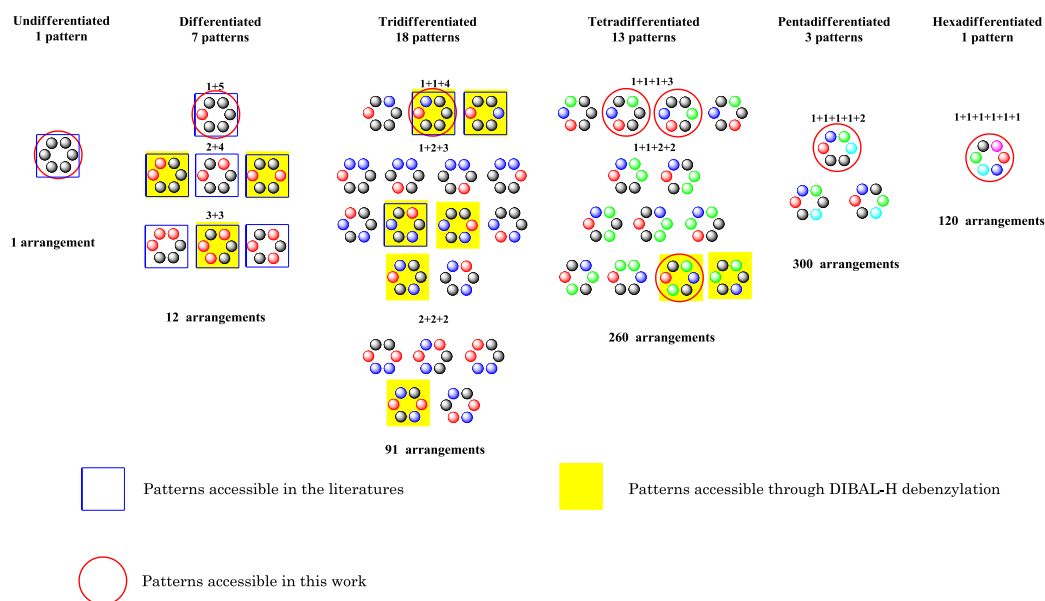
It is also possible to synthesize another regioisomeric hexadifferentiated cyclodextrin **260** in a shorter sequence (Scheme III-10). Using thionyl chloride in the presence of pyridine, the already existing alcohol on sugar unit **E** was chlorinated after protection of primary amine with Boc group. It was followed by the methallyl bridge removal and the azidation of amine, giving hexadifferentiated cyclodextrin **260**.



**Scheme III-10:** Further chemical transformations of hexadifferentiated cyclodextrin **246**

## 5. Conclusion

In this chapter, based on our well-established site-directing debenzoylation rules, the ultimate hexadifferentiation of  $\alpha$ -cyclodextrin was accomplished, as well as pentadifferentiation and two new tetradifferentiation unreached before (Figure III-4). This illustrated that the DIBAL-H-mediated debenzoylation and the attached site-directing rules have the capacity to realize the poly-hetero-functionalization of cyclodextrins with high efficiency. We believe that this achievement on cyclodextrins should give the inspiration on the functionalization of this class of  $C_n$  concave cycles.



**Figure III-4: Functionalization patterns**

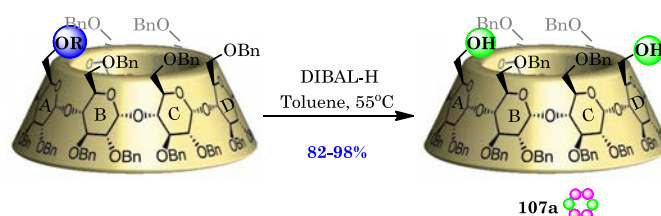
## **CHAPTER IV**

# **DIBAL-H INDUCED SELECTIVE FUNCTIONALIZATION OF SULFUR- AND SELENIUM-DERIVED $\alpha$ -CYCLODEXTRINS: NEW SITE-DIRECTING RULES**



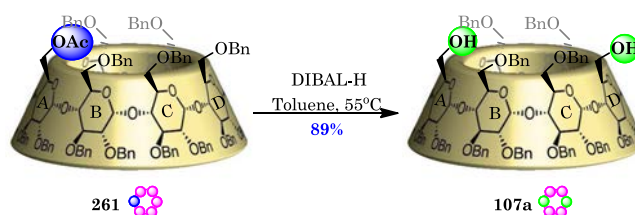
## 1. Introduction

DIBAL-H-mediated debenzoylation is an efficient method for the functionalization of cyclodextrins, by which, benzyl groups on perbenzoylated  $\alpha$ -cyclodextrin or monol- $\alpha$ -cyclodextrin can be removed regioselectively, affording a unique diol-cyclodextrin **107a** with excellent yields<sup>100</sup> (Scheme IV-1).



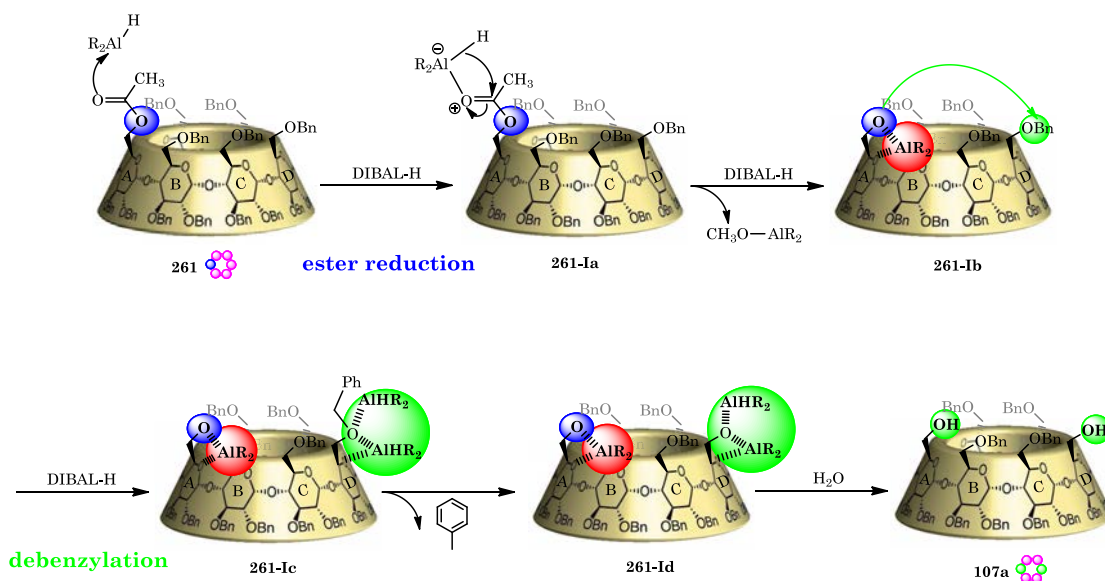
**Scheme IV-1:** DIBAL-H-mediated de-*O*-benzoylation on the primary rim of cyclodextrins

Monoacetate-cyclodextrin **261**, was prepared from acetylation of monol-cyclodextrin **130** with acetic anhydride in pyridine. It was submitted to the action of DIBAL-H in toluene, as we imagined, giving diol-cyclodextrin **107a** as a single product in 89% yield (Scheme IV-2).



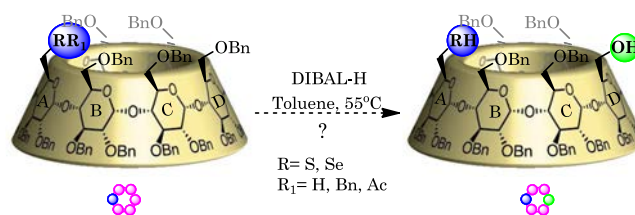
**Scheme IV-2:** Diol-cyclodextrin formed from monoacetate-cyclodextrin **261** by DIBAL-H

In the case of the perbenzoylated or monol-cyclodextrins, the reason for the debenzoylation to take place on the diametrically opposed position (glucose unit **D**), is the steric hindrance of the aluminum chelation during the first debenzoylation (for perbenzoylated-CD) or the initial deprotonation (for monol-CD). Similarly, in the case of monoacetate-cyclodextrin **261**, the steric crowding is caused by ester reduction with DIBAL-H (**261-Ib**, Scheme IV-3).



**Scheme IV-3:** Proposed mechanism for the formation of diol-cyclodextrin from monoacetate-cyclodextrin **261** by DIBAL-H

Now, we can synthesize diol-cyclodextrin **107a** from perbenzylated, monol- or monoacetate-cyclodextrins in good yields. All these reactions result from the ability of oxygen atoms to coordinate with aluminum reagents. Sulfur and selenium are in the same group as oxygen, belonging to chalcogen, and to the best of our knowledge, the action of DIBAL-H on sulfur- or selenium-derived cyclodextrins is still underexplored. We therefore envisaged to employ the reactivity of DIBAL-H on sulfur- and selenium-derived cyclodextrins (Scheme IV-4).

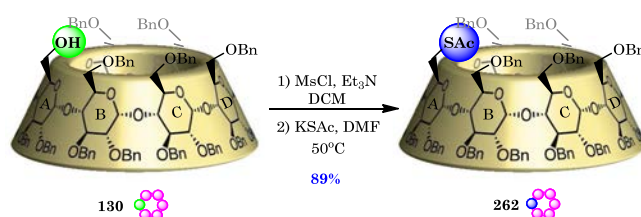


**Scheme IV-4:** Debenzylation of sulfur- or selenium-derived cyclodextrins by DIBAL-H

## 2. DIBAL-H induced selective functionalization of sulfur-derived $\alpha$ -cyclodextrins

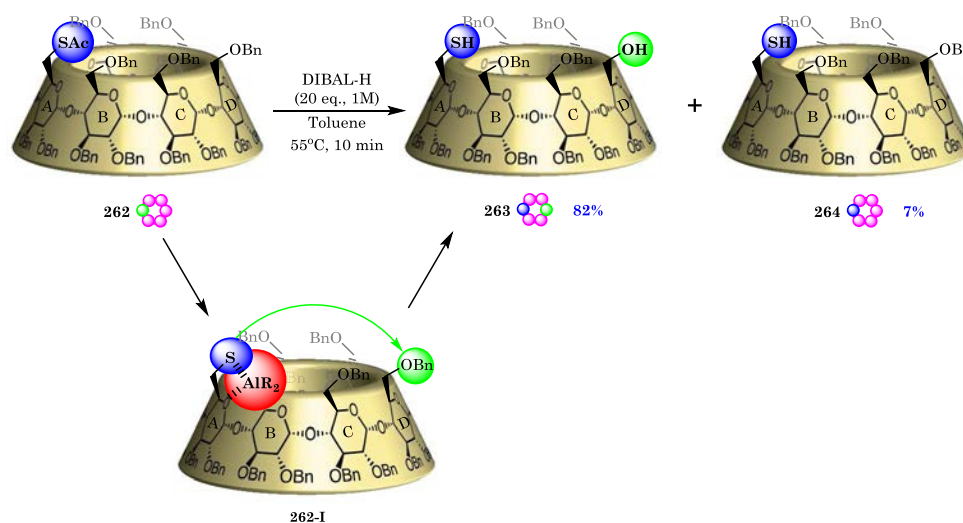
### 2.1 Thioester-reduction/debenzylation

Introduction of the sulfur atom was firstly operated by nucleophilic substitution using thioacetate (Scheme IV-5). A mesyl group was introduced by reaction of cyclodextrin **130** with methanesulfonyl chloride in the presence of triethylamine. It was followed by a nucleophilic substitution reaction with potassium thioacetate in DMF at 50°C, giving thioacetate-cyclodextrin **262** in 89% yield.



Scheme IV-5: Synthesis of thioacetate-cyclodextrin **262**

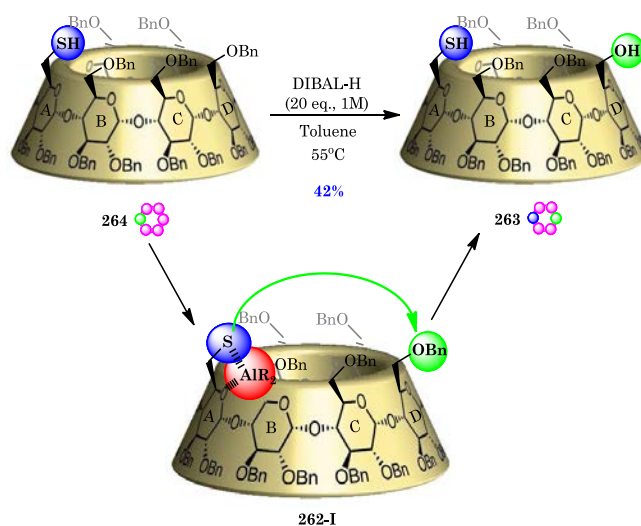
Once thioacetate-cyclodextrin **262** was prepared, a preliminary test demonstrated that AD-thiol-monol-cyclodextrin **263** was generated in 42% yield, with 12% yield of thiol-cyclodextrin **264** and a mixture of diol-cyclodextrins. Careful control of the reaction time (10 min), allowed to reach an excellent yield of 82% (Scheme IV-6). During this process, thioacetate was firstly reduced by DIBAL-H to form the sterically hindered aluminum complex (**262-I**), which oriented the debenzoylation on the farthest position **D**.



Scheme IV-6: Synthesis of thiol-monol-cyclodextrin by the action of DIBAL-H



Cyclodextrin **264** was prepared from cyclodextrin **262** by Zemplin deacetylation conditions. It then underwent the action of DIBAL-H to give cyclodextrin **263** in 42% yield. The mechanism resembles that in the case of monol-cyclodextrin **130**. The steric hindrance was formed by deprotonation of thiol with DIBAL-H (Scheme IV-7).



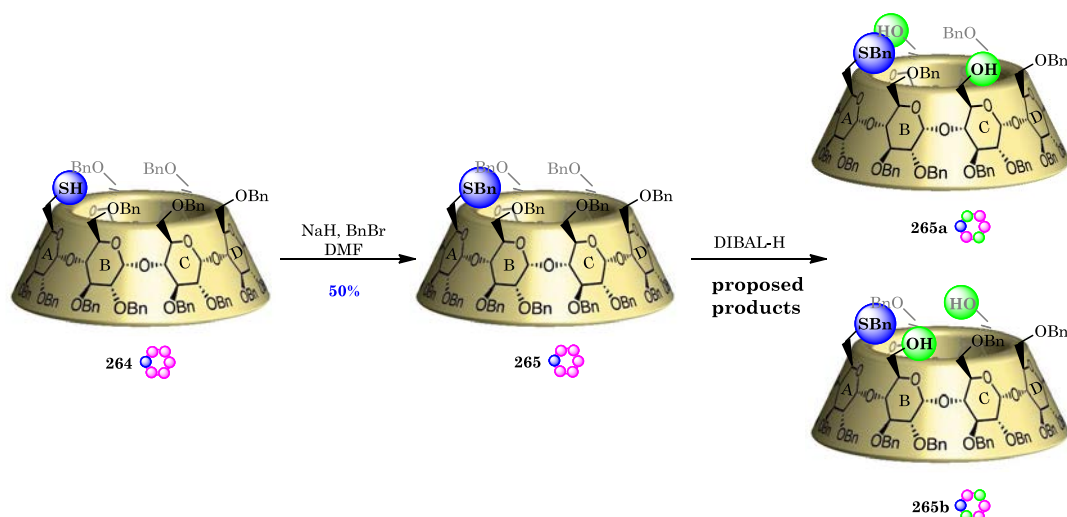
**Scheme IV-7:** Synthesis of thiol-monol-cyclodextrin from thiol-cyclodextrin by DIBAL-H

Consequently, a new site-directing debenzilation rule was uncovered. The steric hindrance caused by ester reduction or thiol deprotonation of DIBAL-H, can orient the debenzilation selectively. This paves the way to prepare cyclodextrin patterns containing thiol and hydroxyl groups.

## 2.2 The difference of reactivity of SBn and OBn groups in DIBAL-H debenzilation

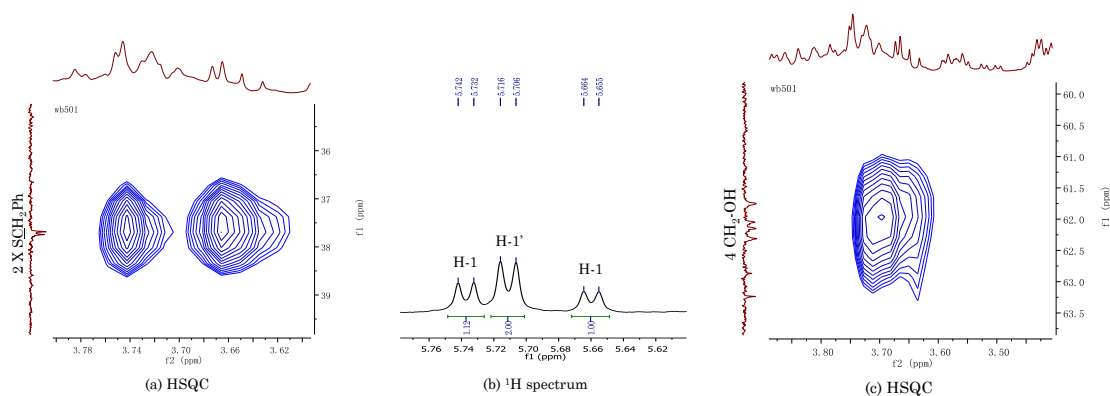
Gratifyingly, introduction of thiol or thioacetate groups on the primary rim of cyclodextrins, gave encouraging results during DIBAL-H-mediated debenzilation. Then, thiobenzyl group was imported to study the difference of reactivity between the *O*-benzyl and the *S*-benzyl groups.

Thiobenzyl-cyclodextrin **265** was prepared by benzylation of thiol-cyclodextrin **264** with benzyl bromide in the presence of sodium hydride in DMF. Then, cyclodextrin **265** was subjected to the action of DIBAL-H (Scheme IV-8). In the course of this reaction, mass spectrometry was employed to monitor the process of the reaction. When the di-debenzylated product was the major product, the reaction was quenched and a sequence of work-up and purification, gave a mixture of inseparable di-debenzylated regioisomeric products **265a** and **265b**.



**Scheme IV-8:** Synthesis of thiobenzyl-cyclodextrin and DIBAL-H debenzylation

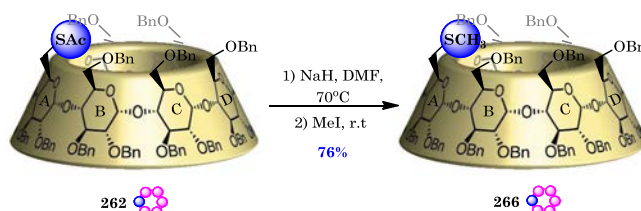
In order to investigate this reaction, a series of NMR spectra were made. As shown in Figure IV-2, the benzyl group attached to the sulfur atom was untouched (Figure IV-2a). On the basis of  $^1\text{H}$  NMR analysis, there were two products obtained with a ratio of 1:2 under the action of DIBAL-H (Figure IV-2b). Figure IV-2c showed that 4 alcohols were released according to the characteristic chemical shifts (62 ppm) of primary carbons attached to the hydroxyls.



**Figure IV-2:** NMR (400 MHz, 300 K,  $\text{CDCl}_3$ ) spectral analysis of thiobenzyl-cyclodextrin **265** under the action of DIBAL-H. (a) Correlation of S-benzylic carbons and their protons; (b)  $^1\text{H}$  spectrum of H-1s; (c) Correlation of C-6s and the corresponding H-6s

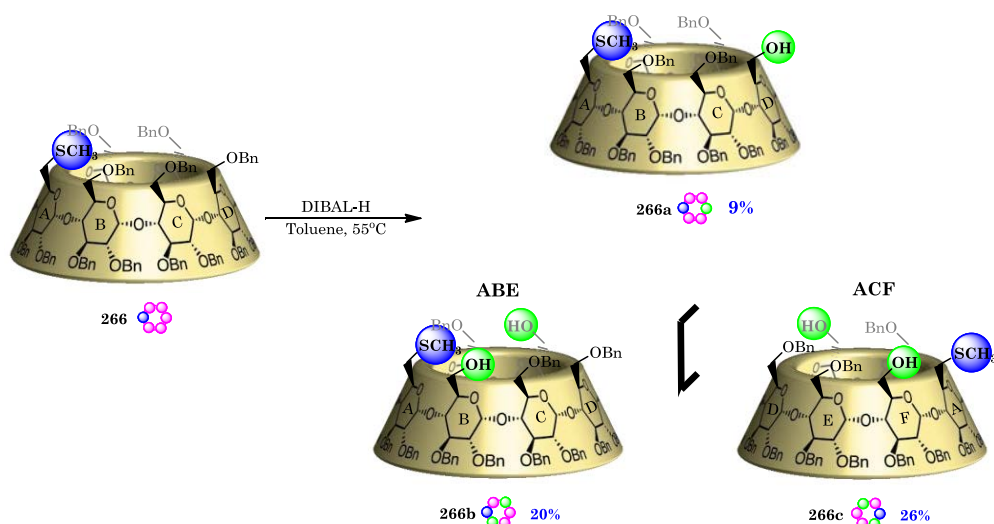
Based on the NMR spectral analysis, we speculated that the benzyl group attached to the sulfur atom was immune to the action of DIBAL-H. To confirm this assumption, an alternative cyclodextrin **266** was synthesized with a methyl group attached to the sulfur atom.

Cyclodextrin **266** was synthesized using a method developed by Krief<sup>136</sup>. It was used initially in chemoselective reduction of organoselenocyanates to selenolates with metal hydrides. We tried this method on thioacetate-cyclodextrin **262**, by reaction with sodium hydride in DMF at 70°C for 30 min to give the corresponding sodium thiolate, which was then involved in the subsequent alkylation with methyl iodide to produce thiomethyl-cyclodextrin **266** in 76% yield (Scheme IV-9).



**Scheme IV-9:** Synthesis of thiomethyl-cyclodextrin **266**

Cyclodextrin **266** underwent the action of DIBAL-H using similar conditions as in the case of thiobenzyl-cyclodextrin **265**. After being stirred for 30 min, mass spectrometry showed that di-debenzylated products were the major products. Importantly, at first glance, mass spectrum indicated that the methyl group attached to the sulfur atom was immune to the action of DIBAL-H. By means of chromatographical purification, together with mono-debenzylated cyclodextrin **266a**, two di-debenzylated cyclodextrin **266b** and **266c** were obtained with a ratio of 3:4, in 20% and 26% yields, respectively (Scheme IV-10).



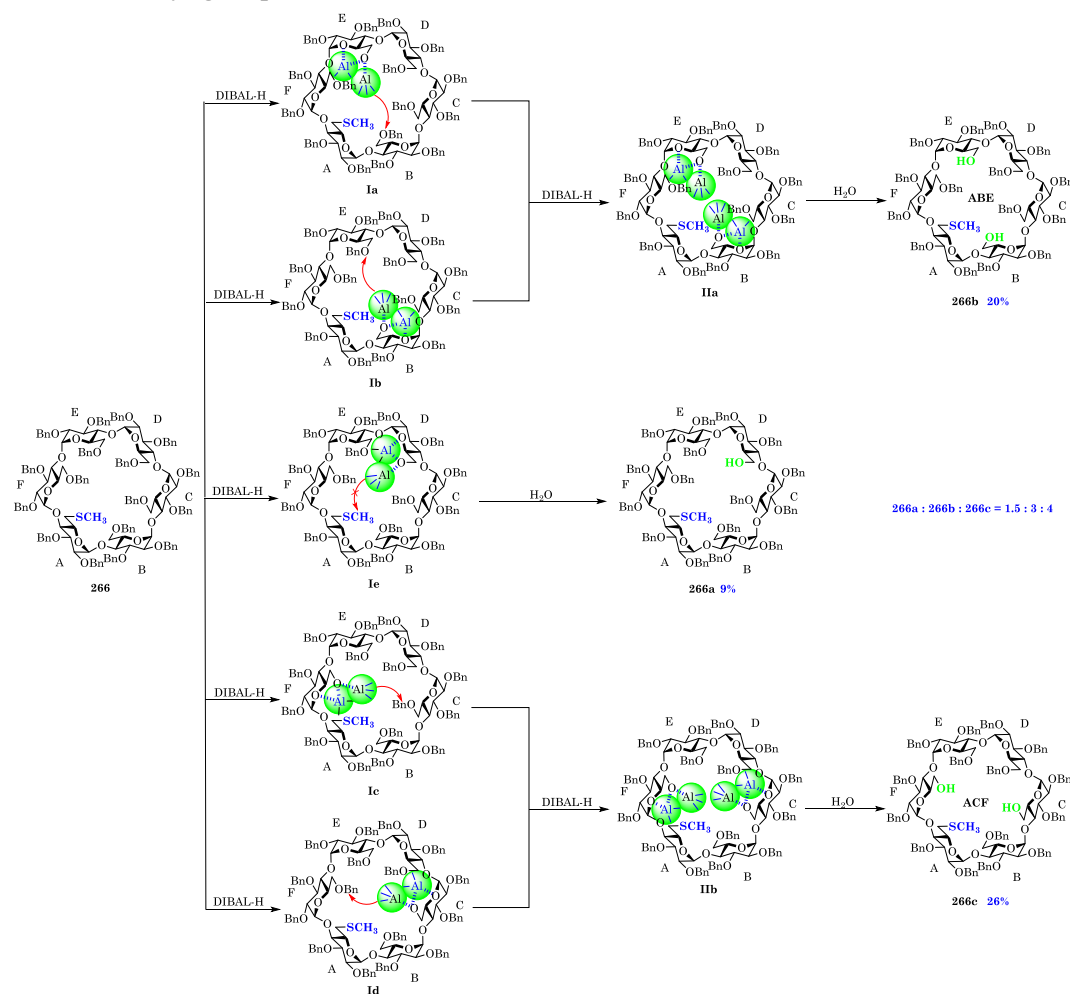
**Scheme IV-10:** The action of DIBAL-H on thiomethyl-cyclodextrin

The structures of these isomers were thoroughly characterized by NMR spectroscopy. Cyclodextrin derivative **266b** bears a free hydroxyl on the counterclockwise position (sugar unit **B**) to sugar unit **A** and another hydroxyl on the diametrically opposed position (sugar

<sup>136</sup> A. Krief, C. Delmotte, W. Dumont, *Tetrahedron*, **1997**, 53, 12147.

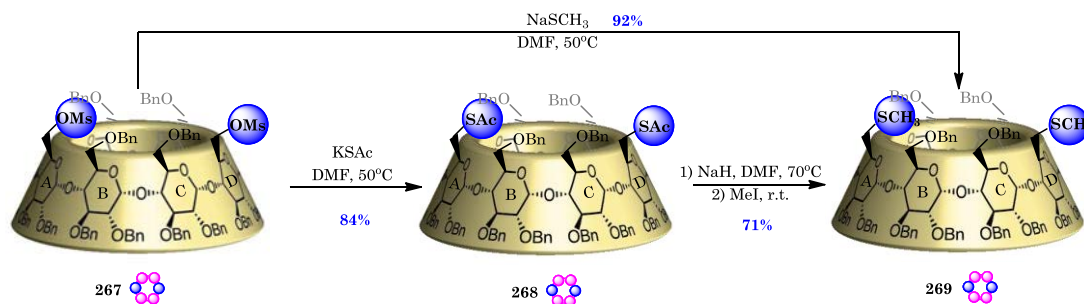
unit **E**) to sugar unit **B**. On the contrary, cyclodextrin **266c** was the pseudo-enantiomer of cyclodextrin **266b**, with a hydroxyl on the clockwise position (sugar unit **F**) and another one on the diametrically opposite position (sugar unit **C**) to the first hydroxyl. The structure of mono-debenzylated cyclodextrin **266a** was verified by comparison with product formed by the selective benzylation of thiol group of cyclodextrin **263**, indicating that a benzyl group was removed on the diametrically opposed position of sugar unit **A**.

In order to explain this outcome, we proposed a plausible mechanism. Thiomethyl group has no coordination with aluminum reagents, perhaps because of the weak reaction between the soft base thiomethyl and the hard acid aluminum reagent. Thus the first debenzylation might happen simultaneously on five different positions, i.e. sugar units **B**, **C**, **D**, **E** and **F** to form intermediates **Ia**, **Ib**, **Ic**, **Id** and **Ie** (Scheme IV-11). Then due to the steric hindrance caused by the first debenzylation, the following aluminum reagents attach to the diametrically opposed positions. Intermediates **Ia** and **Ib** were thus transformed into the same intermediate **IIa**. Likewise, intermediate **IIb** was generated by the action of DIBAL-H with intermediates **Ic** or **Id**. Finally the hydrolysis gave cyclodextrin derivatives **266b** and **266c**. For aluminum complex **Ie**, the debenzylation just stopped at the monol stage because of its opposed thiomethyl group.



**Scheme IV-11:** Mechanistic proposal for the debenzylation of thiomethyl-cyclodextrin

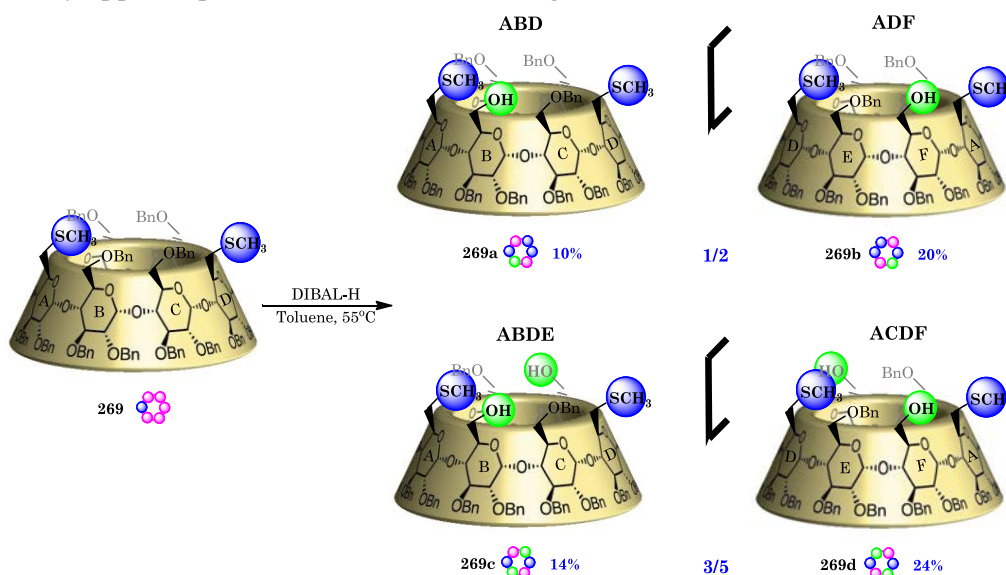
To verify this mechanistic proposal, a  $C_2$ -symmetrical cyclodextrin derivative **269** was prepared with two thiomethyl groups on diametrically opposed positions. Using Krief's method<sup>136</sup>, treatment of dithioacetate cyclodextrin **268** with sodium hydride and sequential methylation, gave cyclodextrin **269** with a yield of 60% in two steps (Scheme IV-12). Alternatively and more efficiently, dimesylated-cyclodextrin **267**, through  $S_N2$  substitution reaction with sodium methanethiolate in DMF, gave cyclodextrin **269** in 92% yield.



**Scheme IV-12:** Synthesis of dithiomethyl-cyclodextrin **269**

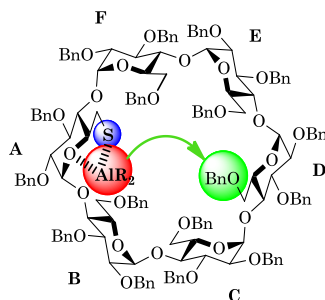
Cyclodextrin **269** reacted with DIBAL-H for 10 min, and mass spectrometry showed that mono-debenzylated product and di-debenzylated product were generated. By chromatographical purification and NMR analysis, four products were obtained, two mono-debenzylated isomers **269a** and **269b** in 10% and 20% yields, two di-debenzylated isomers **269c** and **269d** in 14% and 24% yields, respectively (Scheme IV-13).

This reaction proceeded as in the case of thiomethyl-cyclodextrin **266**, the first debenzylation reaction occurred on both sides (counterclockwise **B** and clockwise **F** sides) of thiomethyl group, giving mono-debenzylated isomers **269a** and **269b**, then the formed sterically hindered aluminum species forced the second debenzylation to take place on the diametrically opposed positions **E** and **C**, affording isomeric diols **269c** and **269d**.



**Scheme IV-13:** The action of DIBAL-H on dithiomethyl-cyclodextrin

Until now, we disclosed that, 1) thioacetate group can orient the debenzoylation on the farthest position due to the formation of the sterically hindered aluminum complex after ester reduction (Figure IV-4); 2) thiol-cyclodextrin behaves towards debenzoylation as monol-cyclodextrin owing to the initial deprotonation by DIBAL-H (Figure IV-4); 3) thiomethyl and thiobenzyl are two functions immune to the action of DIBAL-H probably due to the weak interaction between the soft sulfur base and the hard aluminum acid.

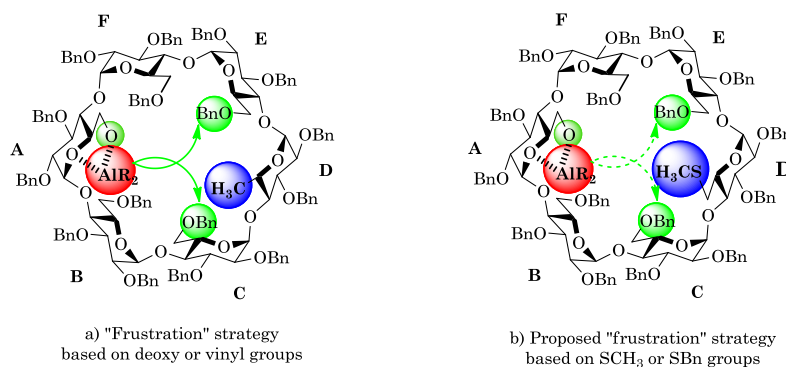


**Figure IV-4:** Site-directing rule based on sulfur-derived cyclodextrins

Aluminum complex was formed either by thioester reduction with DIBAL-H or by DIBAL-H deprotonation of thiol-cyclodextrin.

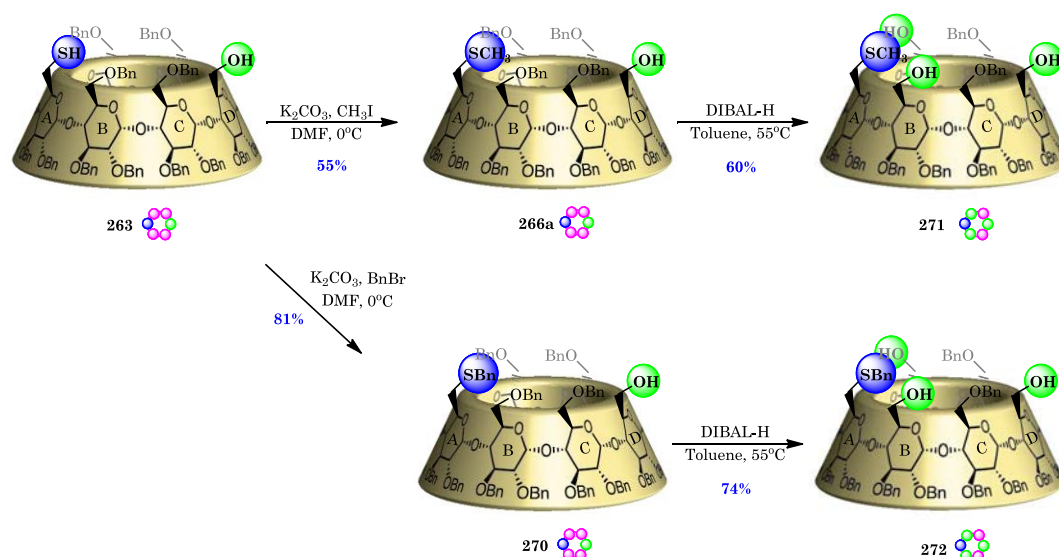
### 2.3 A new “frustration” strategy based on sulfur-derived cyclodextrins

In Chapter II, we showed a “frustration” strategy<sup>106</sup> which combined two strategies, using a deoxy or a vinyl function located on the diametrically opposed position to a free hydroxyl or an azido group. By means of this strategy, a tetradifferentiated cyclodextrin with high degree of complexity was reached (a, Figure IV-5). During the study of the action of DIBAL-H on sulfur-derived cyclodextrins, we found that groups SCH<sub>3</sub> or SBn substituted benzyloxy group on position 6 were immune to the action of DIBAL-H. Inspired by the precedent “frustration” strategy, we speculated that such a strategy might be also operated on the sulfur-derived cyclodextrins (b, Figure IV-5).



**Figure IV-5:** “Frustration” strategy

To verify our hypothesis, two sulfur-derived cyclodextrins **266a** and **270** with SCH<sub>3</sub> and SBn groups diametrically opposed to a free hydroxyl group were synthesized. Taking advantage of the acidic difference between thiol and hydroxyl (pK<sub>a</sub>≈10 for SH, and 15 for OH), using weak base potassium carbonate in DMF, the thiols were selectively deprotonated, this was followed by their alkylations with CH<sub>3</sub>I or BnBr to give cyclodextrins **266a** and **270** in 55% and 81% yields, respectively<sup>137</sup> (Scheme IV-14). The action of DIBAL-H was then performed on cyclodextrin **266a** under usual conditions (1 M DIBAL-H, 20 eq., 55°C), when triol-cyclodextrin was the major product monitored by mass spectrometry, the reaction was stopped and chromatographical purification gave a unique product in 60% yield. To our delight, NMR spectral characterization indicated that a triol cyclodextrin **271** was obtained with two released free alcohols on both sides of thiomethyl function. Likewise, thiobenzyl-derived cyclodextrin **270** also gave the same result, another triol-cyclodextrin **272** in 74% yield.



**Scheme IV-14:** Synthesis of triol-cyclodextrins by new “frustration” strategy

Hence, these results expand the previously depicted “frustration” strategy, allowing the access to tridifferentiated cyclodextrins with three alcohols in a very regioselective manner.

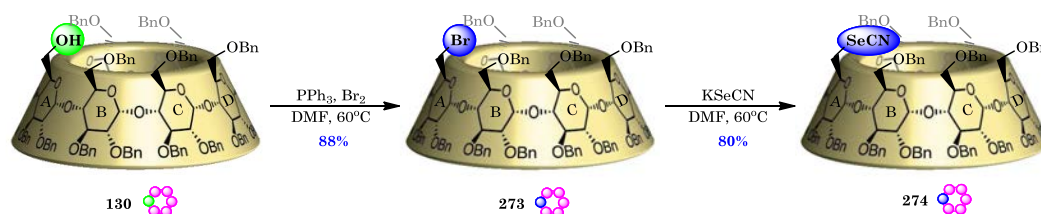
### 3. DIBAL-H induced selective functionalization of selenium-derived $\alpha$ -cyclodextrins

Some quite encouraging results have been afforded when sulfur-derived cyclodextrins underwent the action of DIBAL-H, allowing to reach different cyclodextrin derivatives. To highlight the versatility of this method, selenoacetate was introduced on the primary rim of cyclodextrin in several steps to see whether it had a similar site-directing effect as in the case

<sup>137</sup> D. Tsuchiya, M. Tabata, K. Moriyama, H. Togo, *Tetrahedron*, **2012**, 68, 6849.

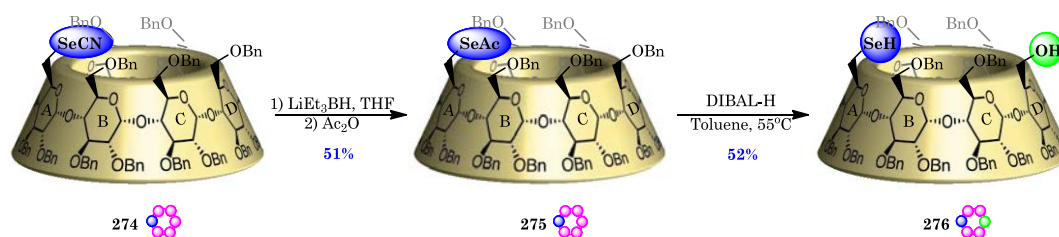
of thioacetate-cyclodextrin.

A sequence of reactions were carried out to access selenoacetate cyclodextrin. Bromo-cyclodextrin **273** was prepared in 88% yield by Appel Reaction<sup>73</sup>, using bromine in the presence of triphenylphosphine at 60°C. It was followed by a direct substitution reaction of selenocyanate in DMF, giving cyclodextrin **274** in 80% yield<sup>138</sup> (Scheme IV-15).



**Scheme IV-15:** Synthesis of selenocyanate-cyclodextrin

The selenocyanate **274** was converted into the corresponding selenoacetate **275**. By reduction with  $\text{LiEt}_3\text{BH}$  (super-hydride) followed treatment with acetic anhydride, cyclodextrin **275** was obtained in 51% yield<sup>139</sup>. Then it was subjected to the action of DIBAL-H, the sole mono-debenzylated product **276** was obtained in 52% yield (Scheme IV-16). Through the NMR analysis, its structure was elucidated as A-selenol-D-alcohol cyclodextrin **276**. Initially, the selenoester was reduced by DIBAL-H, which thereafter induced the debenzylation on the diametrically opposed position. In this case, although with a slightly lower yield, the outcome proved firmly that ester-reduction/debenzylation can be another site-directing method and efficiently applied to the functionalization of cyclodextrins.



**Scheme IV-16:** Selenoacetate-induced debenzylation by DIBAL-H

We have indicated that, SBn group was immune to the action of DIBAL-H. When cyclodextrin **265** reacted with DIBAL-H, a mixture of inseparable isomers were obtained. Hence, we will study whether SeBn group has a similar behavior with regard to the action of DIBAL-H.

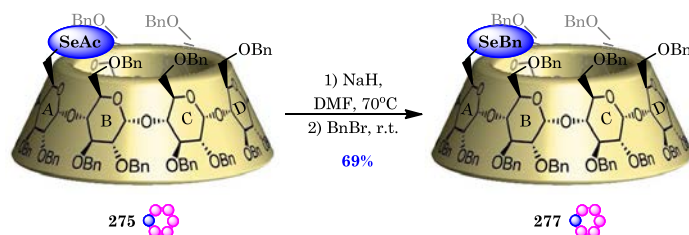
Selenobenzyl-cyclodextrin was synthesized using the same conditions<sup>136</sup> as in the case of thiomethyl-cyclodextrin **266**. Treatment of cyclodextrin **275** in the presence of sodium

<sup>138</sup> Y. Lee, G. M. Morales, L. Yu, *Angew. Chem. Int. Ed.*, **2005**, 44, 4228.

<sup>139</sup> Y. Ie, T. Hirose, A. Yao, T. Yamada, N. Takagi, M. Kawai, Y. Aso, *Phys. Chem. Chem. Phys.*, **2009**, 11, 4949.

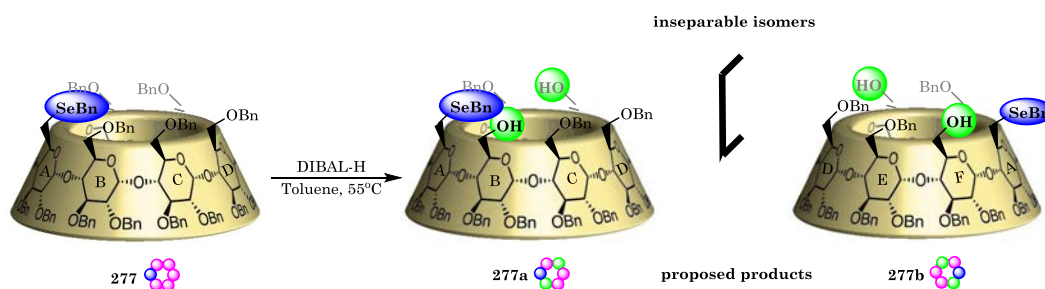


hydride, and followed benzylation with benzyl bromide, gave cyclodextrin **277** in 69% yield (Scheme IV-17).



**Scheme IV-17:** Synthesis of selenobenzyl-cyclodextrin

Cyclodextrin **277** underwent the action of DIBAL-H under the same conditions (1 M, 20 eq.  $55^\circ\text{C}$ ), after being reacted for 45 min, mass spectrum indicated that di-debenzylated products were the major components of the reaction mixture (Scheme IV-18). With the help of NMR characterization, we confirmed that benzyl group attached to selenium atom was untouched during the reaction of DIBAL-H. According to the previously disclosed mechanism, we proposed that the formed diol-cyclodextrins were a pair of pseudo-enantiomers **277a** and **277b**.

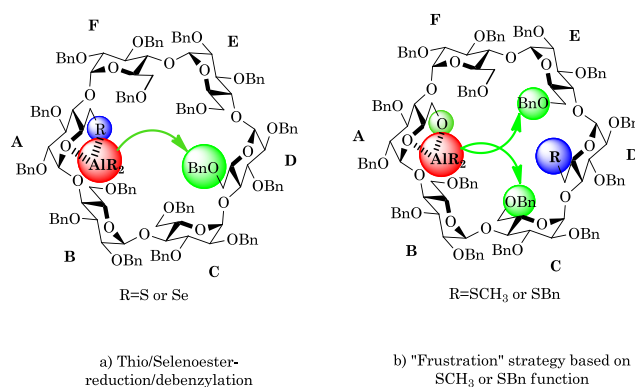


**Scheme IV-18:** DIBAL-H debenylation on selenobenzyl-cyclodextrin

## 4. Conclusion

In conclusion, in this chapter a lot of research work were performed concerning sulfur- and selenium-derived cyclodextrins, and gratifyingly, gave some quite promising results. Besides many sulfur- and selenium-derived cyclodextrins were synthesized in a regioselective fashion, most importantly, two site-directing rules were disclosed:

- 1) Thioacetate or selenoacetate functions can orient a debenzoylation on the farthest position due to the formation of sterically hindered aluminum complex after ester reduction (a, Figure IV-6). As well, thiol-cyclodextrin and selenol-cyclodextrin behavior in debenzoylation is similar to that of monol-cyclodextrin owing to the initial deprotonation by DIBAL-H (a, Figure IV-6);
- 2) On the basis of the immunity of  $\text{SCH}_3$  or  $\text{SBn}$  to the action of DIBAL-H, a new “frustration” rule was depicted. The existing hydroxyl can induce a double-debenzoylation on both sides of  $\text{SCH}_3$  or  $\text{SBn}$  functions (b, Figure IV-6). We believe that this site directing rule can also work on cyclodextrins with the hydroxyl group replaced by an azido group, or  $\text{SeCH}_3$  and  $\text{SeBn}$  derived cyclodextrins.



**Figure IV-6:** Site-directing rules based on sulfur- and selenium-derived cyclodextrins



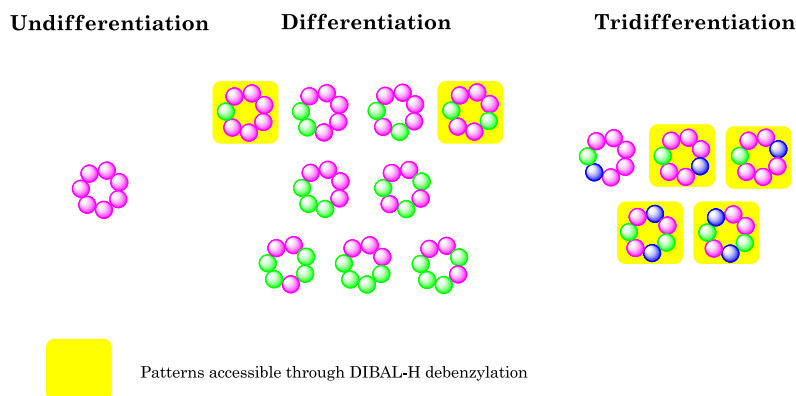
## **CHAPTER V**

# **MULTIDIFFERENTIATION OF $\beta$ -CYCLODEXTRIN, TOWARDS HEPTADIFFERENTIATED PATTERNS**



## 1. Introduction

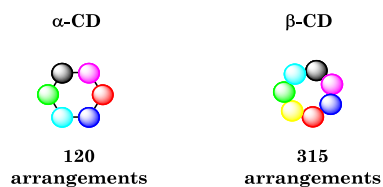
Functionalization of  $\alpha$ -cyclodextrin has progressed in the last decade, especially after the development of DIBAL-H-mediated debenzylation and the attached site-directing rules. Functionalized derivatives displaying up to hexadifferentiated patterns, have been reached and some of them have been used in diverse fields. However, functionalization of  $\beta$ -cyclodextrin is still a difficult task with few functionalization patterns (Figure V-1) accessible.



**Figure V-1:** Accessible functionalization patterns of  $\beta$ -cyclodextrin

(All corresponding  $\beta$ -cyclodextrin derivatives showed in Chapter II)

The difficulty of functionalization of  $\beta$ -cyclodextrin is well illustrated by combinatorial calculation. In the case of hexadifferentiation of  $\alpha$ -cyclodextrin, the combinatorial calculation demonstrates that when six different functional groups are introduced on the primary rim of  $\alpha$ -cyclodextrin, there are **120** arrangements, while for heptadifferentiation of  $\beta$ -cyclodextrin, much more arrangements (**315** arrangements) are accessible (Figure V-2). Furthermore, the odd number of glucose units in  $\beta$ -cyclodextrin compared to  $\alpha$ -cyclodextrin also multiplies the difficulties of the functionalization patterns.



**Figure V-2:** Hexa- and heptadifferentiated patterns of cyclodextrins

In Chapter III, hexadifferentiation of  $\alpha$ -cyclodextrin has been fulfilled by well-delineated site-directing rules based on DIBAL-H-mediated debenzylation reaction, which highlighted the versatility of this method. Hence, in this chapter, taking advantage of this method and

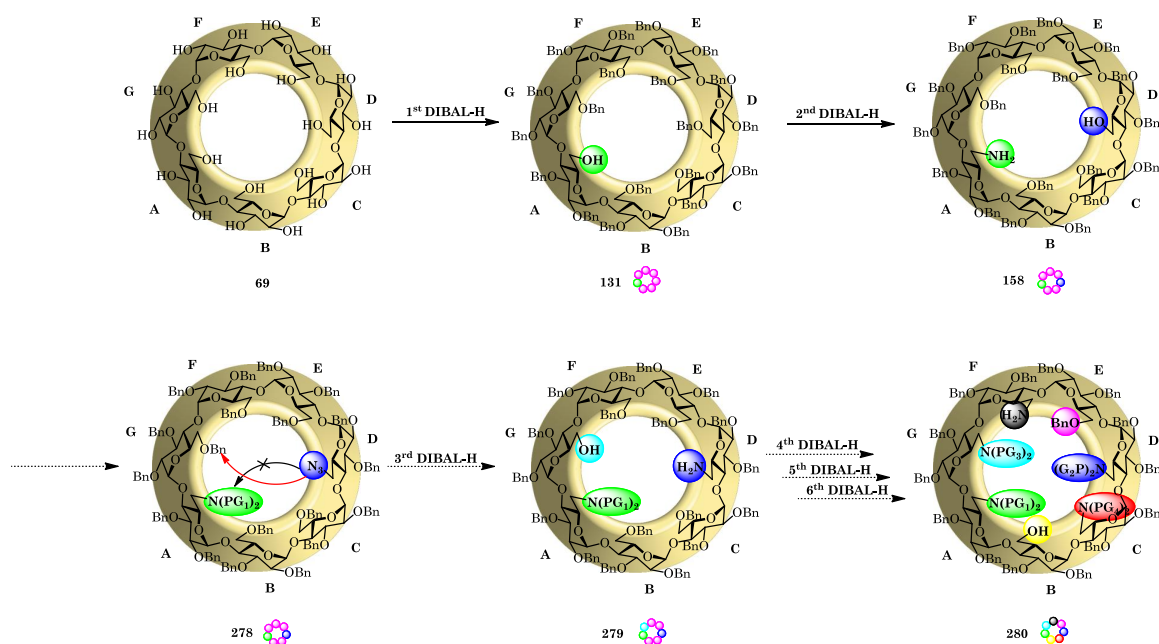
combining the available site-directing rules, we envisage the possibility to access  $\beta$ -cyclodextrin derivatives with higher level of complexity, even towards heptadifferentiated  $\beta$ -cyclodextrin, with 7 different functional groups on its primary rim.

## 2. The amine strategy

Polydifferentiation of cyclodextrins relies on a single mono-debenzylation during a single DIBAL-H-mediated debenylation reaction. On this basis, hexadifferentiation of  $\alpha$ -cyclodextrin has been realized by means of 5 successive debenylation reactions. However, because of the odd number of glucose units and the bigger size of  $\beta$ -cyclodextrin, some site-directing rules are not well applicable, such as symmetrical bridge strategy, giving a mixture of regioisomers<sup>111</sup>. Nevertheless, tandem azide-reduction/debenzylation strategy has proved to be a highly efficient site-directing method for the functionalization of cyclodextrins. Taking advantage of this method, we devised a synthetic strategy to achieve the heptadifferentiation of  $\beta$ -cyclodextrin (Scheme V-1). Cyclodextrin **158** is synthesized starting from native  $\beta$ -cyclodextrin **69** through two DIBAL-H-mediated debenylation reactions<sup>104</sup>. The amine of cyclodextrin **158** could be functionalized by reductive amination<sup>140</sup> with an aldehyde to form a tertiary amine, which is supposed to be inert to the action of DIBAL-H. Subsequent chemical transformations convert the free alcohol into an azide, would give cyclodextrin **278**. Then a tandem azide-reduction/debenzylation (namely third debenylation) will be performed, affording product **279** with a selective debenylation on sugar unit **G** due to the inertness of the tertiary amine towards DIBAL-H. Subsequently, following a repetitive strategy of reductive amination with different aldehydes, azidation and tandem azide-reduction/debenzylation would afforded the ultimate heptadifferentiated  $\beta$ -cyclodextrin **280** possessing different amines on its primary rim.

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<sup>140</sup> A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.*, **1996**, 61, 3849.

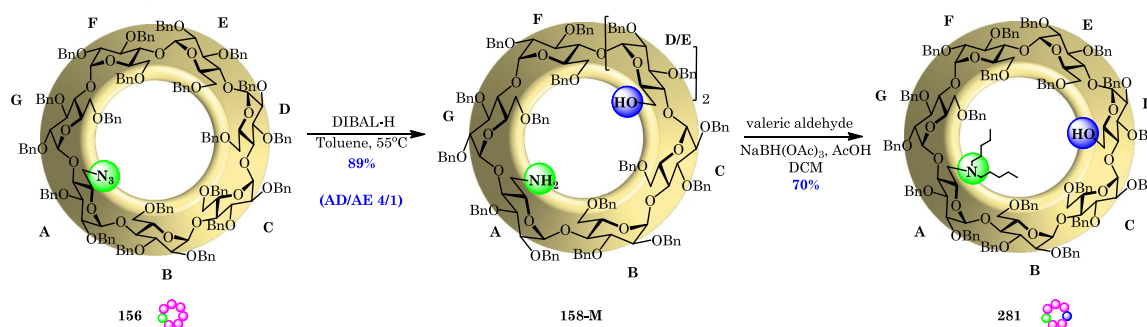


**Scheme V-1:** Synthetic strategy towards heptadifferentiated  $\beta$ -cyclodextrin by 6 successive DIBAL-H-mediated debenzylations (Plain arrows mean the previous reactions; dash arrows mean new reactions presented in this work.)

## 2.1 Alkyl chain strategy based on tandem azide-reduction/ debenzylation

According to the devised strategy (Scheme V-I), different aldehydes will be used to transform the primary amines into tertiary inert ones. In this part, different aldehydes with straight alkyl chains were chosen.

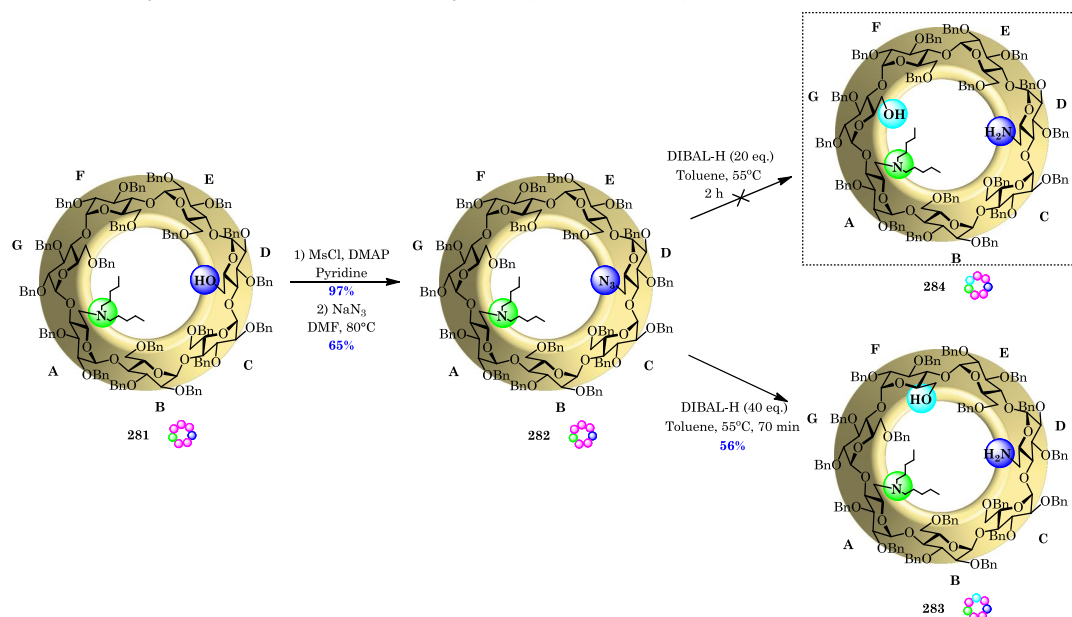
Monoazido- $\beta$ -cyclodextrin **156** was prepared according to our previously reported procedures<sup>104</sup>: mesylation of  $\beta$ -monol cyclodextrin **131** and followed azidation. It was then submitted to the action of DIBAL-H, giving an inseparable mixture (**158-M**) of amino-alcohol cyclodextrins in 89% yield with a ratio of 4:1 (Scheme V-2). This outcome was attributed to the odd number of glucose units of  $\beta$ -cyclodextrin. After protection of the amine with alkyls, the regioisomers could be isolated. The amine was protected by reductive amination<sup>140</sup> with valeric aldehyde and  $\text{NaBH}(\text{OAc})_3$  as the reducing agent, affording the major AD-isomer **281** (Scheme V-2).



**Scheme V-2:** Debzilylation and the amine protection with valeric aldehyde



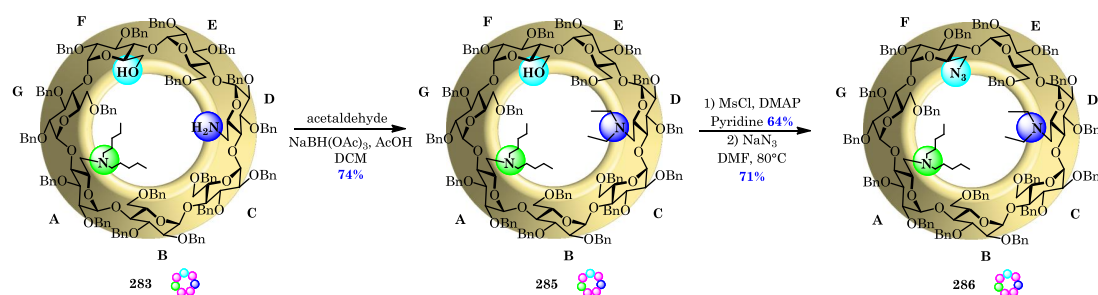
As we mentioned in the synthetic strategy, cyclodextrin **281** was then converted into azido-cyclodextrin **282** in 78% yield (Scheme V-3). The following azide-reduction debenzylation would give D-amino-G-alcohol-cyclodextrin **284**. Consequently, cyclodextrin **282** underwent the action of DIBAL-H under the usual conditions (20 equivalents of DIBAL-H, 1 mol/L, 55°C). However, the reaction did not give the expected amino-alcohol-cyclodextrin, but rather get stuck at the azide-reduction stage. Raising the reaction conditions to 40 equivalents of DIBAL-H, afforded the unexpected amino-alcohol-cyclodextrin **283** in 56% yield (Scheme V-3).



**Scheme V-3:** Second tandem azide-reduction/debenzylation

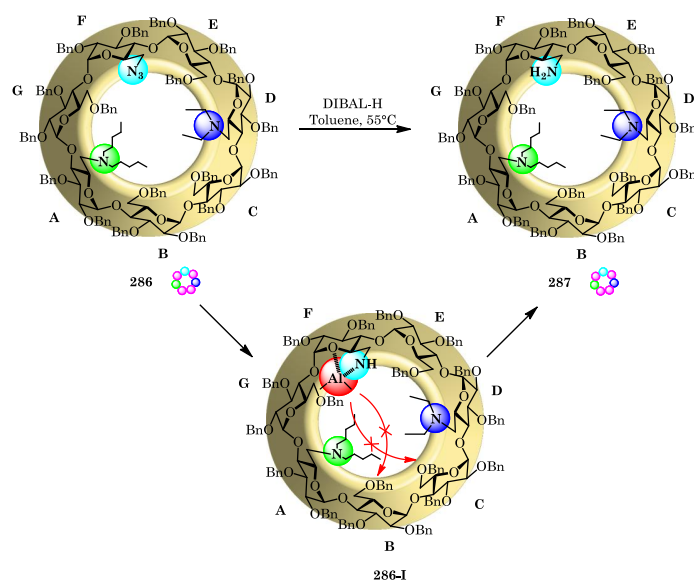
Its structure was elucidated by a **typical NMR characterization procedure**: as shown in Figure V-3. Firstly, all the C-1s and H-1s were identified through HSQC with characteristic chemical shifts of the acetal carbons around 100 ppm (Figure V-3a). As shown in Figure V-3b, sugars **D** and **F** were identified through their C-6D and C-6F characteristically upfield shifted (43 and 60 ppm respectively, compared to 30 ppm). Combining COSY and TOCSY 2D experiments, all the other protons of each unit were attributed since we identified all the H-1s. For example, Figure V-3c showed all the protons of sugars **A** and **D**. In sugar **A**, NOESY indicated a cross-correlation between H-6A and the secondary protons of pentyl groups (Figure V-3d). The correlations between C-6B, C-6C, C-6E, C-6G and their benzylic protons were observed in HMBC (Figure V-3e). Once all the protons of cyclodextrin were attributed, the order of all sugar cycles is determined through NOESY cross coupling between H-4s and H-1s of adjacent sugar units (Figure V-3f). Surprisingly, NOESY spectrum demonstrated that, the debenzylation did not occur on sugar unit **G**, but on sugar unit **F**. The steric hindrance and the flexibility of dipentyl chains might explain this result, hampered the debenzylation on sugar unit **G**, adjacent to sugar unit **A**.





**Scheme V-4:** Synthesis of azido-cyclodextrin **113**

Cyclodextrin **286** was reacted with 40 equivalents of DIBAL-H at 55°C (Scheme V-5) and followed by mass spectrometry. The azide was reduced completely in 15 min, but after 45 min we did not observe any debenzylated product. Therefore, another 20 equivalents of DIBAL-H was added and after another 45 min, mass spectrometry indicated that, amino-cyclodextrin **287** was still the major product, together with traces of debenzylated product. To explain this result, we supposed that the introduction of pentyl and ethyl groups (**286-I**) might prevent the debenzylation because of their steric hindrance and flexibilities.



**Scheme V-5:** DIBAL-H-mediated debenzylation on cyclodextrin **286**

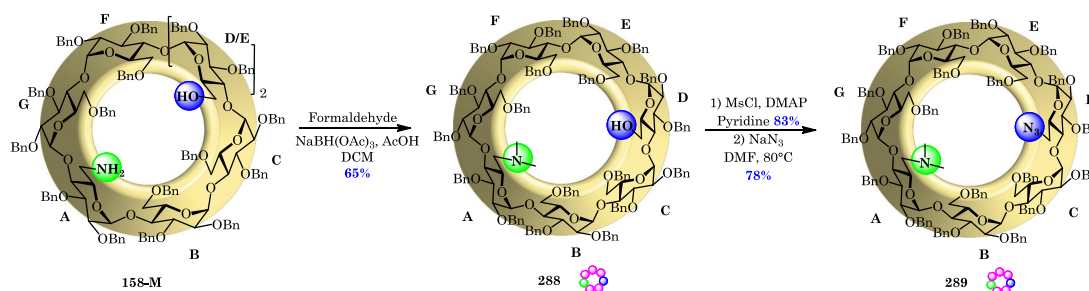
Hence, based on the obtained results, the introduction of larger linear alkyl chains might prevent adjacent debenzylation due to their steric hindrance and flexibilities.

## 2.2 Less hindered linear alkyl-amines and cyclic amines combined strategy

Linear alkyl chains produce an important steric hindrance because they can rotate freely, which might disturb the debenzylation on the primary rim of  $\beta$ -cyclodextrin. To overcome this problem, in this section formaldehyde and glutaraldehyde were employed to form the less

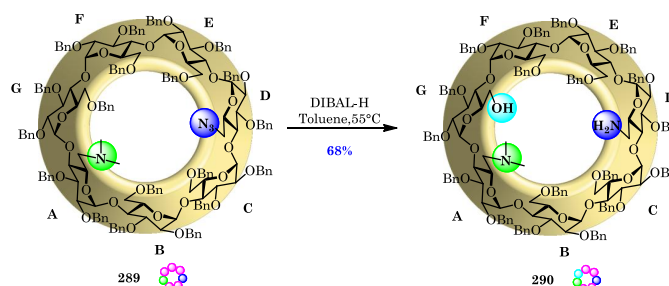
hindered dimethyl protected amine or less flexible *N*-piperidine ring, which could facilitate the further tandem azide-reduction/debenzylation.

So amino-alcohol cyclodextrins **158-M** were modified by reductive amination using formaldehyde, giving AD-isomer **288** in 65% yield (Scheme V-6). Cyclodextrin **289** was prepared for the subsequent debenzoylation reaction by the mesylation and azidation of cyclodextrin **288**.



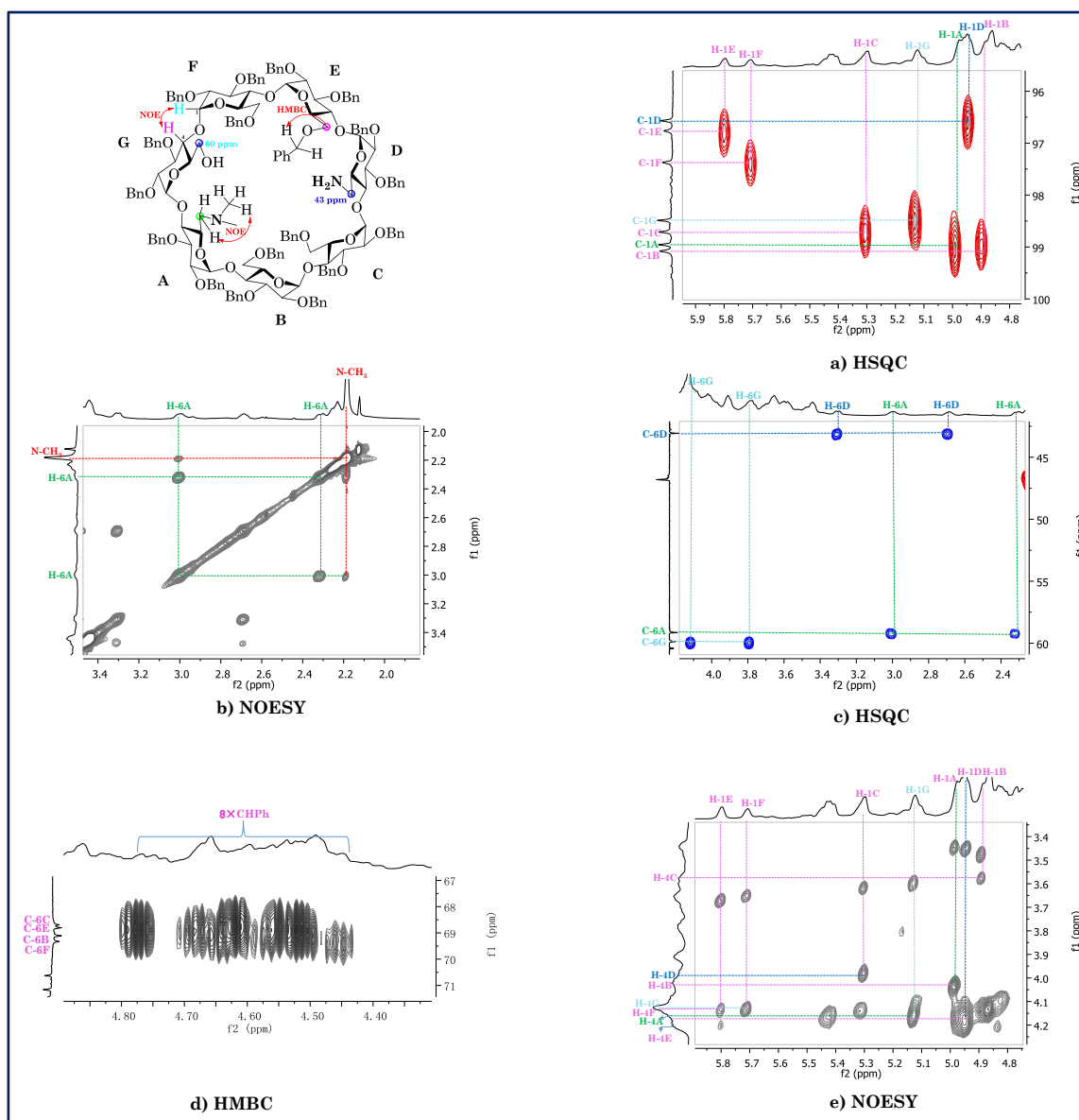
**Scheme V-6: Synthesis of azido-cyclodextrin 289**

Cyclodextrin **289** underwent DIBAL-H-mediated debenzoylation under the same conditions as in the case of dipentyl-cyclodextrin **282** (Scheme V-3), giving cyclodextrin **290** in 68% yield (Scheme V-7).



**Scheme V-7: Azide-reduction/debenzylation to access tetradifferentiated  $\beta$ -cyclodextrin 290**

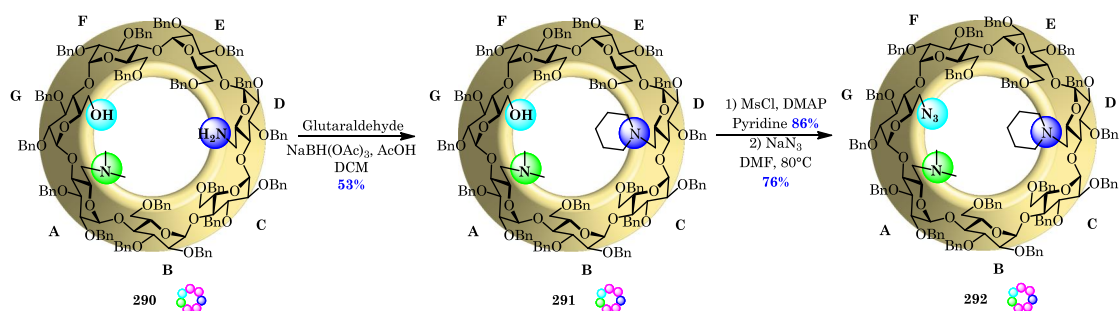
Its structure was confirmed by NMR spectral analysis (Figure V-4) as did in the case of cyclodextrin **283**. The results demonstrated that debenzoylation reaction took place on sugar unit **G** as we imagined, probably due to the lesser steric hindrance of methyl groups on sugar unit **A**, compared to pentyl groups in cyclodextrin **282**.



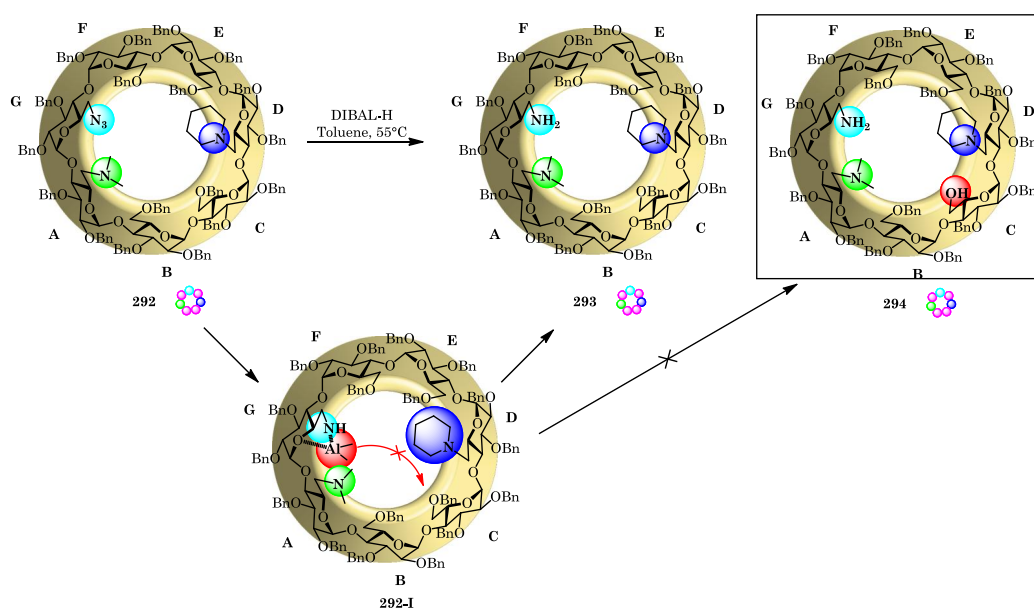
**Figure V-4:** NMR (600 MHz, 300K,  $\text{CDCl}_3$ ) analysis of cyclodextrin **290**

- (a) Correlations of C-1s and H-1s in HSQC; (b) Correlations of H-6A and  $\text{NCH}_3$  in NOESY; (c) Correlations of C-6s and H-6s in HSQC; (d) Correlations of C-6s and benzylic protons in HMBC; (e) Correlations of H-1s and vicinal H-4s in NOESY.

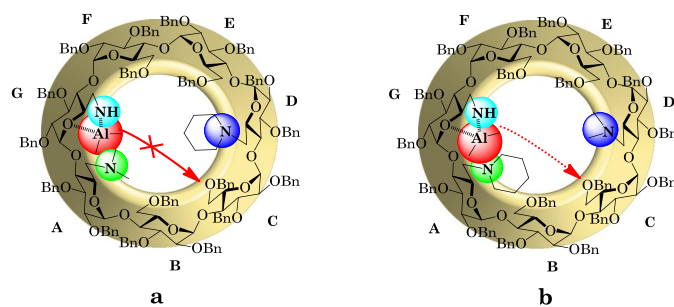
With cyclodextrin **290** in hand, a sequence of chemical transformations: reductive amination by glutaraldehyde, mesylation and azidation, gave azido-cyclodextrin **292** (Scheme V-8).

Scheme V-8: Synthesis of azido-cyclodextrin **292**

The tandem azide-reduction/debenzylation was then performed on cyclodextrin **292** (Scheme V-9). Initially, 50 equivalents of DIBAL-H was employed. After 30 min, mass spectrometry showed that amino-cyclodextrin **293** was the major product with traces of debenzylated product **294**. Therefore, same amount of DIBAL-H was added and after another 1 h, the reaction did not progress. Finally, even total addition of 150 equivalents of DIBAL-H, amino-cyclodextrin **293** was still the major product. In this case, the steric hindrance of piperidine ring might be the reason that prevented the debenzylation.

Scheme V-9: DIBAL-H-mediated debenzylation on cyclodextrin **292**

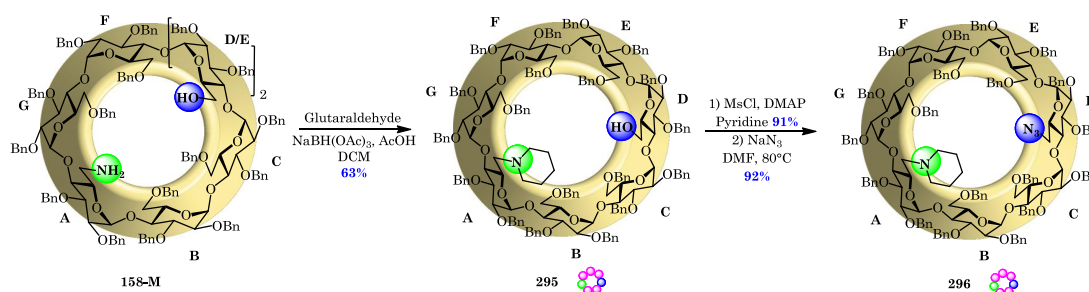
Since piperidine ring on sugar unit **D** probably hampered the debenzylation (Figure V-5a), a new synthetic strategy was devised, switching the protection order of amines, i.e. using methyl as the protection for sugar unit **D**, and piperidine ring for sugar unit **A** (Figure V-5b). Thus, the dimethyl protected amine on sugar unit **D** has less hindrance which might favor the subsequent debenzylation on sugar unit **C**.



**Figure V-5:** Mechanism for DIBAL-H-mediated debenzoylation

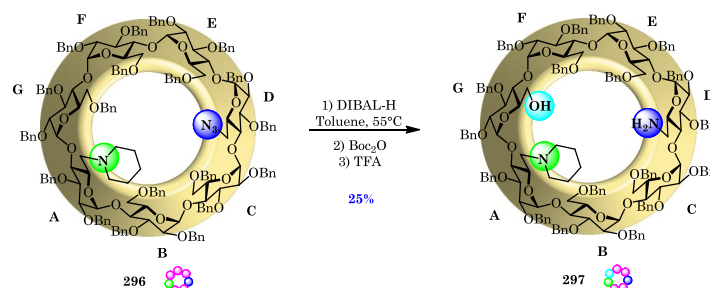
- a) *N*-piperidine ring prevents the debenzoylation on sugar unit C; b) dimethyl group on sugar unit D might favor debenzoylation on sugar unit C.

Cyclodextrin **296** (Scheme V-10) with piperidine ring was prepared in a sequence of reductive amination by glutaraldehyde, mesylation and azidation.



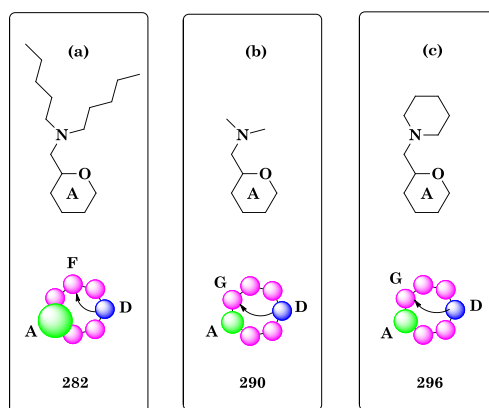
**Scheme V-10:** Synthesis of *N*-piperidine-azido-cyclodextrin

Subsequently, cyclodextrin **296** bearing an azide on sugar unit D was subjected to the action of DIBAL-H (Scheme V-11) under the conditions (1.0 M, 50 equivalents of DIBAL-H, 55 °C) as did in the case of cyclodextrin **282** (Scheme V-3). Mass spectrometry was employed to monitor the reaction process, demonstrating that amino-monol-cyclodextrin **297** was the major product together with amino-cyclodextrin and amino-diol-cyclodextrin. Because of the similar polarities of these three products, the pure product was isolated only after the Boc protection of the amine. Finally, removal of Boc group gave the desired cyclodextrin **297** with 25% yield in 3 steps.



**Scheme V-11:** DIBAL-H-mediated debenzoylation on cyclodextrin **296**

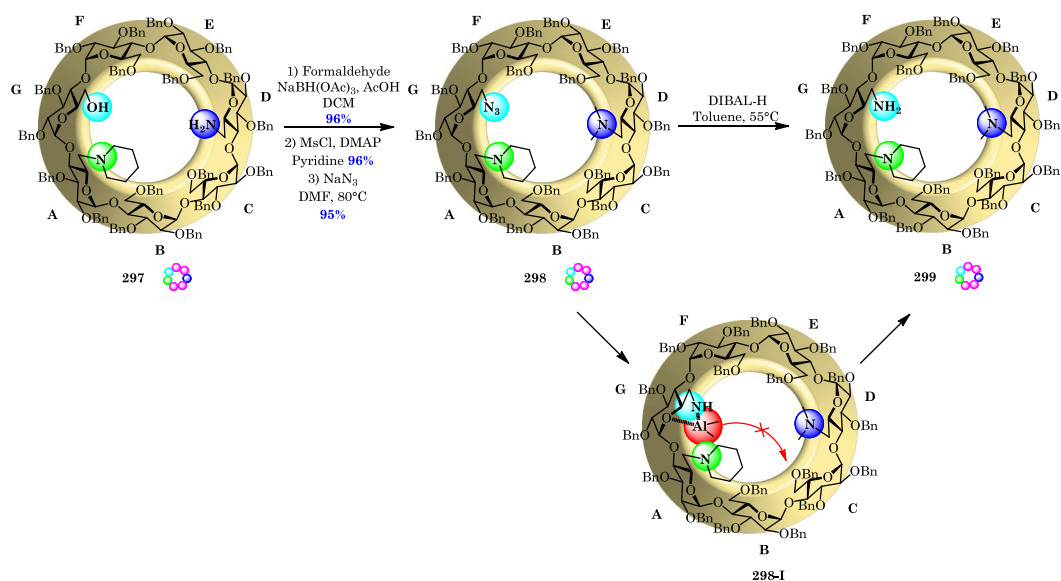
The structure of cyclodextrin **297** was characterized as well by means of NMR spectroscopy, indicating that the debenzylation proceeded on sugar unit **G** as in the case of cyclodextrin **290** (Scheme V-7). As we supposed, larger linear alkyl chain (Figure V-5a) hampers the debenzylation on the clockwise adjacent position. In contrast, the less sterically hindered alkyl groups (Figure V-5b, c) favor this kind of debenzylation.



**Figure V-5:** Rationlization of the debenzylation results induced by alkyl groups

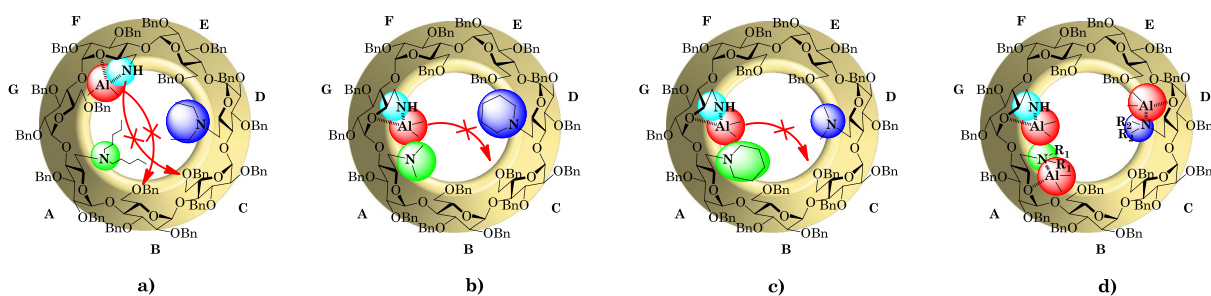
The free amine of cyclodextrin **297** was then protected by methyl groups, and the free alcohol was transformed into an azide using conventional procedures to give cyclodextrin **298** (Scheme V-12). Afterwards, another tandem azide-reduction/debenzylation was attempted on cyclodextrin **298**. Initially, 50 equivalents of DIBAL-H was employed. Frustratingly, as in the case of cyclodextrin **292**, after 30 min, amino-cyclodextrin **299** was the major product with traces of debenzylated product. Another 50 equivalents of DIBAL-H was added and after another 1 h, the major product remains the amino-cyclodextrin **299**, together with traces of amino-alcohol cyclodextrin. In the case of cyclodextrin **292** (dimethyl protection firstly), we attributed the frustration of debenzylation to the steric hindrance of the piperidine ring. We envisaged that the less hindered dimethyl group for the protection of amine on sugar unit **D** would favor the debenzylation reaction on sugar unit **C**, diametrically opposed to unit **G**. However, beyond our expectation, the debenzylation reaction was still unfavorable even under harsh conditions.





**Scheme V-12:** Synthesis of azido-cyclodextrin **298** and the following debenzylation

On the basis of the obtained results, we came to the conclusion that multi-alkyl protected amine strategies cannot afford expected heptadifferentiation on  $\beta$ -cyclodextrin. Instead, it gave the tetradifferentiated motif (Figure V-6). At the outset, we attributed this frustration to the steric hindrance and flexible rotation of the linear alkyl chains (pentyl or ethyl in Figure V-6a). However, when less sterically hindered methyl or less flexible piperidine ring (Figure V-6b and V-6c) were introduced, the same problem still existed. To explain this outcome, we envisage that, the lone electron pairs of the amine probably coordinate with DIBAL-H (Figure V-6d), increasing the whole hindrance on the primary rim of  $\beta$ -cyclodextrin, which is unfavorable to the further DIBAL-H-mediated debenzylation.

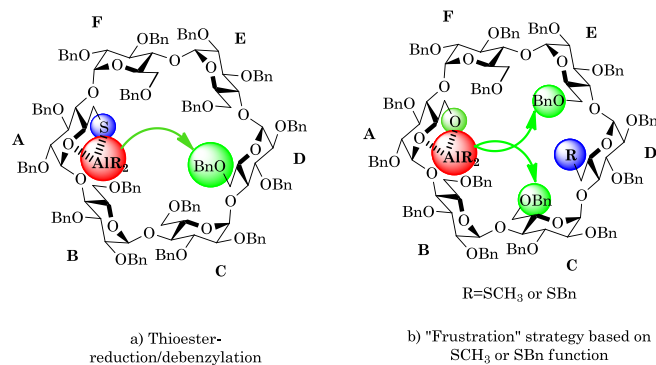


**Figure V-6:** Explanation for the frustration of alkyl-protected amine strategies

### 3. The thioether strategy

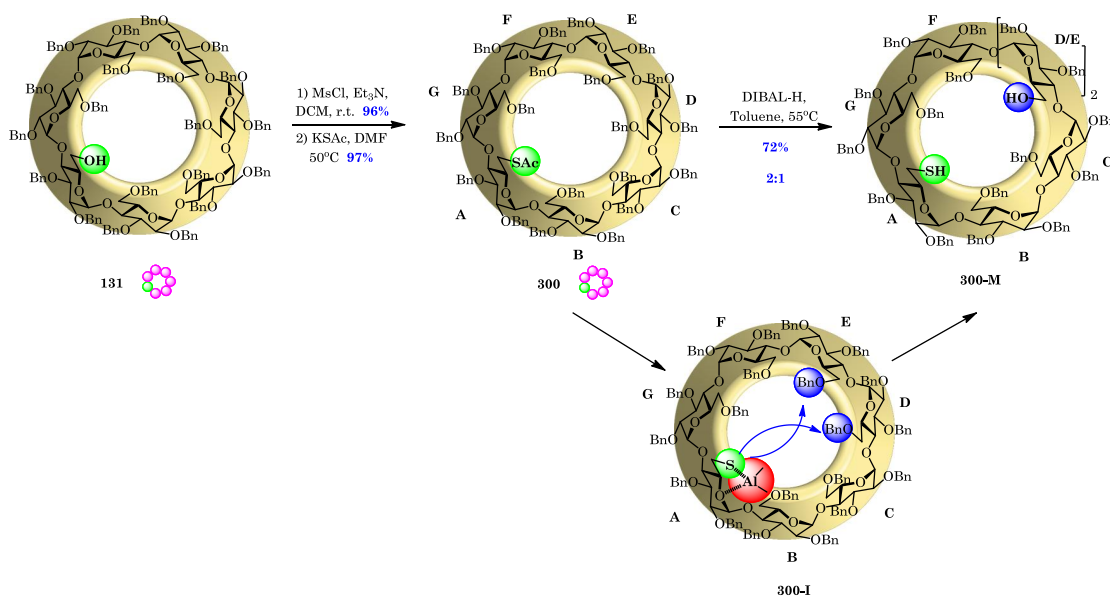
The amine-protection strategy is a dead-end towards heptadifferentiation of  $\beta$ -cyclodextrin, probably due to steric hindrance (in the case of dipentyl-amino-cyclodextrin **282**) caused by the introduced protecting groups or coordination of aluminum reagents by the amines. To solve this problem, new functionalities are necessary, which need to meet some requirements: 1) new functionalities have the capability of orienting debenzylation

regioselectively; 2) protecting groups must be less sterically hindered and immune to the action of DIBAL-H. In Chapter IV, we have shown that SAc group can induce debenzoylation regioselectively (Figure V-7a), and that SCH<sub>3</sub> and SBn are immune to the action of DIBAL-H (Figure V-7b). Therefore, these site-directing groups could be applied on  $\beta$ -cyclodextrin to reach heptadifferentiation of  $\beta$ -cyclodextrin.



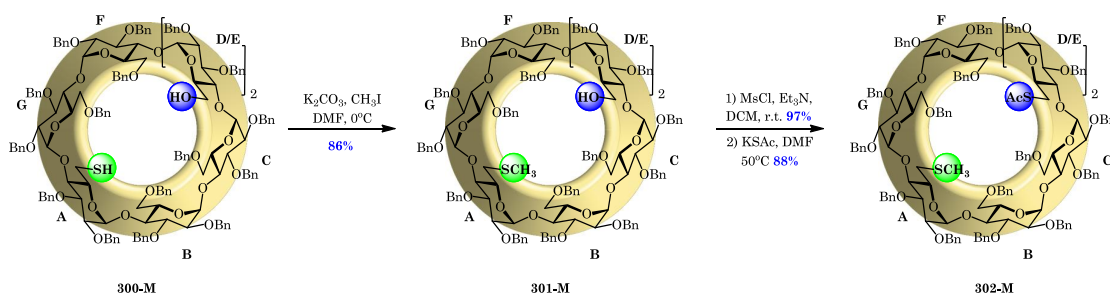
**Figure V-7:** Site-directing rules based on sulfur-derived cyclodextrins

As usually, first debenzoylation gave monol- $\beta$ -cyclodextrin **131** in an excellent yield, which was then converted into thioacetate-cyclodextrin **300** in 93% yield (Scheme V-13). Cyclodextrin **300** underwent thioester-reduction/debenzoylation to give an inseparable mixture (**300-M**) of thiol-monol-cyclodextrin isomers in 72% yield, with a ratio of 2:1 on the basis of <sup>1</sup>H NMR analysis. In this case, asymmetry of  $\beta$ -cyclodextrin accounted for the formation of two regioisomers.



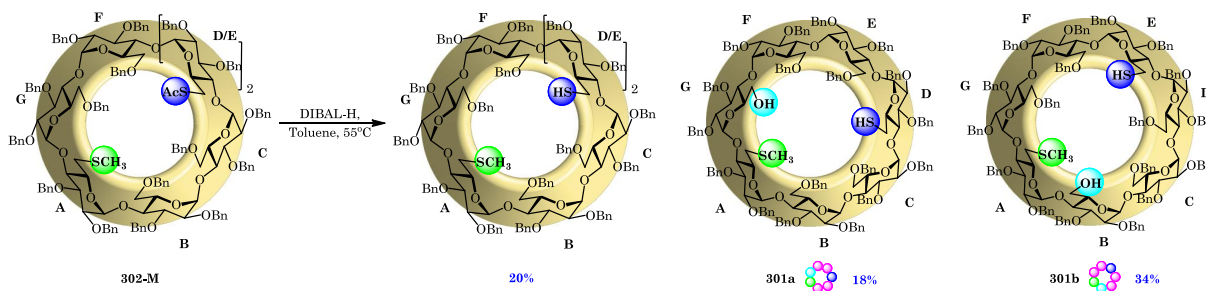
**Scheme V-13:** Formation of thiol-monol-cyclodextrins by tandem thioester-reduction/debenzoylation

Since a mixture of cyclodextrin isomers was obtained, the free thiols of the two isomers were then protected using methyl iodide under weak basic conditions in 86% yield (Scheme V-14). It was followed by mesylation and subsequent thioacetate anion substitution to give a mixture (**302-M**) of cyclodextrin isomers in 85% yield, possessing site-directing group SAc on sugar unit **D** or **E**. During each step of the chemical transformations, the regioisomeric products were submitted to chromatographical purification, trying to get a single pure product. To our disappointment, these two regioisomers could not be isolated.



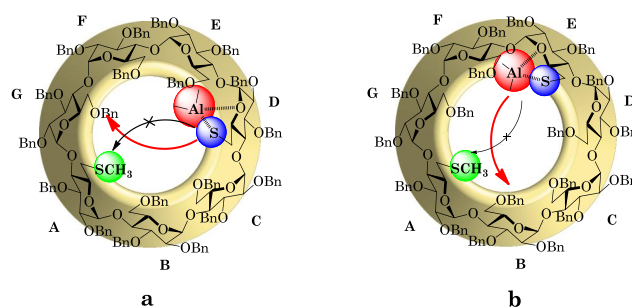
**Scheme V-14:** Synthesis of thioacetate-cyclodextrins

The mixture of thioacetate cyclodextrins was subjected to the action of DIBAL-H (Scheme V-15). Gratifyingly, two pure mono-debenzylated products **301a** and **301b** were obtained, together with an inseparable mixture of thiol-cyclodextrins (20%), which can also be used to prepare cyclodextrin **301a** and **301b**.



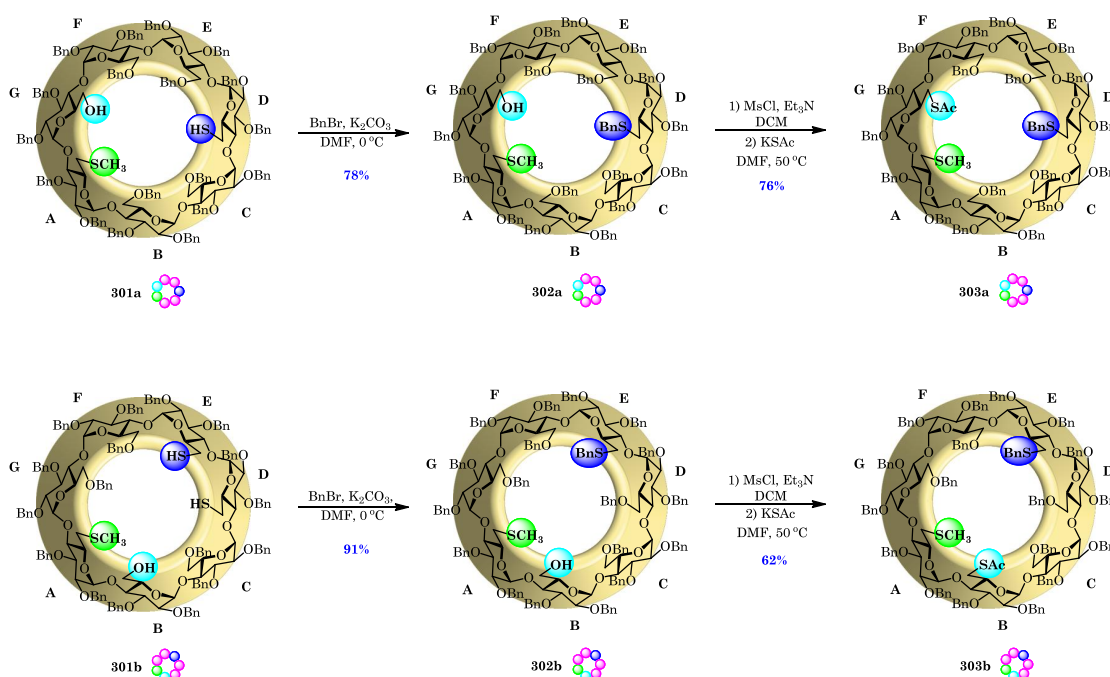
**Scheme V-15:** Formation of tetradifferentiated cyclodextrins

The structures of cyclodextrins **301a** and **301b** were elucidated by NMR analysis, demonstrating that cyclodextrin **301a** was the isomer with a thiol and an alcohol on sugar units **D** and **G**, respectively. Correspondingly, cyclodextrin **301b** was the product with a thiol and an alcohol on sugar units **E** and **B**. Based on this, it was reconfirmed that thioester-mediated debenzylation happened on the farthest position because of steric hindrance induced by ester reduction (Figure V-8).



**Figure V-8:** Mechanisms for the formation of cyclodextrin **301a** and **301b**

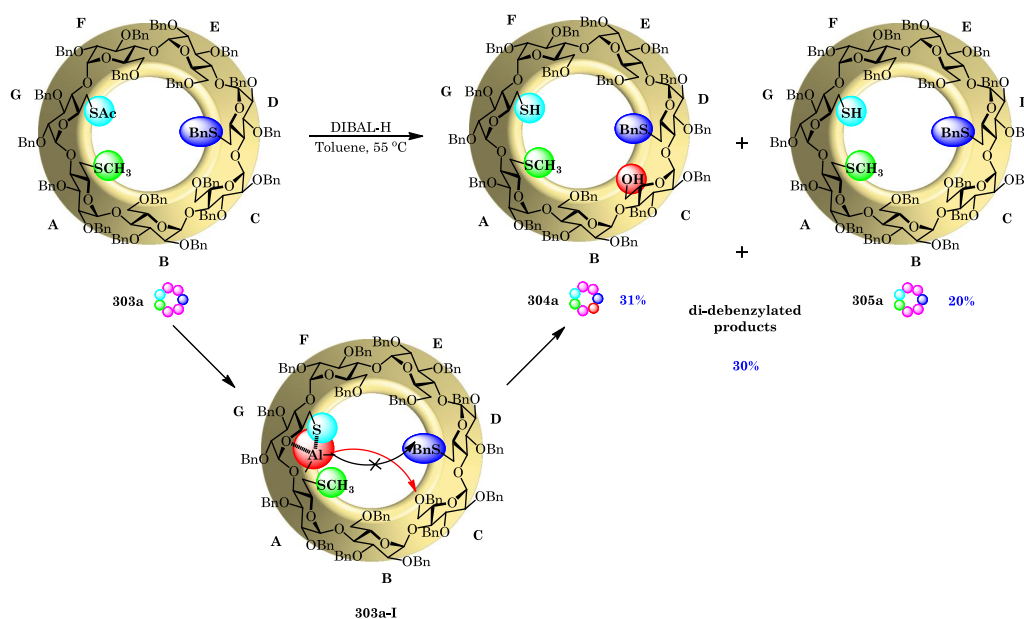
The free thiol of tetradifferentiated cyclodextrin **301a** was then benzylated in 78% yield (Scheme V-16). The followed mesylation and thioacetate anion substitution gave cyclodextrin **303a** with a SAc group on sugar unit **G** to direct another thioester-reduction/debenzylation. The same chemical transformation performed on cyclodextrin **301b**, giving cyclodextrin **303b** with a SAc group on sugar unit **B** (Scheme V-16)



**Scheme V-16:** Synthesis of cyclodextrin **303a** and **303b**

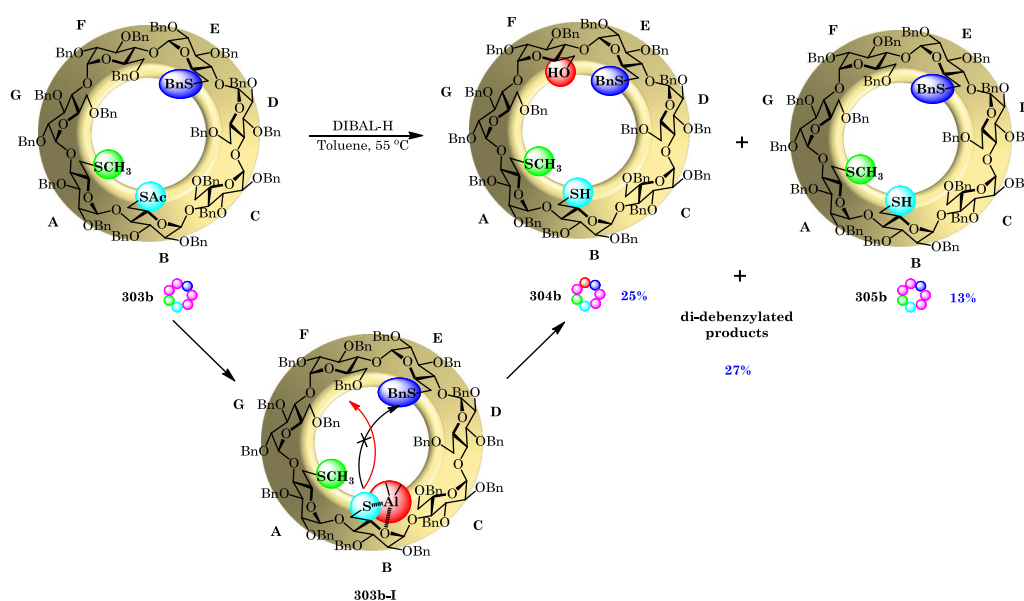
Introduction of a new SAc group would orient a regioselective debenylation according to our previously established rule. Consequently, cyclodextrin **303a** was submitted to the action of DIBAL-H. After 30 min, mass spectrometry demonstrated that mono-debenzylated product **304a** was the major product, together with thiol-cyclodextrin **305a** and a mixture of di-debenzylated products (Scheme V-17). As shown before, regioselectivity of this reaction can be explained by the formation of **303a-I** after ester reduction. Although the yield of

cyclodextrin **304a** is slightly lower, at least this reaction does work. We believe that the yield can be increased by controlling the reaction time.

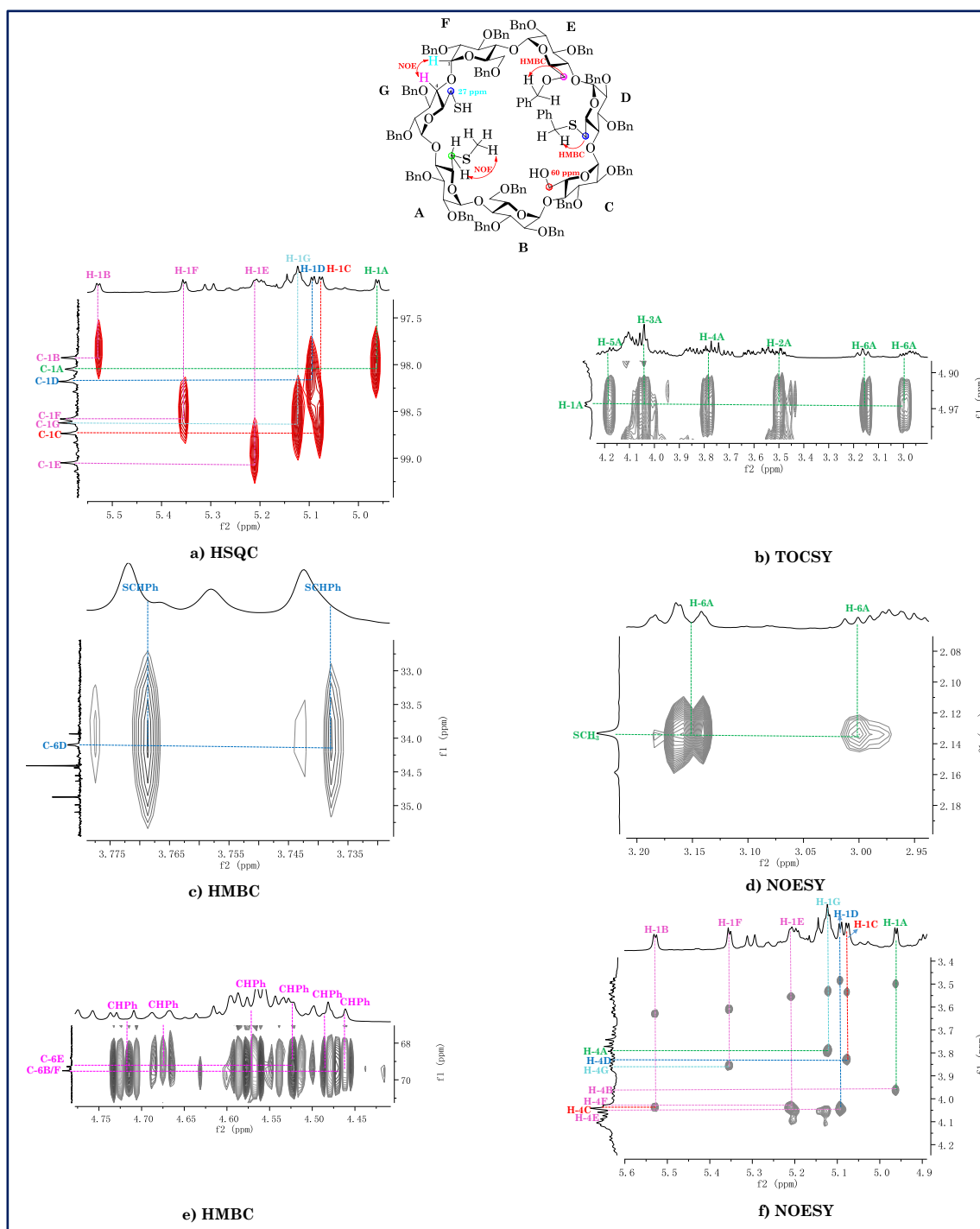


**Scheme V-17:** Synthesis of pentadifferentiated  $\beta$ -cyclodextrin **304a**

The structure of cyclodextrin **304a** was well characterized by typical NMR characteristically procedures (Figure V-9), demonstrating that the benzyl group was removed on sugar unit **C**. Cyclodextrin **303b** underwent the action of DIBAL-H, giving another pentadifferentiated cyclodextrin **304b** (Scheme V-18) with removal of a benzyl group on sugar unit **F** because of the formation of hindered aluminum derivative and the immunity of SBn group to DIBAL-H (**303b-I**).



**Scheme V-18:** Synthesis of pentadifferentiated  $\beta$ -cyclodextrin **304b**



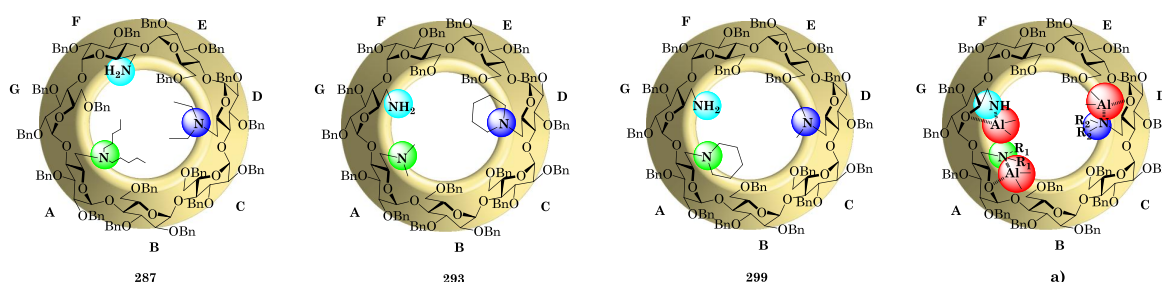
**Figure V-9:** NMR (600 MHz, 300 K, CDCl<sub>3</sub>) analysis of cyclodextrin 304a

- (a) Correlations of C-1s and H-1s in HSQC; (b) Protons of sugar unit A in TOCSY; (c) Correlations of C-6D and benzylic protons in HMBC; (d) Correlations of H-6A and SCH<sub>3</sub> in NOESY; (e) Correlations of C-6B,E,F and their benzylic protons in HMBC; (f) Correlations of H-1s and vicinal H-4s in NOESY.

## 4. Conclusion

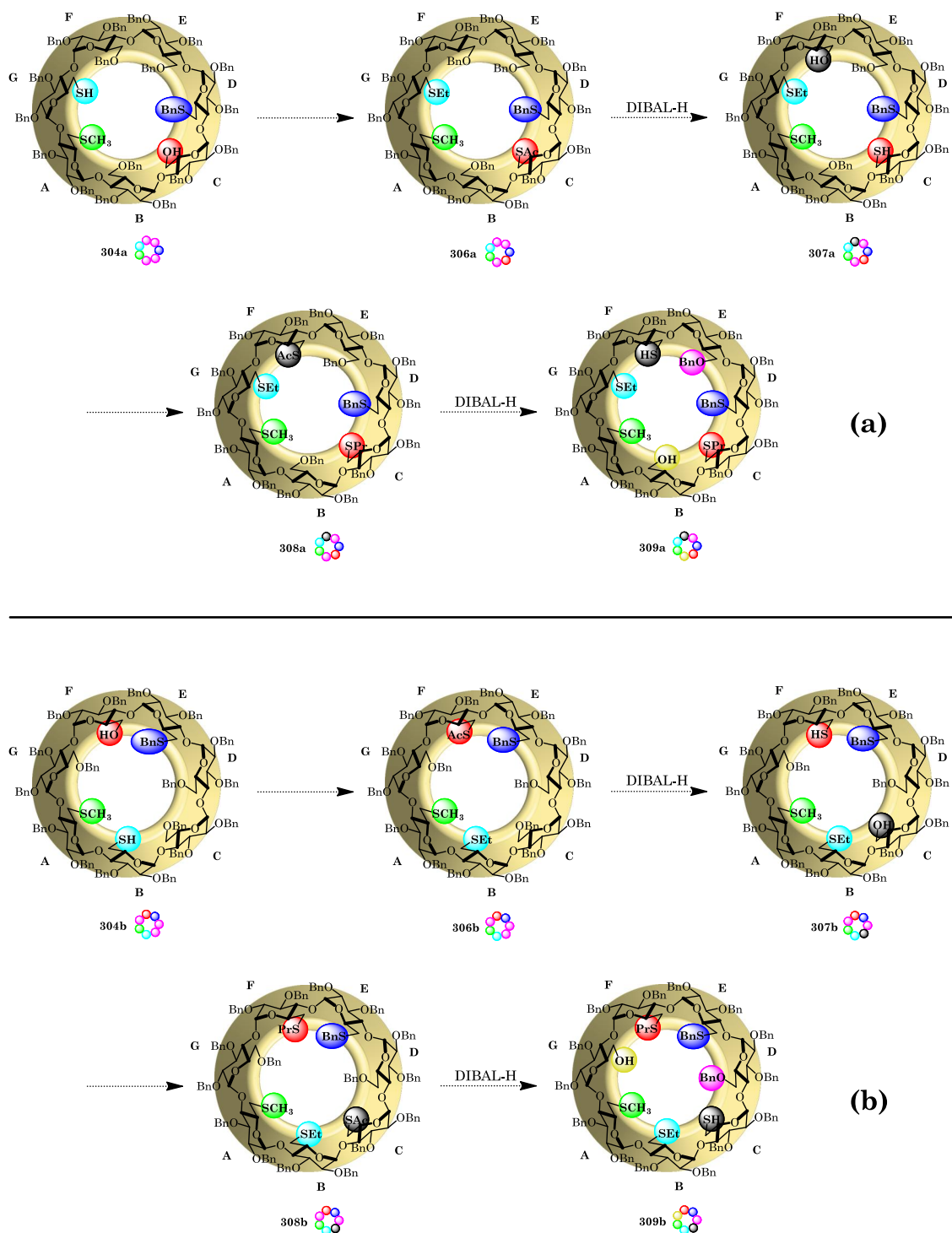
In this chapter, much efforts have been paid to polydifferentiate  $\beta$ -cyclodextrin, towards its heptadifferentiation. Two strategies were employed:

- 1) Based on tandem azide-reduction/debenzylation and using alkyl groups as the protection of the formed amine, only tetradifferentiated  $\beta$ -cyclodextrins (Figure V-10) were obtained. Further DIBAL-H-mediated debenzylation were prevented. We attributed these results to the coordination between lone electron pairs on nitrogen atoms and aluminum reagents (Figure V-10a).



**Figure V-10:** Accessible tetradifferentiated  $\beta$ -cyclodextrins

- 2) To overcome this problem, another strategy was devised. In Chapter IV, we developed a new site-directing strategy, namely thioester-reduction/debenzylation. It is also well applicable to the functionalization of  $\beta$ -cyclodextrin. Using this site-directing rule and appropriate protecting groups, some different derivatives, even more complicated pentadifferentiated  $\beta$ -cyclodextrins **304a** and **304b** were synthesized, which was unreached before. In the future, the obtained cyclodextrin **304a** should be subjected to two successive tandem thioester-reduction/debenzylation (Scheme V-19), to give the ultimate heptadifferentiated  $\beta$ -cyclodextrin **309a** with 7 different chemical groups on its primary rim. By using similar methods, another regioisomeric heptadifferentiated cyclodextrin **309b** could also be afforded starting from pentadifferentiated cyclodextrin **304b**.



**Scheme V-19:** Synthetic routes towards heptadifferentiated  $\beta$ -cyclodextrins **309a** and **309b**  
 (a) Synthesis from pentadifferentiated cyclodextrin **304a**; (b) synthesis from pentadifferentiated cyclodextrin **304b**



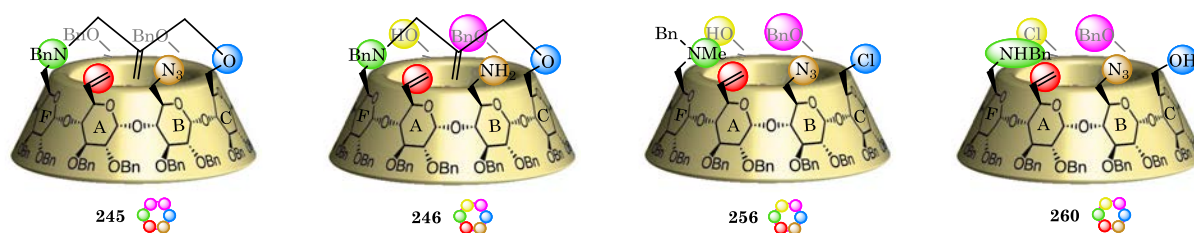


# **GENERAL CONCLUSION**



In this thesis, we aimed at the complete differentiation of  $\alpha$  and  $\beta$ -cyclodextrins. We already realized: hexadifferentiation of  $\alpha$ -cyclodextrin, and establishment of new site-directing rules based on sulfur- and selenium-derived cyclodextrins. Finally, polydifferentiation of  $\beta$ -cyclodextrin was studied, which opens a route towards heptadifferentiated pattern.

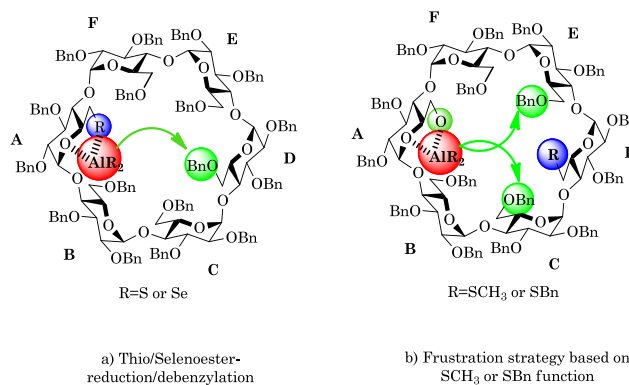
Based on the DIBAL-H-mediated debenzoylation, combining the previously delineated site-directing rules, unprecedented penta- and ultimate hexadifferentiated  $\alpha$ -cyclodextrins (Figure G-1) were reached. Further chemical transformations gave two regioisomeric products with six orthogonal functions: amine, alkene, azide, alcohol, ether and chloride.



**Figure G-1:** penta- and hexadifferentiated  $\alpha$ -cyclodextrin patterns

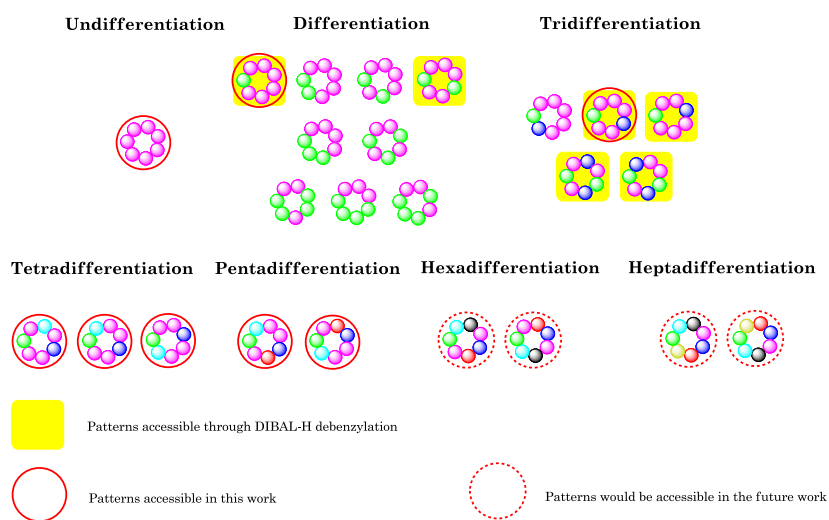
Then in Chapter IV, a detailed study was performed on the action of DIBAL-H on sulfur- and selenium-derived cyclodextrins. Two new site-directing reactions were established:

- 1) Thio/selenoester-reduction/debenzoylation (Figure G-2a). Thioacetate or selenoacetate has the capability to orient the debenzoylation on the farthest position because of the formation of sterically hindered aluminum complexes after ester reduction;
- 2) New “frustration” strategy (Figure G-2b) based on the immunity of thioether to the action of DIBAL-H. Substituting a benzyloxy group on the diametrically opposed position of a hydroxyl group with a thioether, the existing hydroxyl can induce a double-debenzoylation on both sides of the thioether.

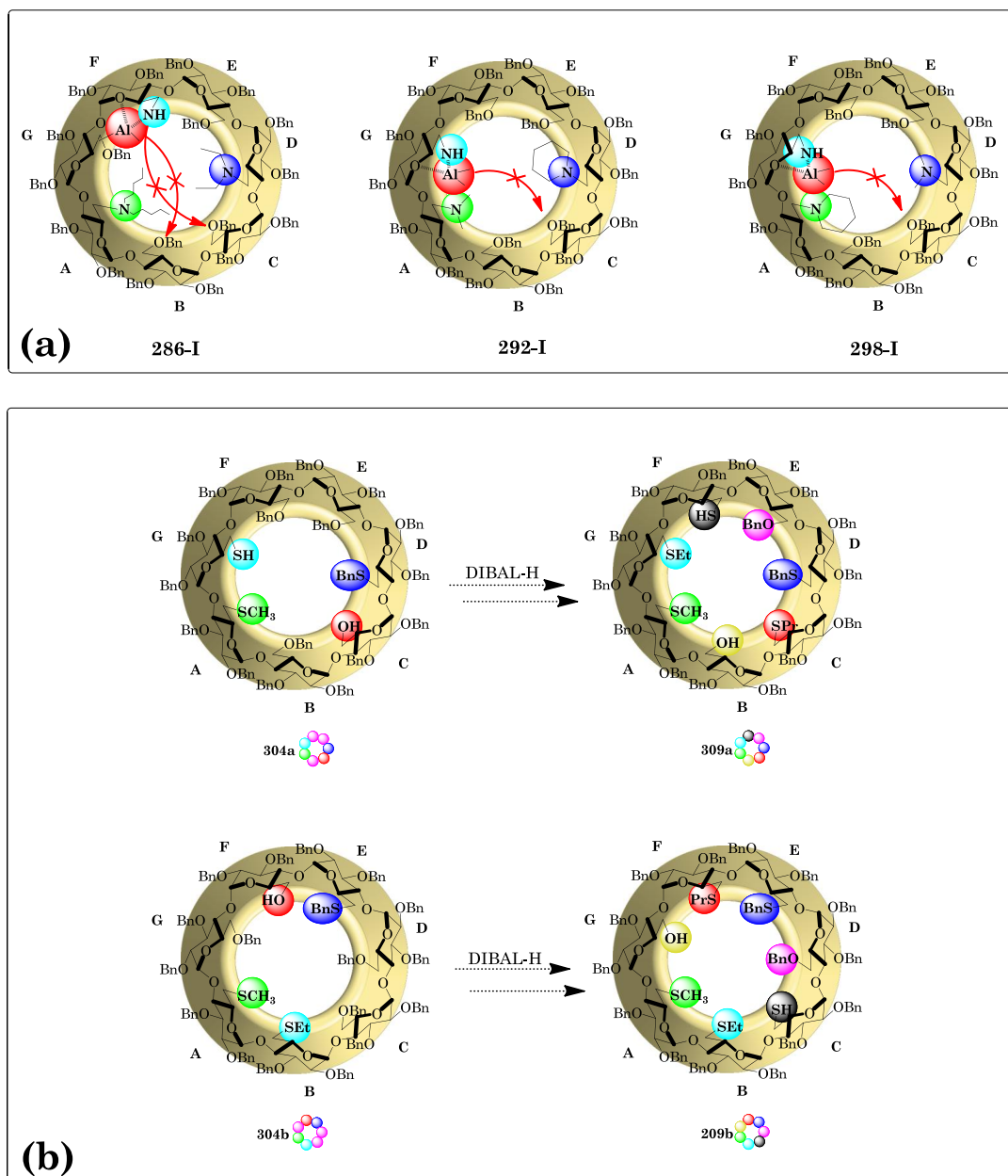


**Figure G-2:** Site-directing rules based on sulfur- and selenium-derived cyclodextrins

Last, in Chapter V, polydifferentiation of  $\beta$ -cyclodextrin was studied, and some patterns (Figure G-3) with higher level of complexity were accessed. Concerning the heptadifferentiation of  $\beta$ -cyclodextrin, initially, tandem azide-reduction debenylation was employed and different aldehydes were used for the protection of the amine. However, multi-alkyl protected amine strategies cannot give heptadifferentiated pattern possibly due to the coordination between lone pair electrons on nitrogen atoms and aluminum reagents (Figure G-4a). Nevertheless, using sulfur-derived site-directing strategy, some encouraging results were obtained, giving pentadifferentiated  $\beta$ -cyclodextrins unreached before. We believed that using this strategy, the ultimate heptadifferentiated  $\beta$ -cyclodextrins (Figure G-4b) with thioethers on its primary rim should be realized.



**Figure G-3:** Accessible functionalization patterns of  $\beta$ -cyclodextrin



**Figure G-4:** Strategies used towards heptadifferentiation of  $\beta$ -cyclodextrin.

(a) Amine strategy based on tandem azide-reduction/debenzylation; (b) thioether strategy based on tandem thioester-reduction/debenzylation



# **APPENDIX**





## 1. Combinatorics

Number of necklaces with  $n$  beads and  $k$  colors (i.e. containing one to  $k$  colors):<sup>1</sup>

$$N_k(n) = \frac{1}{n} \sum_{i=1}^{\nu(n)} \varphi(d_i) k^{n/d_i}$$

where  $d_i$  are the divisors of  $n$ ,  $\nu(n)$  is the number of divisors of  $n$  and  $\varphi(d)$  is the Euler's totient function define by:

$$\begin{aligned} \varphi: \mathbb{N}^* &\rightarrow \mathbb{N}^* \\ n &\mapsto \text{card}(\{m \in \mathbb{N}^* | m \leq n \text{ and } m \text{ relatively prime to } n\}) \end{aligned}$$

It is possible to generate those necklaces of  $n$  beads of  $k$  colors using: <http://www.jasondavies.com/necklaces/>

Starting from this, one can deduce the number of necklaces with  $n$  beads and exactly  $k$  colors.:

$$R_k(n) = N_k(n) - \sum_{i=1}^{k-1} \binom{k}{i} R_i(n)$$

Indeed, for a given  $k$ , the value  $N_k(n)$  includes the templates with  $k-1$ ,  $k-2 \dots 1$  colors. Thus, to have exactly  $k$  colors, one must subtract the number of combination of lower rank.

For  $i$  colors, there are  $\binom{k}{i} = \frac{k!}{i!(k-i)!}$  ways to choose among the  $k$  colors, so the number of

combination to subtract is  $\binom{k}{i} R_i(n)$ , and one must do that for all  $i$  such that  $0 < i < k$ .

Applying this formula for  $n = 6$  gives

$$R_1(6) = N_1(6) - \sum_{i=1}^0 \binom{1}{i} R_i(6)$$

$$R_1(6) = 1 - 0$$

$$\boxed{R_1(6) = 1}$$

$$R_2(6) = N_2(6) - \sum_{i=1}^1 \binom{2}{i} R_i(6)$$

$$R_2(6) = 14 - \binom{2}{1} R_1(6) = 14 - 2 \times 1$$

$$\boxed{R_2(6) = 12}$$

$$R_3(6) = N_3(6) - \sum_{i=1}^2 \binom{3}{i} R_i(6)$$

$$R_3(6) = 130 - \binom{3}{1} R_1(6) - \binom{3}{2} R_2(6)$$

$$R_3(6) = 130 - 3 \times 1 - 3 \times 12$$

$$\boxed{R_3(6) = 91}$$

$$R_4(6) = N_4(6) - \sum_{i=1}^3 \binom{4}{i} R_i(6)$$

$$R_4(6) = 700 - \binom{4}{1} R_1(6) - \binom{4}{2} R_2(6) - \binom{4}{3} R_3(6)$$

$$R_4(6) = 700 - 4 \times 1 - 6 \times 12 - 4 \times 91$$

$$\boxed{R_4(6) = 260}$$

$$R_5(6) = N_5(6) - \sum_{i=1}^4 \binom{5}{i} R_i(6)$$

$$R_5(6) = 2635 - \binom{5}{1} R_1(6) - \binom{5}{2} R_2(6) - \binom{5}{3} R_3(6) - \binom{5}{4} R_4(6)$$

$$R_5(6) = 2635 - 5 \times 1 - 10 \times 12 - 10 \times 91 - 5 \times 260$$

$$\boxed{R_5(6) = 300}$$

$$R_6(6) = N_6(6) - \sum_{i=1}^5 \binom{6}{i} R_i(6)$$

$$R_6(6) = 7826 - \binom{6}{1} R_1(6) - \binom{6}{2} R_2(6) - \binom{6}{3} R_3(6) - \binom{6}{4} R_4(6) - \binom{6}{5} R_5(6)$$

$$R_6(6) = 7826 - 6 \times 1 - 15 \times 12 - 20 \times 91 - 15 \times 260 - 6 \times 300$$

$$\boxed{R_6(6) = 120}$$

## 2. Characteristic analysis of hexadifferentiated $\alpha$ -cyclodextrin 246 by NMR spectroscopy

Complete attribution was done as explained hereafter on the hexa-differentiated  $\alpha$ -cyclodextrin in  $\text{CDCl}_3$  at 600 MHz and 300 K using  $^1\text{H}$ ,  $^{13}\text{C}$ , DEPT 135, HSQC, 2D COSY, 2D TOCSY, 2D NOESY and HMBC.

1. First, the H-1s protons were attributed using HSQC cross-correlation with C-1s whose chemical shifts are characteristic (*ca.* 100 ppm).

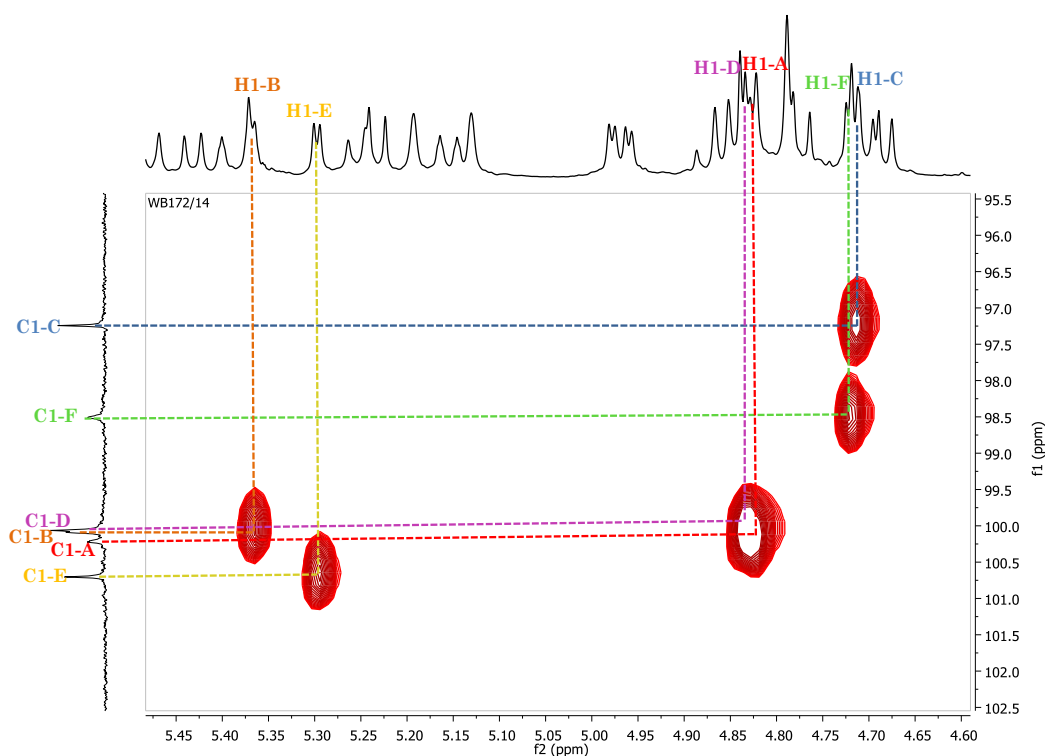


Figure A-1: HSQC spectrum of the C-1/H-1 region

- Using 2D COSY and 2D TOCSY, all protons of each glycosidic unit were attributed and labeled according to their corresponding H-1.

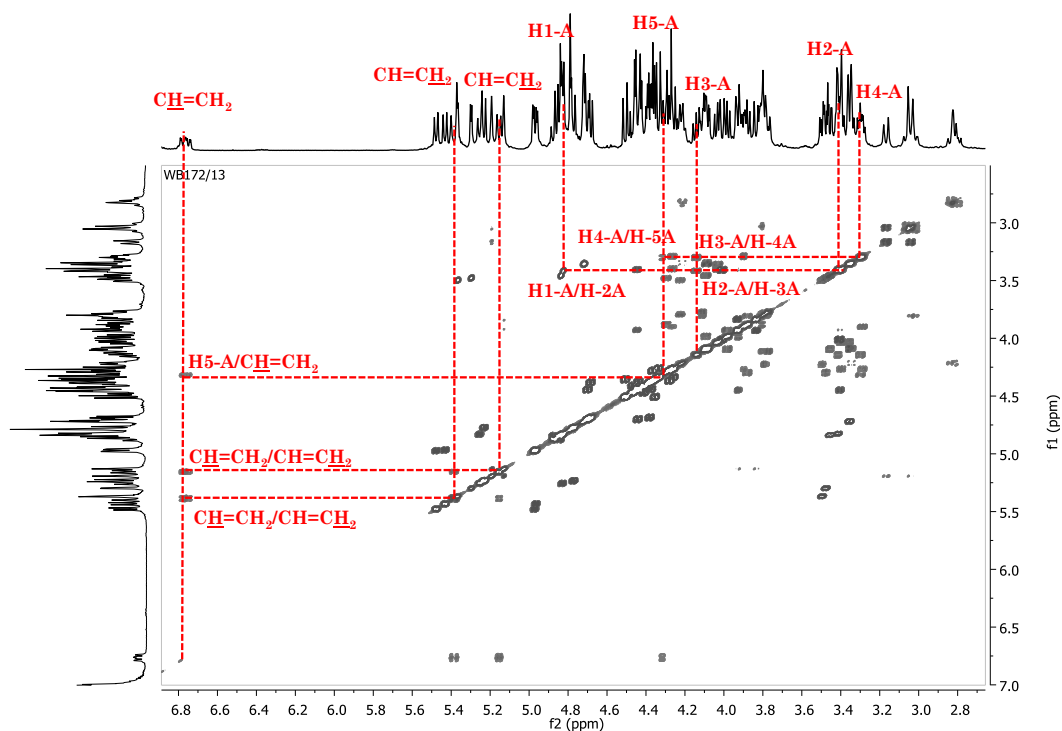


Figure A-2: 2D COSY of unit A

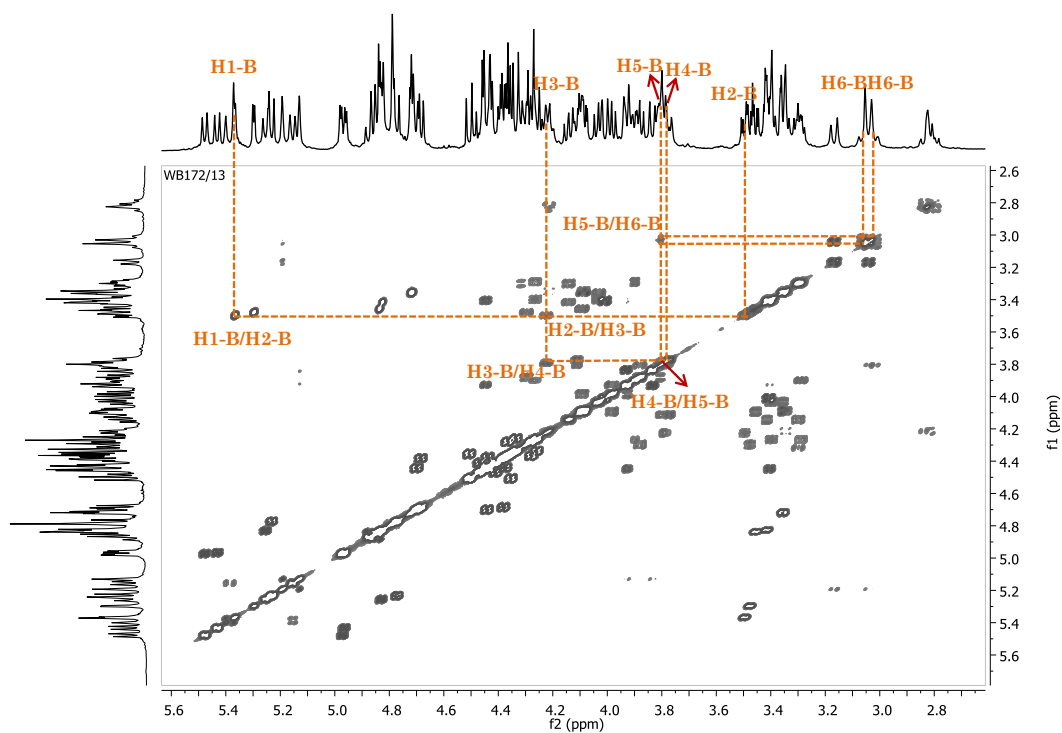


Figure A-3: 2D COSY of unit B

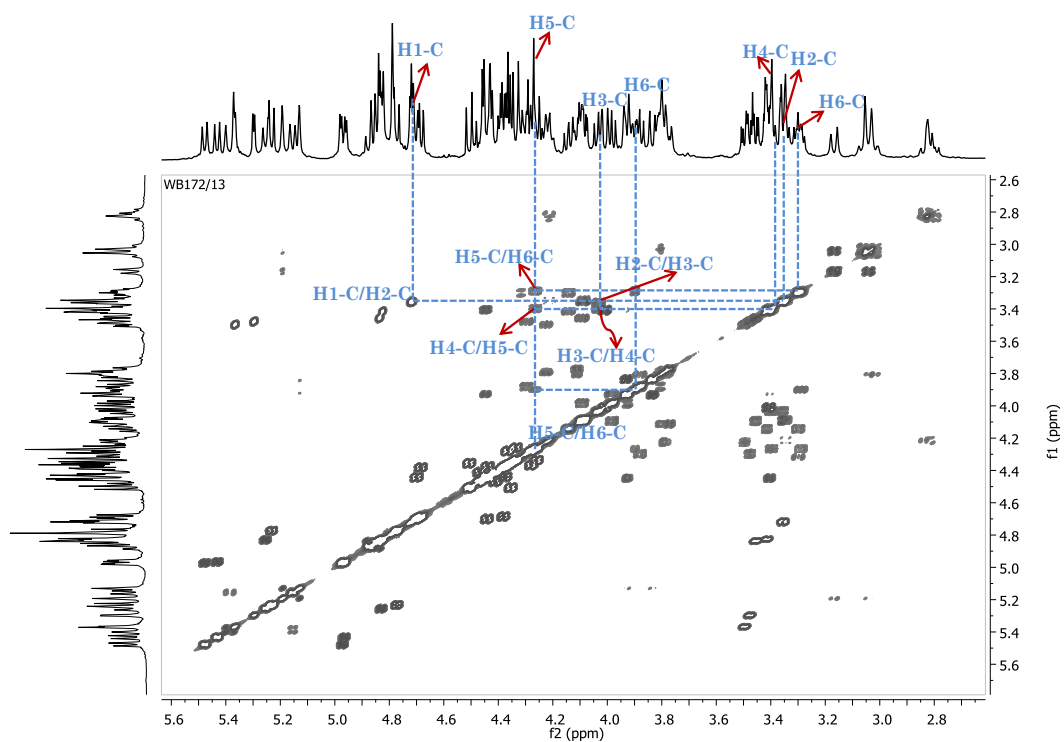


Figure A-4: 2D COSY of unit C

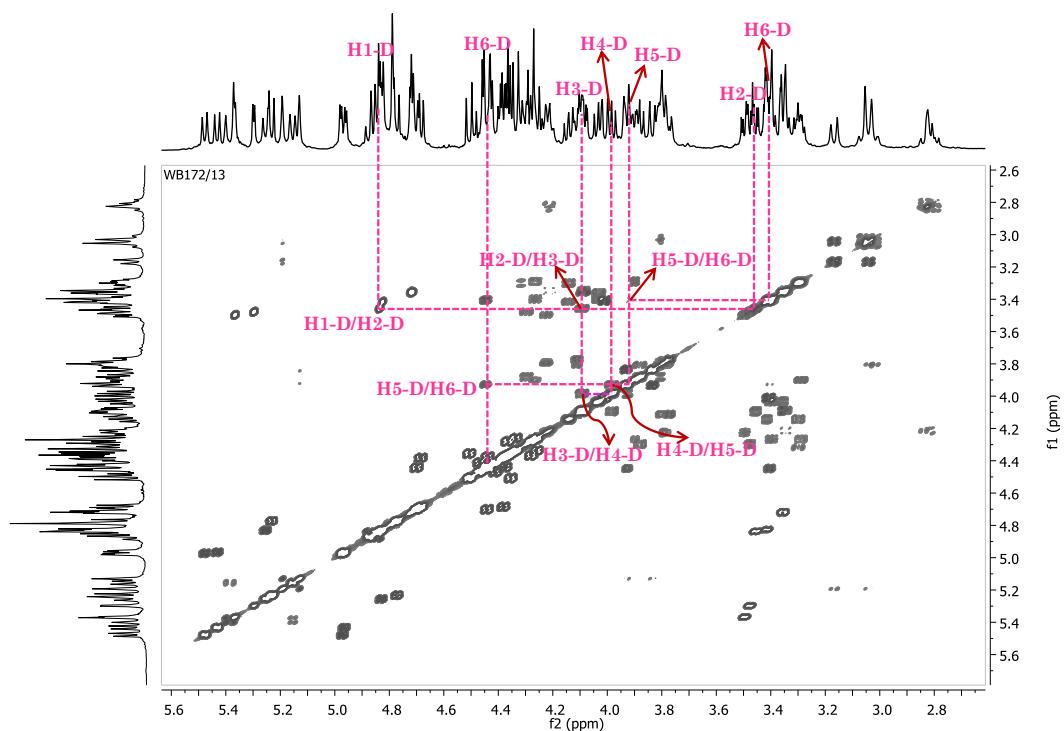


Figure A-5: 2D COSY of unit D

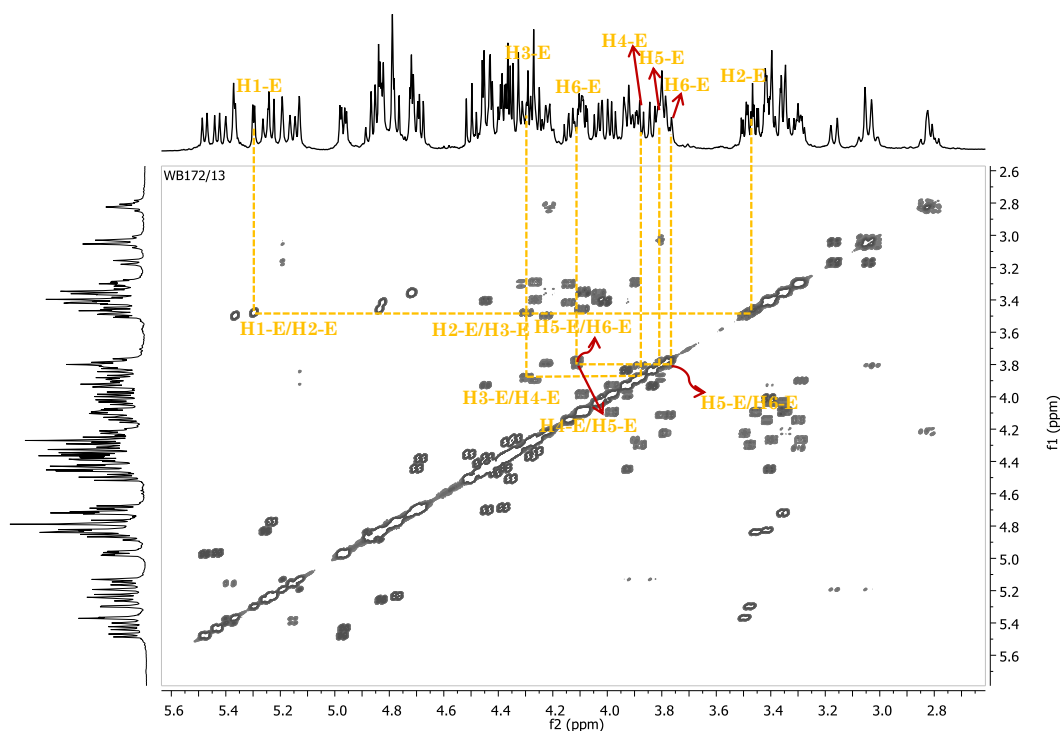


Figure A-6: 2D COSY of unit E

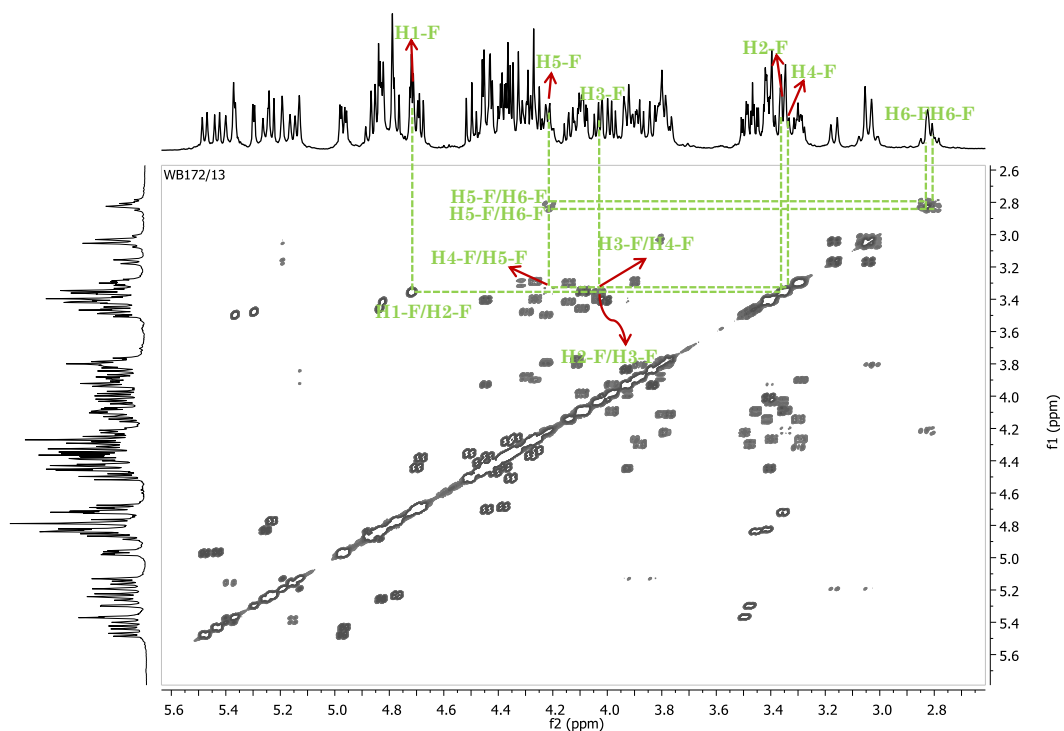


Figure A-7: 2D COSY of unit F

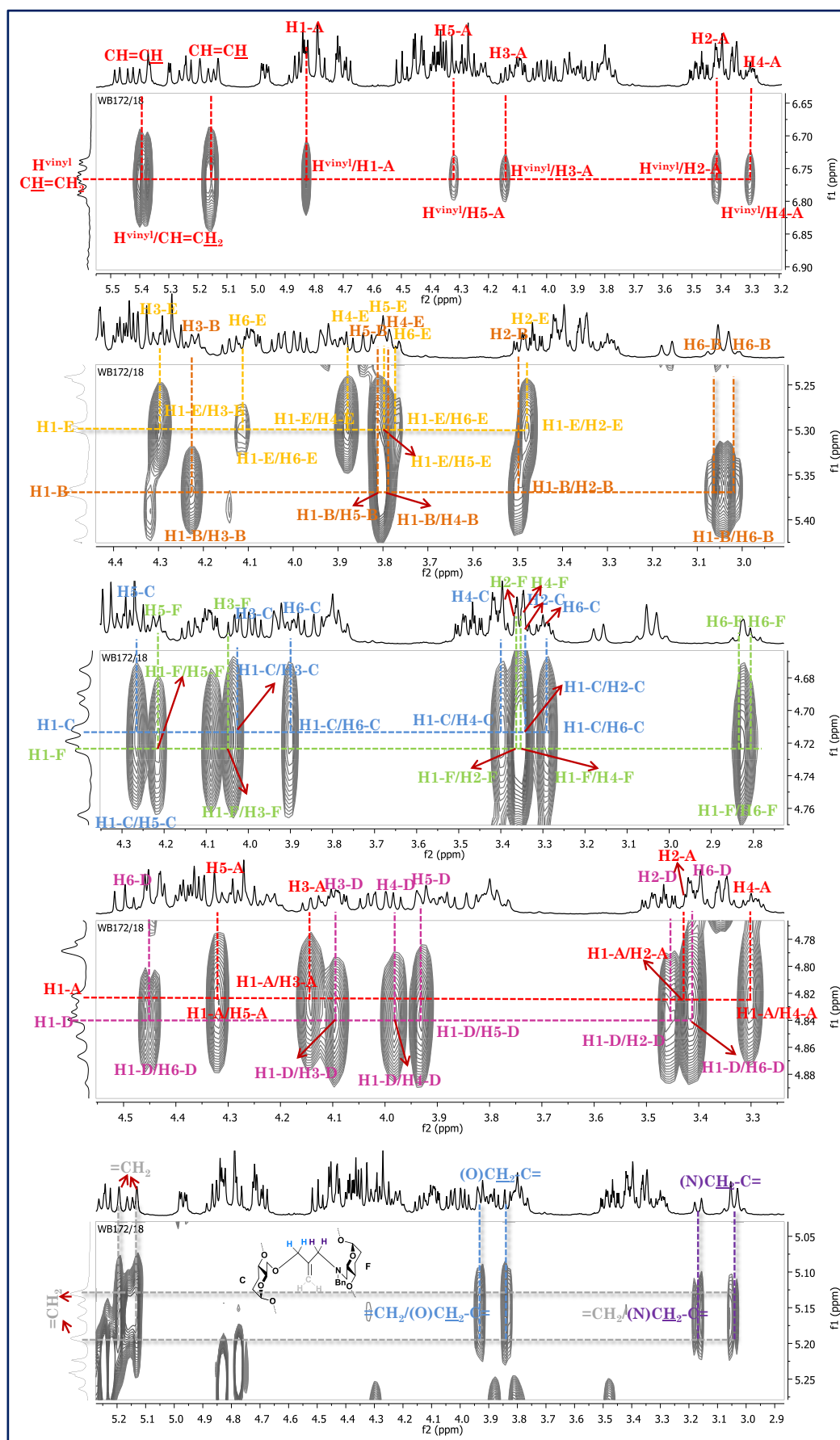


Figure A-8: 2D TCOSY (240 ms)



3. All the secondary carbons C6s were attributed using HSQC cross-coupling with the corresponding protons.

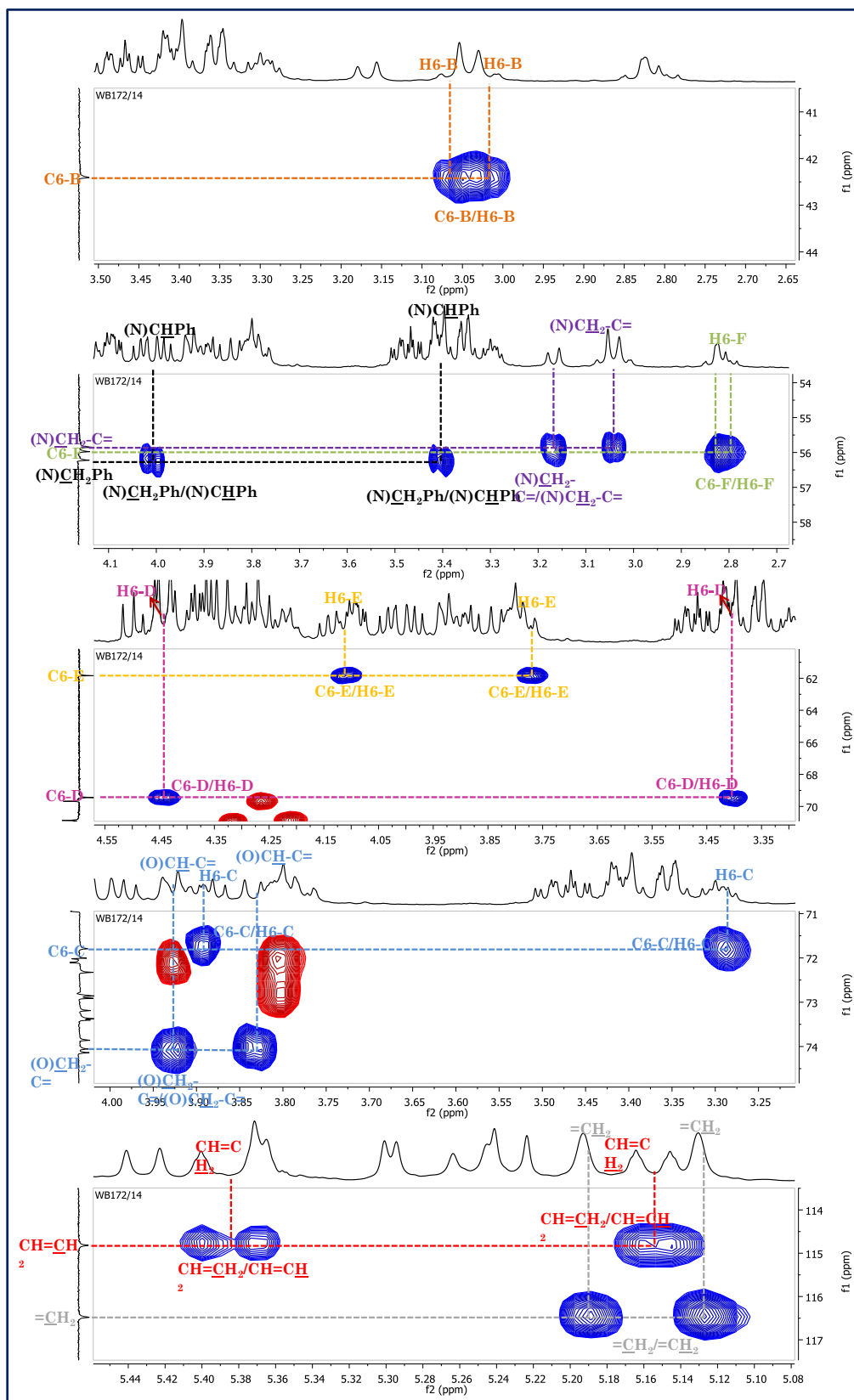
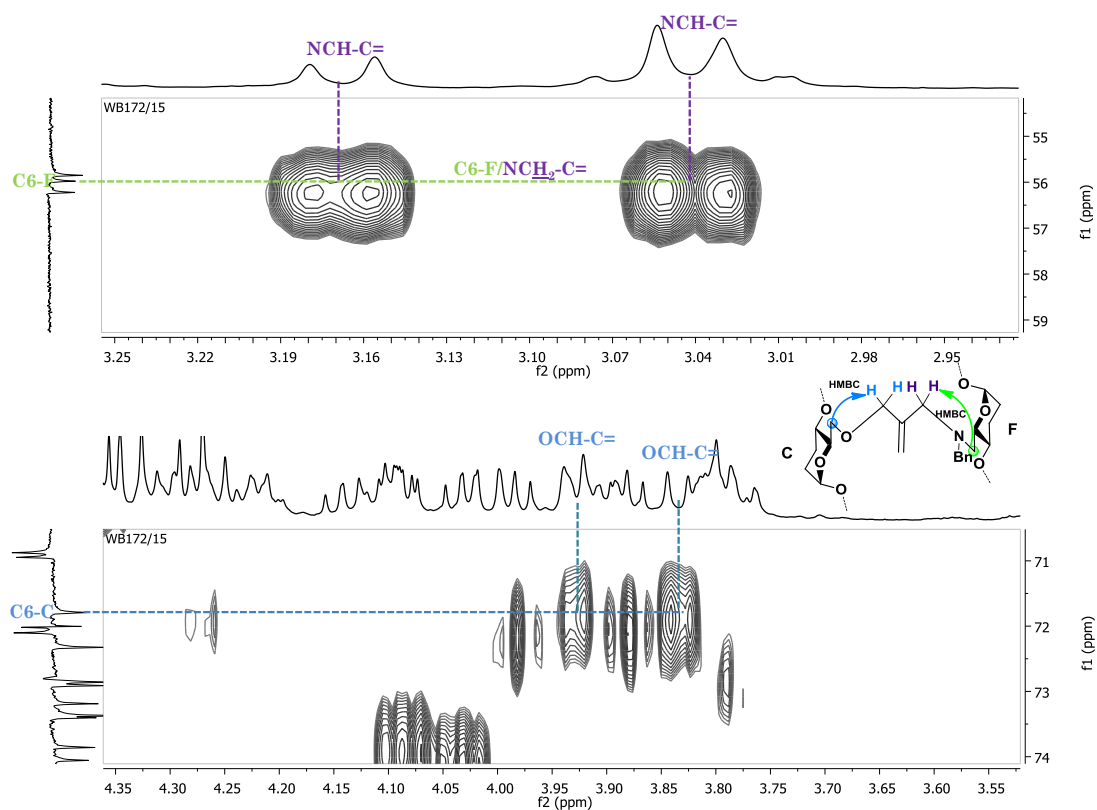


Figure A-9: HSQC spectrum of the secondary carbons with their protons

4. Using HMBC cross-correlation, the allylic protons on the bridge can be determined by the correlations between the C-6F, C-6C and the protons respectively (Figure A-10). Besides, the correlation with the terminal alkene carbon can also attribute the allylic protons (Figure A-11). For the glycosidic unit F and D with the benzyl groups, they can be identified in HMBC by the correlation between the C-6 and the benzylic protons (Figure A-12)



**Figure A-10:** HMBC spectrum of C-6C, C-6F and the allylic protons region.  
(Upper: HMBC correlation of C-6F and allylic protons. Bottom: HMBC correlation of C-6C and allylic protons)

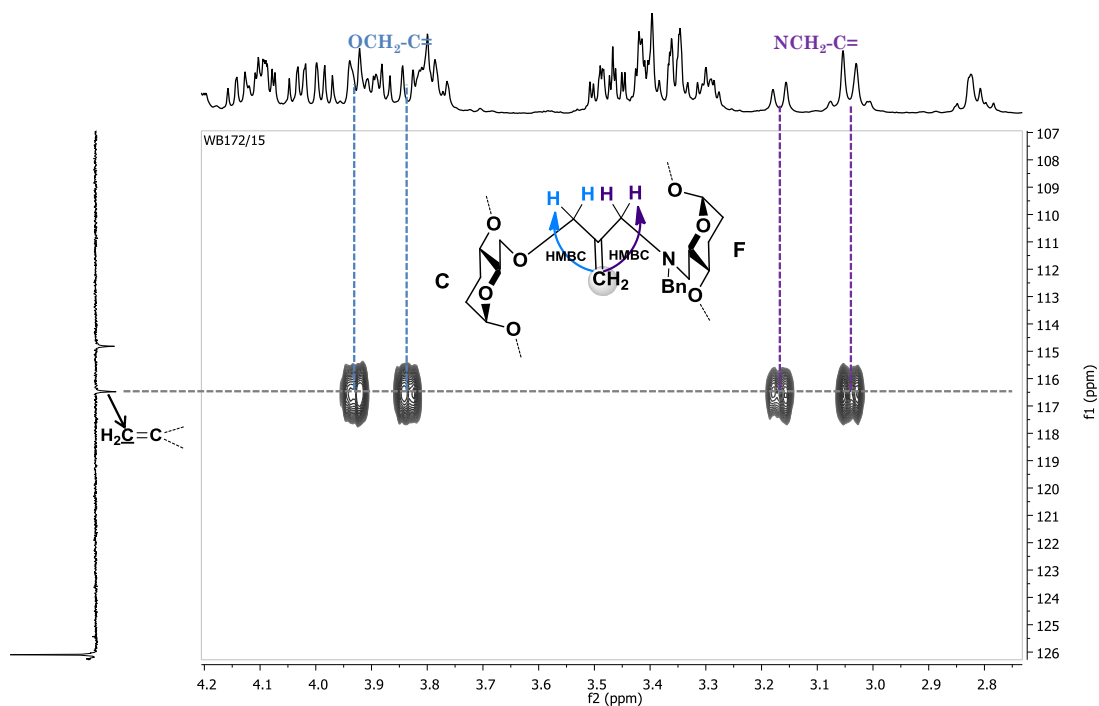


Figure A-11: HMBC spectrum of terminal alkene carbon and allylic protons region

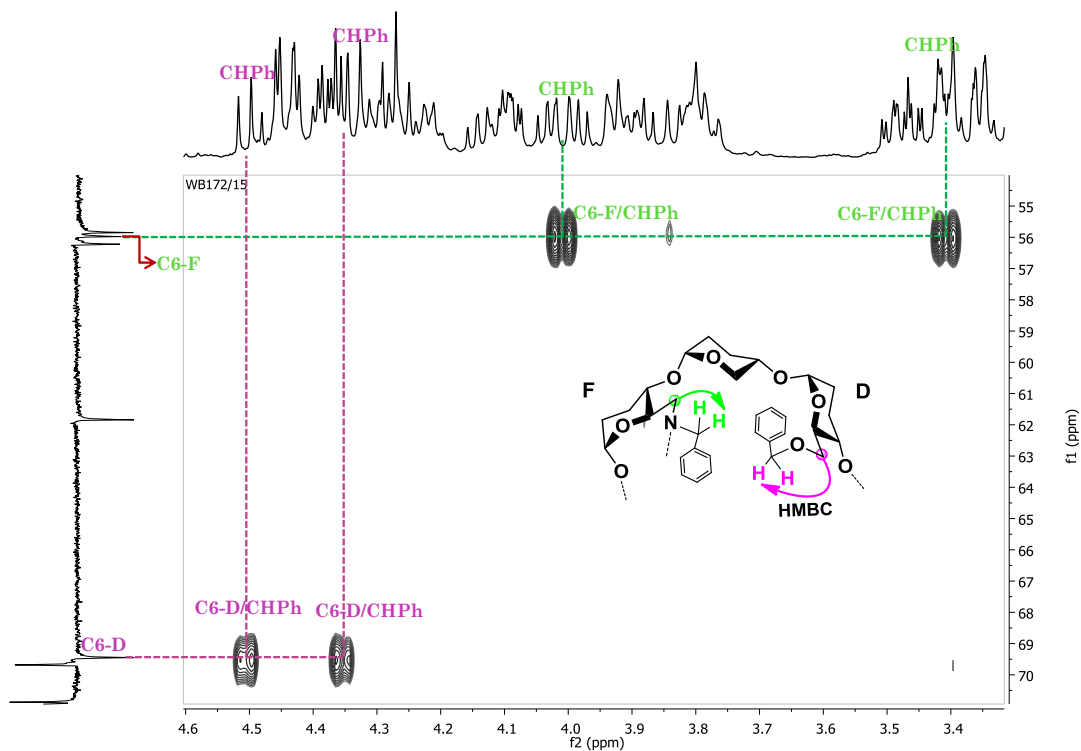


Figure A-12: HMBC spectrum of C-6D, C-6F and benzylic protons region

5. At last, the connection order of the glucosidic units was determined using NOE between H-1s and their vicinal H-4s. Furthermore, it can be verified by cross-correlation between C-1s and their vicinal H-4s in HMBC.

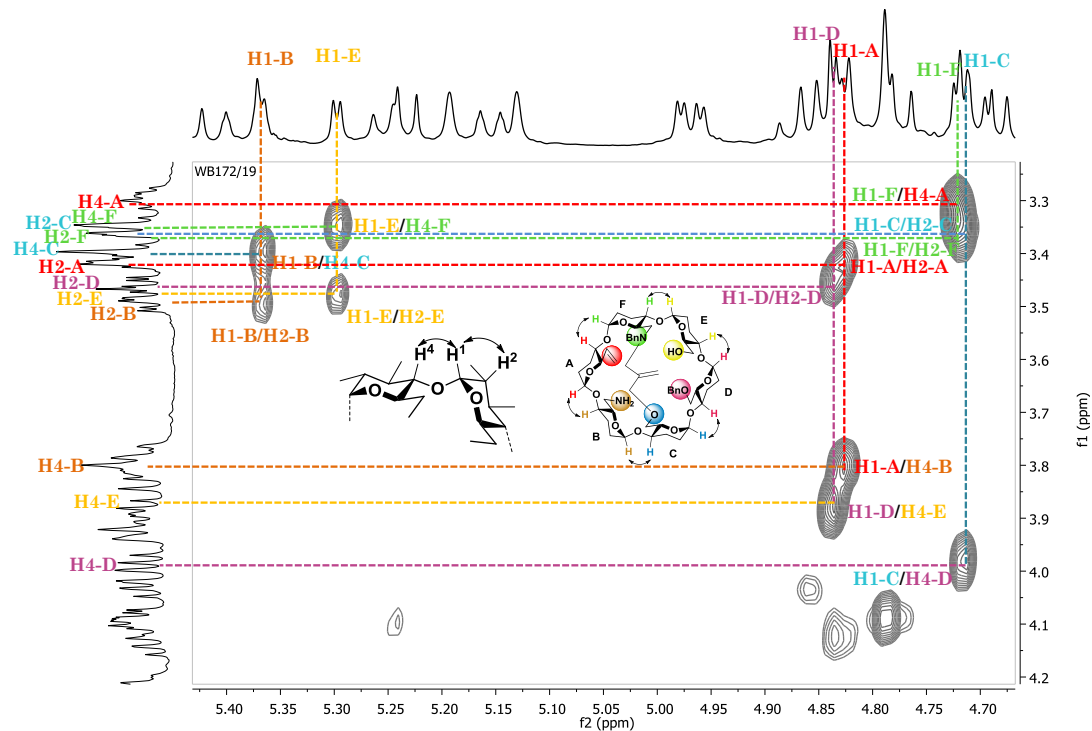


Figure A-13: NOESY spectrum of the H-1/H-2 and H-1/H-4 region

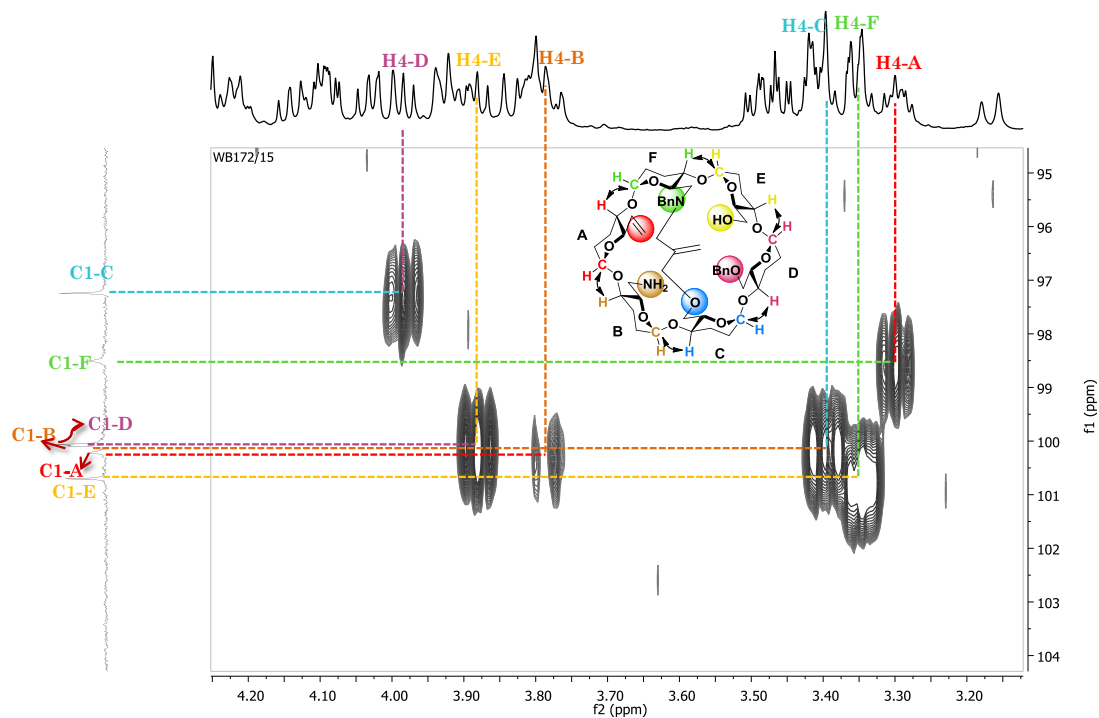


Figure A-14: HMBC spectrum of the C-1/H-4 region

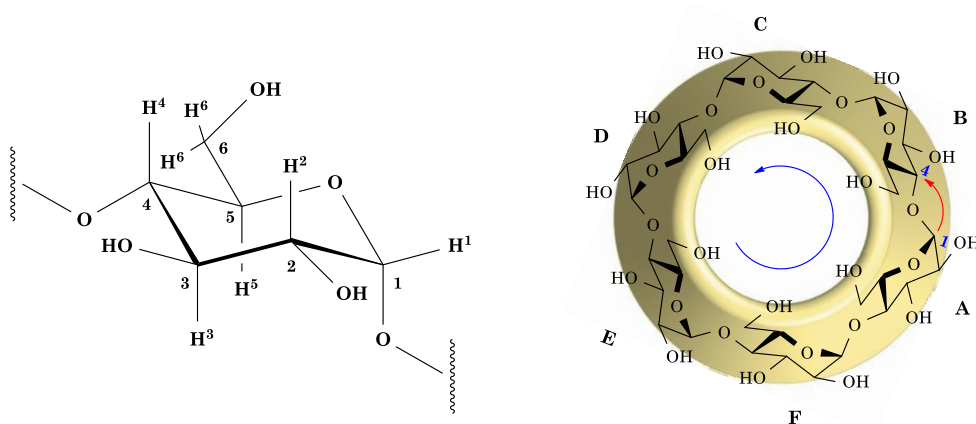


# **EXPERIMENTAL PART**



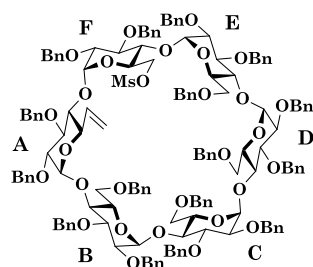
## General information

Dichloromethane was freshly distilled from  $P_2O_5$ , toluene from sodium and THF from sodium/benzophenone. Reactants were purchased from commercial sources and used without further purification. HRMS were recorded on a Bruker microTOF spectrometer, using Tuning-Mix as reference. Optical rotations were measured on a Perkin-Elmer 341 digital polarimeter or a Jasco P-2000 polarimeter with a path length of 1 dm. NMR spectra were recorded on a Bruker Avance II 600 MHz or Bruker AM- 400 MHz using residual  $CHCl_3$  signal as internal reference ( $\delta(^1H) = 7.26$  ppm and  $\delta(^{13}C) = 77.16$  ppm). Assignments were aided by COSY, HSQC, NOESY, TOCSY and HMBC experiments.





**6<sup>A</sup>-Deoxy-6<sup>A</sup>-Vinyl-6<sup>F</sup>-O-Methylsulfonyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>-Hexadeca-O-Benzyl- $\alpha$ -cyclodextrin (241a)**



To a solution of vinyl-alcohol **166** (200 mg, 0.083 mmol, 1 eq.) in  $\text{CH}_2\text{Cl}_2$  (3 mL) were added  $\text{Et}_3\text{N}$  (24  $\mu\text{L}$ , 0.166 mmol, 2 eq.) and  $\text{MsCl}$  (14  $\mu\text{L}$ , 0.166 mmol, 2 eq.) at  $0^\circ\text{C}$ . The reaction mixture was stirred at r.t. for 1 h under nitrogen, then water (3 mL) was added, the phases were separated and the aqueous layers were extracted with dichloromethane (3 $\times$ 3 mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. Silica gel

flash chromatography of the residue (CyH/EtOAc: 5/1) afforded mono-mesylated  $\alpha$ -cyclodextrin **241a** (203 mg, 98%) as a white foam.

$\alpha_{\text{D}} = +32.0$  (c 1.0,  $\text{CHCl}_3$ ).

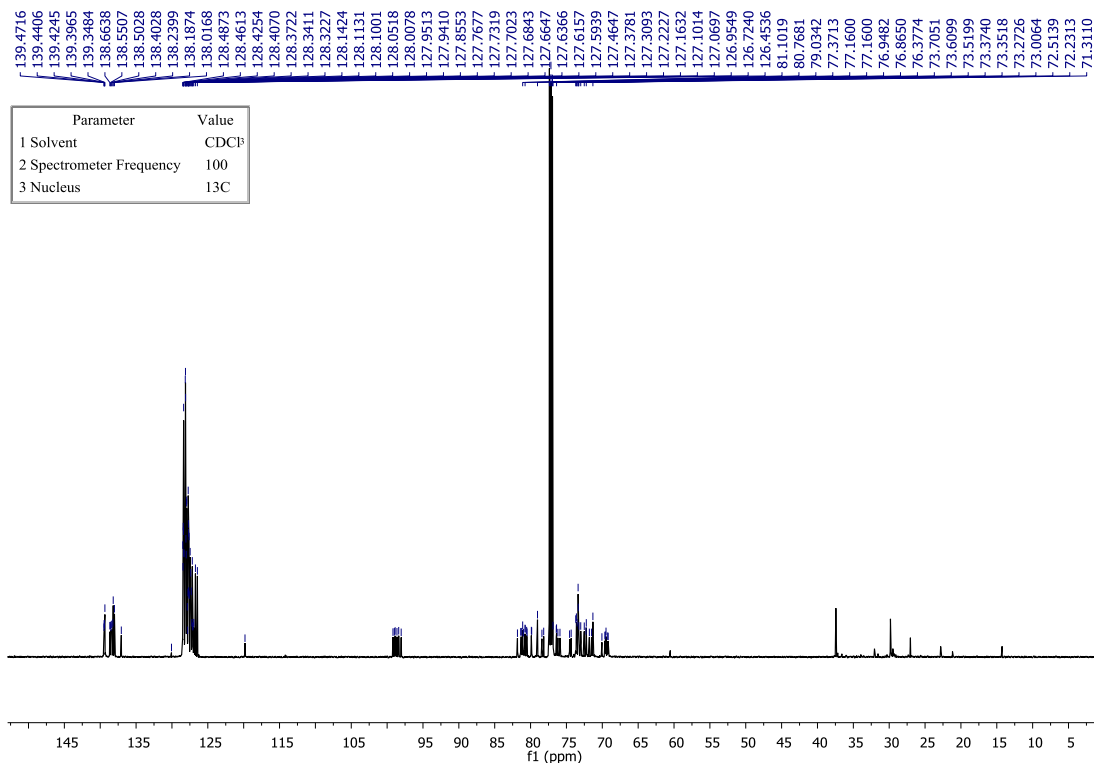
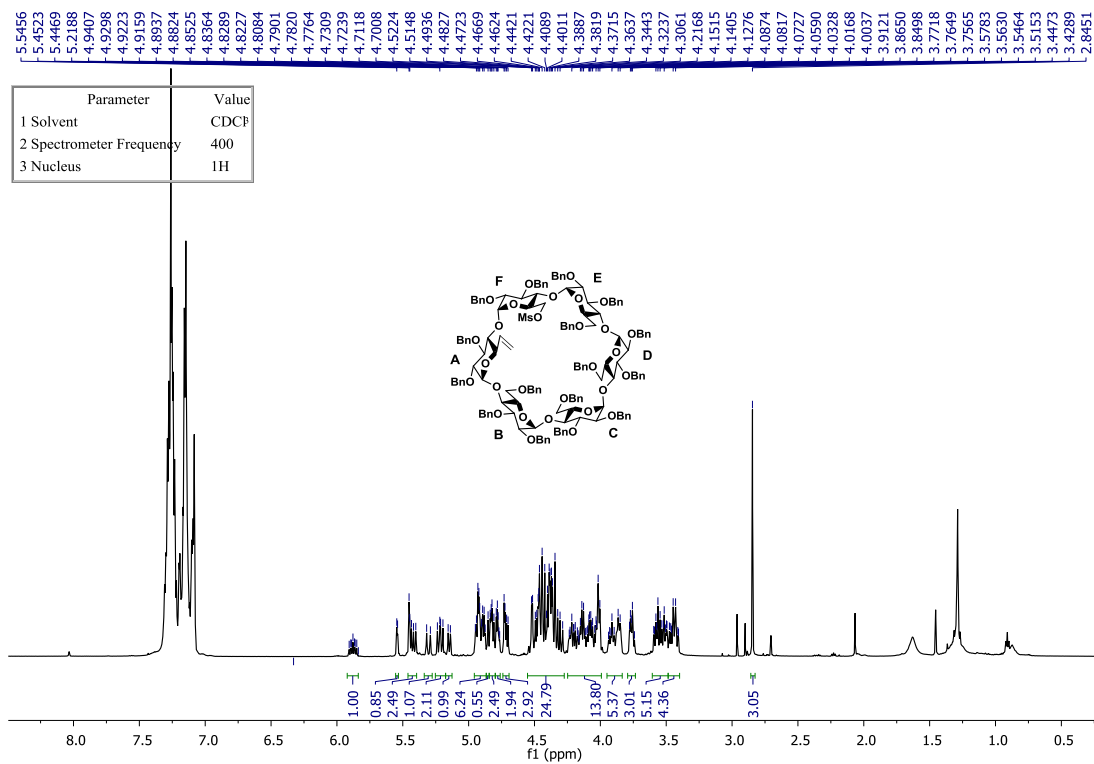
$R_f = 0.57$  (CyH/EtOAc: 2/1)

**$^1\text{H NMR}$**  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.30-7.07 (m, 80H, 80 $\times$ H-Ar), 5.87 (ddd, 1H,  $^3J_{5,6} = 7.4$  Hz,  $^3J_{\text{cis}} = 9.9$  Hz,  $^3J_{\text{trans}} = 16.9$  Hz,  $\text{CH}=\text{CH}_2$ ), 5.54 (d, 1H,  $^3J_{1,2} = 3.6$  Hz, H-1), 5.44 (d, 1H,  $^3J_{1,2} = 3.8$  Hz, H-1), 5.42 (d, 1H,  $^2J = 10.8$  Hz, CHPh), 5.40 (d, 1H,  $^2J = 10.4$  Hz, CHPh), 5.27 (bd, 1H,  $^3J_{\text{trans}} = 17.2$  Hz,  $\text{CH}=\text{CH}_2$ ), 5.21 (d, H,  $^2J = 11.0$  Hz, CHPh), 5.18 (d, H,  $^2J = 10.9$  Hz, CHPh), 5.13 (bd, 1H,  $^3J_{\text{cis}} = 10.3$  Hz,  $\text{CH}=\text{CH}_2$ ), 4.93-4.68 (m, 13H, 4 $\times$ H-1, 8 $\times$ CHPh, H-6), 4.50-4.28 (m, 20H, H-5, H-6, 18 $\times$ CHPh), 4.25-3.98 (m, 14H, 6 $\times$ H-3, 4 $\times$ H-4, 2 $\times$ H-5, 2 $\times$ H-6), 3.92-3.82 (m, 5H, 3 $\times$ H-5, 2 $\times$ H-6), 3.77-3.71 (m, 3H, 2 $\times$ H-4, H-6), 3.58-3.37 (m, 9H, 6 $\times$ H-2, 3 $\times$ H-6), 2.82 (s, 3H, S- $\text{CH}_3$ ).

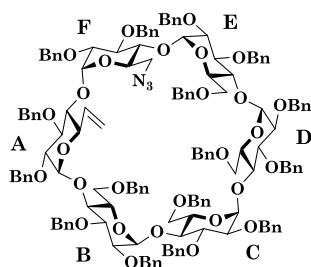
**$^{13}\text{C NMR}$**  ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  139.46, 139.43(2C), 139.42, 139.39(2C), 139.34, 138.67, 138.56, 138.51, 138.39, 138.24, 138.19, 138.16, 138.01, 138.00 (16 $\times$ C-Ar<sup>quat</sup>), 137.07 ( $\text{CH}=\text{CH}_2$ ), 128.49-126.44 (m, 80 $\times$ C-Ar<sup>tert</sup>), 119.82 ( $\text{CH}=\text{CH}_2$ ), 99.18, 98.99, 98.88, 98.63, 98.36, 98.05 (6 $\times$ C-1), 81.83 (C-4), 81.37, 81.33 (2 $\times$ C-3), 81.20, 81.09, 81.05 (3 $\times$ C-4), 80.99 (C-2), 80.74(2C), 80.54, 80.48 (4 $\times$ C-3), 79.85, 79.83, 79.01, 78.38, 78.14 (5 $\times$ C-2), 77.36(2C) (C-4), 76.43, 76.40, 76.21, 75.93, 74.55, 74.34, 73.70, 73.60, 73.52, 73.37(2C), 73.33, 73.27, 73.00, 72.49 (15 $\times$  $\text{CH}_2\text{Ph}$ ), 72.25 (C-5), 72.20 ( $\text{CH}_2\text{Ph}$ ), 71.79, 71.46, 71.29(2C) (4 $\times$ C-5), 70.06, 69.61, 69.57 (3 $\times$ C-6), 69.47 (C-5), 69.28, 69.14 (2 $\times$ C-6), 37.43 (S- $\text{CH}_3$ )

**HRMS (ESI)**: Calcd. For  $\text{C}_{150}\text{H}_{158}\text{O}_{31}\text{SNa}$  [ $\text{M}+\text{Na}$ ]<sup>+</sup>: 2510.0354; Found: 2510.0400 (+1.8 ppm).

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>F</sup>-Dideoxy-6<sup>A</sup>-Vinyl-6<sup>F</sup>-Azido-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>-Hexadeca-  
O-Benzyl- $\alpha$ -cyclodextrin (**241**)**



To a solution of mono-mesylated  $\alpha$ -cyclodextrin **241a** (580 mg, 0.233 mmol, 1 eq.) in DMF (4 mL) was added NaN<sub>3</sub> (60.6 mg, 0.932 mmol, 4 eq.) at r.t. The reaction mixture was stirred at 80°C for 12 h under nitrogen, then cooled down to r.t. and evaporated to dryness. The crude was dissolved in ethyl acetate (10 mL), washed with water (5 mL) and the aqueous layers were extracted with ethyl acetate (3×10 mL). The combined organic layers were dried

over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 5/1) afforded azido-cyclodextrin **241** (530 mg, 93%) as a white foam.

$\alpha_D = +32.3$  (c 1.0, CHCl<sub>3</sub>).

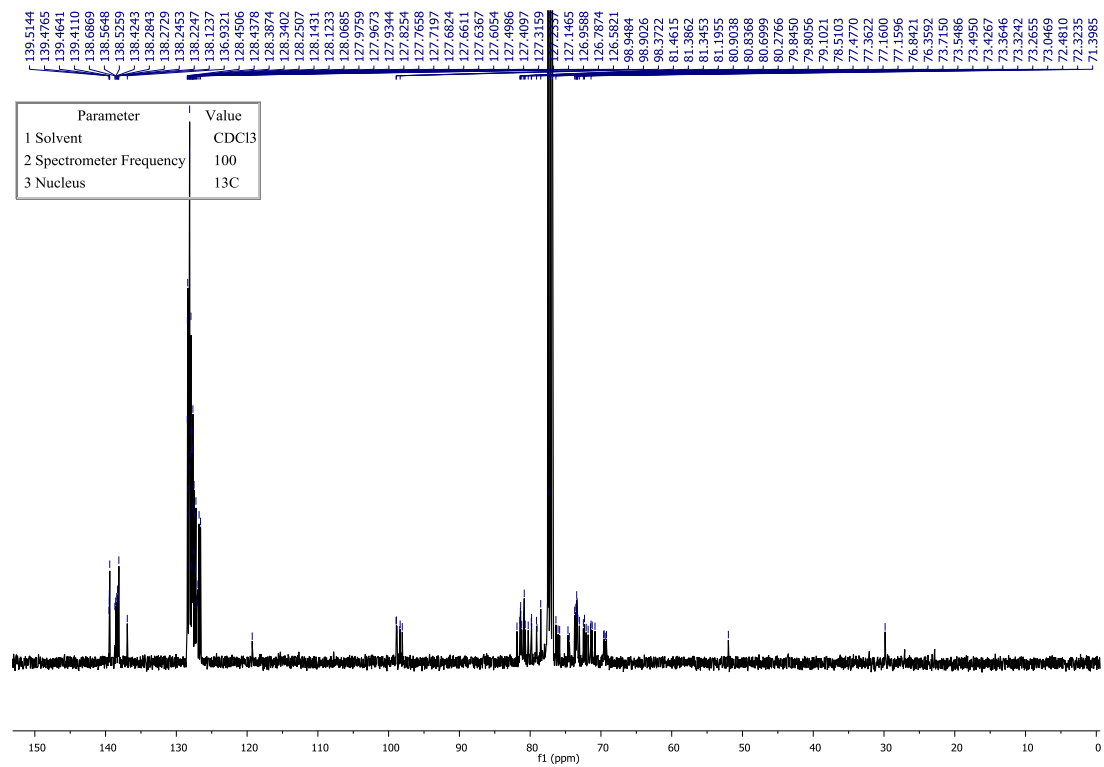
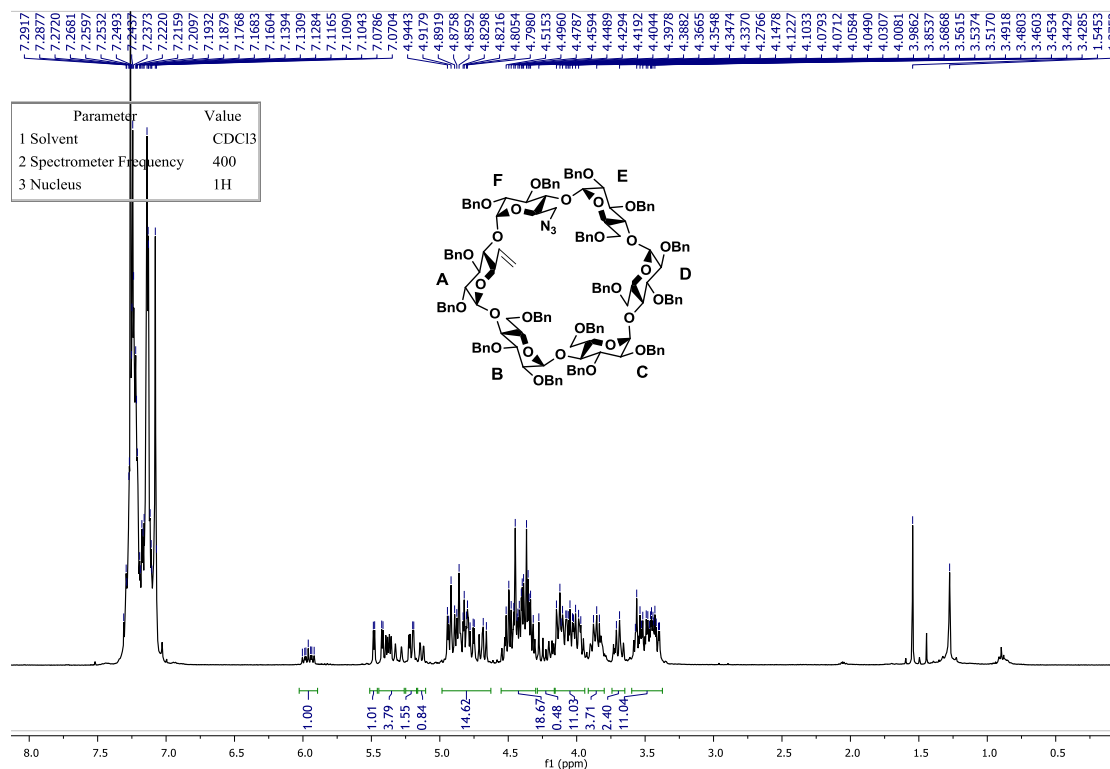
$R_f = 0.77$  (CyH/EtOAc: 2/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.29-7.07 (m, 80H, 80×H-Ar), 5.96 (ddd, 1H, <sup>3</sup>J<sub>5,6</sub> = 7.0 Hz, <sup>3</sup>J<sub>cis</sub> = 10.3 Hz, <sup>3</sup>J<sub>trans</sub> = 17.2 Hz, CH=CH<sub>2</sub>), 5.48 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.8 Hz, H-1), 5.41 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.8 Hz, H-1), 5.38 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 5.36 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 5.30 (bd, 1H, <sup>3</sup>J<sub>trans</sub> = 17.1 Hz, CH=CH<sub>2</sub>), 5.20 (d, 2H, <sup>2</sup>J = 10.9 Hz, 2×CHPh), 5.12 (bd, 1H, <sup>3</sup>J<sub>cis</sub> = 10.9 Hz, CH=CH<sub>2</sub>), 4.94-4.73 (m, 12H, 4×H-1, 8×CHPh), 4.70 (d, 1H, <sup>2</sup>J = 11.9 Hz, CHPh), 4.67 (d, 1H, <sup>2</sup>J = 11.9 Hz, CHPh), 4.51-4.27 (m, 19H, H-5, 18×CHPh), 4.14-3.97 (m, 14H, 6×H-3, 3×H-4, 2×H-5, 3×H-6), 3.90-3.83 (m, 5H, H-4, 3×H-5, H-6), 3.73-3.65 (m, 3H, H-4, 2×H-6), 3.58-3.39 (m, 11H, 6×H-2, H-4, 4×H-6).

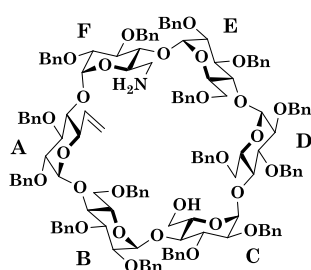
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.51(2C), 139.47, 139.46, 139.41(2C), 138.68, 138.56, 138.52, 138.42, 138.28, 138.27, 138.24, 138.22, 138.12(2C) (16×C-Ar<sup>quat</sup>), 136.93 (CH=CH<sub>2</sub>), 128.45-126.58 (m, 80×C-Ar<sup>tert</sup>), 119.27 (CH=CH<sub>2</sub>), 98.94, 98.90, 98.80, 98.43, 98.37, 98.07 (6×C-1), 81.86, 81.46, 81.38 (3×C-4), 81.34, 81.19, 80.90, 80.83, 80.69, 80.27 (6×C-3), 79.84, 79.80, 79.10, 79.03, 78.51(2C) (6×C-2), 77.36(2C) (2×C-4), 76.35(2C), 76.05, 75.83, 74.65, 74.46, 73.71, 73.54, 73.49, 73.42, 73.36, 73.32, 73.26, 73.04, 72.48, 72.32 (16×CH<sub>2</sub>Ph), 72.08, 71.81, 71.47, 71.39, 71.23 (5×C-5), 70.83(2C) (C-4, C-5), 69.61, 69.54, 69.39, 69.21, 51.99 (5×C-6).

**HRMS (ESI):** Calcd. For C<sub>149</sub>H<sub>155</sub>N<sub>3</sub>O<sub>28</sub>Na [M+Na]<sup>+</sup>: 2457.0706; Found: 2457.0689 (-0.7 ppm).

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>F</sup>-Dideoxy-6<sup>A</sup>-Vinyl-6<sup>F</sup>-Amino-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>D</sup>,6<sup>E</sup>-Pentadeca-  
O-Benzyl- $\alpha$ -cyclodextrin (**242**)**



DIBAL-H (1.5 M in toluene, 1.5 mL, 2.16 mmol, 15 eq.) was slowly added to a solution of cyclodextrin **241** (350 mg, 0.15 mmol, 1 eq.) in toluene (0.72 mL) under nitrogen at r.t. The reaction mixture was stirred at 50°C. When the formation of the monol as the major product (20 min), heating was stopped, diethyl ether (45 mL) was added and the mixture was cooled down to 0°C. Water (173  $\mu$ L) was added dropwise, then NaOH aq.sol. 15% (173  $\mu$ L) and a second portion of water (432  $\mu$ L) were added. The mixture was vigorously stirred at r.t. for 20 min, then MgSO<sub>4</sub> (180 mg) was added and the mixture was stirred for 60 min. The precipitate was filtered and washed abundantly with diethyl ether (5 $\times$ 15 mL). The combined organic layers were concentrated. Silica gel flash chromatography (CyH/EtOAc 3:1, then DCM/MeOH 98:2) gave cyclodextrin **242** (260 mg, 78%) as a white foam.

$\alpha_D = +43.6$  (c 1.0, CHCl<sub>3</sub>)

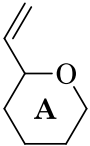
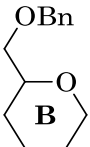
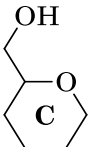
$R_f = 0.30$  (DCM/MeOH: 95/5)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.29-7.06 (m, 75H, 75 $\times$ H-Ar), 6.09 (ddd, 1H, <sup>3</sup>J<sub>5,6</sub> = 5.5 Hz, <sup>3</sup>J<sub>cis</sub> = 10.6 Hz, <sup>3</sup>J<sub>trans</sub> = 16.5 Hz, CH=CH<sub>2</sub>), 5.49 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1B), 5.47 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1E), 5.38 (d, 1H, <sup>2</sup>J = 10.2 Hz, CHPh), 5.35 (d, 1H, <sup>2</sup>J = 11.0 Hz, CHPh), 5.28 (bd, 1H, <sup>3</sup>J<sub>trans</sub> = 17.3 Hz, CH=CH<sub>2</sub>), 5.11 (bd, 1H, <sup>3</sup>J<sub>cis</sub> = 10.2 Hz, CH=CH<sub>2</sub>), 5.10 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 5.06 (d, 1H, <sup>2</sup>J = 10.6 Hz, CHPh), 4.91 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1C), 4.90 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1F), 4.89 (d, 1H, <sup>2</sup>J = 11.3 Hz, CHPh), 4.87 (d, 1H, <sup>2</sup>J = 10.5 Hz, CHPh), 4.81 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 4.78 (d, 1H, <sup>2</sup>J = 10.8 Hz, CHPh), 4.76 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.8 Hz, H-1D), 4.73-4.79 (m, 3H, H-1A, 2 $\times$ CHPh), 4.55-4.37 (m, 20H, 20 $\times$ CHPh), 4.34 (dd, 1H, <sup>3</sup>J<sub>4,5</sub> = 3.8 Hz, <sup>3</sup>J<sub>5,6</sub> = 9.8 Hz, H-5A), 4.15-3.80 (m, 19H, H-3A, H-3B, H-3C, H-3D, H-3E, H-3F, H-4B, H-4C, H-4D, H-4E, H-5B, H-5C, H-5D, H-5E, H-5F, H-6B, H-6E, 2 $\times$ H-6D), 3.74-3.64 (m, 5H, H-4F, H-6B, H-6C, H-6D, H-6E), 3.56 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.6 Hz, H-2B), 3.55 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.8 Hz, H-2E), 3.45 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.6 Hz, H-2C), 3.43-3.39 (m, 3H, H-2D, H-2F, H-4A), 3.37 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.6 Hz, H-2A), 2.96 (dd, 1H, <sup>2</sup>J<sub>6,6'</sub> = 13.1 Hz, <sup>3</sup>J<sub>6,NH</sub> = 2.5 Hz, H-6F), 2.77 (dd, 1H, <sup>2</sup>J<sub>6,6'</sub> = 13.2 Hz, <sup>3</sup>J<sub>6,NH</sub> = 6.2 Hz, H-6F)

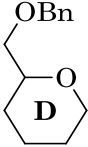
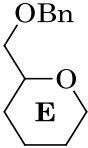
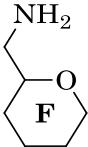
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.49, 139.46, 139.44, 139.41(2C), 139.38, 138.67, 138.63, 138.54, 138.42, 138.31, 138.21(2C), 138.14(2C) (15 $\times$ C-Ar<sup>quat.</sup>), 136.20 (CH=CH<sub>2</sub>), 128.47-126.74 (m, 75 $\times$ C-Ar<sup>tert.</sup>), 117.84 (CH=CH<sub>2</sub>), 98.39, 98.18(2C), 98.22, 97.99, 97.61 (C-1A, C-1D, C-1E, C-1B, C-1C, C-1F), 84.99 (C-4A), 81.77, 88.44 (C-3C, C-3F), 81.36 81.26 (C-4B, C-4E), 81.05, 80.90, 80.85, 80.83, (C-3D, C-3A, C-3E, C-3B), 80.36 (C-4D), 80.04, 79.67, 79.28(2C), 78.24(2C) (C-2D, C-2C, C-2F, C-2A, C-2B, C-2E), 77.63, 76.30 (C-4F, C-4C), 76.20, 76.12, 76.10, 75.83, 74.57(2C), 73.66, 73.55, 73.50, 73.47, 73.40, 72.93, 72.90, 72.68(2C) (15 $\times$ CH<sub>2</sub>Ph), 72.03, 71.89(2C), 71.66, 71.38, 71.14 (C-5E, C-5C, C-5D, C-5B, C-5F, C-5A), 69.98, 69.74, 69.28, 61.53, 43.46 (C-6D, C-6E, C-6B, C-6C, C-6F)

**HRMS (ESI):** Calcd. For C<sub>142</sub>H<sub>152</sub>NO<sub>28</sub> [M+H]<sup>+</sup>: 2319.0517; Found: 2319.0495 (- 0.9ppm)

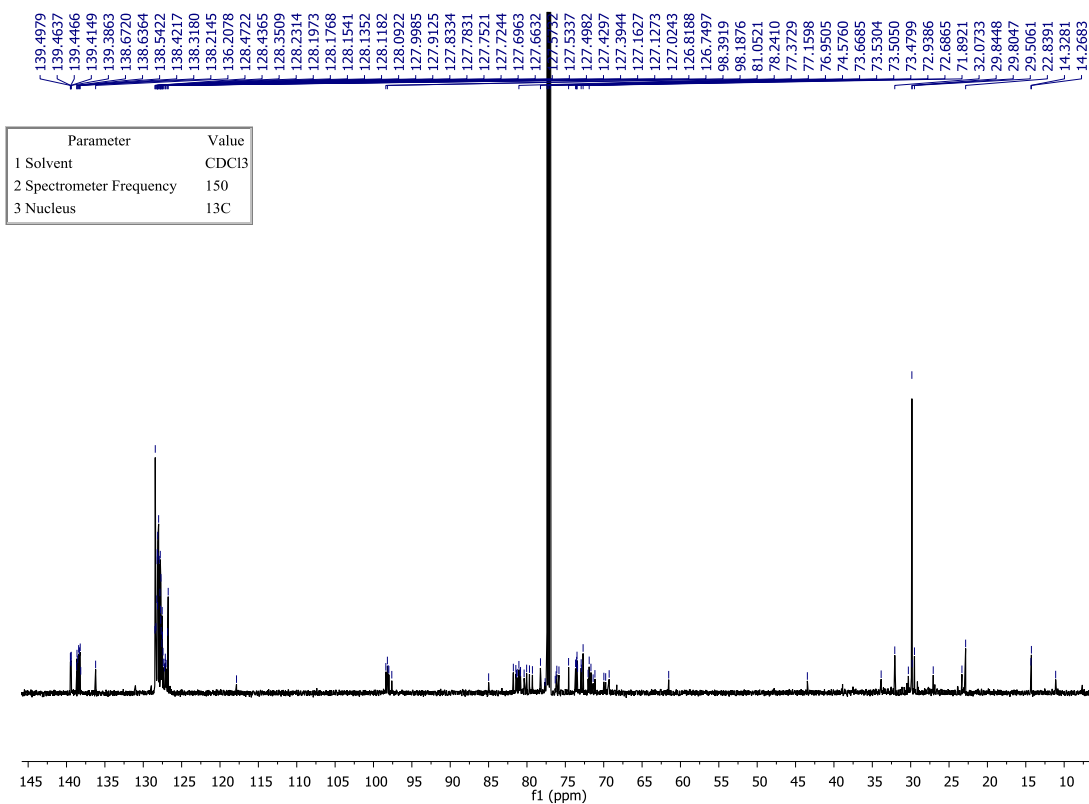
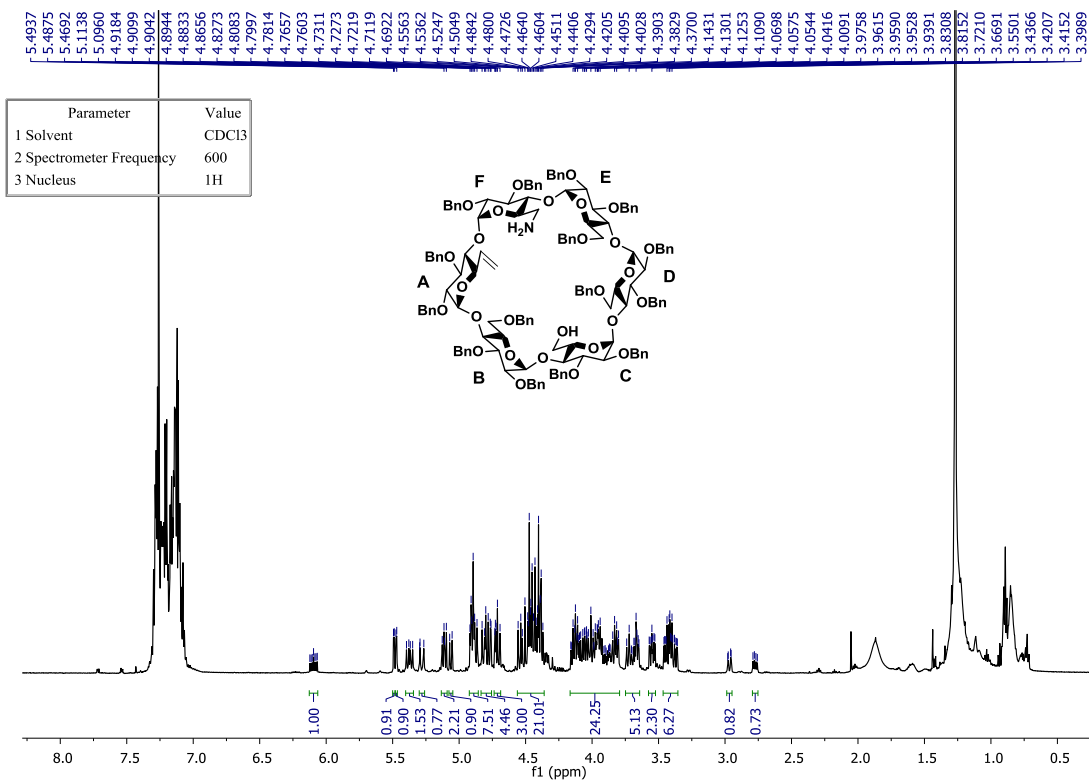
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>A</b></p>	H-1A	4.725	NOE:3.925	H-4B
	C-1A	98.392		
	H-2A	3.375		
	C-2A	79.288		
	H-3A	4.041		
	C-3A	80.904		
	H-4A	3.423	HMBC: 97.616	C-1F
	C-4A	84.995		
	H-5A	4.340		
	C-5A	71.145		
	CH=CH <sub>2</sub>	5.279		
		5.116		
	CH=C <sub>H</sub> 2	117.849		
	CH=CH <sub>2</sub>	6.095		
CH=CH <sub>2</sub>	136.208			
 <p style="text-align: center;"><b>B</b></p>	H-1B	5.491	NOE:3.669	H-4C
	C-1B	98.109		
	H-2B	3.561		
	C-2B	78.241		
	H-3B	4.145		
	C-3B	80.835		
	H-4B	3.925	HMBC: 98.390	C-1A
	C-4B	81.359		
	H-5B	4.017		
	C-5B	71.660		
	H-6B	3.658		
		4.001		
C-6B	69.287			
 <p style="text-align: center;"><b>C</b></p>	H-1C	4.918	NOE:3.829	H-4D
	C-1C	97.996		
	H-2C	3.449		
	C-2C	79.674		
	H-3C	4.113		
	C-3C	81.780		
	H-4C	3.818	HMBC: 98.109	C-1B
	C-4C	76.307		
	H-5C	3.944		
	C-5C	71.890		
	H-6C	3.816		
		3.722		
C-6C	61.532			

**EXPERIMENTAL PART**

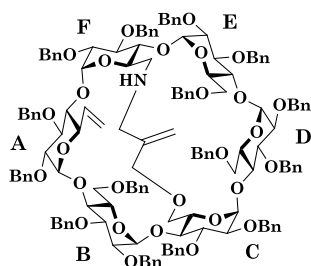
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>D</b></p>	H-1D	4.763	NOE:3.973	H-4E
	C-1D	98.188		
	H-2D	3.406		
	C-2D	80.044		
	H-3D	4.042		
	C-3D	81.054		
	H-4D	3.829	HMBC 97.997:	C-1C
	C-4D	80.370		
	H-5D	3.960		
	C-5D	71.890		
	H-6D	3.711		
		3.892		
C-6D	69.981			
 <p style="text-align: center;"><b>E</b></p>	H-1E	5.472	NOE:3.669	H-4F
	C-1E	98.188		
	H-2E	3.538		
	C-2E	78.241		
	H-3E	4.139		
	C-3E	80.862		
	H-4E	3.980	HMBC: 98.190	C-1D
	C-4E	81.270		
	H-5E	3.860		
	C-5E	72.022		
	H-6E	3.682		
		4.121		
C-6E	69.742			
 <p style="text-align: center;"><b>F</b></p>	H-1F	4.910	NOE:3.410	H-4A
	C-1F	97.613		
	H-2F	3.414		
	C-2F	79.288		
	H-3F	4.085		
	C-3F	81.450		
	H-4F	3.688	HMBC: 98.190	C-1E
	C-4F	77.660		
	H-5F	3.954		
	C-5F	71.376		
	H-6F	2.966		
		2.774		
C-6F	43.356			

EXPERIMENTAL PART





**6<sup>A</sup>,6<sup>F</sup>-Dideoxy-6<sup>A</sup>-Vinyl-6<sup>C</sup>-O-6<sup>F</sup>-N-(prop-2-ene-1,3-dienyl)-2<sup>A-F</sup>,3<sup>A-F</sup>,  
6<sup>B</sup>,6<sup>D</sup>,6<sup>E</sup>-Pentadeca-O-Benzyl- $\alpha$ -cyclodextrin (**243**)**



Sodium hydride (60% w/w in oil, 137.5 mg, 3.483 mmol, 6 eq.) was added at r.t. under argon to a solution of amino-alcohol **242** (1.33 g, 0.573 mmol, 1 eq.) in dry DMF (16 mL). The reaction mixture was stirred for 30 min, and then 3-chloro-2-chloromethyl-1-propene (0.073 mL, 0.630 mmol, 1.1 eq.) was added. After 12 h of stirring, MeOH (5 mL) was slowly added and the solvents were removed.

The residue was dissolved in EtOAc (20 mL) and washed with a saturated aqueous solution of NH<sub>4</sub>Cl (20 mL). The aqueous layers were extracted with EtOAc (3×20 mL), and the organic layers were combined, dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc 3:1, then DCM/MeOH 98:2) gave bridged- $\alpha$ -cyclodextrin **243** (867 mg, 72%) as a white foam.

$\alpha_D = +30.1$  (c 1.0, CHCl<sub>3</sub>)

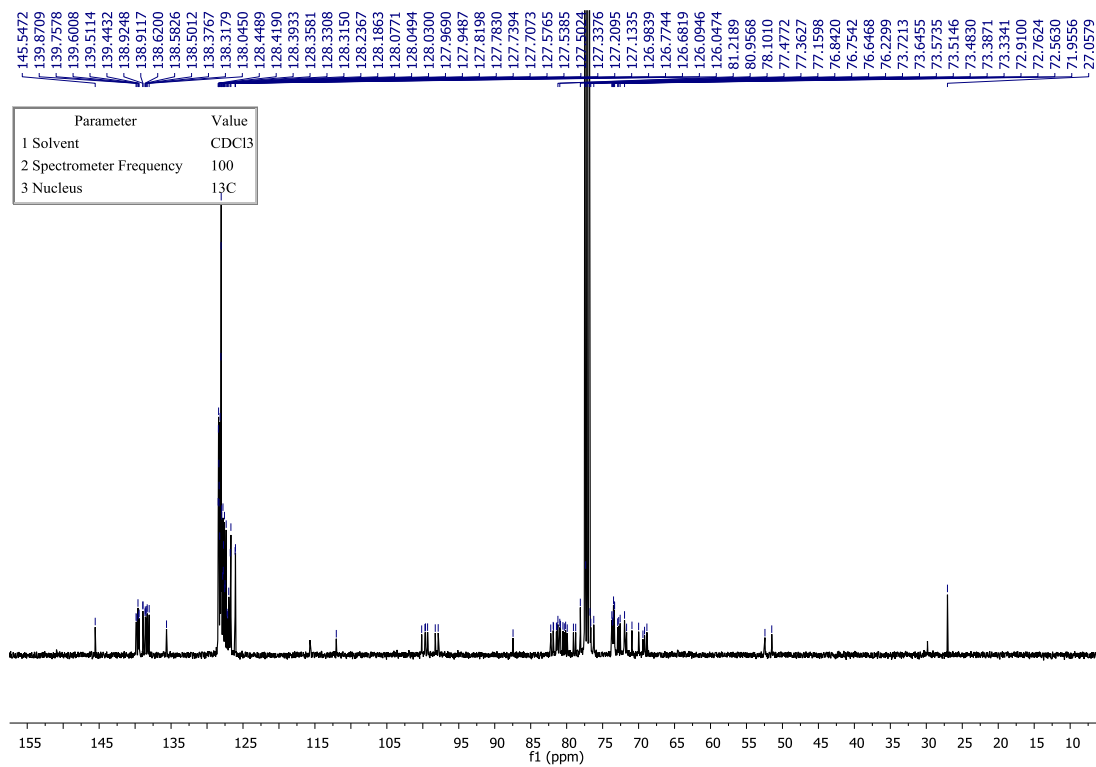
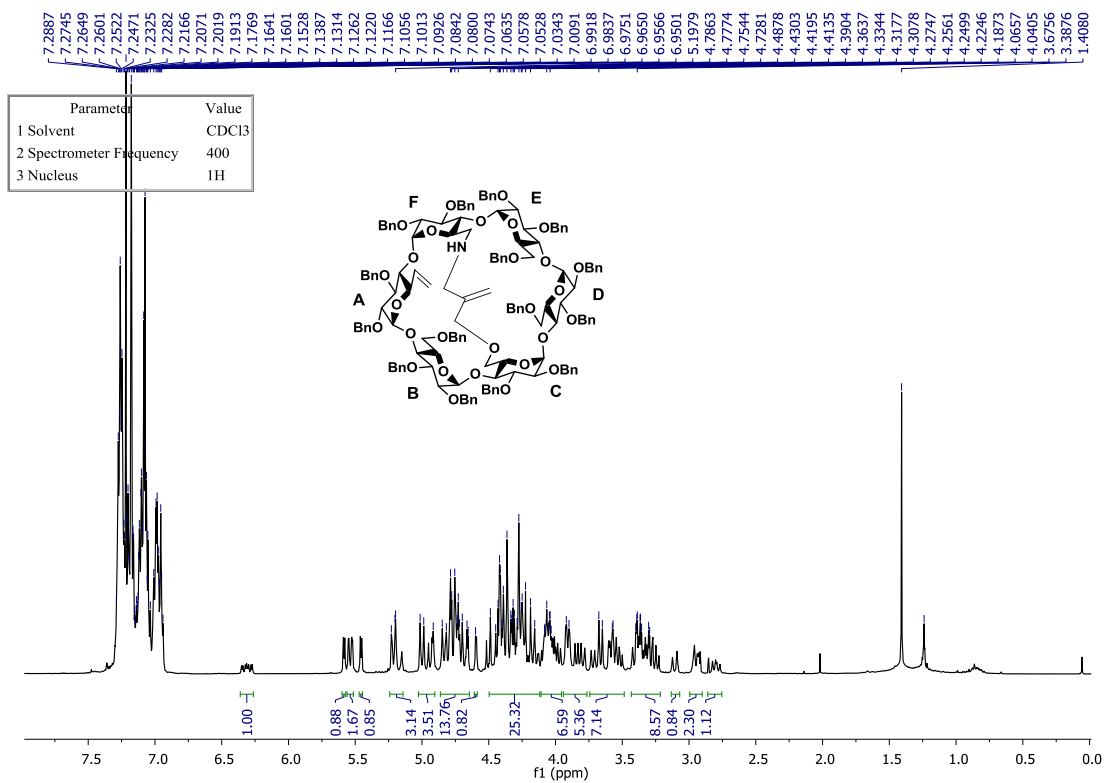
$R_f = 0.87$  (DCM/MeOH: 95/5)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.28-6.93 (m, 75H, 75×H-Ar), 6.31 (ddd, 1H, <sup>3</sup>J<sub>5,6</sub>=3.7 Hz, <sup>3</sup>J<sub>cis</sub>=10.9 Hz, <sup>3</sup>J<sub>trans</sub>=14.7 Hz, CH=CH<sub>2</sub>), 5.58 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=4.0 Hz, H-1), 5.53 (d, 2H, <sup>2</sup>J=10.4 Hz, 2×CHPh), 5.45 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=4.2 Hz, H-1), 5.21 (d, 2H, <sup>2</sup>J=10.5 Hz, 2×CHPh), 5.17 (bd, 1H, <sup>3</sup>J<sub>trans</sub>=18.0 Hz, CH=CH<sub>2</sub>), 5.01-4.91 (m, 4H, CH=CH<sub>2</sub>, 2×CHPh, =CH), 4.84-4.69 (m, 12H, 2×H-1, 9×CHPh, =CH), 4.65 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.4 Hz, H-1), 4.59 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.4 Hz, H-1), 4.51-4.12 (m, 22H, 2×H-3, 3×H-5, 2×H-6, 15×CHPh), 4.10-3.96 (m, 8H, 4×H-3, 3×H-4, H-6), 3.92-3.78 (m, 5H, H-4, 3×H-5, OCH-C=), 3.73-3.64 (m, 3H, 2×H-6, OCH-C=), 3.60-3.50 (m, 4H, 2×H-2, H-4, H-6), 3.42-3.22 (m, 7H, 4×H-2, H-4, 2×H-6), 3.10 (d, 1H, <sup>2</sup>J=13.3 Hz, NCH-C=), 2.97-2.91 (m, 2H, NCH-C=, H-6), 2.79 (dd, 1H, <sup>3</sup>J<sub>5,6</sub>=9.4 Hz, <sup>2</sup>J<sub>6,6'</sub>=13.0 Hz, H-6).

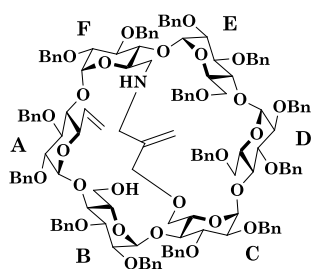
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  145.51 (C=CH<sub>2</sub>), 139.87, 139.75, 139.60 (2C), 139.51, 139.44, 138.92, 138.91, 138.62, 138.58, 138.50, 138.37, 138.31, 138.06, 138.04 (15×C-Ar<sup>quat.</sup>), 135.63 (CH=CH<sub>2</sub>), 128.44-126.04 (m, 75×C-Ar<sup>tert.</sup>), 116.03 (CH=CH<sub>2</sub>), 112.02 (C=CH<sub>2</sub>), 100.15, 99.70, 99.62, 99.33, 98.27, 97.86 (6×C-1), 87.45 (C-4), 82.21 (C-3), 81.86, 81.82 (2×C-4), 81.42, 81.31, 81.21, 81.19 (4×C-3), 80.95 (C-4), 80.86 (C-3), 80.52, 80.33, 80.14, 79.92, 79.05, 78.74 (6×C-2), 70.81 (2C) (2×C-4), 76.75, 76.64, 76.22 (2C), 73.72 (2C), 73.64, 73.57, 73.51 (9×CH<sub>2</sub>Ph), 73.38 (OCH<sub>2</sub>-C=), 73.33, 72.91 (2C), 72.76, 72.56 (2C) (6×CH<sub>2</sub>Ph), 72.00 (C-5), 71.95 (C-6), 71.92, 71.66, 70.92, 69.99 (4×C-5), 69.39, 69.17, 69.12 (3×C-6), 68.84 (C-5), 52.43 (C-6), 51.48 (NCH<sub>2</sub>-C=).

HRMS (ESI): Calcd. For C<sub>146</sub>H<sub>156</sub>NO<sub>28</sub> [M+H]<sup>+</sup>:2371.0886; Found: 2371.0808 (-2.4 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>F</sup>-Dideoxy-6<sup>A</sup>-Vinyl-6<sup>C</sup>-O-6<sup>F</sup>-N-(prop-2-ene-1,3-dienyl)-2<sup>A-F</sup>,3<sup>A-F</sup>,  
6<sup>D</sup>,6<sup>E</sup>-Tetradeca-O-Benzyl- $\alpha$ -cyclodextrin (244)**



DIBAL-H (1.5 M in toluene, 3.4 mL, 5.05 mmol, 15 eq.) was slowly added to a solution of bridge- $\alpha$ -cyclodextrin **243** (800 mg, 0.34 mmol, 1 eq.) in toluene (1.69 mL) under nitrogen at r.t. The reaction mixture was stirred under nitrogen reflux at 45°C. The formation of the monol as the major product was monitored by TLC (30 min). Heating was stopped, diethyl ether (45 mL) was added and the mixture was cooled down to 0°C. Water (340  $\mu$ L) was added

dropwise, then NaOH aq.sol. 15% (340  $\mu$ L) and a second portion of water (500  $\mu$ L) were added. The mixture was vigorously stirred at r.t. for 20 min, then MgSO<sub>4</sub> (180 mg) was added and the mixture was stirred for 60 min. The precipitate was filtered and washed abundantly with diethyl ether (5 $\times$ 15 mL). The combined organic layers were concentrated under vacuum. Silica gel flash chromatography of the residue (CyH/EtOAc 4:1, then CyH/EtOAc 3:1) gave the bridge-alcohol **244** (427 mg, 56%) as a white foam.

$\alpha_D = +32.8$  (c 1.0, CHCl<sub>3</sub>)

$R_f = 0.41$  (CyH/EtOAc: 2:1.5)

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.33-7.98 (m, 70H, 70 $\times$ H-Ar), 6.33 (ddd, 1H,  $^3J_{5,6} = 3.6$  Hz,  $^3J_{cis} = 11.0$  Hz,  $^3J_{trans} = 15.5$  Hz, CH=CH<sub>2</sub>), 5.63 (d, 1H,  $^3J_{1,2} = 3.8$  Hz, H-1E), 5.58 (d, 1H,  $^2J = 10.2$  Hz, CHPh), 5.53 (d, 1H,  $^2J = 10.6$  Hz, CHPh), 5.36 (d, 1H,  $^3J_{1,2} = 3.6$  Hz, H-1B), 5.32 (bd, 1H,  $^3J_{trans} = 17.4$  Hz, CH=CH<sub>2</sub>), 5.27 (dd, 2H,  $^2J = 10.3$  Hz, 2 $\times$ CHPh), 5.08 (bd, 1H,  $^3J_{cis} = 11.3$  Hz, CH=CH<sub>2</sub>), 5.03 (d, 1H,  $^2J = 10.3$  Hz, CHPh), 4.98 (d, 1H,  $^2J = 10.9$  Hz, CHPh), 4.97 (d, 2H,  $^2J = 4.2$  Hz, 2 $\times$ CH), 4.88-4.70(m, 11H, H-1A, H-1D, H-1C, 8 $\times$ CHPh), 4.65 (d, 1H,  $^3J_{1,2} = 2.3$  Hz, H-1F), 4.51-4.21 (m, 20H, 14 $\times$ CHPh, H-3B, H-3E, H-5A, H-5C, H-5F, H-6D), 4.18-4.04 (m, 7H, H-3A, H-3C, H-3D, H-3F, H-4E, H-6B, H-6E), 3.97-3.84 (m, 8H, H-4B, H-4D, H-5B, H-5D, H-5E, H-6B, 2 $\times$ OCH-C=), 3.76 (d, 1H,  $^2J = 10.6$  Hz, H-6E), 3.67 (d, 1H,  $^2J = 11.0$  Hz, H-6C), 3.63 (dd, 1H,  $^3J_{1,2} = 4.2$  Hz,  $^3J_{2,3} = 9.7$  Hz, H-2E), 3.56 (t, 1H,  $^3J = 9.0$  Hz, H-4F), 3.53 (dd, 1H,  $^3J_{1,2} = 4.2$  Hz,  $^3J_{2,3} = 9.9$  Hz, H-2B), 3.47 (d, 1H,  $^2J_{6,6'} = 11.0$  Hz, H-6D), 3.44-3.33 (m, 7H, H-2A, H-2C, H-2D, H-2F, H-4A, H-4C, H-6C), 3.16 (bd, 1H,  $^2J = 13.9$  Hz, NCH-C=), 3.00 (t, 2H, H-6F, NCH-C=), 2.83 (dd, 1H,  $^3J_{5,6} = 9.7$  Hz,  $^2J_{6,6'} = 12.2$  Hz, H-6F)

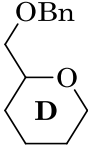
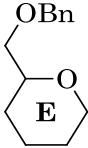
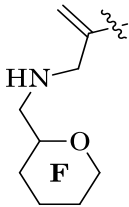
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 150 MHz):  $\delta$  145.34 (C=CH<sub>2</sub>), 139.86, 139.74, 139.58, 139.53, 139.51, 139.38, 138.91, 138.71, 138.60, 138.47, 138.41, 138.36, 138.04, 138.03 (14 $\times$ C-Ar<sup>quat.</sup>), 135.27 (CH=CH<sub>2</sub>), 128.46-126.05 (m, 70 $\times$ C-Ar<sup>tert.</sup>), 116.15 (CH=CH<sub>2</sub>), 112.33 (=CH<sub>2</sub>), 110.35, 100.03, 99.58, 99.42, 98.25, 97.66 (C-1B, C-1A, C-1E, C-1D, C-1C, C-1F), 87.07, 82.18, 81.86(2C) (C-4A, C-4B, C-4D, C-4E), 81.38, 81.36, 81.07, 81.04 (C-3F, C-3E, C-3D, C-3C), 80.89 (C-2F), 80.88 (C-3B), 80.59 (C-2C), 80.43 (C-3A), 80.29, 79.99 (C-4F, C-4C), 79.07, 78.50, 78.13, 77.96 (C-2D, C-2A, C-2E, C-2B), 76.79, 76.51, 76.25, 76.08, 74.09, 73.70 (6 $\times$ CH<sub>2</sub>Ph), 73.52 (OCH<sub>2</sub>-C=), 73.39, 73.34(2C), 72.90, 72.86, 72.66 (6 $\times$ CH<sub>2</sub>Ph), 72.26, 72.00 (C-5B, C-5D), 71.97(2C) (2 $\times$ CH<sub>2</sub>Ph), 71.90 (C-5E), 71.82 (C-6C), 71.03, 70.05 (C-5A, C-5F), 69.36, 69.18 (C-6E, C-6D), 68.97 (C-5C), 62.03, 52.40 (C-6B, C-6F), 51.65 (NCH<sub>2</sub>-C=).

**HRMS (ESI)**: Calcd. For C<sub>139</sub>H<sub>150</sub>NO<sub>28</sub> [M+H]<sup>+</sup>: 2281.0402; Found: 2281.0339 (- 2.8 ppm)

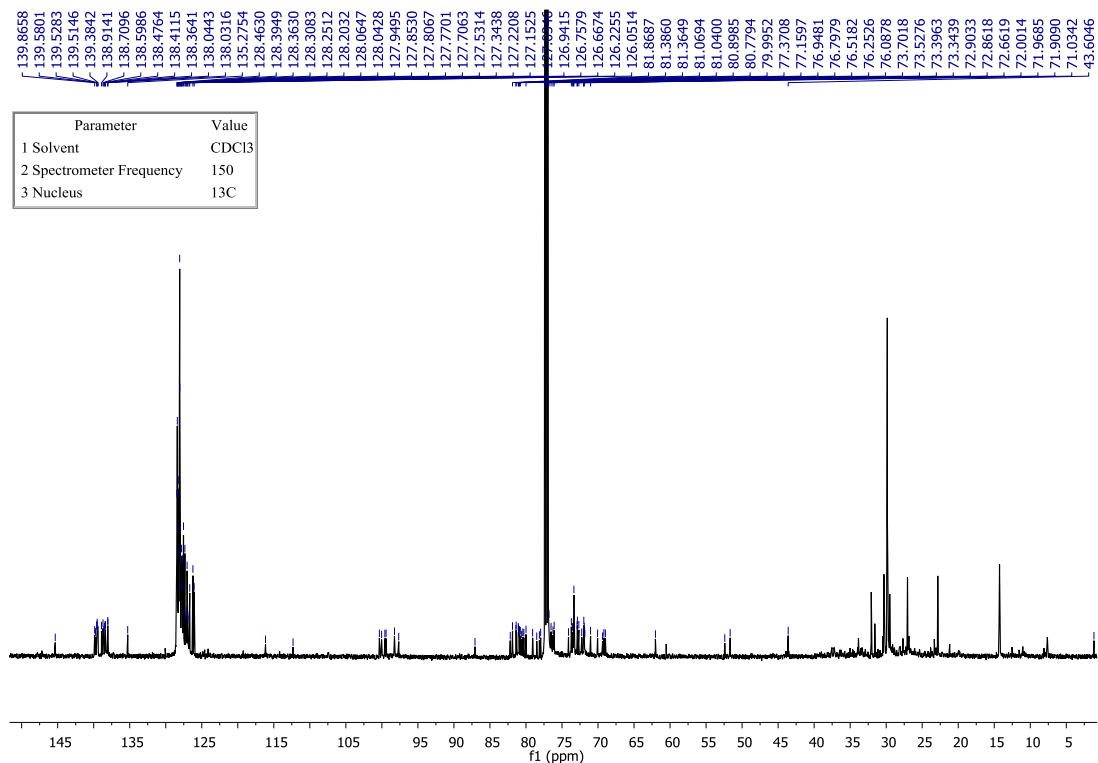
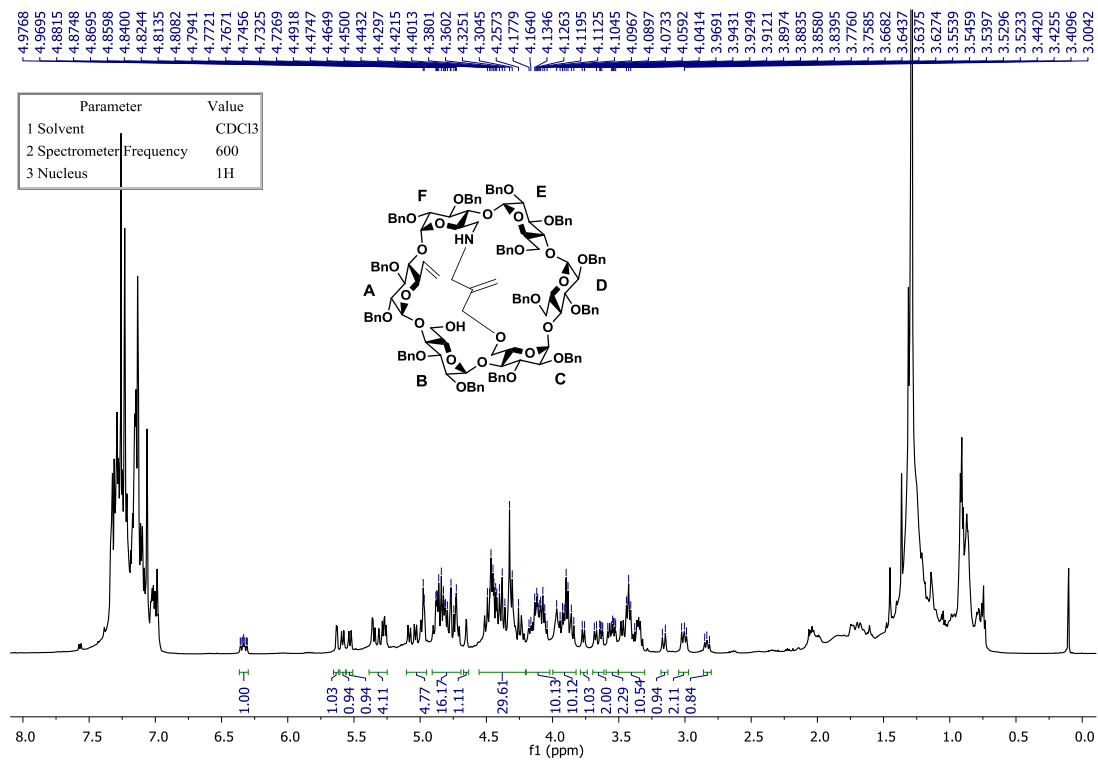
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
<p style="text-align: center;"><b>A</b></p>	H-1A	4.725	NOE:3.925	H-4B
	C-1A	98.392		
	H-2A	3.375		
	C-2A	79.288		
	H-3A	4.041		
	C-3A	80.904		
	H-4A	3.423	HMBC: 97.616	C-1F
	C-4A	84.995		
	H-5A	4.340		
	C-5A	71.145		
	CH=CH <sub>2</sub>	5.279		
		5.116		
	CH=CH <sub>2</sub>	117.849		
	CH=CH <sub>2</sub>	6.095		
CH=CH <sub>2</sub>	136.208			
<p style="text-align: center;"><b>B</b></p>	H-1B	5.491	NOE:3.669	H-4C
	C-1B	98.109		
	H-2B	3.561		
	C-2B	78.241		
	H-3B	4.145		
	C-3B	80.835		
	H-4B	3.925	HMBC: 98.390	C-1A
	C-4B	81.359		
	H-5B	4.017		
	C-5B	71.660		
	H-6B	3.658		
		4.001		
C-6B	69.287			
<p style="text-align: center;"><b>C</b></p>	H-1C	4.918	NOE:3.829	H-4D
	C-1C	97.996		
	H-2C	3.449		
	C-2C	79.674		
	H-3C	4.113		
	C-3C	81.780		
	H-4C	3.818	HMBC: 98.109	C-1B
	C-4C	76.307		
	H-5C	3.944		
	C-5C	71.890		
	H-6C	3.816		
		3.722		
C-6C	61.532			

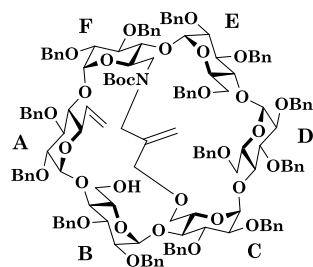
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	4.763	NOE:3.973	H-4E
	C-1D	98.188		
	H-2D	3.406		
	C-2D	80.044		
	H-3D	4.042		
	C-3D	81.054		
	H-4D	3.829	HMBC 97.997:	C-1C
	C-4D	80.370		
	H-5D	3.960		
	C-5D	71.890		
	H-6D	3.711		
		3.892		
C-6D	69.981			
	H-1E	5.472	NOE:3.669	H-4F
	C-1E	98.188		
	H-2E	3.538		
	C-2E	78.241		
	H-3E	4.139		
	C-3E	80.862		
	H-4E	3.980	HMBC: 98.190	C-1D
	C-4E	81.270		
	H-5E	3.860		
	C-5E	72.022		
	H-6E	3.682		
		4.121		
C-6E	69.742			
	H-1F	4.910	NOE:3.410	H-4A
	C-1F	97.613		
	H-2F	3.414		
	C-2F	79.288		
	H-3F	4.085		
	C-3F	81.450		
	H-4F	3.688	HMBC: 98.190	C-1E
	C-4F	77.660		
	H-5F	3.954		
	C-5F	71.376		
	H-6F	2.966		
		2.774		
C-6F	43.356			

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>F</sup>-Dideoxy-6<sup>A</sup>-Vinyl-6<sup>C</sup>-O-6<sup>F</sup>-(Boc)*N*-(prop-2-ene-1,3-dienyl)-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>D</sup>,6<sup>E</sup>-Tetradeca-O-Benzyl- $\alpha$ -cyclodextrin (**244a**)**

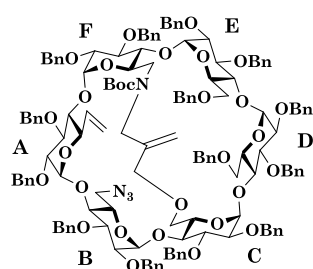


A solution of Boc<sub>2</sub>O (73 mg, 0.33 mmol, 3 eq.) in absolute ethanol (2.5 mL) was added to a solution of  $\alpha$ -cyclodextrin **244** (253 mg, 0.11 mmol, 1 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) at r.t. The reaction mixture was stirred for 12 h, then evaporated under reduced pressure. Silica gel flash chromatography of the residue (CyH/EtOAc 3:1) gave the product **244a** (251 mg, 95%) as a white foam.

$R_f$  = 0.49 (CyH/EtOAc: 2:1)

**HRMS (ESI):** Calcd. For C<sub>144</sub>H<sub>157</sub>NO<sub>30</sub>Na [M+Na]<sup>+</sup>: 2403.0739; Found: 2403.0683 (-2.3 ppm)

**6<sup>A</sup>,6<sup>F</sup>,6<sup>B</sup>-Trideoxy-6<sup>A</sup>-Vinyl-6<sup>B</sup>-Azido-6<sup>C</sup>-O-6<sup>F</sup>-(Boc)*N*-(prop-2-ene-1,3-dienyl)-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>D</sup>,6<sup>E</sup>-Tetradeca-O-Benzyl- $\alpha$ -cyclodextrin (**244b**)**



To a solution of Boc protected  $\alpha$ -cyclodextrin **244a** (251 mg, 0.105 mmol, 1 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) were added Et<sub>3</sub>N (44  $\mu$ L, 0.315 mmol, 3 eq.) and MsCl (24  $\mu$ L, 0.315 mmol, 3 eq.) at 0°C. The reaction mixture was stirred at r.t. for 12 h under nitrogen, then water (2 mL) was added, the phases were separated and the aqueous layers were extracted with dichloromethane (3 $\times$ 4 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated to

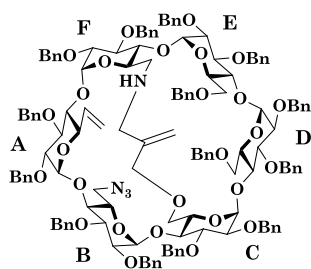
afford the mono-mesylated  $\alpha$ -cyclodextrin as a white foam.

NaN<sub>3</sub> (34 mg, 0.525 mmol, 5 eq.) was added to a solution of mono-mesylated  $\alpha$ -cyclodextrin in DMF (4 mL) at r.t. The reaction mixture was stirred at 80°C for 12 h under nitrogen, then cooled down to r.t. and evaporated to dryness. The crude was dissolved in ethyl acetate (10 mL), washed with water (5 mL) and the aqueous layers were extracted with ethyl acetate (3 $\times$ 10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 4/1) afforded azido- $\alpha$ -cyclodextrin **244b** (240 mg, 95%) as a white foam with two steps.

$R_f$  = 0.68 (cyclohexane/EtOAc: 2/1)

**HRMS (ESI):** Calcd. For C<sub>144</sub>H<sub>156</sub>N<sub>4</sub>O<sub>29</sub>Na [M+Na]<sup>+</sup>: 2428.0782; Found: 2428.0747 (-1.4 ppm)

**6<sup>A</sup>,6<sup>F</sup>,6<sup>B</sup>-Trideoxy-6<sup>A</sup>-Vinyl-6<sup>B</sup>-Azido-6<sup>C</sup>-O-6<sup>F</sup>-N-(prop-2-ene-1,3-dienyl)-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>D</sup>,6<sup>E</sup>-Tetradeca-O-Benzyl- $\alpha$ -cyclodextrin (**244c**)**



Cyclodextrin **244b** (240 mg, 0.1 mmol, 1 eq.) was dissolved in dichloromethane (4 mL) and TFA (1.5 mL) was added at 0°C for 1.5 h. Dichloromethane (10 mL) and saturated aqueous solution of NaHCO<sub>3</sub> (10 mL) were added at the same temperature and the solution was stirred for 1 h. Then the layers were separated and the aqueous layers were extracted with dichloromethane (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered

and concentrated *in vacuo*. Silica gel flash chromatography of the residue (CyH/EtOAc: 4/1) afforded the cyclodextrin **244c** (200 mg, 87%) as a white foam.

$\alpha_D = +56.6$  (c 1.0, CHCl<sub>3</sub>)

$R_f = 0.51$  (CyH/EtOAc: 2:1)

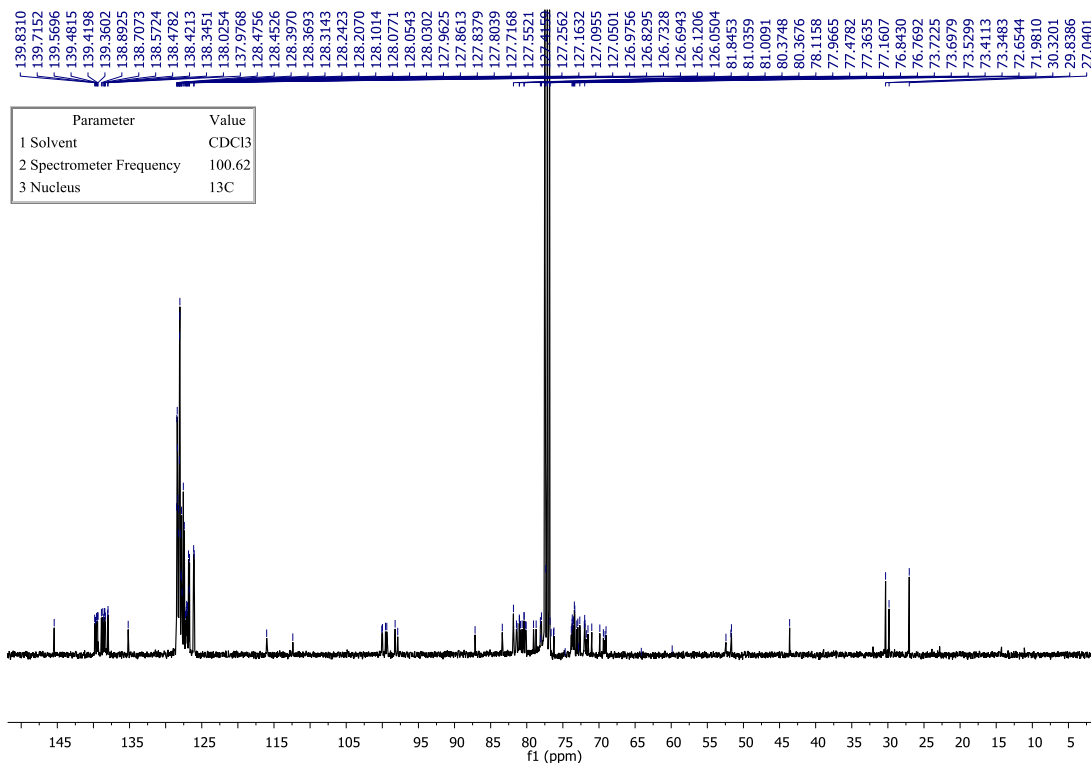
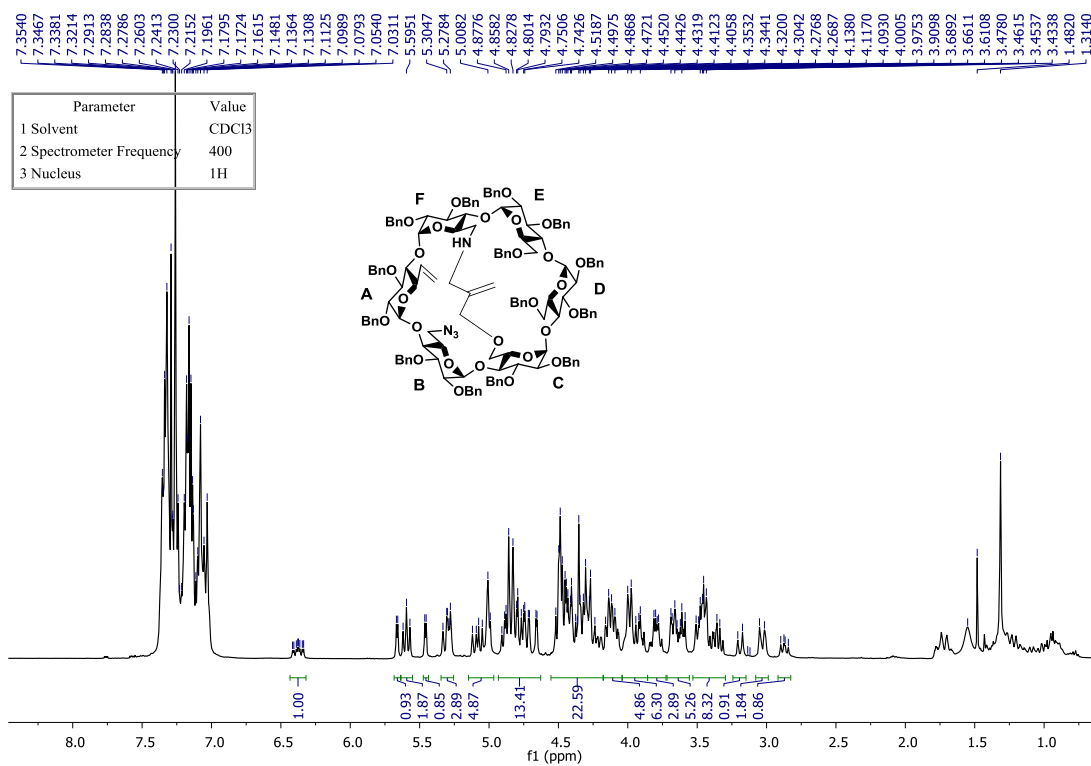
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.53-7.03 (m, 70H, 70×H-Ar), 6.37 (ddd, 1H, <sup>3</sup>J<sub>5,6</sub> = 3.8 Hz, <sup>3</sup>J<sub>cis</sub> = 11.0 Hz, <sup>3</sup>J<sub>trans</sub> = 14.9 Hz, CH=CH<sub>2</sub>), 5.66 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.9 Hz, H-1), 5.58 (t, 2H, <sup>2</sup>J = 9.9 Hz, 2×CHPh), 5.46 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 5.33-5.27 (m, 3H, 2×CHPh, CH=CH<sub>2</sub>), 5.11 (bd, 1H, <sup>3</sup>J<sub>cis</sub> = 11.2 Hz, CH=CH<sub>2</sub>), 5.06 (d, 1H, <sup>2</sup>J = 10.6 Hz, CHPh), 5.04-4.99 (m, 3H, CHPh, 2×=CH), 4.98-4.83 (m, 3H, 3×CHPh), 4.80 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1), 4.78 (d, 1H, <sup>2</sup>J = 10.2 Hz, CHPh), 4.75 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1), 4.71 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, H-1), 4.66 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1), 4.52-4.19 (m, 20H, 2×H-3, 3×H-5, 2×H-6, 14×CHPh), 4.16-4.07 (m, 5H, 4×H-3, H-4), 4.00-3.88 (m, 6H, H-4, 3×H-5, 2×OCH-C=), 3.84-3.76 (m, 3H, H-4, 2×H-6), 3.69-3.58 (m, 5H, 2×H-2, H-4, 2×H-6), 3.51-3.12 (m, 8H, 4×H-2, 2×H-4, 2×H-6), 3.19 (bd, 1H, <sup>2</sup>J = 13.5 Hz, NCH-C=), 3.03 (d, 2H, H-6, NCH-C=), 2.87 (dd, 1H, <sup>3</sup>J<sub>5,6</sub> = 9.3 Hz, <sup>2</sup>J<sub>6,6'</sub> = 12.2 Hz, H-6).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  145.43 (C=CH<sub>2</sub>), 139.83, 139.71, 139.57, 139.48, 139.42, 139.36, 138.89, 138.70, 138.57, 138.48, 138.42, 138.34, 138.02, 137.79 (14×C-Ar<sup>quat</sup>), 135.19 (CH=CH<sub>2</sub>), 128.47-126.05 (70×C-Ar<sup>tert</sup>), 116.01 (CH=CH<sub>2</sub>), 112.39 (=CH<sub>2</sub>), 110.07, 99.98, 99.56, 99.38, 98.23, 97.87 (6×C-1), 87.16, 83.39, 81.84(2C) (4×C-4), 81.43, 81.34, 81.04, 81.01, 80.87, 80.64 (6×C-3), 80.37(2C) (2×C-2), 80.19, 80.08 (2×C-4), 79.06, 78.70, 78.11, 77.97(4×C-2), 76.77, 76.63, 76.30, 76.23, 73.83, 73.72, 73.30 (7×CH<sub>2</sub>Ph), 75.62 (OCH<sub>2</sub>-C=), 73.53, 73.41, 73.35, 73.07, 72.93, 72.65 (6×CH<sub>2</sub>Ph), 72.03 (C-5), 71.98 (CH<sub>2</sub>Ph), 71.90 (C-5), 71.74 (C-6), 71.53, 70.99, 69.88 (3×C-5), 69.39, 69.15 (2×C-6), 69.03 (C-5), 52.42, 51.74 (2×C-6), 51.66 (NCH<sub>2</sub>-C=).

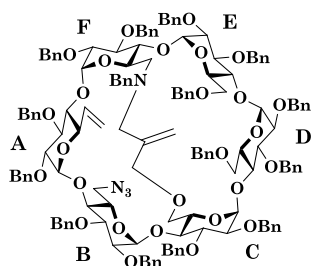
**HRMS (ESI)**: Calcd. For C<sub>139</sub>H<sub>149</sub>N<sub>4</sub>O<sub>27</sub> [M+H]<sup>+</sup>: 2306.0366; Found: 2306.0404 (+ 1.6 ppm)



EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>B</sup>,6<sup>E</sup>-Trideoxy-6<sup>A</sup>-Vinyl-6<sup>B</sup>-Azido-6<sup>C</sup>-O-6<sup>F</sup>-(Benzyl)N-(prop-2-ene-1,3-dienyl)-2<sup>A</sup>-F,3<sup>A</sup>-F,6<sup>D</sup>,6<sup>E</sup>-Tetradeca-O-Benzyl- $\alpha$ -cyclodextrin (245)**



NaH (60% w/w in oil, 92 mg, 2.3 mmol, 20 eq.) was added to a solution of azido- $\alpha$ -cyclodextrin 244c (265 mg, 0.115 mmol, 1 eq.) in DMF (10 mL) under nitrogen at r. t. The reaction mixture was stirred for 30 min, then benzyl iodide (287  $\mu$ L, 2.3 mmol, 20 eq.) was added dropwise. After stirring overnight, the reaction mixture was then carefully hydrolysed with water (10 mL) and the solvents were removed *in vacuo*. The residue was dissolved in ethyl acetate (10 mL) and washed with water (10 mL). The aqueous layers were extracted with ethyl acetate (3 $\times$ 10 mL) and the combined organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated. After purification by silica gel chromatography (CyH/EtOAc 98:2, then 5:1), the benzylated  $\alpha$ -cyclodextrin 245 (200 mg, 73%) was obtained as a white foam.

$\alpha_D = +37.1$  (c 1.0, CHCl<sub>3</sub>)  
 $R_f = 0.75$  (CyH/EtOAc: 3:1)

$\alpha_D = +37.1$  (c 1.0, CHCl<sub>3</sub>)

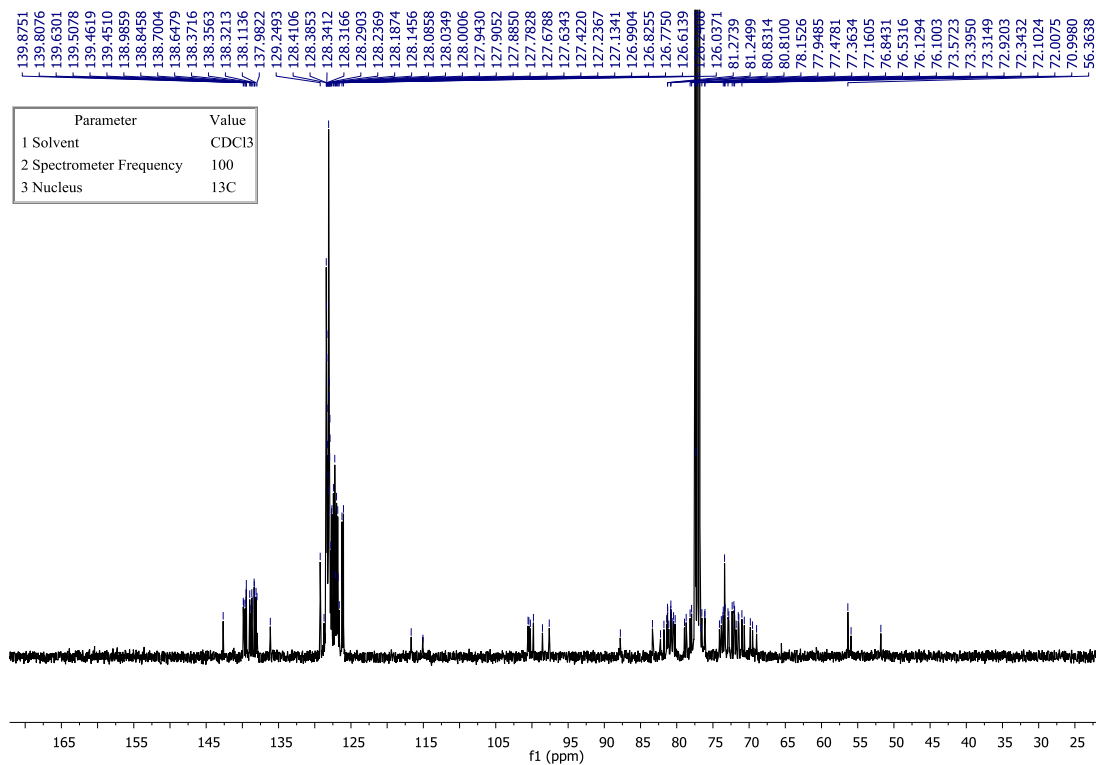
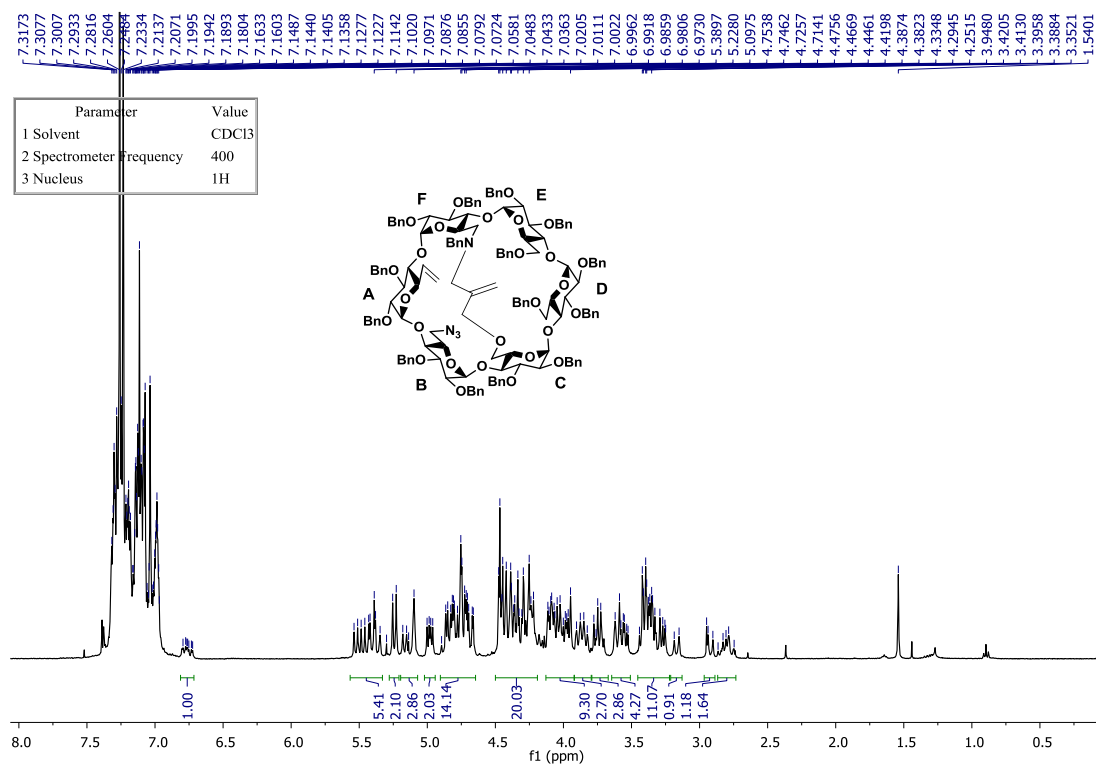
$R_f = 0.75$  (CyH/EtOAc: 3:1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.32-6.97 (m, 75H, 75 $\times$ H-Ar), 6.76 (ddd, 1H, <sup>3</sup>J<sub>5,6</sub> = 3.4 Hz, <sup>3</sup>J<sub>cis</sub> = 11.0 Hz, <sup>3</sup>J<sub>trans</sub> = 14.5 Hz, CH=CH<sub>2</sub>), 5.52 (d, 1H, <sup>2</sup>J = 10.6 Hz, CHPh), 5.43 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 4.1 Hz, H-1), 5.38 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.8 Hz, H-1), 5.36 (bd, 1H, <sup>3</sup>J<sub>trans</sub> = 17.4 Hz, CH=CH<sub>2</sub>), 5.24 (d, 2H, <sup>2</sup>J = 10.5 Hz, 2 $\times$ CHPh), 5.18-5.10 (m, 3H, <sup>3</sup>J<sub>cis</sub> = 11.0 Hz, CH=CH<sub>2</sub>, 2 $\times$ =CH), 4.98 (dd, 2H, <sup>2</sup>J = 10.4 Hz, 2 $\times$ CHPh), 4.86-4.70 (m, 11H, 3 $\times$ H-1, 8 $\times$ CHPh), 4.67 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1), 4.47-4.19 (m, 22H, 3 $\times$ H-3, 3 $\times$ H-5, H-6, 15 $\times$ CHPh), 4.11-3.95 (m, 10H, 3 $\times$ H-3, 3 $\times$ H-4, H-5, H-6, CHPh, OCH-C=), 3.90-3.83 (m, 3H, 2 $\times$ H-5, H-6), 3.78-3.70 (m, 3H, H-4, H-6, OCH-C=), 3.62-3.53 (m, 4H, 2 $\times$ H-2, 2 $\times$ H-6), 3.44-3.25 (m, 9H, 4 $\times$ H-2, 2 $\times$ H-4, 2 $\times$ H-6, CHPh), 3.17 (bd, 1H, <sup>2</sup>J = 14.0 Hz, NCH-C=), 2.92 (bd, 1H, <sup>2</sup>J = 13.9 Hz, NCH-C=), 2.86-2.79 (m, 2H, 2 $\times$ H-6)

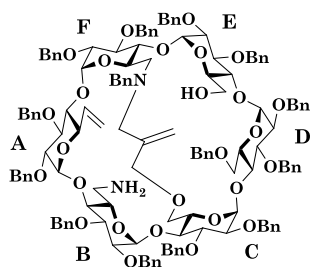
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  142.65 (C=CH<sub>2</sub>), 139.87, 139.81, 139.63, 139.51, 139.46, 139.45, 138.98, 138.84, 138.70, 138.65, 138.37, 138.36, 138.32, 138.11, 137.98 (15 $\times$ C-Ar<sup>quat.</sup>), 136.14 (CH=CH<sub>2</sub>), 129.25-126.04 (75 $\times$ C-Ar<sup>tert.</sup>), 116.68 (=CH<sub>2</sub>), 115.06 (CH=CH<sub>2</sub>), 100.54, 100.42, 100.22, 99.79, 98.55, 97.61 (6 $\times$ C-1), 87.78, 83.35, 82.24, 81.77, 81.39 (5 $\times$ C-4), 81.27 (C-3), 81.25 (C-2), 81.09, 81.83, 80.81, 80.75, 80.54 (5 $\times$ C-3), 80.43 (C-4), 80.21, 78.93, 78.69, 78.15, 77.95 (5 $\times$ C-2), 76.67, 76.53, 76.13, 76.10 74.10 (5 $\times$ CH<sub>2</sub>Ph), 73.84 (OCH<sub>2</sub>-C=), 73.61, 73.57, 73.39(2C), 73.31, 72.92, 72.80, 72.34, 72.10 (9 $\times$ CH<sub>2</sub>Ph), 72.00 (C-5), 71.79 (C-6), 71.50, 71.42, 71.00, 70.67, 69.83 (5 $\times$ C-5), 69.53, 68.97 (2 $\times$ C-6), 56.36(2C) (C-6, CH<sub>2</sub>Ph), 55.92 (NCH<sub>2</sub>-C=), 51.80 (C-6).

HRMS (ESI): Calcd. For C<sub>146</sub>H<sub>155</sub>N<sub>4</sub>O<sub>27</sub> [M+H]<sup>+</sup>: 2396.0823; Found: 2396.0837 (+ 2.1 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>F</sup>,6<sup>B</sup>-Trideoxy-6<sup>A</sup>-Vinyl-6<sup>C</sup>-O-6<sup>F</sup>-(Benzyl)*N*-(Prop-2-ene-1,3-dienyl)-6<sup>B</sup>-Amino-2<sup>A-F</sup>, 3<sup>A-F</sup>,6<sup>D</sup>-Trideca-O-Benzyl- $\alpha$ -cyclodextrin (**246**)**



DIBAL-H (1.5 M in toluene, 0.84 mL, 1.26 mmol, 15 eq.) was added to a solution of cyclodextrin **245** (200 mg, 0.084 mmol, 1 eq.) in toluene (0.42 mL) under nitrogen at r.t. The reaction mixture was stirred at 50°C. When the monol was the major product (60 min), heating was stopped, diethyl ether (45 mL) was added and the mixture was cooled down to 0°C. Water (173  $\mu$ L) was added dropwise, then NaOH aq. sol. 15% (173  $\mu$ L) and a second portion of

water (432  $\mu$ L) were added. The mixture was vigorously stirred at r.t. for 20 min, then MgSO<sub>4</sub> (180 mg) was added and the mixture was stirred for another 60 min. The precipitate was filtered and washed with diethyl ether (5 $\times$ 15 mL). The combined organic layers were concentrated *in vacuum*. Silica gel flash chromatography of the residue (CyH/EtOAc 2:1, then DCM/MeOH 98:2) gave cyclodextrin **246** (135 mg, 70%) as a white foam.

$\alpha_D = +35.5$  (c 1.0, CHCl<sub>3</sub>)

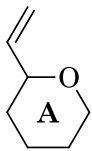
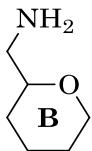
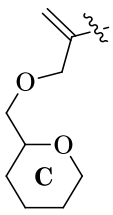
$R_f = 0.55$  (DCM/MeOH: 9/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.31-6.99 (m, 70H, 70 $\times$ H-Ar), 6.76 (ddd, 1H, <sup>3</sup>J<sub>5,6</sub> = 3.2 Hz, <sup>3</sup>J<sub>cis</sub> = 11.0 Hz, <sup>3</sup>J<sub>trans</sub> = 14.5 Hz, CH=CH<sub>2</sub>), 5.48 (d, 1H, <sup>2</sup>J = 10.8 Hz, CHPh), 5.43 (d, 1H, <sup>2</sup>J = 11.0 Hz, CHPh), 5.38 (bd, 1H, <sup>3</sup>J<sub>trans</sub> = 17.3 Hz, CH=CH<sub>2</sub>), 5.37 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1B), 5.30 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1E), 5.25 (d, 1H, <sup>2</sup>J = 11.0 Hz, CHPh), 5.23 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 5.19 (bs, 1H, =CH), 5.15 (bd, 1H, <sup>3</sup>J<sub>cis</sub> = 11.0 Hz, CH=CH<sub>2</sub>), 5.13 (bs, 1H, =CH), 4.97 (dd, 2H, <sup>2</sup>J = 11.0 Hz, 2 $\times$ CHPh), 4.87 (d, 1H, <sup>2</sup>J = 11.0 Hz, CHPh), 4.85 (d, 1H, <sup>2</sup>J = 12.0 Hz, CHPh), 4.84 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, H-1D), 4.83 (d, 1H, <sup>2</sup>J = 11.0 Hz, CHPh), 4.82 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1A), 4.77 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 4.72 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.8 Hz, H-1F), 4.71 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1C), 4.70 (d, 1H, <sup>2</sup>J = 12.0 Hz, CHPh), 4.68 (d, 1H, <sup>2</sup>J = 12.2 Hz, CHPh), 4.51 (d, 1H, <sup>2</sup>J = 11.9 Hz, CHPh), 4.80-4.20 (m, 19H, H-3B, H-3E, H-5A, H-5F, H-5C, H-6D, 13 $\times$ CHPh), 4.16-4.10 (m, 4H, H-3A, H-3D, H-3F, H-6E), 4.04-3.96 (m, H-3C, H-4D, N-CHPh), 3.94-3.76 (m, 9H, H-4E, H-4B, H-5D, H-5E, H-5B, H-6C, H-6E, 2 $\times$ =C-CH), 3.50 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, H-2B), 3.48 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.8 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, H-2E), 3.45 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.4 Hz, H-2D), 3.43-3.28 (m, 9H, H-2A, H-2F, H-2C, H-4C, H-4F, H-4A, H-6C, H-6D, N-CHPh), 3.17 (bd, 1H, <sup>2</sup>J = 14.4 Hz, =C-CH), 3.07-3.00 (m, 3H, 2 $\times$ H-6B, =C-CH), 2.85-2.78 (m, 2H, 2 $\times$ H-6F)

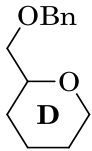
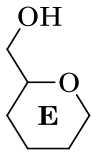
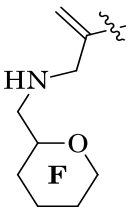
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  142.89 (C=CH<sub>2</sub>), 139.93, 139.81, 139.64, 139.62, 139.48, 139.42, 138.86, 138.80, 138.78, 138.55, 138.40, 138.30, 138.14, 137.99 (14 $\times$ C-Ar<sup>quat</sup>), 136.28 (CH=CH<sub>2</sub>), 129.33-126.10 (70 $\times$ C-Ar<sup>tert</sup>), 116.48 (=CH<sub>2</sub>), 114.82 (CH=CH<sub>2</sub>), 100.70, 100.22, 100.09, 100.06, 98.52, 97.25 (C-1E, C-1A, C-1B, C-1D, C-1F, C-1C), 87.70, 82.99, 82.76, 81.81 (C-4A, C-4F, C-4B, C-4E), 81.43 (C-3C), 81.12 (C-4D), 80.85, 80.75, 80.73, 80.69, 80.66 (C-3E, C-3F, C-3B, C-3D, C-3A), 80.62 (C-2F), 80.39 (C-4C), 80.21, 78.80, 78.69, 78.11, 78.05 (C-2C, C-2A, C-2D, C-2E, C-2B), 76.65, 76.44, 76.09, 75.79, 74.14 (5 $\times$ CH<sub>2</sub>Ph), 74.06 (OCH<sub>2</sub>-C=), 73.86, 73.40, 73.38, 73.19, 72.92, 72.86 (6 $\times$ CH<sub>2</sub>Ph), 72.80 (C-5E), 72.33 (CH<sub>2</sub>Ph), 72.11, 72.02(2C) (C-5D, C-5A, CH<sub>2</sub>Ph), 71.80 (C-6C), 70.95, 70.88, 69.69 (C-5B, C-5F, C-5C), 69.65, 61.85 (C-6D, C-6E), 56.23 (N-CH<sub>2</sub>Ph), 55.98 (C-6F), 55.86 ((NCH<sub>2</sub>-C=), 42.41 (C-6B).

**HRMS (ESI):** Calcd. For C<sub>139</sub>H<sub>151</sub>N<sub>2</sub>O<sub>27</sub> [M+H]<sup>+</sup>: 2281.0557; Found: 2281.0499 (-2.5 ppm)

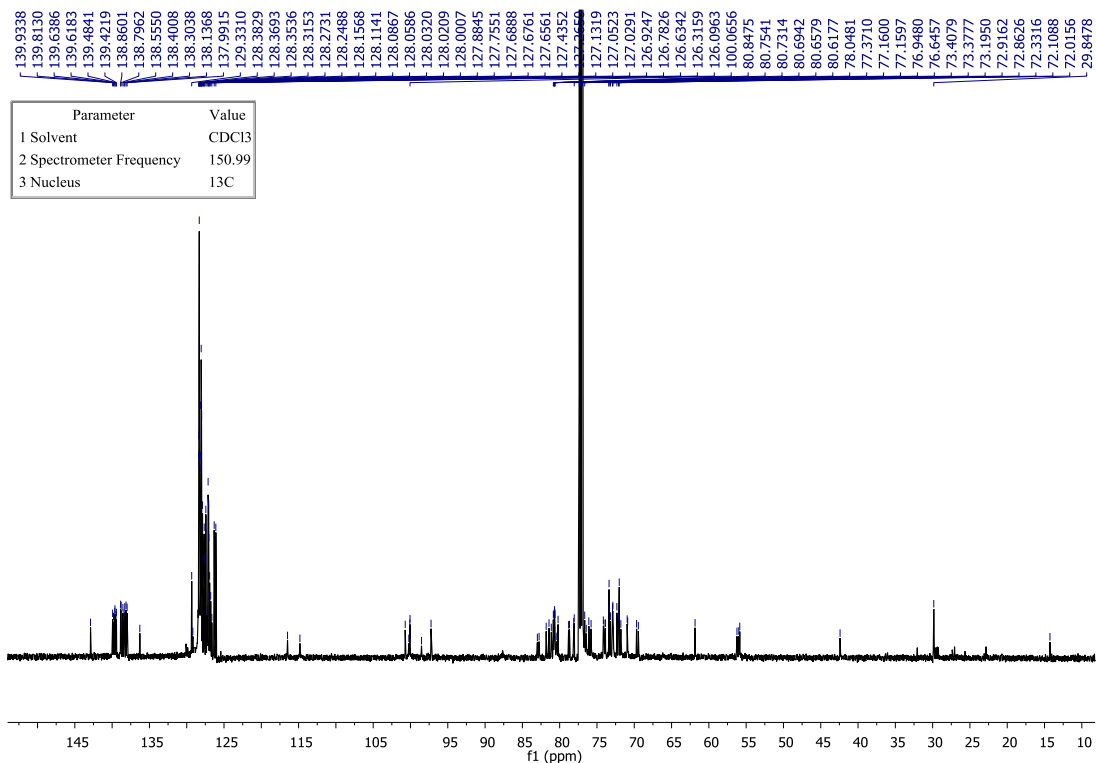
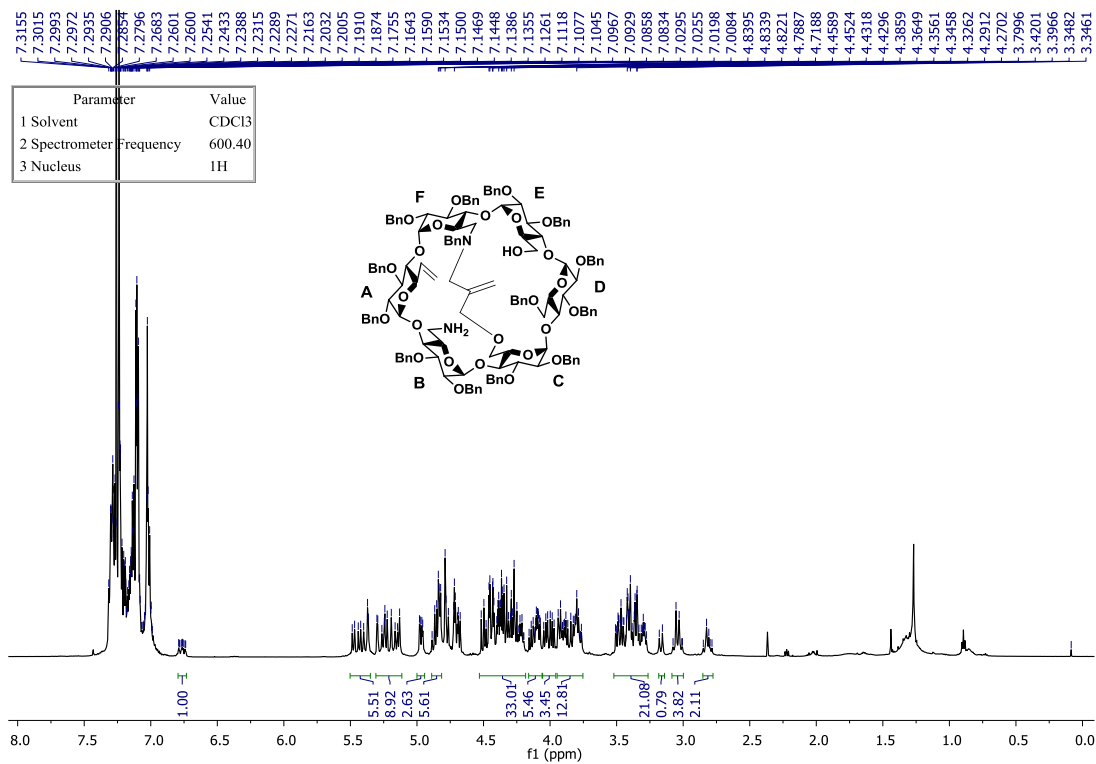
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution	
 <p style="text-align: center;"><b>A</b></p>	H-1A	4.824	NOE:3.800	H-4B	
	C-1A	100.090			
	H-2A	3.412			
	C-2A	78.80			
	H-3A	4.142			
	C-3A	80.66			
	H-4A	3.297			
	C-4A	87.69			
	H-5A	4.317			
	C-5A	72.02			
	CH=CH <sub>2</sub>	5.383			
		5.153			
	CH=CH <sub>2</sub>	114.812			
	CH=CH <sub>2</sub>	6.763			
CH=CH <sub>2</sub>	136.28				
 <p style="text-align: center;"><b>B</b></p>	H-1B	5.367	NOE:3.401	H-4C	
	C-1B	100.066			
	H-2B	3.491			
	C-2B	78.05			
	H-3B	4.218			
	C-3B	80.73			
	H-4B	3.792			
	C-4B	82.76			
	H-5B	3.798			
	C-5B	70.95			
	H-6B	3.040			
		3.040			
	C-6B	42.375			
 <p style="text-align: center;"><b>C</b></p>	H-1C	4.715	NOE:3.986	H-4D	
	C-1C	97.246			
	H-2C	3.355			
	C-2C	80.210			
	H-3C	4.043			
	C-3C	81.430			
	H-4C	3.394			
	C-4C	80.37			
	H-5C	4.255			
	C-5C	69.69			
	H-6C	3.891			
		3.285			
C-6C	71.800				

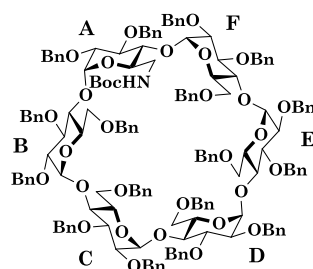
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	4.836	NOE:3.885	H-4E
	C-1D	100.225		
	H-2D	3.458		
	C-2D	78.69		
	H-3D	4.096		
	C-3D	80.70		
	H-4D	3.982		
	C-4D	81.12		
	H-5D	3.930		
	C-5D	72.11		
	H-6D	4.450		
		3.402		
	C-6D	69.449	HMBC:4.51 and 4.35	CH <sub>2</sub> Ph
	H-1E	5.298	NOE:3.350	H-4F
	C-1E	100.707		
	H-2E	3.473		
	C-2E	78.11		
	H-3E	4.294		
	C-3E	80.85		
	H-4E	3.882		
	C-4E	81.81		
	H-5E	3.798		
	C-5E	72.81		
	H-6E	4.111		
		3.767		
	C-6E	61.842		
	H-1F	4.723	NOE:3.316	H-4A
	C-1F	98.520		
	H-2F	3.355		
	C-2F	80.62		
	H-3F	4.091		
	C-3F	80.75		
	H-4F	3.344		
	C-4F	82.99		
	H-5F	4.216		
	C-5F	70.88		
	H-6F	2.819	NOE: 3.16 and 3.05	NCH <sub>2</sub> C=
		2.819	NOE:4.01 and 3.41	NCH <sub>2</sub> Ph
	C-6F	55.984	HMBC:4.01 and 3.41	NCH <sub>2</sub> Ph

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-(Boc)*N*-Amino-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>,6<sup>F</sup>-Heptadeca-  
O-Benzyl- $\alpha$ -cyclodextrin (248)**



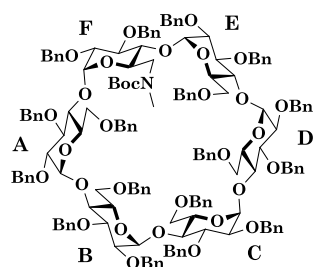
A solution of Boc<sub>2</sub>O (48 mg, 0.22 mmol, 1.1 eq.) in absolute ethanol (1.0 mL) was added to a solution of  $\alpha$ -cyclodextrin **247** (500 mg, 0.2 mmol, 1 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) at r.t. The reaction mixture was stirred for 2 h, then evaporated under reduced pressure. Silica gel flash chromatography of the residue (CyH/EtOAc: 4:1) gave the product **248** (480 mg, 92%) as a white foam.

$$\alpha_D = +36.8 \text{ (} c \text{ 1.0, CHCl}_3 \text{)}$$

$R_f$  = 0.60 (CyH/EtOAc: 3/1);

**HRMS (ESI):** Calcd. For C<sub>160</sub>H<sub>171</sub>NNaO<sub>31</sub> [M+Na]<sup>+</sup>: 2625.1606; Found: 2625.1727 (+4.6 ppm).

**6<sup>A</sup>-Deoxy-6<sup>A</sup>-(Boc)*N*(Methyl)-Amino-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>,6<sup>F</sup>-Heptadeca-  
O-Benzyl- $\alpha$ -cyclodextrin (248a)**



NaH (60% w/w in oil, 13 mg, 0.32 mmol, 8 eq.) was added to a solution of  $\alpha$ -cyclodextrin **248** (100 mg, 0.04 mmol, 1 eq.) in DMF (1.5 mL) under nitrogen at 0°C. The reaction mixture was stirred for 30 min, then CH<sub>3</sub>I (5  $\mu$ L, 0.08 mmol, 2 eq.) was added dropwise. After stirring overnight, the reaction mixture was then carefully hydrolysed with water (2 mL) and the solvents were removed in vacuum. The residue was dissolved in ethyl acetate (3 mL) and

washed with water (3 mL). The aqueous layers were extracted with ethyl acetate (3 $\times$ 3 mL) and the combined organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under vacuum. After purification by silica gel chromatography (CyH/EtOAc: 5:1), methylated  $\alpha$ -cyclodextrin **248a** (100 mg, 95%) was obtained as a white foam.

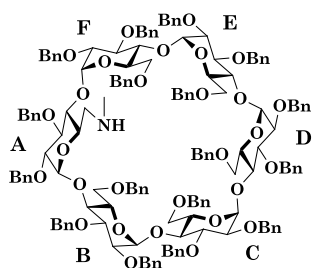
$$\alpha_D = +34.3 \text{ (} c \text{ 1.0, CHCl}_3 \text{)}$$

$R_f$  = 0.60 (CyH/EtOAc: 3/1);

**HRMS (ESI):** Calcd. For C<sub>161</sub>H<sub>173</sub>NNaO<sub>31</sub> [M+Na]<sup>+</sup>: 2639.1880; Found: 2639.1884 (+0.2 ppm).



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-N(Methyl)-Amino-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>,6<sup>F</sup>-Heptadeca-O-Benzyl- $\alpha$ -cyclodextrin (249)**



The  $\alpha$ -cyclodextrin **248a** (100 mg, 0.04 mmol, 1 eq.) was dissolved in dichloromethane (5 mL) and TFA (1.5 mL) was added at 0°C for 1.5 h. Dichloromethane (10 mL) and saturated aqueous solution of NaHCO<sub>3</sub> (10 mL) were added at the same temperature and the solution was stirred during 1 h. Then the layers were separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Silica gel flash chromatography of the residue (CyH/EtOAc: 3/1, then DCM/MeOH: 98/2) afforded cyclodextrin **249** (80 mg, 79%) as a white foam.

$\alpha_D = +31.2$  (c 1.0, CHCl<sub>3</sub>).

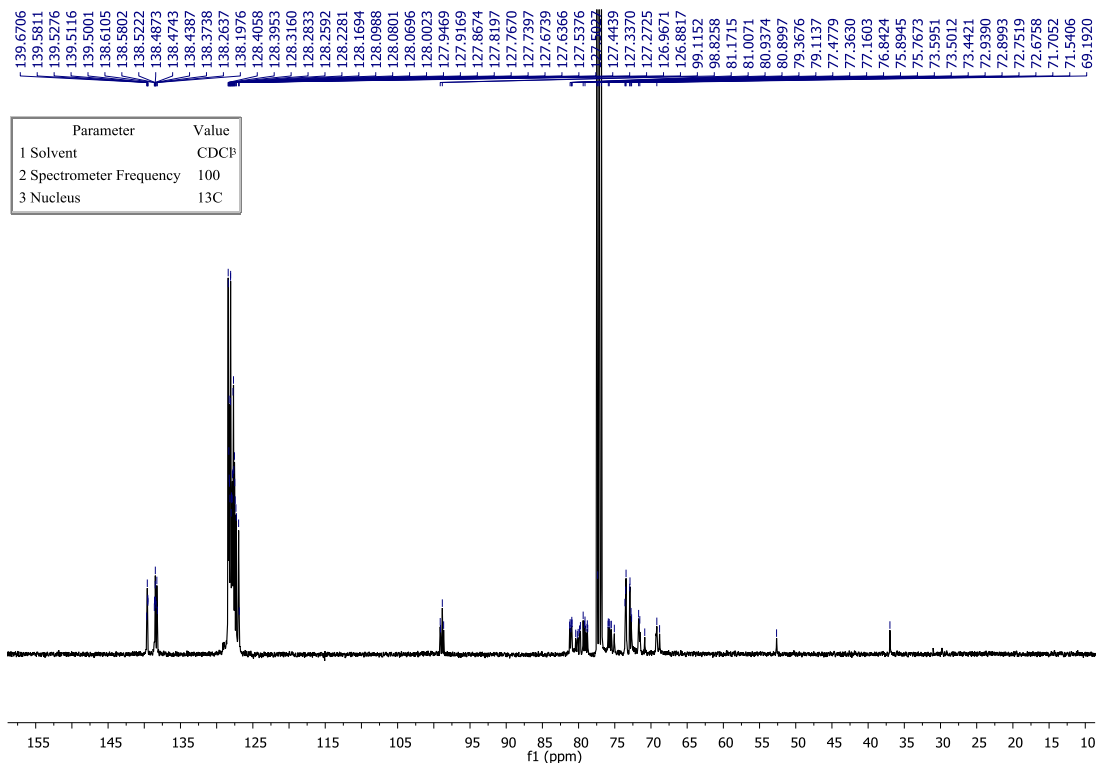
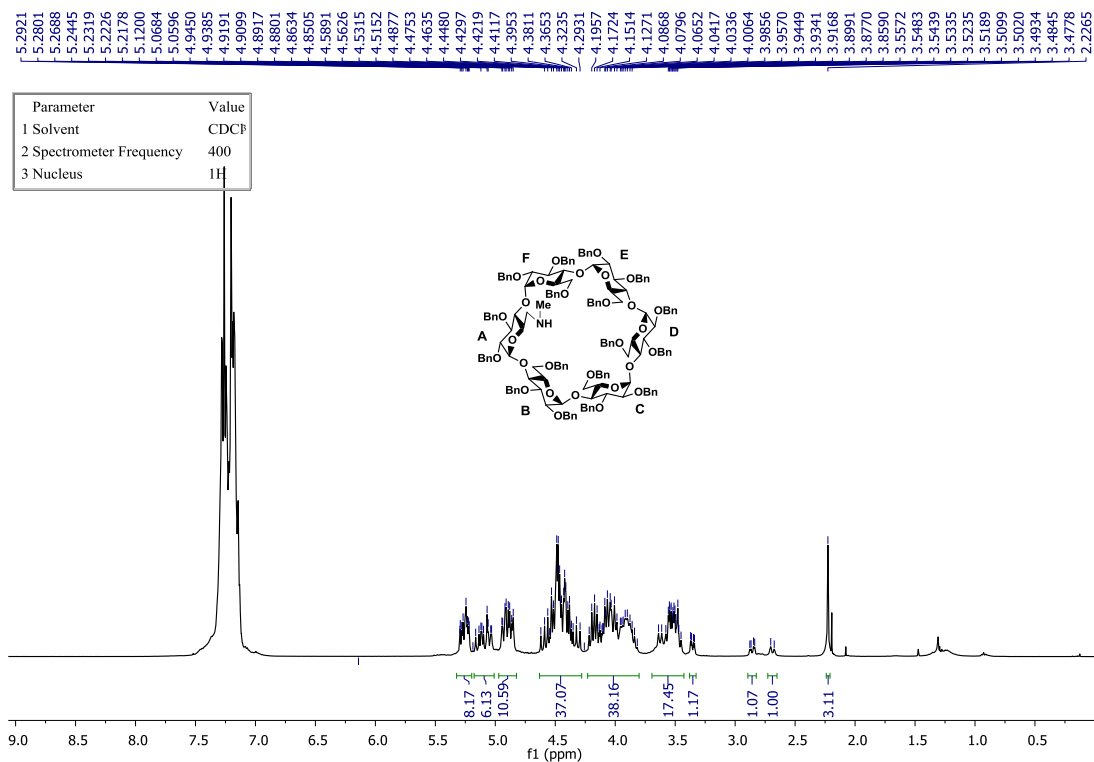
$R_f = 0.41$  (DCM/MeOH: 95/5).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.29-7.13 (m, 85H, 85×H-Ar), 5.28 (d, 1H, <sup>2</sup>J=10.4 Hz, CHPh), 5.26 (d, 1H, <sup>2</sup>J=11.0 Hz, CHPh), 5.25 (d, 1H, <sup>2</sup>J=10.0 Hz, CHPh), 5.34-5.22 (m, 2H, 2×H-1), 5.15 (d, 1H, <sup>2</sup>J=11.0 Hz, CHPh), 5.11 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.0 Hz, H-1), 5.08 (d, 1H, <sup>2</sup>J=11.4 Hz, CHPh), 5.06 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.7 Hz, H-1), 5.03 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=2.7 Hz, H-1), 4.95-4.85 (m, 8H, H-1, 7×CHPh), 4.62-4.29 (m, 22H, 22×CHPh), 4.22-3.82 (m, 22H, 6×H-3, 6×H-4, 6×H-5, 4×H-6), 3.64-3.45 (m, 11H, 5×H-2, 6×H-6), 3.35 (dd, 1H, <sup>3</sup>J<sub>1,2</sub>=3.3 Hz, <sup>3</sup>J<sub>2,3</sub>=9.7 Hz, H-2), 2.86 (dd, 1H, <sup>3</sup>J<sub>5,6</sub>=4.0 Hz, <sup>2</sup>J<sub>6,6'</sub>=12.5 Hz, H-6), 2.67 (d, 1H, <sup>2</sup>J=11.6 Hz, H-6), 2.23 (s, 3H, N-CH<sub>3</sub>)

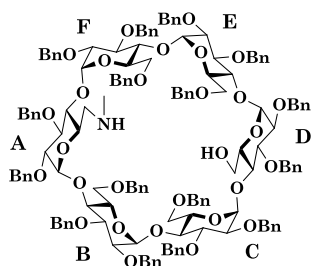
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.67, 139.58(2C), 139.51, 139.50, 138.61, 138.58, 138.52, 138.49, 138.47(2C), 138.44, 138.37, 138.26(2C), 138.20 (17×C-Ar<sup>quat.</sup>), 128.41-126.88 (85×C-Ar<sup>tert.</sup>), 99.12, 99.08, 98.83(3C), 98.64, (6×C-1), 81.24, 81.17, 81.07, 81.01, 80.94, 80.90 (6×C-3), 80.40, 80.18, 80.06, 79.87, 79.75 (5×C-4), 79.37(2C) (C-4, C-2), 79.18, 79.11, 78.98, 78.79, 78.74 (5×C-2), 75.93, 75.90, 75.77, 75.67, 75.48, 75.06, 73.60, 73.54, 73.50, 73.44(2C), 72.94(2C), 72.90(2C), 72.75, 72.68 (17×CH<sub>2</sub>Ph), 71.75, 71.71, 71.67, 71.63, 71.54, 70.85 (6×C-5), 69.29, 69.24, 69.19, 69.16, 68.81, 52.65 (6×C-6), 36.99 (N-CH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>156</sub>H<sub>166</sub>NO<sub>29</sub> [M+H]<sup>+</sup>: 2517.1604; Found: 2517.1540 (-2.6 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-N(Methyl)-Amino-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>-Hexadeca-  
O-Benzyl- $\alpha$ -cyclodextrin (**250**)**



DIBAL-H (0.8 mL, 1.2 mmol, 1.5 M in toluene, 15 eq.) was slowly added to a solution of Methyl-amino- $\alpha$ -cyclodextrin **249** (200 mg, 0.08 mmol, 1 eq.) in toluene (0.4 mL) under nitrogen at r.t. The reaction mixture was stirred at 55°C for 30 min, until TLC indicated formation of mono-alcohol as a major product, and then cooled to r.t. and poured into ice/water. Aqueous HCl (2 mL, 1 M) and EtOAc (2 mL) were added, and the solution was stirred for 1 h.

The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Silica gel chromatography of the residue (DCM/MeOH: 98/2) gave cyclodextrin **250** (126 mg, 65%) as white foams.

$\alpha_D = +31.3$  (c 1.0, CHCl<sub>3</sub>).

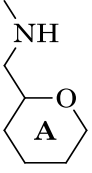
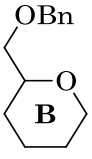
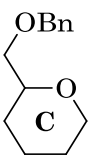
$R_f = 0.41$  (DCM/MeOH: 95/5).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.46-6.12 (m, 80H, 80×H-Ar.), 5.89 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 2.8 Hz, H-1C), 5.74 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1F), 5.58 (d, 2H, <sup>2</sup>J = 10.3 Hz, 2×CHPh), 5.29 (d, 2H, <sup>2</sup>J = 10.3 Hz, 2×CHPh), 5.06-5.03 (m, 3H, 3×CHPh), 4.96 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 2.6 Hz, H-1D), 4.95 (d, 1H, <sup>2</sup>J = 10.6 Hz, CHPh), 4.95 (d, 1H, <sup>2</sup>J = 10.8 Hz, CHPh), 4.92 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1B), 4.90-4.84 (m, 4H, H-1E, 3×CHPh), 4.79 (d, 1H, <sup>2</sup>J = 11.5 Hz, CHPh), 4.70 (d, 1H, <sup>2</sup>J = 11.8 Hz, CHPh), 4.65-4.48 (m, 16H, H-1A, 15×CHPh), 4.37 (d, 1H, <sup>2</sup>J = 11.7 Hz, CHPh), 4.35 (d, 1H, <sup>2</sup>J = 10.2 Hz, CHPh), 4.33 (d, 1H, <sup>2</sup>J = 10.9 Hz, CHPh), 4.32-4.28 (m, 3H, H-3C, H-3F, H-6E), 4.25-4.06 (m, 12H, H-3A, H-3B, H-3D, H-4E, H-4C, H-3E, H-4F, H-5C, H-5D, H-5E, H-6C, H-6F), 4.02-3.83 (m, 9H, H-4B, H-4D, H-5A, H-5B, H-5F, H-6B, H-6C, H-6D, H-6F), 3.75 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 11.0 Hz, H-6D), 3.69 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, <sup>3</sup>J<sub>2,3</sub> = 10.0 Hz, H-2C), 3.68-3.65 (m, 2H, H-2F, H-4A), 3.63 (bd, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.6 Hz, H-6E), 3.60-3.52 (m, 4H, H-2B, H-2D, H-2E, H-6B), 3.36 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 2.8 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, H-2A), 2.82 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 11.6 Hz, H-6A), 2.60 (m, 1H, H-6A), 2.21 (s, 3H, N-CH<sub>3</sub>).

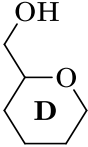
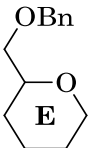
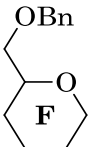
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.65, 139.62, 139.57, 139.43, 139.31, 139.19, 138.88, 138.79, 138.57, 138.47, 138.38, 138.28, 138.21, 138.11, 138.08, 137.91 (16×C-Ar<sup>quat.</sup>), 128.40-126.34 (80×C-Ar<sup>tert.</sup>), 98.61, 98.56(2C), 98.23, 97.24, 96.65 (C-1B, C-1A, C-1F, C-1E, C-1C, C-1D), 82.51 (C-3D), 81.66, 81.30, 81.22 (C-4B, C-4F, C-4C), 81.14, 81.02, 80.98(2C), 80.79 (C-3A, C-3E, C-3F, C-3C, C-3B), 80.08, 79.96 (C-2D, C-2A), 79.83 (C-4E), 79.12, 79.00 (C-2B, C-2E), 78.47 (C-4A), 78.36, 77.82 (C-2C, C-2F), 76.47(2C), 76.17, 76.07, 74.35, 73.90, 73.59, 73.56 (8×CH<sub>2</sub>Ph), 73.46(2C) (CH<sub>2</sub>Ph, C-5A), 73.42, 73.40, 73.38, 73.07, 72.86, 72.52, 72.39 (7×CH<sub>2</sub>Ph), 72.00, 71.72, 71.52, 71.49, 71.44 (C-5F, C-5B, C-5E, C-5C, C-5D), 69.95 (C-6E), 69.71(2C) (C-4D, C-6F), 69.59, 68.78, 61.05, 54.43 (C-6C, C-6B, C-6D, C-6A), 36.91 (N-CH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>149</sub>H<sub>160</sub>NO<sub>29</sub> [M+H]<sup>+</sup>: 2427.1023; Found: 2427.1071 (+2.0 ppm)

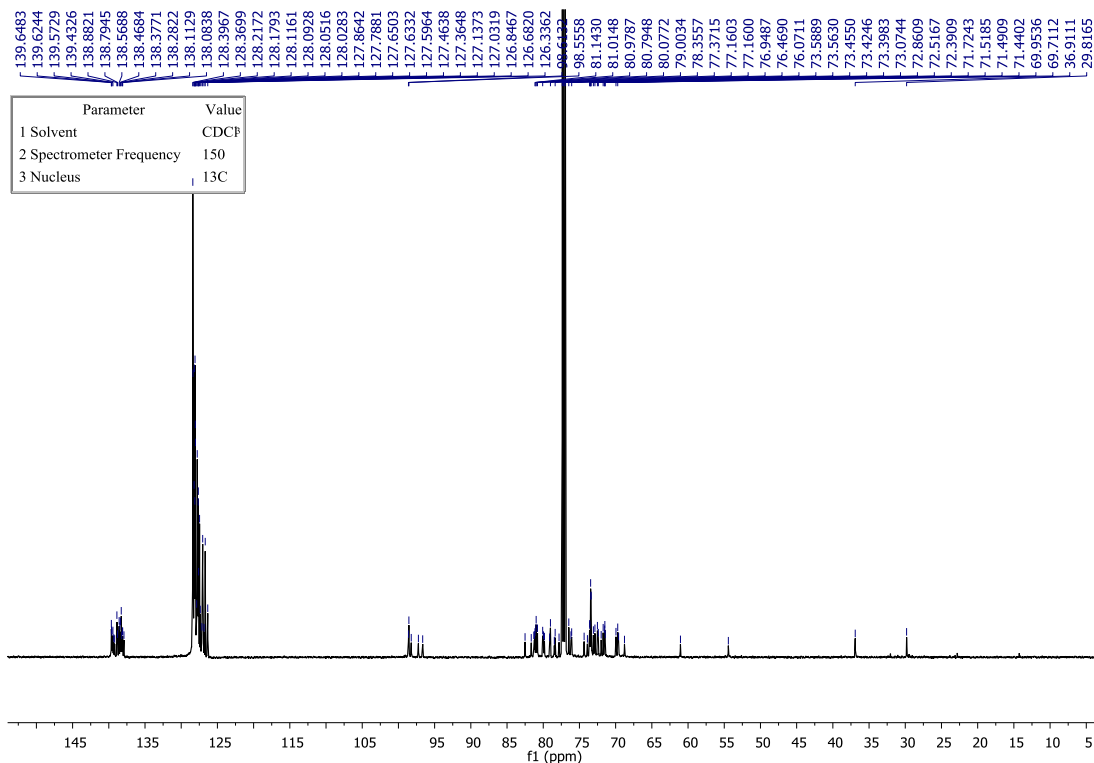
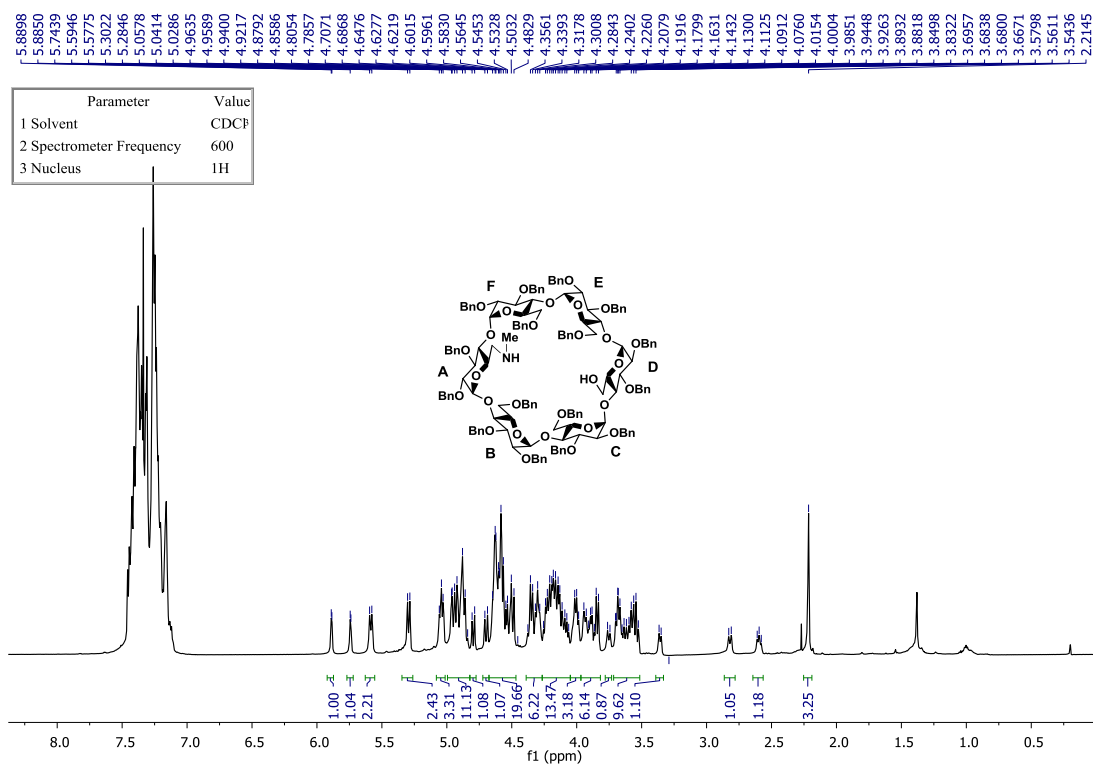
**EXPERIMENTAL PART**

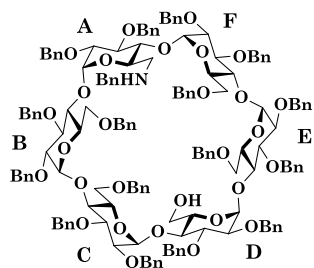
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>A</b></p>	H-1A	4.630	NOE:3.876 ppm	H-4B
	C-1A	98.556		
	H-2A	3.357		
	C-2A	79.963		
	H-3A	4.126		
	C-3A	81.143		
	H-4A	3.662	NOE:5.741 ppm	H-1F
	C-4A	78.470		
	H-5A	3.977		
	C-5A	73.455		
	H-6A	2.819		
		2.592		
C-6A	54.434			
 <p style="text-align: center;"><b>B</b></p>	H-1B	4.912	NOE:4.126 ppm	H-4C
	C-1B	98.613		
	H-2B	3.531		
	C-2B	79.116		
	H-3B	4.179		
	C-3B	80.795		
	H-4B	3.876	NOE: 4.630 ppm	H-1A
	C-4B	81.656		
	H-5B	4.021		
	C-5B	71.724		
	H-6B	3.893		
		3.584		
C-6B	68.779			
 <p style="text-align: center;"><b>C</b></p>	H-1C	5.887	NOE:3.933 ppm	H-4D
	C-1C	97.241		
	H-2C	3.691		
	C-2C	78.356		
	H-3C	4.293		
	C-3C	80.979		
	H-4C	4.126	NOE:4.912 ppm	H-1B
	C-4C	81.219		
	H-5C	4.165		
	C-5C	71.491		
	H-6C	3.838		
		4.219		
C-6C	69.590			

**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	4.961	NOE: 4.236 ppm	H-4E
	C-1D	96.648		
	H-2D	3.573		
	C-2D	80.077		
	H-3D	4.209		
	C-3D	82.512		
	H-4D	3.933	NOE: 5.887 ppm	H-1C
	C-4D	69.711		
	H-5D	4.186		
	C-5D	71.440		
	H-6D	3.926		
		3.753		
C-6D	61.047			
	H-1E	4.882	NOE: 4.073 ppm	H-4F
	C-1E	98.230		
	H-2E	3.552		
	C-2E	79.003		
	H-3E	4.165		
	C-3E	81.015		
	H-4E	4.236	NOE: 4.961 ppm	H-1D
	C-4E	79.833		
	H-5E	4.097		
	C-5E	71.519		
	H-6E	3.622		
		4.284		
C-6E	69.954			
	H-1F	5.741	NOE: 3.662 ppm	H-4A
	C-1F	98.556		
	H-2F	3.674		
	C-2F	77.817		
	H-3F	4.297		
	C-3F	80.979		
	H-4F	4.073	NOE: 4.882 ppm	H-1E
	C-4F	81.300		
	H-5F	3.932		
	C-5F	71.998		
	H-6F	4.144		
		3.834		
C-6F	69.711			

EXPERIMENTAL PART



**6<sup>A</sup>-deoxy-6<sup>A</sup>-(Benzyl)*N*-Amino-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>-****Hexadeca-*O*-Benzyl- $\alpha$ -cyclodextrin (**251**)**

$\text{Pd}^0(\text{PPh}_3)_4$  (4 mg, 0.003 mmol, 0.1 eq.) was added to a solution of  $\alpha$ -cyclodextrin **245** (76 mg, 0.030 mmol, 1 eq.) in degassed THF (2 mL) at r.t. under argon. A 1 M solution of anhydrous  $\text{ZnCl}_2$  in THF (0.45 mL, 0.45 mmol, 15 eq.) was added dropwise and the reaction mixture was stirred for 10 min. After addition of  $\text{Et}_3\text{SiH}$  (0.45 mL, 0.45 mmol, 15 eq.), the reaction mixture was refluxed at 80 °C under argon for 3 h, diluted with EtOAc (5 mL), poured on water (5

mL). Layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were dried with  $\text{MgSO}_4$ , filtered and concentrated. Silica gel chromatography column (CyH/EtOAc 3/1) gave  $\alpha$ -cyclodextrin **251** (50 mg, 65%) as a white foam.

$\alpha_D = +37.0$  (c 1.0,  $\text{CHCl}_3$ )

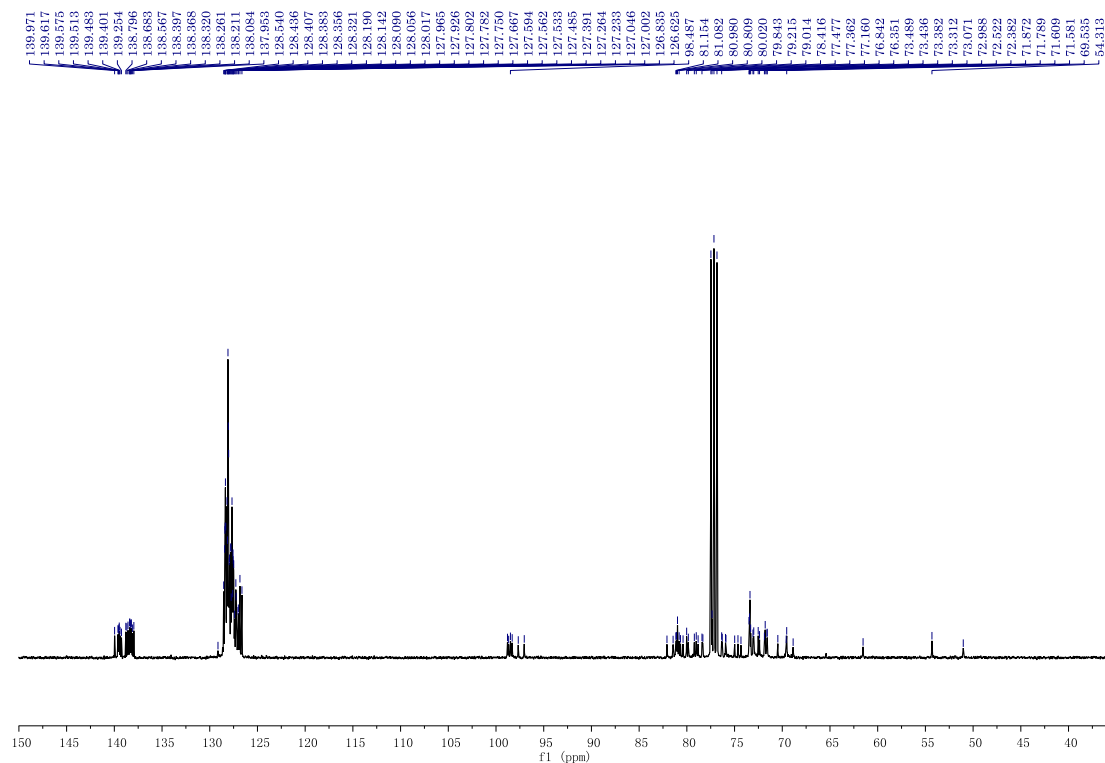
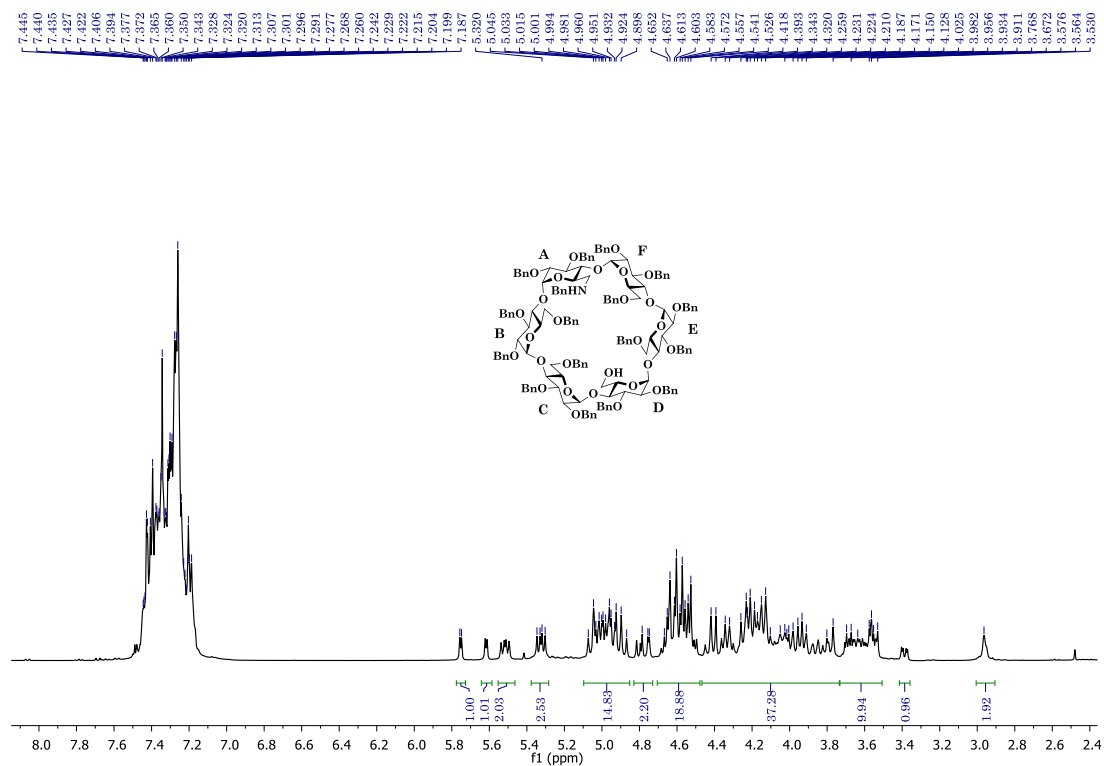
$R_f = 0.57$  (CyH/ EtOAc: 2/1)

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.44-7.18 (m, 85H, 85×H-Ar), 5.75 (d, 1H,  $^3J_{1,2} = 3.7$  Hz, H-1), 5.62 (d, 1H,  $^3J_{1,2} = 3.5$  Hz, H-1), 5.52 (d, 1H,  $^2J = 10.4$  Hz, CHPh), 5.51 (d, 1H,  $^2J = 10.5$  Hz, CHPh), 5.33 (d, 1H,  $^2J = 10.5$  Hz, CHPh), 5.32 (d, 1H,  $^2J = 10.5$  Hz, CHPh), 5.07-4.87 (m, 12H, 3×H-1, 9×CHPh), 4.80 (d, 1H,  $^2J = 11.9$  Hz, CHPh), 4.75 (d, 1H,  $^3J_{1,2} = 3.2$  Hz, H-1), 4.67-4.39 (m, 17H, 17×CHPh), 4.36-3.91 (m, 23H, CHPh, 6×H-3, 6×H-4, 6×H-5, 4×H-6), 3.88-3.76 (m, 5H, 3×H-6, 2×NCHPh), 3.70-3.53 (m, 8H, 3×H-6, 5×H-2), 3.38 (dd, 1H,  $^3J_{1,2} = 3.3$  Hz,  $^3J_{2,3} = 9.3$  Hz, H-2), 2.96 (m, 2H, 2×H-6),

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  139.97, 139.62, 139.57, 139.51, 139.48, 139.40, 139.25, 138.80, 138.68, 138.57, 138.40, 138.37, 138.32, 138.26, 138.21, 138.08, 137.95 (17×C-Ar<sup>quat.</sup>), 128.54-126.62 (85×C-Ar<sup>tert.</sup>), 98.80, 98.68, 98.49, 98.30, 97.66, 97.04 (6×C-1), 82.08, 81.44 (2×C-4), 81.54, 81.08, 80.98(2C), 80.81, 80.67 (7×C-3), 80.40 (C-4), 80.02(2C) (C-4, C-2), 79.84, 79.22, 79.01 (3×C-2), 78.82 (C-4), 78.42, 78.32 (2×C-2), 76.35, 76.29, 75.95, 75.90 (4×CH<sub>2</sub>Ph), 74.99 (C-4), 74.64, 74.33, 73.49, 73.44, 73.38(3C), 73.31, 73.07, 72.99, 72.52, 72.38 (12×CH<sub>2</sub>Ph), 71.87, 71.80(2C), 71.61, 71.58, 70.46 (6×C-5), 69.59, 69.54(2C), 68.86, 61.53 (5×C-6), 54.31 (NCH<sub>2</sub>Ph), 51.03 (C-6)

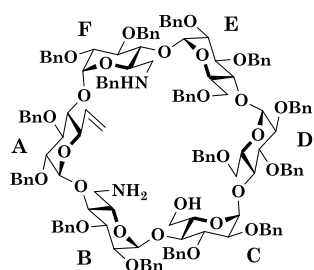
**HRMS (ESI):** Calcd. For  $\text{C}_{155}\text{H}_{164}\text{NO}_{29}$   $[\text{M}+\text{H}]^+$ : 2503.1537; Found: 2503.1384 (-6.1 ppm)

EXPERIMENTAL PART





**6<sup>A</sup>,6<sup>B</sup>,6<sup>F</sup>-Trideoxy-6<sup>A</sup>-Vinyl-6<sup>B</sup>-Amino-6<sup>F</sup>-(Benzyl)*N*-Amino-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>D</sup>,6<sup>E</sup>-Tetradeca-*O*-Benzyl- $\alpha$ -cyclodextrin (**252**)**



$\text{Pd}^0(\text{PPh}_3)_4$  (3 mg, 0.002 mmol, 0.1 eq.) was added to a solution of  $\alpha$ -cyclodextrin **245** (60 mg, 0.025 mmol, 1 eq.) in degassed THF (2 mL) at r.t. under argon. A 1 M solution of anhydrous  $\text{ZnCl}_2$  in THF (0.75 mL, 0.75 mmol, 30 eq.) was added dropwise and the reaction mixture was stirred for 10 min. After addition of  $\text{Et}_3\text{SiH}$  (0.21 mL, 0.75 mmol, 30 eq.), the reaction mixture was refluxed at 80 °C under argon for 3 h, diluted with EtOAc (5 mL), poured on water (5

mL). Layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were dried with  $\text{MgSO}_4$ , filtered and concentrated. Silica gel chromatography column (CyH/EtOAc 3/1, then DCM/MeOH 98/2) gave cyclodextrin **252** (46 mg, 78%) as a white foam.

$\alpha_D^{20} = +59.4$  (c 1.0,  $\text{CHCl}_3$ )

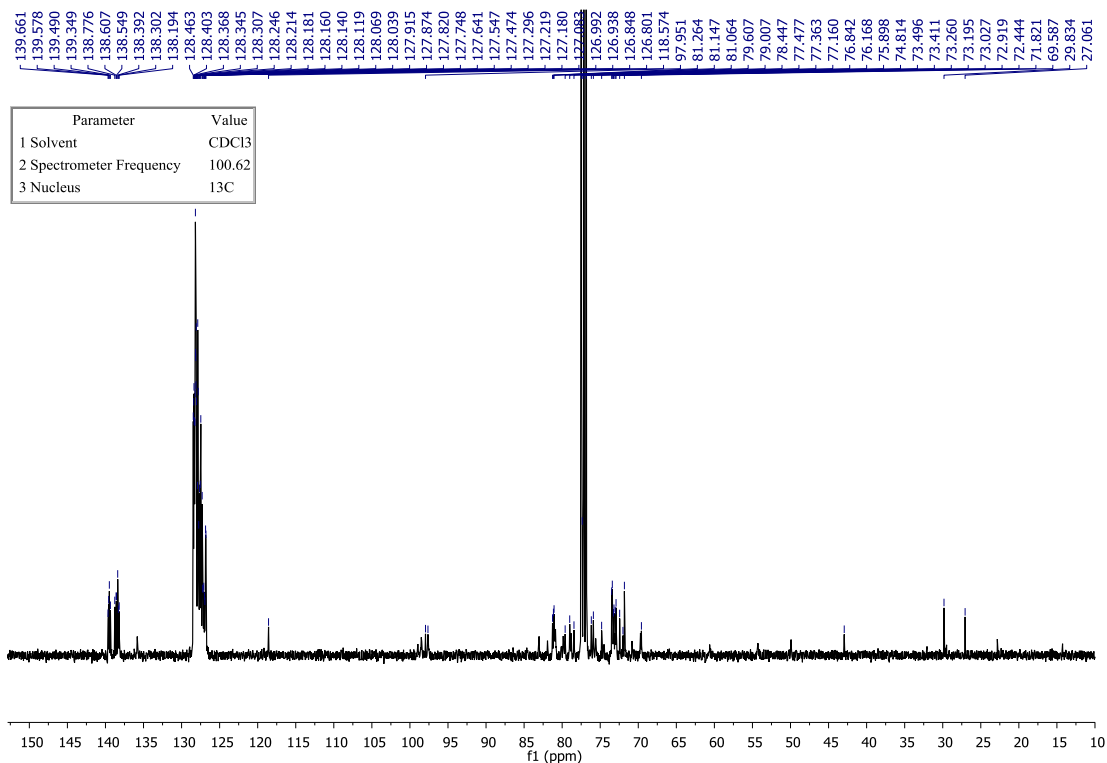
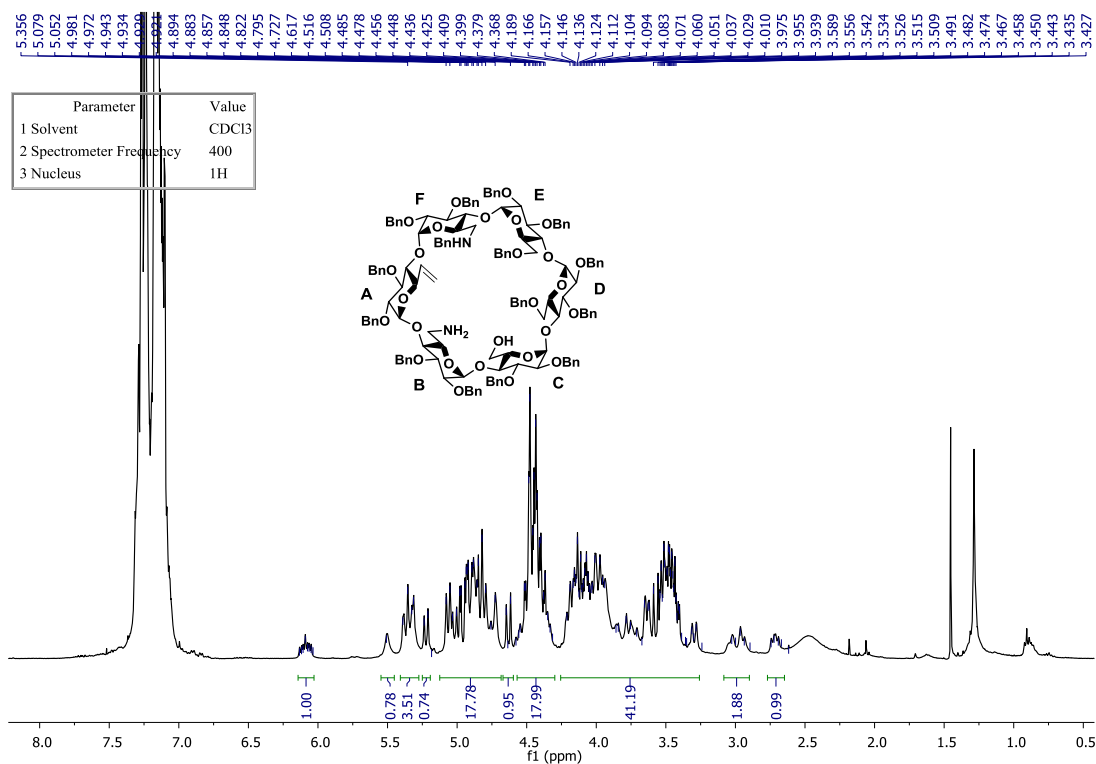
$R_f = 0.27$  (DCM/MeOH: 95/5)

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.30-7.10 (m, 75H, 75×H-Ar), 6.09 (ddd, 1H,  $^3J_{5,6} = 5.8$  Hz,  $^3J_{\text{cis}} = 10.6$  Hz,  $^3J_{\text{trans}} = 16.7$  Hz,  $\text{CH}=\text{CH}_2$ ), 5.50 (d, 1H,  $^3J_{1,2} = 3.5$  Hz, H-1), 5.38 (d, 1H,  $^3J_{1,2} = 3.0$  Hz, H-1), 5.35-5.31 (m, 4H, 3×CHPh,  $\text{CH}=\text{CH}_2$ ), 5.22 (d, 1H,  $^2J = 10.6$  Hz, CHPh), 5.07 (bd, 1H,  $^3J_{\text{cis}} = 11.1$  Hz,  $\text{CH}=\text{CH}_2$ ), 5.06 (bd, 1H,  $^2J = 11.1$  Hz, CHPh), 5.02 (d, 1H,  $^2J = 11.8$  Hz, CHPh), 4.98 (d, 1H,  $^3J_{1,2} = 3.5$  Hz, H-1), 4.94-4.73 (m, 6H, 3×CHPh, 3×H-1), 4.63 (d, 1H,  $^2J = 12.2$  Hz, CHPh), 4.55-4.33 (m, 19H, 18×CHPh, H-5), 4.21-3.93 (m, 17H, 6×H-3, 4×H-4, 4×H-5, 3×H-6), 3.85-3.67 (m, 3H, H-5, H-6, NCHPh), 3.65-3.40 (m, 11H, 6×H-2, 2×H-4, 2×H-6, NCHPh), 3.30 (d, 1H, H-6), 3.30 (m, 2H, 2×H-6), 2.72 (dd, 1H,  $^3J_{5,6} = 8.9$  Hz,  $^2J_{6,6'} = 12.6$  Hz, H-6)

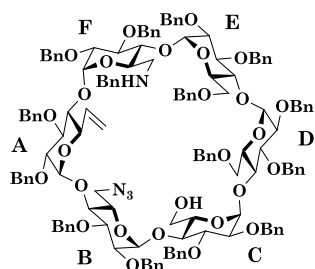
$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  139.66, 139.58(2C), 139.49(2C), 139.47, 139.35, 138.78, 138.61, 138.55, 138.39(2C), 138.36, 138.30, 138.19 (15×C-Ar<sup>quat.</sup>), 135.82 ( $\text{CH}=\text{CH}_2$ ), 128.46-126.81 (75×C-Ar<sup>tetr.</sup>), 118.56 ( $\text{CH}=\text{CH}_2$ ), 98.96, 98.50(2C), 97.95(2C), 97.63 (6×C-1), 84.56, 83.03 (2×C-4), 81.93(2C) (2×C-3), 81.26(2C) (C-4, C-3), 81.15(2C) (2×C-3), 81.06(2C), 81.00 (3×C-4), 80.88 (C-3), 79.85, 79.60, 79.00(2C), 78.81, 78.44 (6×C-2), 71.17, 75.90, 75.60, 74.81, 74.50, 73.50(2C), 73.41(2C), 73.26, 73.19, 73.03, 72.92, 72.45 (14×CH<sub>2</sub>Ph), 72.01, 71.82(2C), 71.23, 70.81(2C), (6×C-5), 69.70, 69.59, 60.70 (3×C-6), 54.11 (NCH<sub>2</sub>Ph), 49.97, 42.97 (2×C-6),

**HRMS (ESI)**: Calcd. For  $\text{C}_{142}\text{H}_{153}\text{N}_2\text{O}_{27}$   $[\text{M}+\text{H}]^+$ : 2318.0714; Found: 2318.0655 (-2.5 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>B</sup>,6<sup>F</sup>-Trideoxy-6<sup>A</sup>-Vinyl-6<sup>B</sup>-Azido-6<sup>F</sup>-(Benzyl)*N*-Amino-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>D</sup>,  
6<sup>E</sup>-Tetradeca-*O*-Benzyl- $\alpha$ -cyclodextrin (**253**)**



Imidazole-1-sulfonyl azide hydrochloride (4 mg, 0.020 mmol, 1.5 eq.) was added to  $\alpha$ -cyclodextrin **252** (30 mg, 0.013 mmol, 1 eq.),  $K_2CO_3$  (4 mg, 0.039 mmol, 3 eq.) and  $CuSO_4 \cdot 5H_2O$  (0.2 mg, 0.6  $\mu$ mol, 0.05 eq.) in MeCN (2 mL), and the reaction mixture was stirred at r.t overnight. After removal of the solvent, the residue was diluted with water (10 mL), acidified with HCl (1M) and extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers

were dried with  $MgSO_4$ , filtered and concentrated. Silica gel chromatography column (CyH/EtOAc 4/1) gave cyclodextrin **253** (24 mg, 79%) as a white foam.

$\alpha_D = +34.5$  (c 1.0,  $CHCl_3$ )

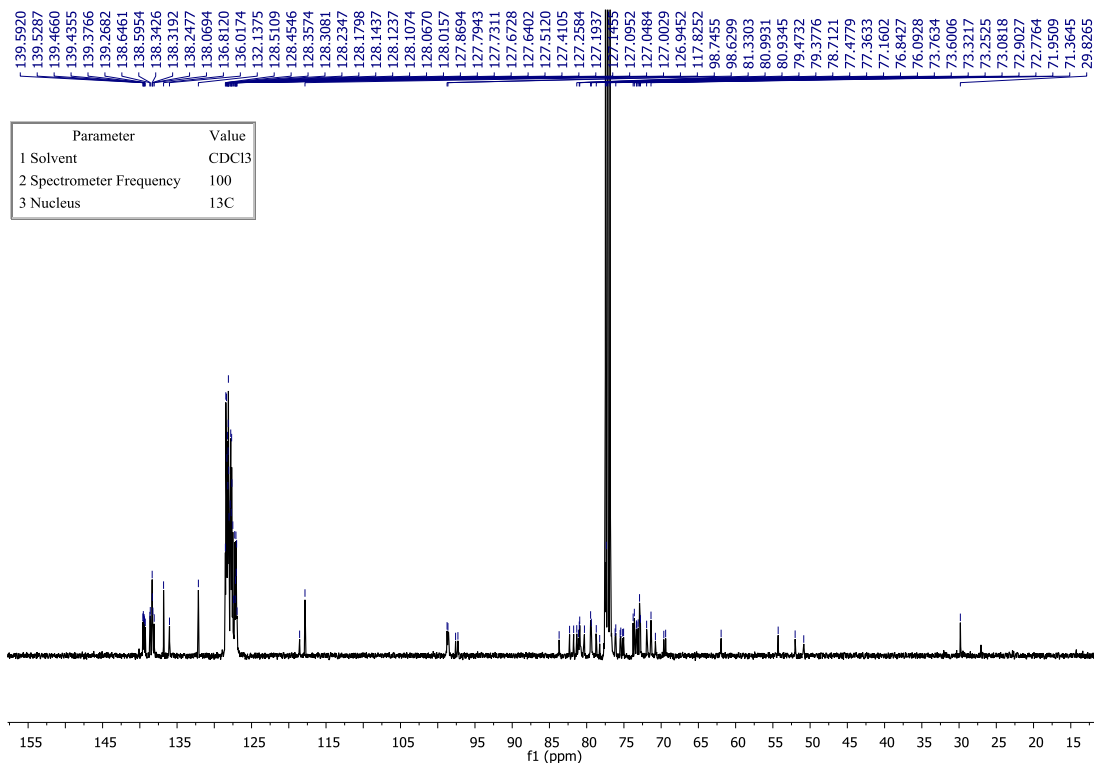
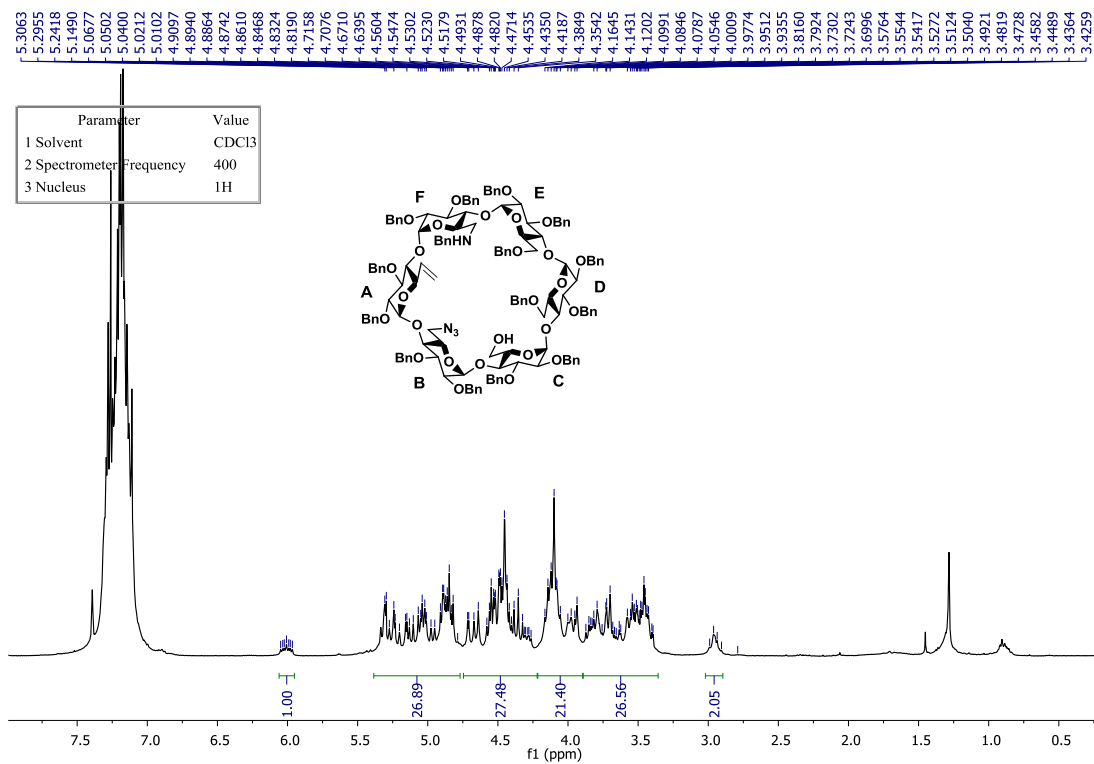
$R_f = 0.46$  (CyH/EtOAc 2/1)

<sup>1</sup>H NMR ( $CDCl_3$ , 400 MHz):  $\delta$  7.31-7.11 (m, 75H, 75 $\times$ H-Ar), 6.01 (ddd, 1H,  $^3J_{5,6} = 6.0$  Hz,  $^3J_{cis} = 10.6$  Hz,  $^3J_{trans} = 16.2$  Hz,  $\underline{CH=CH_2}$ ), 5.31 (d, 1H,  $^2J = 11.0$  Hz, CHPh), 5.30 (d, 1H,  $^3J_{1,2} = 4.3$  Hz, H-1), 5.29 (d, 1H,  $^2J = 11.0$  Hz, CHPh), 5.26 (d, 1H,  $^3J_{1,2} = 3.9$  Hz, H-1), 5.22 (bd, 1H,  $^3J_{trans} = 15.9$  Hz,  $\underline{CH=CH_2}$ ), 5.15 (d, 1H,  $^3J_{1,2} = 4.3$  Hz, H-1), 5.12 (d, 1H,  $^2J = 10.9$  Hz, CHPh), 5.07-5.01 (m, 4H, H-1, 3 $\times$ CHPh), 4.96 (bd, 1H,  $^3J_{cis} = 10.8$  Hz,  $\underline{CH=CH_2}$ ), 4.91-4.82 (m, 7H, H-1, 6 $\times$ CHPh), 4.71 (d, 1H,  $^3J_{1,2} = 3.3$  Hz, H-1), 4.65 (bd, 2H,  $^2J = 11.7$  Hz, 2 $\times$ CHPh), 4.58-4.26 (m, 15H, 14 $\times$ CHPh, H-5), 4.16-4.06 (m, 11H, 6 $\times$ H-3, H-4, 2 $\times$ H-5, 2 $\times$ H-6), 4.00-3.93 (m, 4H, H-4, 3 $\times$ H-5), 3.87-3.76 (m, 4H, 2 $\times$ H-4, 2 $\times$ H-6), 3.75-3.62 (m, 4H, H-4, 2 $\times$ H-6, NCHPh), 3.60-3.89 (m, 10H, 6 $\times$ H-2, H-4, 2 $\times$ H-6, NCHPh), 2.95 (m, 2H, 2 $\times$ H-6)

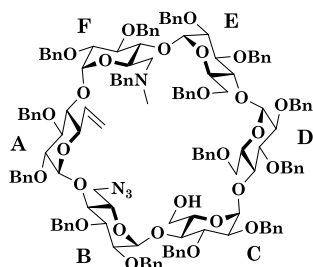
<sup>13</sup>C NMR ( $CDCl_3$ , 100 MHz):  $\delta$  139.59, 139.53, 139.47, 139.44, 139.38, 139.27, 138.65, 138.60(2C), 138.34(2C), 138.32, 138.30, 138.25, 138.07 (15 $\times$ C-Ar<sup>quat.</sup>), 136.02 ( $\underline{CH=CH_2}$ ), 128.51-126.95 (75 $\times$ C-Ar<sup>tert.</sup>), 118.55 ( $\underline{CH=CH_2}$ ), 98.75, 98.65, 98.63, 98.55, 97.60, 97.29 (6 $\times$ C-1), 83.70, 82.30 (2 $\times$ C-4), 81.75, 81.33 (2 $\times$ C-3), 81.11 (C-4), 80.99, 80.93, 80.90 (3 $\times$ C-3), 80.81 (C-4), 80.30 (C-3), 79.47(2C), 79.38, 79.35, 78.76, 78.71 (6 $\times$ C-2), 78.25, 77.68 (2 $\times$ C-4), 76.18, 76.09, 75.50, 75.42, 75.17, 75.04, 73.76, 73.60, 73.32, 73.25, 73.08, 72.90(2C), 72.78 (14 $\times$ CH<sub>2</sub>Ph), 71.95, 71.89, 71.38, 71.36, 71.34, 70.77 (6 $\times$ C-5), 69.64, 69.40, 61.95 (3 $\times$ C-6), 54.29 (NCH<sub>2</sub>Ph), 52.01, 50.85 (2 $\times$ C-6)

HRMS (ESI): Calcd. For  $C_{142}H_{151}N_4O_{27}$  [M+H]<sup>+</sup>: 2344.0480; Found: 2344.0560 (+ 3.4 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>B</sup>,6<sup>F</sup>-Trideoxy-6<sup>A</sup>-Vinyl-6<sup>B</sup>-Azido-6<sup>F</sup>-(Benzyl)*N*(Methyl)-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>D</sup>,6<sup>E</sup>-Tetradeca-*O*-Benzyl- $\alpha$ -cyclodextrin (**254**)**



Formaldehyde (37% in water, 0.004 mL, 0.048 mmol, 3 eq.) was added to a solution of cyclodextrin **253** (37 mg, 0.016 mmol, 1 eq.) in acetonitrile (2 mL) under nitrogen at r.t. The reaction mixture was stirred for 1 h, then NaBH(OAc)<sub>3</sub> (13 mg, 0.064 mmol, 4 eq.) and AcOH (0.001 mL, 0.016 mmol, 1 eq.) were added. After stirred overnight. The sat. NaHCO<sub>3</sub> (5 mL) was added and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×5mL). The

combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc: 4/1) afforded cyclodextrin **254** (30 mg, 79%) as a white foam.

$\alpha_D = +35.0$  (c 1.0, CHCl<sub>3</sub>)

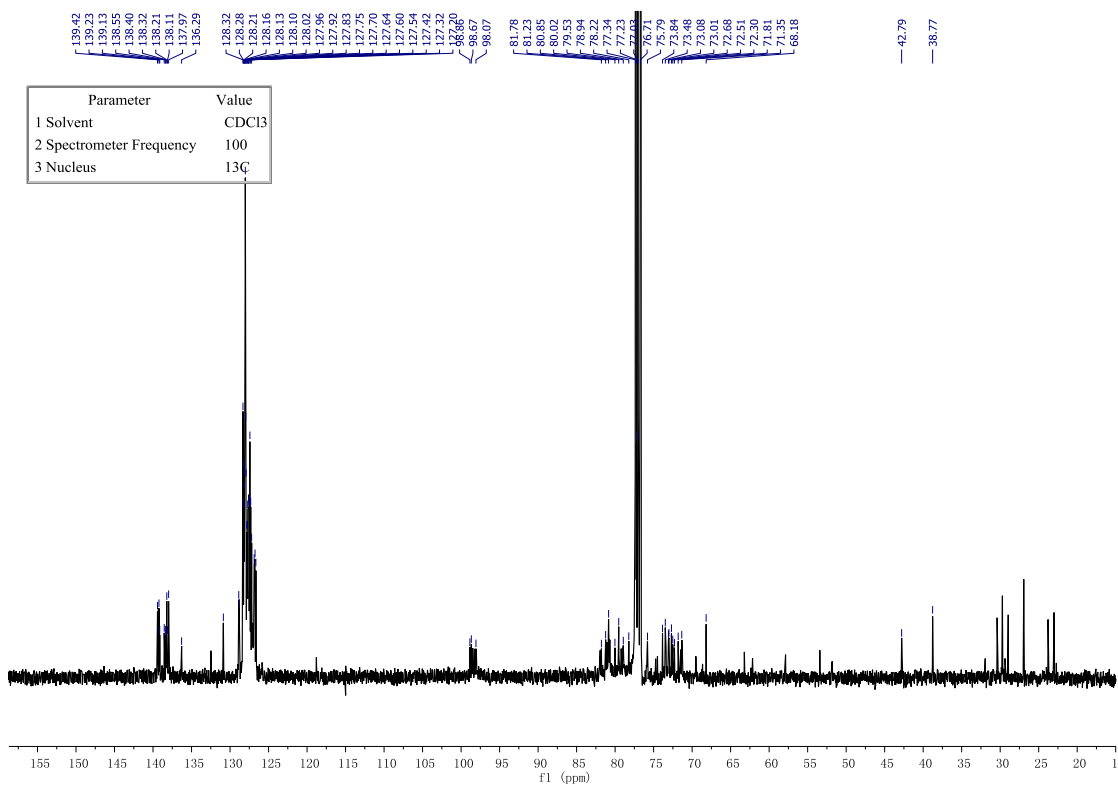
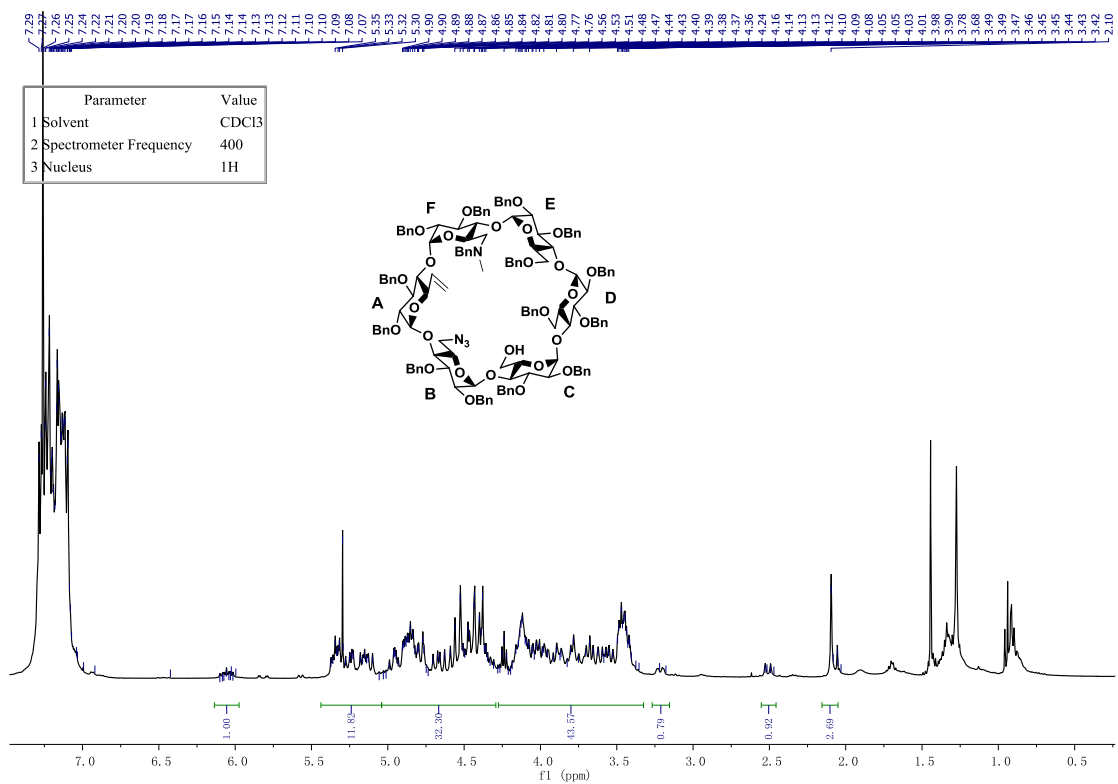
$R_f = 0.43$  (CyH/EtOAc 2/1)

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.28-7.11 (m, 75H, 75×H-Ar), 6.06 (ddd, 1H, <sup>3</sup>*J*<sub>5,6</sub> = 6.2 Hz, <sup>3</sup>*J*<sub>cis</sub> = 10.4 Hz, <sup>3</sup>*J*<sub>trans</sub> = 16.9 Hz, CH=CH<sub>2</sub>), 5.37 (d, 1H, <sup>2</sup>*J* = 11.4 Hz, CHPh), 5.34 (bd, 1H, <sup>3</sup>*J*<sub>trans</sub> = 16.6 Hz, CH=CH<sub>2</sub>), 5.33 (d, 1H, <sup>3</sup>*J*<sub>1,2</sub> = 3.4 Hz, H-1), 5.32 (d, 1H, <sup>3</sup>*J*<sub>1,2</sub> = 3.8 Hz, H-1), 5.26 (d, 1H, <sup>2</sup>*J* = 11.4 Hz, CHPh), 5.23 (d, 1H, <sup>3</sup>*J*<sub>1,2</sub> = 3.3 Hz, H-1), 5.18 (d, 1H, <sup>2</sup>*J* = 11.4 Hz, CHPh), 5.16 (bd, 1H, <sup>3</sup>*J*<sub>cis</sub> = 9.4 Hz, CH=CH<sub>2</sub>), 5.13 (d, 1H, <sup>2</sup>*J* = 10.4 Hz, CHPh), 4.99-4.77 (m, 8H, 2×H-1, 6×CHPh), 4.76 (d, 1H, <sup>3</sup>*J*<sub>1,2</sub> = 3.3 Hz, H-1), 4.70-4.30 (m, 19H, 18×CHPh, H-5), 4.16-3.95 (m, 12H, 6×H-3, 2×H-4, 3×H-5, H-6), 3.92-3.75 (m, 7H, 2×H-4, 2×H-5, H-6, 2×NCHPh), 3.70-3.53 (m, 6H, 2×H-4, 4×H-6), 3.49-3.41 (m, 8H, 6×H-2, 2×H-6), 3.21 (dd, 1H, <sup>3</sup>*J*<sub>5,6</sub> = 8.9 Hz, <sup>2</sup>*J*<sub>6,6'</sub> = 13.9 Hz, H-6), 2.51 (d, 1H, <sup>2</sup>*J*<sub>6,6'</sub> = 13.9 Hz, H-6), 2.09 (s, 3H, NCH<sub>3</sub>)

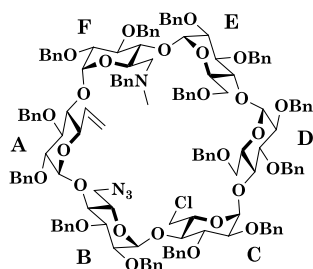
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.46, 139.44, 139.42(2C), 139.23(2C), 139.13, 138.55, 138.40, 138.32, 138.21(2C), 138.12, 137.97(2C) (15×C-Ar<sup>quat.</sup>), 136.29 (CH=CH<sub>2</sub>), 128.80-126.52 (75×C-Ar<sup>tert.</sup>), 118.74 (CH=CH<sub>2</sub>), 98.86, 98.67, 98.49, 98.25, 98.07, 98.00 (6×C-1), 81.94 (C-4), 81.78, 81.23 (2×C-3), 81.19 (C-4), 81.08, 81.05 (2×C-3), 80.85(2C) (2×C-4), 80.80, 80.69 (2×C-3), 80.02 (C-4), 79.53(2C), 79.21, 79.01, 78.94, 78.22 (6×C-2), 77.83 (C-4), 75.92, 75.85, 75.79, 75.77, 74.75, 74.50, 73.85, 73.48, 73.38, 73.08, 73.01, 72.68, 72.65, 72.51 (14×CH<sub>2</sub>Ph), 72.30, 71.81, 71.48, 71.35, 71.31, 71.27 (6×C-5), 69.50, 68.65, 63.22 (3×C-6), 62.15 (NCH<sub>2</sub>Ph), 57.88, 51.82 (2×C-6), 42.79 (NCH<sub>3</sub>)

**HRMS (ESI)**: Calcd. For C<sub>143</sub>H<sub>153</sub>N<sub>4</sub>O<sub>27</sub> [M+H]<sup>+</sup>: 2358.0704 ; Found: 2358.0717 (+ 0.5 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>F</sup>-Tetradeoxy-6<sup>A</sup>-Vinyl-6<sup>B</sup>-Azido-6<sup>C</sup>-Chloro-6<sup>F</sup>-(Benzyl)*N*(Methyl)-  
2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>D</sup>,6<sup>E</sup>-Tetradeca-*O*-Benzyl- $\alpha$ -cyclodextrin (**255**)**



Thionyl chloride (2  $\mu$ L, 0.026 mmol, 2 eq.) was added to a solution of cyclodextrin **254** (30 mg, 0.013 mmol, 1 eq.) in pyridine (2 mL) at r.t.. The reaction mixture was stirred for 2 h. Water (5 mL) and EtOAc (5 mL) were added, then the organic phase was extracted with HCl (1M) and sat. NaHCO<sub>3</sub>. The combined organic layers were dried with MgSO<sub>4</sub>, filtered and concentrated. Silica gel chromatography column (CyH/EtOAc 5/1) gave cyclodextrin **255** (10 mg, 39%) as a white foam.

$\alpha_D = +35.5$  (c 1.0, CHCl<sub>3</sub>)

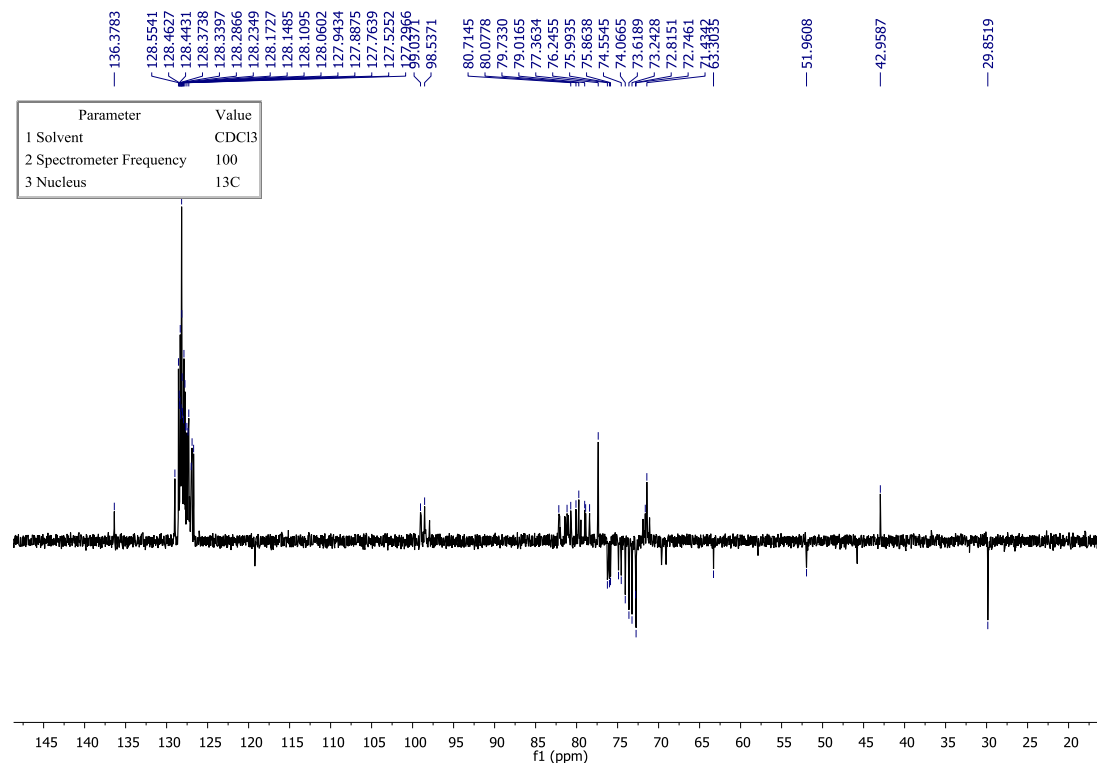
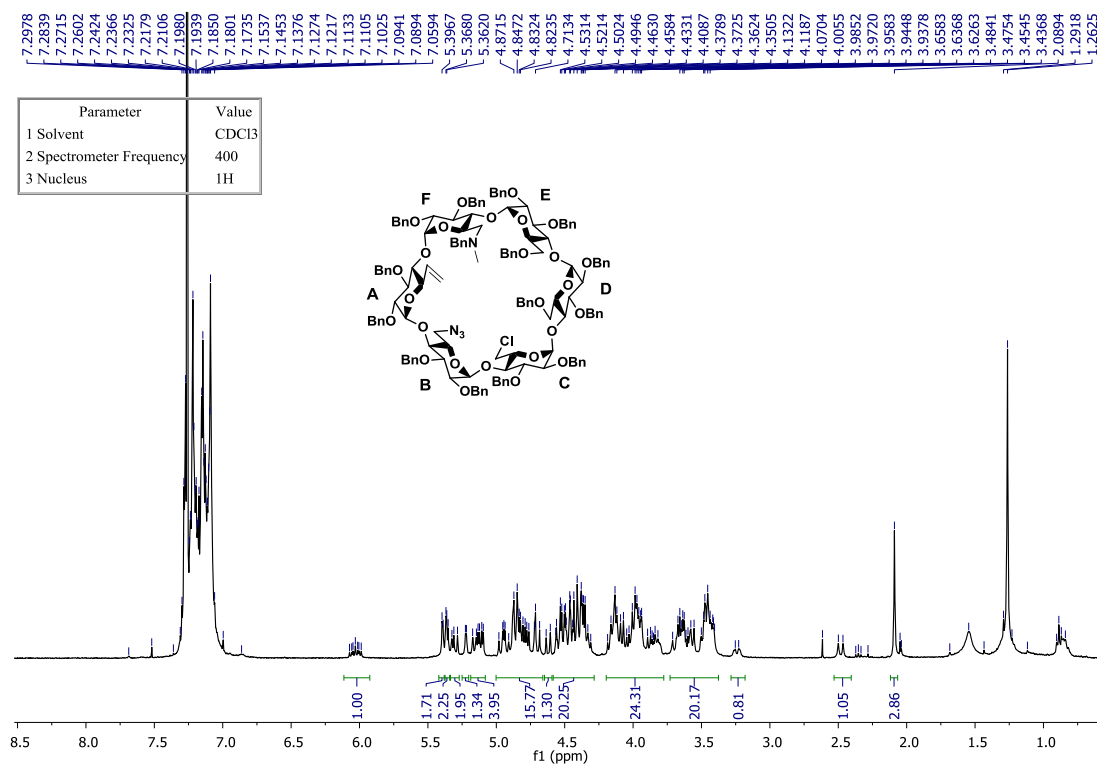
$R_f = 0.50$  (CyH/EtOAc 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.30-7.06 (m, 75H, 75 $\times$ H-Ar), 6.03 (ddd, 1H, <sup>3</sup>J<sub>5,6</sub> = 6.4 Hz, <sup>3</sup>J<sub>cis</sub> = 10.3 Hz, <sup>3</sup>J<sub>trans</sub> = 17.0 Hz, CH=CH<sub>2</sub>), 5.39 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1), 5.38 (d, 1H, <sup>2</sup>J = 11.4 Hz, CHPh), 5.36 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.9 Hz, H-1), 5.34 (bd, 1H, <sup>3</sup>J<sub>trans</sub> = 15.5 Hz, CH=CH<sub>2</sub>), 5.30 (d, 1H, <sup>2</sup>J = 10.6 Hz, CHPh), 5.22 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1), 5.16 (bd, 1H, <sup>3</sup>J<sub>cis</sub> = 11.0 Hz, CH=CH<sub>2</sub>), 5.12 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 5.11 (d, 1H, <sup>2</sup>J = 10.9 Hz, CHPh), 4.97 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 4.94 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 4.91-4.76 (m, 8H, H-1, 7 $\times$ CHPh), 4.72 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1), 4.70 (d, 1H, <sup>2</sup>J = 11.9 Hz, CHPh), 4.62 (d, 1H, <sup>2</sup>J = 12.3 Hz, CHPh), 4.56-4.31 (m, 15H, 14 $\times$ CHPh, H-5), 4.19-4.03 (m, 7H, 6 $\times$ H-3, H-5), 4.01-3.94 (m, 7H, 2 $\times$ H-4, 2 $\times$ H-5, 3 $\times$ H-6), 3.89-3.80 (m, 4H, 2 $\times$ H-4, 2 $\times$ H-5), 3.71-3.55 (m, 7H, 2 $\times$ H-4, 4 $\times$ H-6, NCHPh), 3.50-3.40 (m, 8H, 6 $\times$ H-2, H-6, NCHPh), 3.23 (dd, 1H, <sup>3</sup>J<sub>5,6</sub> = 5.1 Hz, <sup>2</sup>J<sub>66</sub> = 14.6 Hz, H-6), 2.48 (d, 1H, <sup>2</sup>J<sub>66</sub> = 14.3 Hz, H-6), 2.09 (s, 3H, NCH<sub>3</sub>)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.63(2C), 139.58, 139.48, 139.36(2C), 139.25, 138.66, 138.47, 138.44, 138.37, 138.29, 138.23, 138.18, 138.07 (15 $\times$ C-Ar<sup>quat.</sup>), 136.38 (CH=CH<sub>2</sub>), 128.99-126.71 (75 $\times$ C-Ar<sup>tert</sup>), 119.24 (CH=CH<sub>2</sub>), 99.04, 98.95, 98.58, 98.54, 98.43, 97.93 (6 $\times$ C-1), 82.19, 82.17 (2 $\times$ C-4), 82.05, 81.45, 81.42, 81.17, 81.10 (5 $\times$ C-3), 81.00, 80.97 (2 $\times$ C-4), 80.71 (C-3), 80.01 (C-4), 79.73(2C), 79.48, 79.02, 78.90, 78.42 (6 $\times$ C-2), 77.45 (C-4), 76.24, 76.16, 75.99, 75.86, 74.89, 74.55, 74.07, 73.62, 73.60, 73.24(2C), 72.81, 72.75(2C) (14 $\times$ CH<sub>2</sub>Ph), 71.90, 71.62, 71.46, 71.43(2C), 73.10 (6 $\times$ C-5), 69.64, 69.09 (2 $\times$ C-6), 63.30 (NCH<sub>2</sub>Ph), 57.95, 51.96, 45.80 (3 $\times$ C-6), 42.96 (NCH<sub>3</sub>)

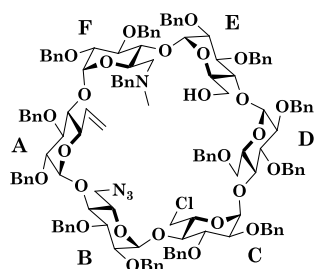
HRMS (ESI): Calcd. For C<sub>143</sub>H<sub>152</sub>ClN<sub>4</sub>O<sub>26</sub> [M+H]<sup>+</sup>: 2376.0330; Found: 2376.0378 (+4.8 ppm)

EXPERIMENTAL PART





**6<sup>A</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>F</sup>-Tetradecoxy-6<sup>A</sup>-Vinyl-6<sup>B</sup>-Azido-6<sup>C</sup>-Chloro-6<sup>F</sup>-(Benzyl)*N*(Methyl)-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>D</sup>-Trideca-*O*-Benzyl- $\alpha$ -cyclodextrin (**256**)**



DIBAL-H (1.5 M in toluene, 0.2 mL, 0.303 mmol, 60 eq.) was added slowly to a solution of azido- $\alpha$ -cyclodextrin **255** (12 mg, 0.005 mmol, 1 eq.) in toluene (0.3 mL) under nitrogen at r.t. The reaction mixture was stirred under nitrogen reflux at 50°C. The formation of the monol as the major product was monitored by MS (90 min). Heating was stopped, diethyl ether (5 mL) was added and the mixture was cooled down to 0°C. Water (100  $\mu$ L) was added dropwise, then NaOH aq.sol. 15% (100  $\mu$ L) and a second portion of water (200  $\mu$ L) were added. The mixture was vigorously stirred at r.t. for 20 min, then MgSO<sub>4</sub> (90 mg) was added and the mixture was stirred for 60 min. The precipitate was filtered and washed abundantly with diethyl ether (5 $\times$ 5 mL). The combined organic layers were concentrated and dried to give a mixture of amino-, amino-monol and amino-diol cyclodextrin (10 mg).

Imidazole-1-sulfonyl azide hydrochloride (1.6 mg, 0.008 mmol, 1.5 eq.) was added to  $\alpha$ -cyclodextrin mixture (10 mg, 0.005 mmol, 1 eq.), K<sub>2</sub>CO<sub>3</sub> (1.5 mg, 0.015 mmol, 3 eq.) and CuSO<sub>4</sub>·5H<sub>2</sub>O (0.06 mg, 0.25  $\mu$ mol, 0.05 eq.) in MeCN (2 mL) and the reaction mixture was stirred at r.t for 3 h. After removal of the solvent, the residue was diluted with water (5 mL), acidified with HCl (1M) and extracted with EtOAc (3 $\times$ 5 mL). The combined organic layers were dried with MgSO<sub>4</sub>, filtered and concentrated. Silica gel chromatography column (CyH/EtOAc 5/1) gave cyclodextrin **256** (4 mg, 40%) as a white foam.

$\alpha_D = +23.2$  (c 0.1, CHCl<sub>3</sub>)

$R_f = 0.50$  (CyH/EtOAc 3/1)

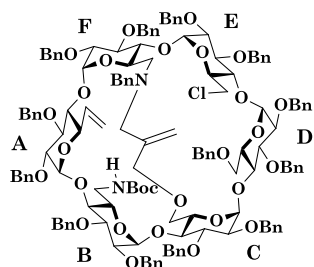
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  7.32-7.12 (m, 70H, 70 $\times$ H-Ar), 6.06 (ddd, 1H, <sup>3</sup>J<sub>5,6</sub> = 6.4 Hz, <sup>3</sup>J<sub>cis</sub> = 10.0 Hz, <sup>3</sup>J<sub>trans</sub> = 17.0 Hz, CH=CH<sub>2</sub>), 5.61 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1), 5.49 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1), 5.47 (d, 1H, <sup>2</sup>J = 10.9 Hz, CHPh), 5.40 (d, 2H, <sup>2</sup>J = 10.1 Hz, 2 $\times$ CHPh), 5.38 (bd, 1H, <sup>3</sup>J<sub>trans</sub> = 17.1 Hz, CH=CH<sub>2</sub>), 5.21 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1), 5.19 (bd, 1H, <sup>3</sup>J<sub>cis</sub> = 11.3 Hz, CH=CH<sub>2</sub>), 5.18 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 5.16 (d, 1H, <sup>2</sup>J = 10.5 Hz, CHPh), 4.93-4.70 (m, 10H, 3 $\times$ H-1, 8 $\times$ CHPh), 4.64-4.33 (m, 16H, H-5, 15 $\times$ CHPh), 4.23-3.87 (m, 18H, 6 $\times$ H-3, 4 $\times$ H-4, 5 $\times$ H-5, 3 $\times$ H-6), 3.79 (m, 2H, H-6, NCHPh), 3.71-3.46 (m, 12H, 5 $\times$ H-2, 2 $\times$ H-4, 4 $\times$ H-6, NCHPh), 3.34 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.8 Hz, H-2), 3.25 (dd, 1H, <sup>2</sup>J<sub>5,6</sub> = 5.1 Hz, <sup>2</sup>J<sub>6,6</sub> = 13.9 Hz, H-6), 2.55 (d, 1H, <sup>2</sup>J<sub>6,6</sub> = 14.3 Hz, H-6), 2.13 (s, 3H, N-CH<sub>3</sub>)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz):  $\delta$  139.58, 139.50, 139.44, 139.32, 139.29(2C), 139.20, 139.08, 138.72, 138.28, 138.19, 138.06, 137.98, 137.91 (14 $\times$ C-Ar<sup>quat.</sup>), 136.48 (CH=CH<sub>2</sub>), 128.94-126.98 (70 $\times$ C-Ar<sup>tert.</sup>), 118.85 (CH=CH<sub>2</sub>), 99.27, 98.49, 98.36, 98.20, 97.83, 97.78 (6 $\times$ C-1), 82.96, 82.15, 81.82 (3 $\times$ C-4), 81.48, 81.32, 81.16, 81.09, 80.86, 80.62 (6 $\times$ C-3), 80.21, 80.04 (2 $\times$ C-4), 79.75, 79.72, 79.19, 79.16, 78.74, 77.84 (6 $\times$ C-2), 76.45, 76.33(2C), 76.15 (4 $\times$ CH<sub>2</sub>Ph), 75.01 (C-4), 74.45, 74.32, 73.72, 73.57, 73.41, 73.38, 72.82, 72.64, 72.63 (9 $\times$ CH<sub>2</sub>Ph), 71.85, 71.71, 71.59, 71.04, 70.97, 70.93 (6 $\times$ C-5), 69.08 (C-6), 63.27 (N-CH<sub>2</sub>Ph), 61.79, 57.90, 52.13, 45.86 (4 $\times$ C-6), 43.01 (N-CH<sub>3</sub>)

HRMS (ESI): Calcd. For C<sub>136</sub>H<sub>146</sub>ClN<sub>4</sub>O<sub>26</sub> [M+H]<sup>+</sup>: 2285.9986; Found: 2285.9908 (-3.4 ppm)



**6<sup>A</sup>,6<sup>B</sup>,6<sup>E</sup>,6<sup>F</sup>-Tetra-deoxy-6<sup>A</sup>-Vinyl-6<sup>B</sup>-(Boc)*N*-Amino-6<sup>C</sup>-O-6<sup>F</sup>-(Benzyl)*N*-  
(Prop-2-ene-1,3-dienyl)-6<sup>E</sup>-Chloro-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>D</sup>-Trideca-O-Benzyl- $\alpha$ -cyclodextrin (**258**)**



A solution of Boc<sub>2</sub>O (11 mg, 0.05 mmol, 2 eq.) in ethanol absolute (0.5 mL) was added to a solution of hexa-differentiated  $\alpha$ -cyclodextrin **246** (56 mg, 0.025 mmol, 1 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) at r.t.. The reaction mixture was stirred for 2 h, then evaporated under reduce pression. Silica gel flash chromatography of the residue (CyH/EtOAc 4:1) gave the product **257** (43 mg, 74%) as a white foam.

Thionyl chloride (2  $\mu$ L, 0.029 mmol, 1.5 eq.) was added to a solution of  $\alpha$ -cyclodextrin **257** (43 mg, 0.019 mmol, 1 eq.) in pyridine (2 mL) at r.t.. The reaction mixture was stirred at the same temperature overnight. Water (10 mL) and EtOAc (10 mL) were added, then the organic phase was extracted with HCl (1M) and sat. NaHCO<sub>3</sub>. The combined organic layers were dried with MgSO<sub>4</sub>, filtered and concentrated. Silica gel chromatography column (CyH/EtOAc 5/1) gave the  $\alpha$ -cyclodextrin **258** (20 mg, 46%) as a white foam.

$\alpha_D = +33.8$  (c 1.0, CHCl<sub>3</sub>)

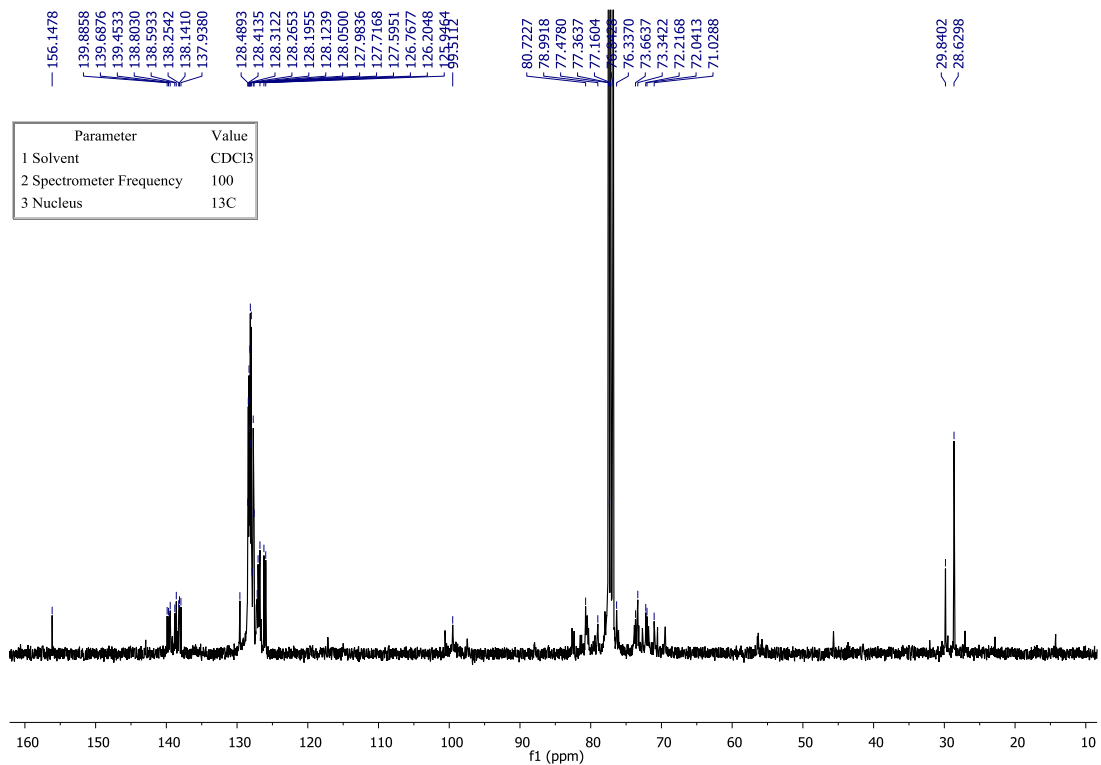
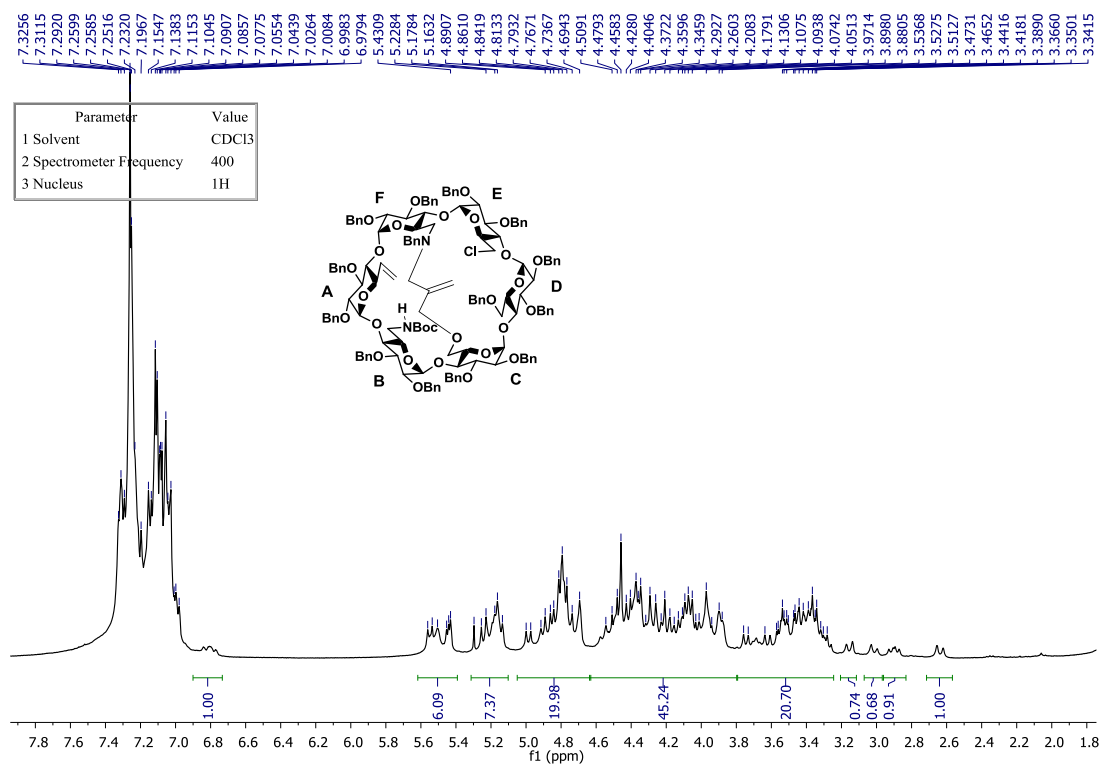
$R_f = 0.54$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.33-6.98 (m, 70H, 70 $\times$ H-Ar), 6.80 (ddd, 1H, <sup>3</sup>J<sub>5,6</sub> = 3.2 Hz, <sup>3</sup>J<sub>cis</sub> = 11.0 Hz, <sup>3</sup>J<sub>trans</sub> = 14.5 Hz, CH=CH<sub>2</sub>), 5.48 (d, 1H, <sup>2</sup>J = 10.8 Hz, CHPh), 5.55 (d, 1H, <sup>2</sup>J = 11.4 Hz, CHPh), 5.52 (bd, 1H, <sup>3</sup>J<sub>trans</sub> = 17.3 Hz, CH=CH<sub>2</sub>), 5.51 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1), 5.44 (d, 1H, <sup>2</sup>J = 9.70 Hz, CHPh), 5.43 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 4.1 Hz, H-1), 5.30-5.13 (m, 6H, H-1, 2 $\times$ CHPh, CH=CH<sub>2</sub>, 2 $\times$  =CH), 4.99 (d, 1H, <sup>2</sup>J = 10.3 Hz, CHPh), 4.92-4.69 (m, 10H, 3 $\times$ H-1, 7 $\times$ CHPh), 4.58-3.88 (m, 34H, 13 $\times$ CHPh, 6 $\times$ H-3, 3 $\times$ H-4, 6 $\times$ H-5, 4 $\times$ H-6, N-CHPh, (O)CH-C=), 3.76-3.26 (m, 15H, 6 $\times$ H-2, 3 $\times$ H-4, 4 $\times$ H-6, (O)CH-C=, N-CHPh), 3.16 (bd, 1H, <sup>2</sup>J = 13.5 Hz, (N)CH-C=), 3.01 (bd, 1H, <sup>2</sup>J = 13.6 Hz, (N)CH-C=), 2.90 (dd, 1H, <sup>3</sup>J<sub>5,6</sub> = 9.8 Hz, <sup>2</sup>J<sub>6,6'</sub> = 14.0 Hz, H-6), 2.64 (bd, 1H, <sup>2</sup>J<sub>6,6'</sub> = 13.9 Hz, H-6) 1.49 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>)

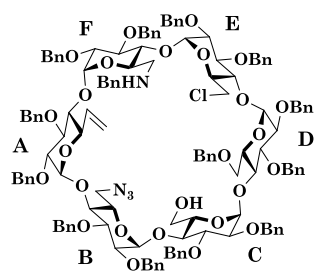
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  156.15 (NH-CO), 142.94 (C=CH<sub>2</sub>), 139.89, 139.69, 139.50, 139.45, 139.41, 139.15, 138.80, 138.59, 138.58, 138.37, 138.25, 138.14(2C), 137.94 (14 $\times$ C-Ar<sup>quat.</sup>), 135.77 (CH=CH<sub>2</sub>), 129.60-125.95 (70 $\times$ C-Ar<sup>tert.</sup>), 117.16 (=CH<sub>2</sub>), 114.83 (CH=CH<sub>2</sub>), 100.62, 99.51(2C), 98.87, 98.68, 97.45 (6 $\times$ C-1), 87.86, 82.61, 82.37, 82.05, 81.49, 81.31(6 $\times$ C-4), 80.72(2C), 80.64, 80.57, 80.50, 80.46 (6 $\times$ C-3), 80.31, 79.61, 79.42, 79.06, 79.00, 77.99 (6 $\times$ C-2), 76.64, 76.34(2C), 76.07, 73.91 (5 $\times$ CH<sub>2</sub>Ph), 73.82 (OCH<sub>2</sub>-C=), 73.66, 73.46, 73.38, 73.34, 73.21, 72.69, 72.22, 72.17 (8 $\times$ CH<sub>2</sub>Ph), 72.04(2C) (2 $\times$ C-5), 71.82 (C-6), 71.03, 70.95, 70.59, 70.55 (4 $\times$ C-5), 69.46 (C-6), 56.41 (C-6), 56.31 (NCH<sub>2</sub>-C=), 55.75 (N-CH<sub>2</sub>Ph), 45.67, 41.48 (2 $\times$ C-6), 31.75 (C(CH<sub>3</sub>)<sub>3</sub>), 28.63 (C(CH<sub>3</sub>)<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>144</sub>H<sub>157</sub>ClN<sub>2</sub>O<sub>28</sub>Na [M+Na]<sup>+</sup>: 2420.0557; Found: 2420.0504 (-2.2 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>B</sup>,6<sup>E</sup>,6<sup>F</sup>-Tetradecoxy-6<sup>A</sup>-Vinyl-6<sup>B</sup>-Azido-6<sup>E</sup>-Chloro-6<sup>F</sup>-(Benzyl)*N*-Amino-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>D</sup>-Trideca-*O*-Benzyl- $\alpha$ -cyclodextrin (**260**)**



$\text{Pd}^0(\text{PPh}_3)_4$  (3mg, 0.002 mmol, 0.3 eq.) was added to a solution of cyclodextrin **258** (20 mg, 0.008 mmol, 1 eq.) in degassed THF (2 mL) at r.t. under argon, then a 1 M solution of anhydrous  $\text{ZnCl}_2$  in THF (0.36 mL, 0.36 mmol, 45 eq.) was added and the reaction mixture was stirred for 10 min. After addition of  $\text{Et}_3\text{SiH}$  (0.58 mL, 0.36 mmol, 45 eq.), the reaction mixture was refluxed at 80 °C under argon overnight, diluted with EtOAc (5 mL), poured on water (5

mL). Layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were dried with  $\text{MgSO}_4$ , filtered and concentrated. Silica gel chromatography column (DCM/MeOH 98/2) gave cyclodextrin **259** (10 mg, 50%) as a white foam.

Imidazole-1-sulfonyl azide hydrochloride (1.4 mg, 0.007 mmol, 1.5 eq.) was added to the cyclodextrin **259** (10 mg, 0.05 mmol, 1 eq.),  $\text{K}_2\text{CO}_3$  (1.3 mg, 0.13 mmol, 3 eq.) and  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (0.06 mg, 0.22  $\mu\text{mol}$ , 0.05 eq.) in MeCN (2 mL) and the reaction mixture was stirred at r.t for 4 h. After removal of the solvent, the residue was diluted with water (5 mL), acidified with HCl (1M) and extracted with EtOAc (3×5 mL). The combined organic layers were dried with  $\text{MgSO}_4$ , filtered and concentrated. Silica gel chromatography column (CyH/EtOAc 5/1) gave azido- $\alpha$ -cyclodextrin **260** (6 mg, 60%) as a white foam.

$\alpha_{\text{D}} = +15.8$  (c 0.1,  $\text{CHCl}_3$ )

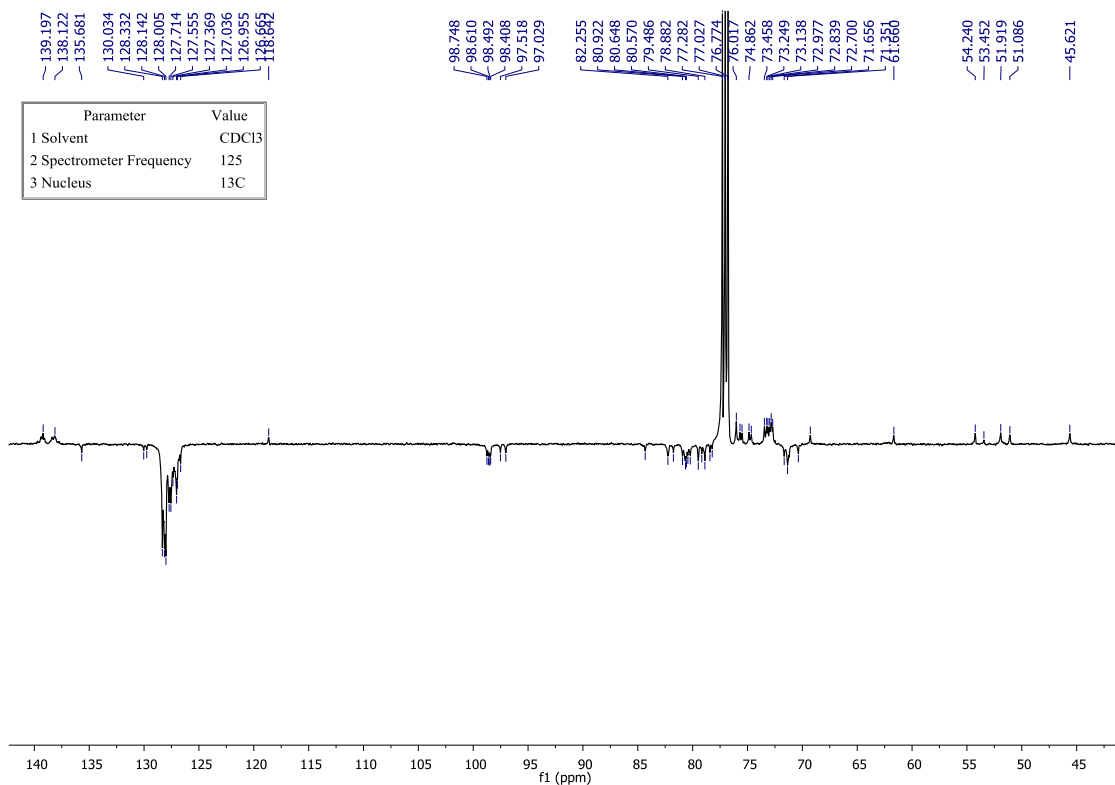
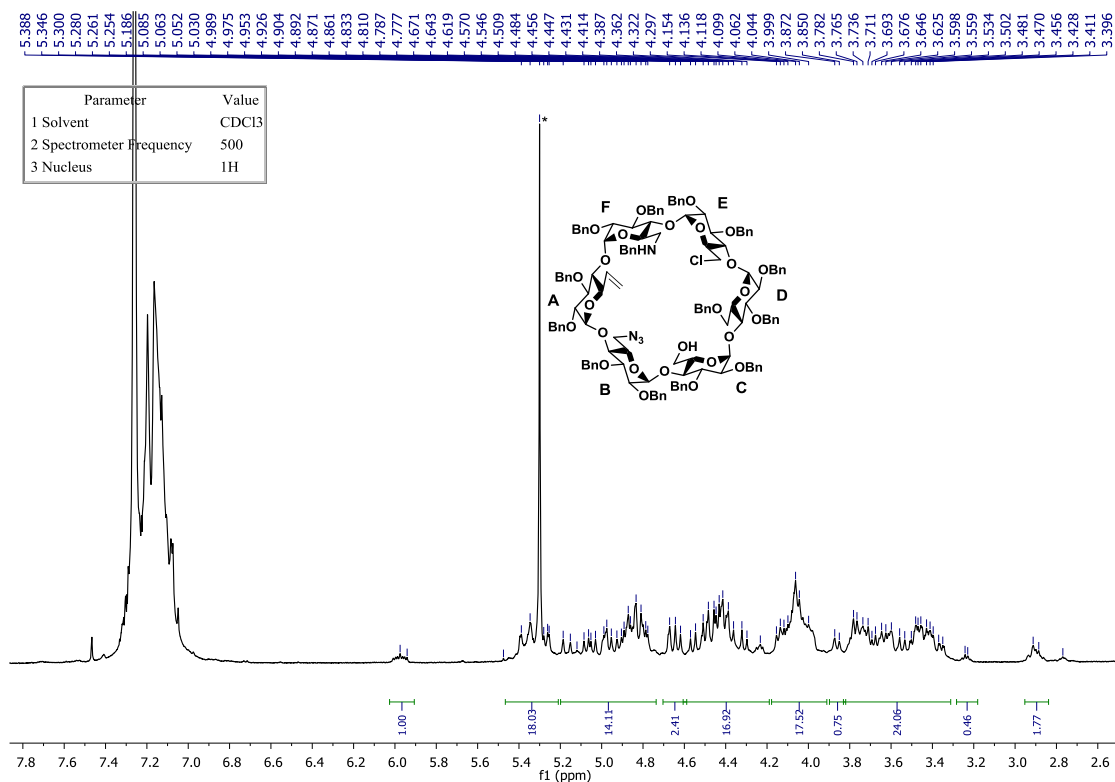
$R_f = 0.37$  (CyH/EtOAc: 5/1)

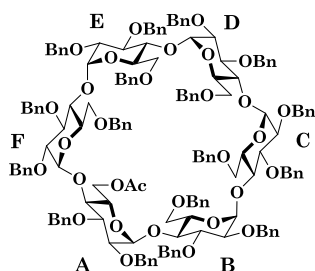
<sup>1</sup>H NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.33-6.98 (m, 70H, 70×H-Ar), 5.98 (ddd, 1H,  $^3J_{5,6} = 5.7$  Hz,  $^3J_{\text{cis}} = 10.7$  Hz,  $^3J_{\text{trans}} = 16.7$  Hz,  $\text{CH}=\text{CH}_2$ ), 5.39 (d, 1H,  $^3J_{1,2} = 3.5$  Hz, H-1), 5.35-5.28 (m, 2H, 2×CHPh), 5.26 (d, 1H,  $^3J_{1,2} = 3.5$  Hz, H-1), 5.17 (bd, 1H,  $^3J_{\text{trans}} = 17.5$  Hz,  $\text{CH}=\text{CH}_2$ ), 5.07 (d, 1H,  $^2J = 11.0$  Hz, CHPh), 5.04 (d, 1H,  $^2J = 11.2$  Hz, CHPh), 4.99 (d, 1H,  $^2J = 10.3$  Hz, CHPh), 4.98 (d, 1H,  $^3J_{1,2} = 3.3$  Hz, H-1), 4.97 (d, 1H,  $^2J = 10.7$  Hz, CHPh), 4.91 (bd, 1H,  $^3J_{\text{cis}} = 11.2$  Hz,  $\text{CH}=\text{CH}_2$ ), 4.89-4.78 (m, 8H, 2×H-1, 6×CHPh), 4.68 (d, 1H,  $^3J_{1,2} = 3.5$  Hz, H-1), 4.63 (d, 1H,  $^2J = 12.0$  Hz, CHPh), 4.56 (d, 1H,  $^2J = 12.2$  Hz, CHPh), 4.52-4.36 (m, 11H, 11×CHPh), 4.31 (d, 1H,  $^2J = 12.0$  Hz, CHPh), 4.24 (dd, 1H,  $^3J_{4,5} = 6.7$  Hz,  $^3J_{5,6} = 9.7$  Hz, H-5), 4.15-3.98 (m, 14H, 6×H-3, H-4, 5×H-5, 2×H-6), 3.86 (d, 1H,  $^2J_{6,6'} = 12.2$  Hz, H-6), 3.78-3.59 (m, 10H, 4×H-4, 5×H-6, N-CHPh), 3.55 (d, 1H,  $^2J = 12.1$  Hz, N-CHPh), 3.49-3.40 (m, 6H, 5×H-2, H-4), 3.36 (dd, 1H,  $^3J_{1,2} = 3.2$  Hz,  $^3J_{2,3} = 9.7$  Hz, H-2), 2.94-2.86 (m, 2H, 2×H-6)

<sup>13</sup>C NMR ( $\text{CDCl}_3$ , 125 MHz):  $\delta$  139.85, 139.54, 139.46, 139.32(2C), 139.20, 138.53, 138.48, 138.40, 138.33, 138.25, 138.23, 138.16, 138.12 (14×C-Ar<sup>quat.</sup>), 135.81 ( $\text{CH}=\text{CH}_2$ ), 128.46-126.79 (70×C-Ar<sup>tert.</sup>), 118.65 ( $\text{CH}=\text{CH}_2$ ), 98.88, 98.74, 98.62, 98.53, 97.65, 97.16 (6×C-1), 84.46, 82.39, 82.33 (3×C-4), 81.88, 81.05 (2×C-3), 80.83 (C-4), 80.78, 80.70, 80.57, 80.34 (4×C-3), 79.61(2C), 79.29 (3×C-2), 79.01(2C) (C-2, C-4), 78.55, 78.35 (2×C-2), 76.86 (C-4), 76.15(2C), 75.81, 75.63, 74.99, 74.79, 73.59, 73.38, 73.27, 73.11, 72.97, 72.94, 72.83 (13×CH<sub>2</sub>Ph), 71.79, 71.47(2C), 71.42, 71.33, 70.50 (6×C-5), 69.41, 61.79 (2×C-6), 54.37 (N-CH<sub>2</sub>Ph), 53.58, 52.05, 51.23 (3×C-6)

HRMS (ESI): Calcd. For  $\text{C}_{135}\text{H}_{144}\text{ClN}_4\text{O}_{26}$   $[\text{M}+\text{H}]^+$ : 2271.9769; Found: 2271.9752 (-0.8 ppm)

EXPERIMENTAL PART



**6A-O-Acetyl-2A-F,3A-F,6B,6C,6D,6E,6F-Heptadeca-O-Benzyl- $\alpha$ -Cyclodextrin (261)**

Acetic anhydrous (0.03 mL, 0.032 mmol, 4 eq.) was added to a solution of monol-cyclodextrin **130** (200 mg, 0.08 mmol, 1 eq.) in pyridine (5 mL) at room temperature. The reaction mixture was stirred overnight at the same temperature. EtOAc (10 mL) and HCl (1 M, 10 mL) were added. The aqueous phases were extracted with ethyl acetate (3×10 mL) and the organic layers were combined, dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 4/1) gave

acetate- $\alpha$ -cyclodextrin **261** (174 mg, 85%) as a white foam.

$\alpha_D = +36.8$  (c 1.0, CHCl<sub>3</sub>)

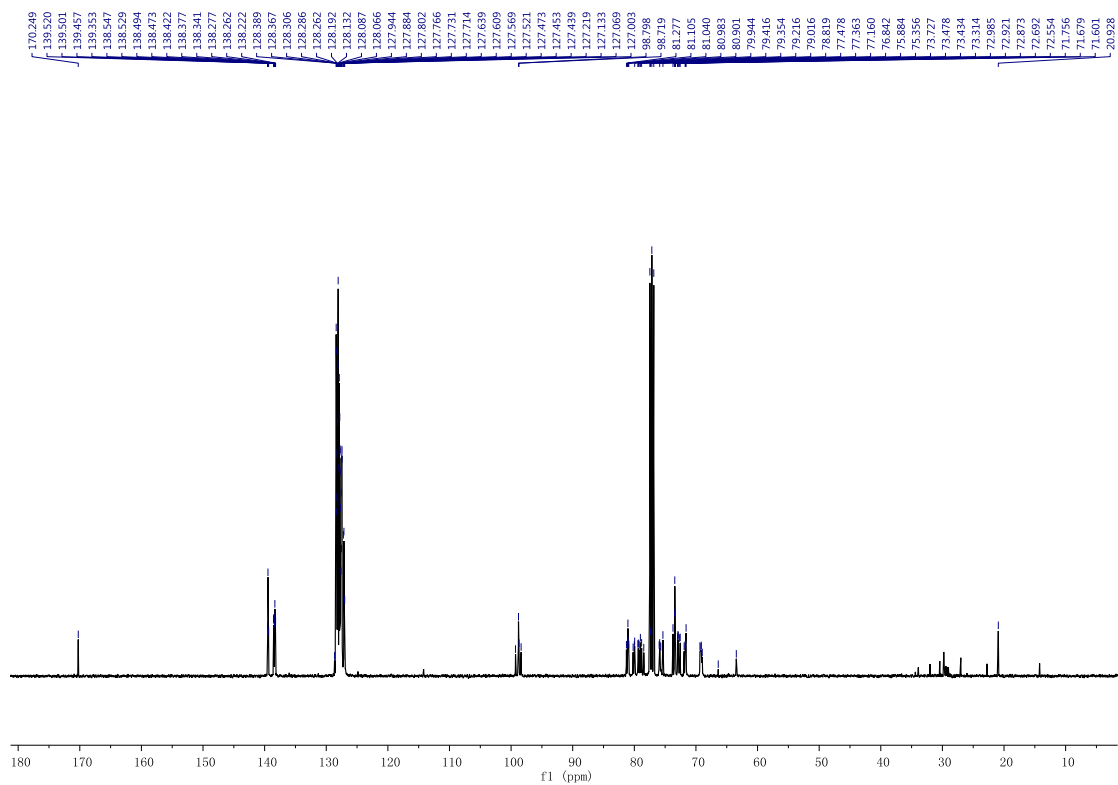
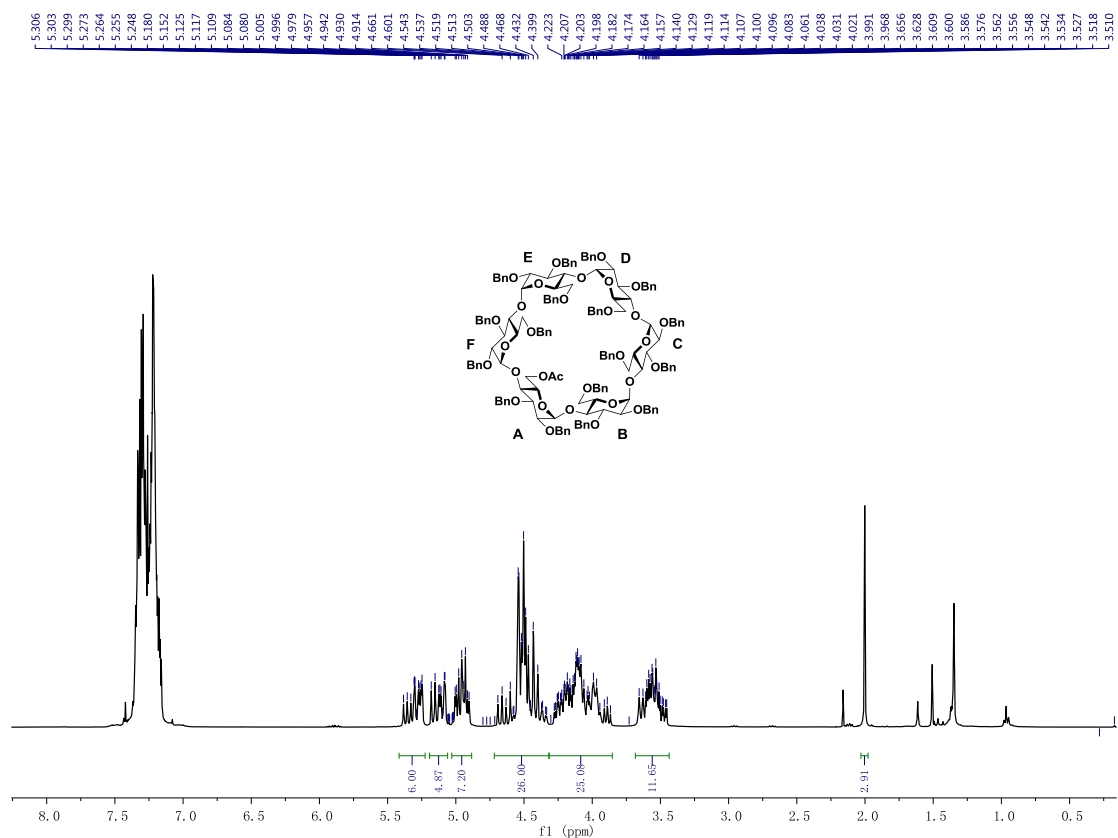
$R_f = 0.48$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.36-7.17 (m, 85H, 85×H-Ar.), 5.37 (d, 1H, <sup>2</sup>J=10.0 Hz, CHPh), 5.33 (d, 1H, <sup>2</sup>J=11.0 Hz, CHPh), 5.60 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.0 Hz, H-1), 5.29 (d, 1H, <sup>2</sup>J=10.6 Hz, CHPh), 5.26 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.6 Hz, H-1), 5.25 (d, 1H, <sup>2</sup>J=10.2 Hz, CHPh), 5.17 (d, 1H, <sup>2</sup>J=11.2 Hz, CHPh), 5.14 (d, 1H, <sup>2</sup>J=10.7 Hz, CHPh), 5.11 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.5 Hz, H-1), 5.09 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.0 Hz, H-1), 5.08 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.1 Hz, H-1), 5.00 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.4 Hz, H-1), 4.98-4.90 (m, 6H, 6×CHPh), 4.69-4.40 (m, 23H, H-6, 22×CHPh), 4.35 (dd, 1H, <sup>3</sup>J<sub>5,6</sub>=4.0 Hz, <sup>2</sup>J<sub>6,6'</sub>=12.2 Hz, H-6), 4.28-3.87 (m, 23H, 6×H-3, 6×H-4, 6×H-5, 5×H-6), 3.66-3.50 (m, 10H, 5×H-2, 5×H-6), 3.47 (dd, 1H, <sup>3</sup>J<sub>1,2</sub>=3.7 Hz, <sup>3</sup>J<sub>2,3</sub>=9.7 Hz, H-2), 2.00 (s, 3H, OC(O)CH<sub>3</sub>)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  170.25 (OC(O)CH<sub>3</sub>), 139.52, 139.50, 139.46(3C), 139.35, 138.55, 138.53, 138.49, 138.47, 138.42, 138.38, 138.34(2C), 138.27, 138.26, 138.22 (17×C-Ar<sup>quat.</sup>), 128.39-127.00 (85×C-Ar<sup>tert.</sup>), 99.28, 98.80(2C), 98.77, 98.72, 98.38 (6×C-1), 81.28, 81.11, 81.04(2C), 80.98, 80.90 (6×C-3), 80.19, 80.00, 79.94, 79.91 (4×C-4), 79.42, 79.25, 79.22, 79.04, 79.02, 78.82 (6×C-2), 78.79, 78.47 (2×C-4), 75.97, 75.88, 75.83, 75.71, 75.36(2C), 73.73, 73.48, 73.45, 73.43(2C), 73.31, 72.99, 72.92, 72.87, 72.69, 72.55 (17×CH<sub>2</sub>Ph), 71.91, 71.76, 71.68, 71.61(3C) (6×C-5), 69.24, 69.20, 69.13, 69.10, 68.98, 63.45 (6×C-6), 20.93 (OC(O)CH<sub>3</sub>)

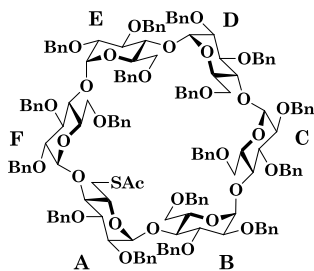
**HRMS (ESI):** Calcd. For C<sub>157</sub>H<sub>164</sub>O<sub>31</sub>Na [M+Na]<sup>1+</sup>: 2568.1233; Found: 2568.1149 (-3.3 ppm)

EXPERIMENTAL PART





**6<sup>A</sup>-Deoxy-6<sup>A</sup>-S-Acetyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>,6<sup>F</sup>-Heptadeca-  
O-Benzyl- $\alpha$ -Cyclodextrin (**262**)**



The *O*-methylsulfonyl-cyclodextrin (1.2 g, 0.460 mmol, 1 eq.) was dissolved in anhydrous DMF (25 mL) under nitrogen. Potassium thioacetate (159 mg, 1.39 mmol, 3 eq.) was added at room temperature. The reaction mixture was stirred overnight at 50°C. EtOAc (25 mL) was added and the organic layers were washed with brine (3×25 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 5/1) gave thioacetate- $\alpha$ -cyclodextrin

**262** (1.1 g, 93%) as a yellowish foam.

$\alpha_D = +43.9$  (c 1.0, CHCl<sub>3</sub>)

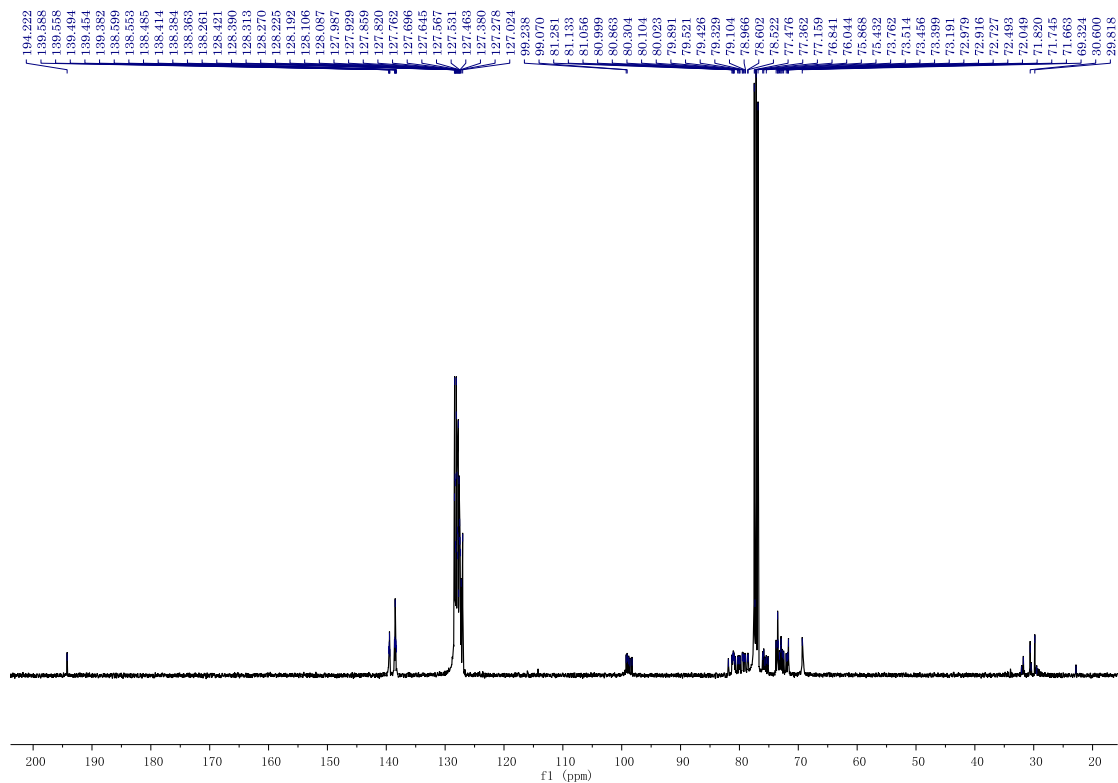
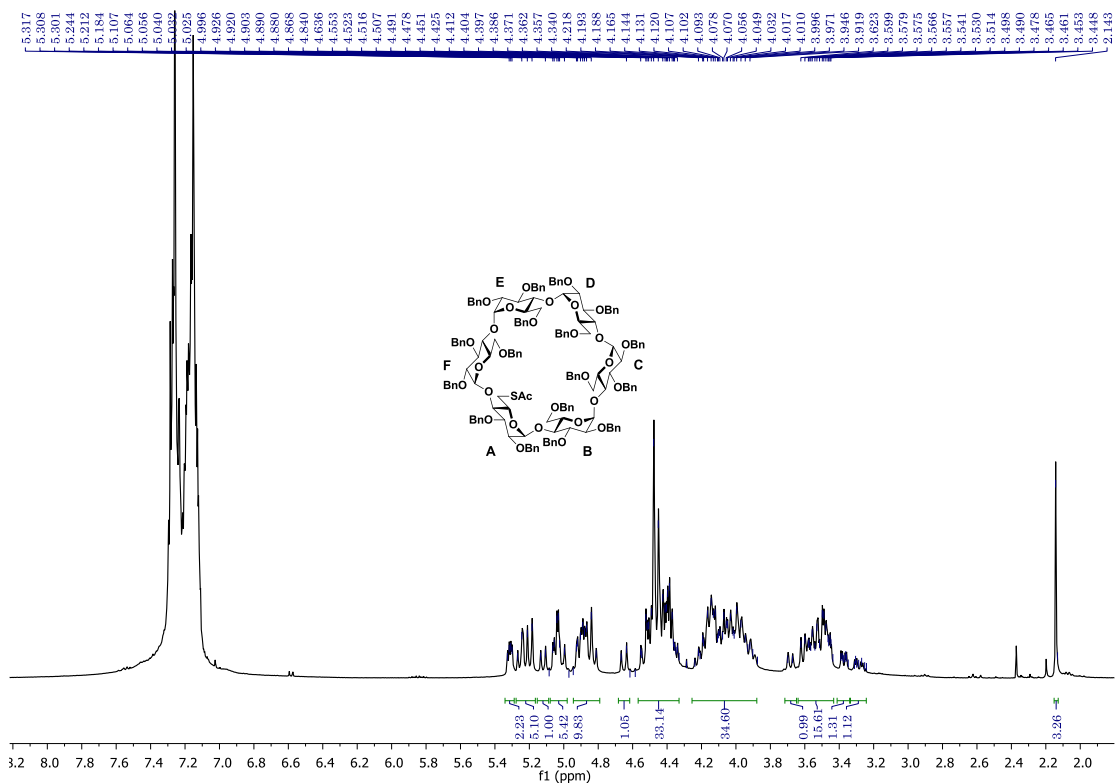
$R_f = 0.61$  (CyH/EtOAc: 3/1)

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.30-7.13 (m, 85H, 85×H-Ar.), 5.32 (d, 1H, <sup>3</sup> $J_{1,2} = 3.8$  Hz, H-1), 5.30 (d, 1H, <sup>3</sup> $J_{1,2} = 3.2$  Hz, H-1), 5.26 (d, 1H, <sup>2</sup> $J = 10.5$  Hz, CHPh), 5.24 (d, 1H, <sup>3</sup> $J_{1,2} = 2.9$  Hz, H-1), 5.20 (d, 2H, <sup>2</sup> $J = 10.8$  Hz, 2×CHPh), 5.12 (d, 1H, <sup>2</sup> $J = 11.1$  Hz, CHPh), 5.06 (d, 1H, <sup>3</sup> $J_{1,2} = 3.2$  Hz, H-1), 5.03 (d, 1H, <sup>3</sup> $J_{1,2} = 3.3$  Hz, H-1), 5.01 (d, 1H, <sup>2</sup> $J = 11.4$  Hz, CHPh), 4.93-4.81 (m, 8H, H-1, 7×CHPh), 4.65 (d, 1H, <sup>2</sup> $J = 11.7$  Hz, CHPh), 4.55-4.34 (m, 21H, 21×CHPh), 4.24-3.89 (m, 22H, 6×H-3, 5×H-4, 6×H-5, 5×H-6), 3.68 (d, 1H, <sup>2</sup> $J_{6,6'} = 10.2$  Hz, H-6), 3.62-3.44 (m, 11H, 5×H-2, H-4, 5×H-6), 3.37 (dd, 1H, <sup>3</sup> $J_{1,2} = 3.4$  Hz, <sup>3</sup> $J_{2,3} = 9.9$  Hz, H-2), 3.28 (dd, 1H, <sup>3</sup> $J_{5,6} = 5.1$  Hz, <sup>2</sup> $J_{6,6'} = 13.9$  Hz, H-6), 2.14 (s, 3H, SC(O)CH<sub>3</sub>)

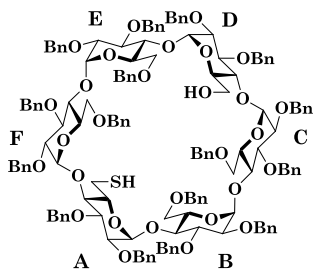
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  194.22 (SC(O)CH<sub>3</sub>), 139.59, 139.56, 139.49, 139.45(2C), 139.38, 138.60, 138.55, 138.51, 138.48(3C), 138.45, 138.41, 138.38, 138.36, 138.26 (17×C-Ar<sup>quat.</sup>), 128.42-127.02 (85×C-Ar<sup>tert.</sup>), 99.24, 99.07, 99.02, 98.81, 98.60, 98.24 (6×C-1), 81.87 (C-4), 81.28, 81.13, 81.06, 81.00, 80.86, 80.73 (6×C-3), 80.30, 80.10, 80.02, 79.89 (4×C-4), 79.52, 79.43, 79.33, 79.10, 78.97, 78.60 (6×C-2), 78.52 (C-4), 76.04, 75.87, 75.84, 75.67, 75.43, 75.13, 73.76, 73.51(2C), 73.46, 73.40, 73.19, 72.98, 72.92(2C), 72.73, 72.49 (17×CH<sub>2</sub>Ph), 72.05, 71.82, 71.74, 71.66(2C), 71.63 (6×C-5), 69.32(2C), 69.29, 69.24, 69.16, 30.60 (6×C-6), 29.82 (SC(O)CH<sub>3</sub>)

**HRMS (ESI)**: Calcd. For C<sub>157</sub>H<sub>164</sub>O<sub>30</sub>SNa [M+Na]<sup>1+</sup>: 2584.0920; Found: 2584.0931 (-0.4 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-Thiol-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>-Hexadeca-  
O-Benzyl- $\alpha$ -Cyclodextrin (**263**)**



DIBAL-H (1.5 M in toluene, 1.7 mL, 2.50 mmol, 20 eq.) was added to a solution of thioacetate-cyclodextrin **262** (320 mg, 0.125 mmol, 1 eq.) in toluene (0.8 mL) under nitrogen at r. t. The reaction mixture was stirred at 55°C with a nitrogen balloon reflux for 10 min, until TLC indicated formation of monol-CD as a major product, and then cooled to r.t. and poured into ice/water. Aqueous HCl (5 mL, 1 M) and EtOAc (5 mL) were added, and the solution was stirred for 1 h. The aqueous layer was extracted with EtOAc (3×5 mL). The

combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Silica gel chromatography of the residue (CyH/EtOAc: 4/1) gave thiol-monol-cyclodextrin **263** (250 mg, 82%) as a yellowish foam.

$\alpha_D = +39.1$  (c 1.0, CHCl<sub>3</sub>)

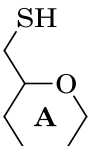
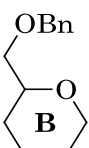
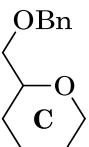
$R_f = 0.46$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.31-7.08 (m, 80H, 85×H-Ar.), 5.53 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, H-1F), 5.52 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, H-1C), 5.39 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh), 5.34 (d, 1H, <sup>2</sup>J = 10.1 Hz, CHPh), 5.21 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 5.19 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 4.91-4.79 (m, 11H, H-1B, H-1D, H-1E, 8×CHPh), 4.75 (d, 1H, <sup>2</sup>J = 11.7 Hz, CHPh), 4.73 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1A), 4.69 (d, 1H, <sup>2</sup>J = 12.1 Hz, CHPh), 4.59-4.32 (m, 18H, 18×CHPh), 4.21 (t, 1H, <sup>3</sup>J<sub>2,3</sub> = <sup>3</sup>J<sub>3,4</sub> = 8.8 Hz, H-3F), 4.19 (t, 1H, <sup>3</sup>J<sub>2,3</sub> = <sup>3</sup>J<sub>3,4</sub> = 8.4 Hz, H-3C), 4.14-3.82 (m, 21H, H-3A, H-3B, H-3D, H-3E, H-4A, H-4B, H-4C, H-4D, H-4E, H-4F, H-5A, H-5B, H-5C, H-5D, H-5E, H-5F, H-6B, H-6C, H-6D, H-6E, H-6F), 3.76 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.7 Hz, H-6C), 3.73 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.7 Hz, H-6C), 3.66-3.62 (m, 3H, H-6B, H-6D, H-6E), 3.57 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, <sup>3</sup>J<sub>2,3</sub> = 8.8 Hz, H-2F), 3.55 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, <sup>3</sup>J<sub>2,3</sub> = 8.4 Hz, H-2C), 3.45 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, H-2E), 3.40 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 2.8 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.5 Hz, H-2D), 3.35 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, H-2A), 2.86-2.76 (m, 2H, 2×H-6A), 2.60 (t, 1H, <sup>3</sup>J<sub>6,OH</sub> = 5.5 Hz, OH), 1.45 (t, 1H, <sup>3</sup>J<sub>6,SH</sub> = 8.0 Hz, SH)

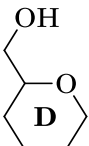
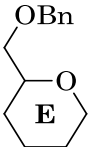
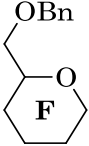
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.53(2C), 139.46(2C), 139.44(2C), 138.68(2C), 138.54, 138.44, 138.39, 138.30, 138.25(2C), 138.17, 138.05 (16×C-Ar<sup>quat</sup>), 128.52-126.67 (80×C-Ar<sup>tert</sup>), 98.69, 98.54, 98.49(2C), 98.35, 98.11 (C-1C, C-1A, C-1B, C-1D, C-1F, C-1E), 81.49 (C-3D), 81.39 (C-4B), 81.14, 81.12, 81.07 (C-3F, C-3C, C-3A), 80.99, 80.92 (C-4C, C-4E), 80.83(2C) (C-3B, C-3E), 80.44 (C-4F), 80.06, 79.75, 79.27, 79.22, 78.29 (C-2A, C-2D, C-2E, C-2B, C-2C), 78.26(2C) (C-2F, C-4A), 76.33, 76.29 (2×CH<sub>2</sub>Ph), 76.06 (C-4D), 75.96, 75.85, 74.57, 74.46, 73.68, 73.63, 73.57, 73.53, 73.48, 73.30, 73.15, 73.14, 72.58(2C) (14×CH<sub>2</sub>Ph), 72.13, 72.08(2C), 71.96, 71.63, 70.56 (C-5F, C-5C, C-5E, C-5D, C-5B, C-5A), 69.80, 69.73, 69.40, 69.38, 61.84, 27.33 (C-6C, C-6F, C-6B, C-6E, C-6D, C-6A)

**HRMS (ESI):** Calcd. For C<sub>148</sub>H<sub>156</sub>O<sub>29</sub>SNa [M+Na]<sup>1+</sup>: 2452.0418; Found: 2452.0345 (-3.0 ppm)

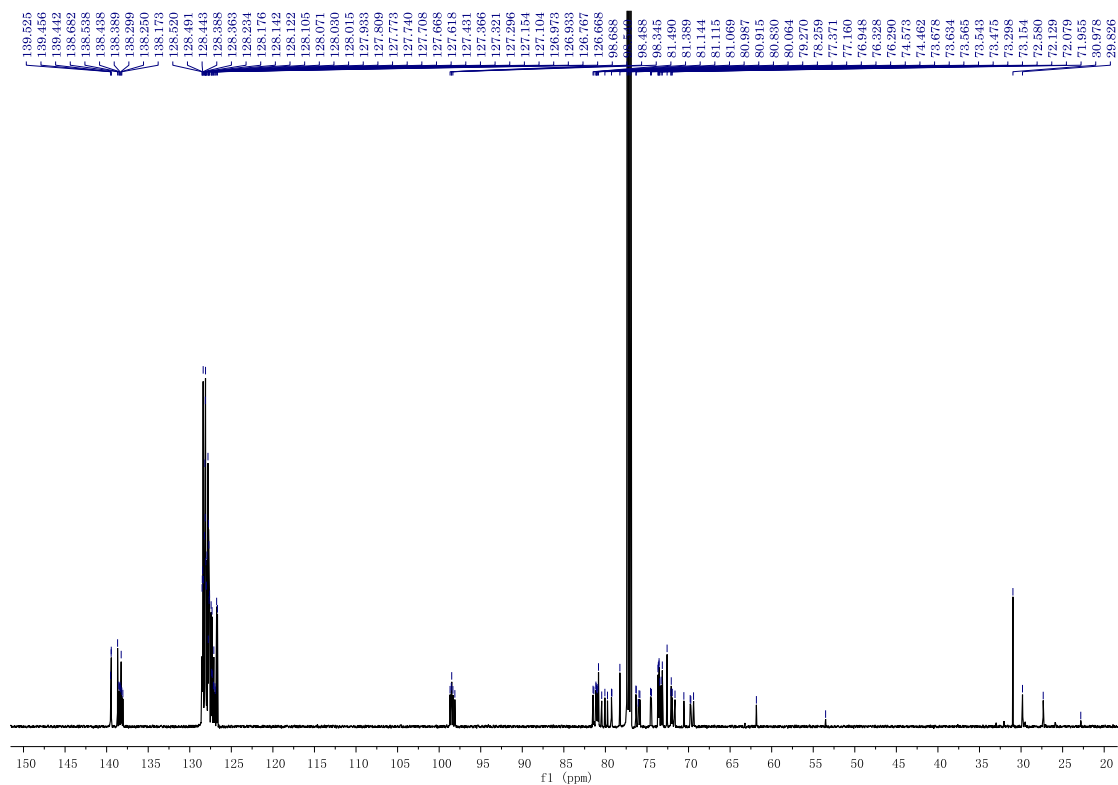
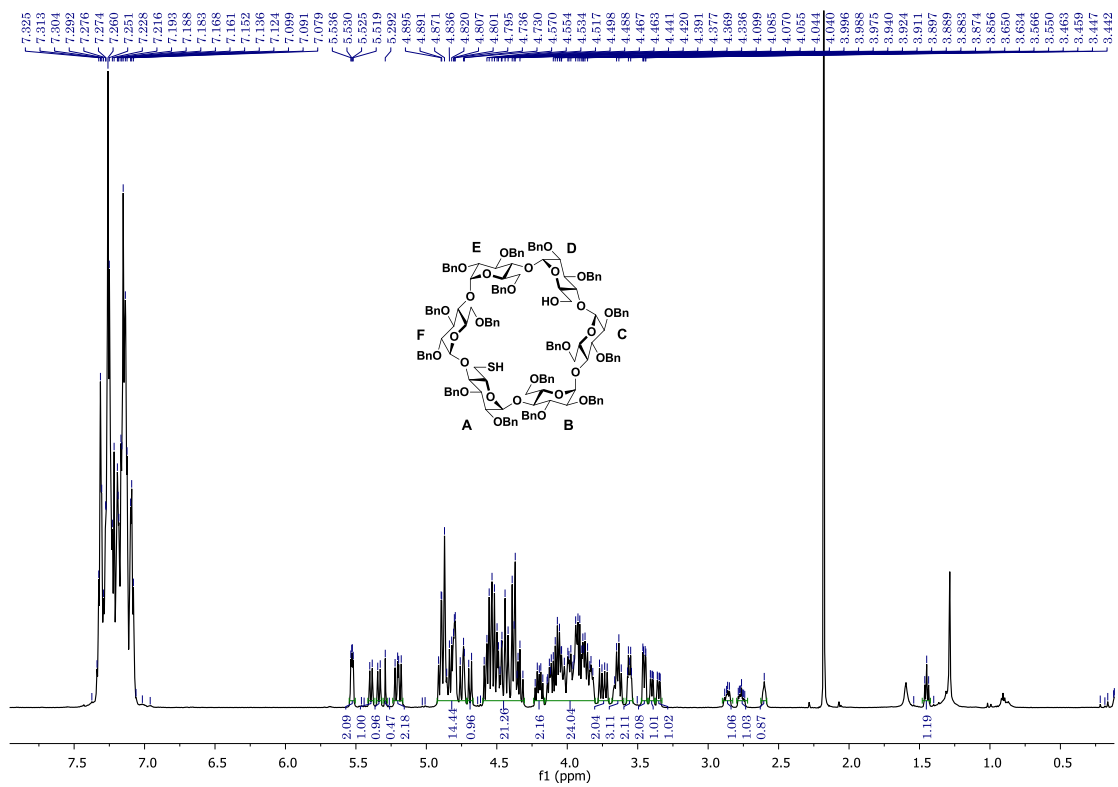
**EXPERIMENTAL PART**

	<b>Attribution</b>	<b>Signal (ppm)</b>	<b>Correlation(ppm)</b>	<b>Attribution</b>
 <p style="text-align: center;"><b>A</b></p>	H-1A	4.749	NOE: 3.865 ppm	H-4B
	C-1A	98.555		
	H-2A	3.350		
	C-2A	80.064		
	H-3A	4.067		
	C-3A	81.096		
	H-4A	3.885	NOE: 5.535 ppm	H-1F
	C-4A	78.259		
	H-5A	4.026		
	C-5A	70.563		
	H-6A	2.865		
		2.761		
C-6A	27.346			
 <p style="text-align: center;"><b>B</b></p>	H-1B	4.879	NOE: 3.917 ppm	H-4C
	C-1B	98.496		
	H-2B	3.452		
	C-2B	79.218		
	H-3B	4.056		
	C-3B	80.830		
	H-4B	3.865	NOE: 4.749 ppm	H-1A
	C-4B	81.405		
	H-5B	3.947		
	C-5B	71.628		
	H-6B	3.996		
		3.653		
C-6B	69.319			
 <p style="text-align: center;"><b>C</b></p>	H-1C	5.522	NOE: 3.908 ppm	H-4D
	C-1C	98.689		
	H-2C	3.555		
	C-2C	78.290		
	H-3C	4.188		
	C-3C	81.115		
	H-4C	3.917	NOE: 4.879 ppm	H-1B
	C-4C	81.987		
	H-5C	3.950		
	C-5C	72.079		
	H-6C	3.766		
		3.962		
C-6C	69.773			

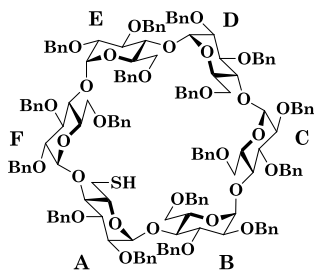
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	4.813	NOE: 3.933 ppm	H-4E
	C-1D	98.496		
	H-2D	3.398		
	C-2D	79.750		
	H-3D	4.115		
	C-3D	81.500		
	H-4D	3.908	NOE: 5.522 ppm	H-1C
	C-4D	76.060		
	H-5D	3.949		
	C-5D	71.955		
	H-6D	3.668		
		3.842		
C-6D	61.793			
	H-1E	4.905	NOE: 4.096 ppm	H-4F
	C-1E	98.096		
	H-2E	3.452		
	C-2E	79.270		
	H-3E	4.036		
	C-3E	80.830		
	H-4E	3.933	NOE: 4.813 ppm	H-1D
	C-4E	80.915		
	H-5E	3.876		
	C-5E	72.079		
	H-6E	4.024		
		3.633		
C-6E	69.355			
	H-1F	5.535	NOE: 3.885 ppm	H-4A
	C-1F	98.335		
	H-2F	3.562		
	C-2F	78.259		
	H-3F	4.214		
	C-3F	81.141		
	H-4F	4.096	NOE: 4.905 ppm	H-1E
	C-4F	80.444		
	H-5F	3.834		
	C-5F	72.129		
	H-6F	4.140		
		3.725		
C-6F	69.698			

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-Thiol-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>,6<sup>F</sup>-Heptadeca-  
O-Benzyl- $\alpha$ -Cyclodextrin (**264**)**



The thioacetate-cyclodextrin **262** (550 mg, 0.215 mmol, 1 eq.) was dissolved in anhydrous THF (3 mL) under nitrogen. Sodium methoxide (19 mM in methanol, 3.4 mL, 0.065 mmol, 0.3 eq.) was added at r.t.. The reaction mixture was stirred at r.t. for 2 h. The reaction was quenched with water (3 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 5/1) gave

thiol- $\alpha$ -cyclodextrin **264** (420 mg, 77%) as a yellowish foam.

$\alpha_D = +45.2$  (c 1.0, CHCl<sub>3</sub>)

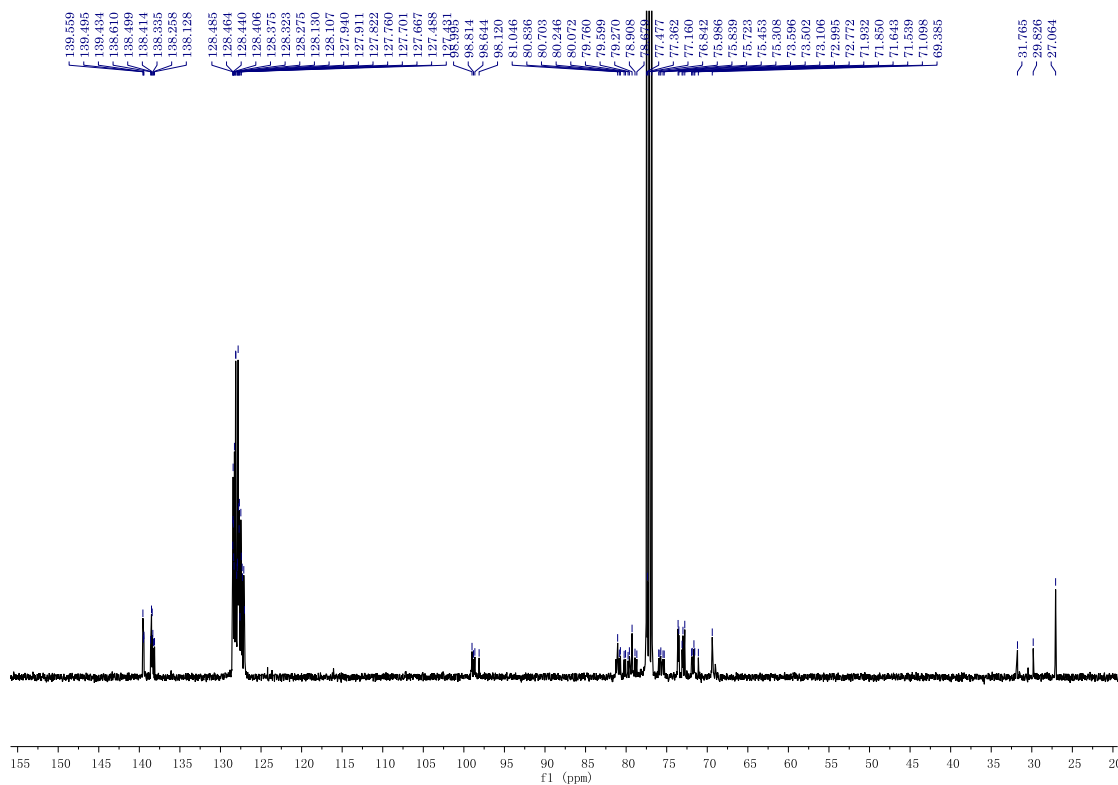
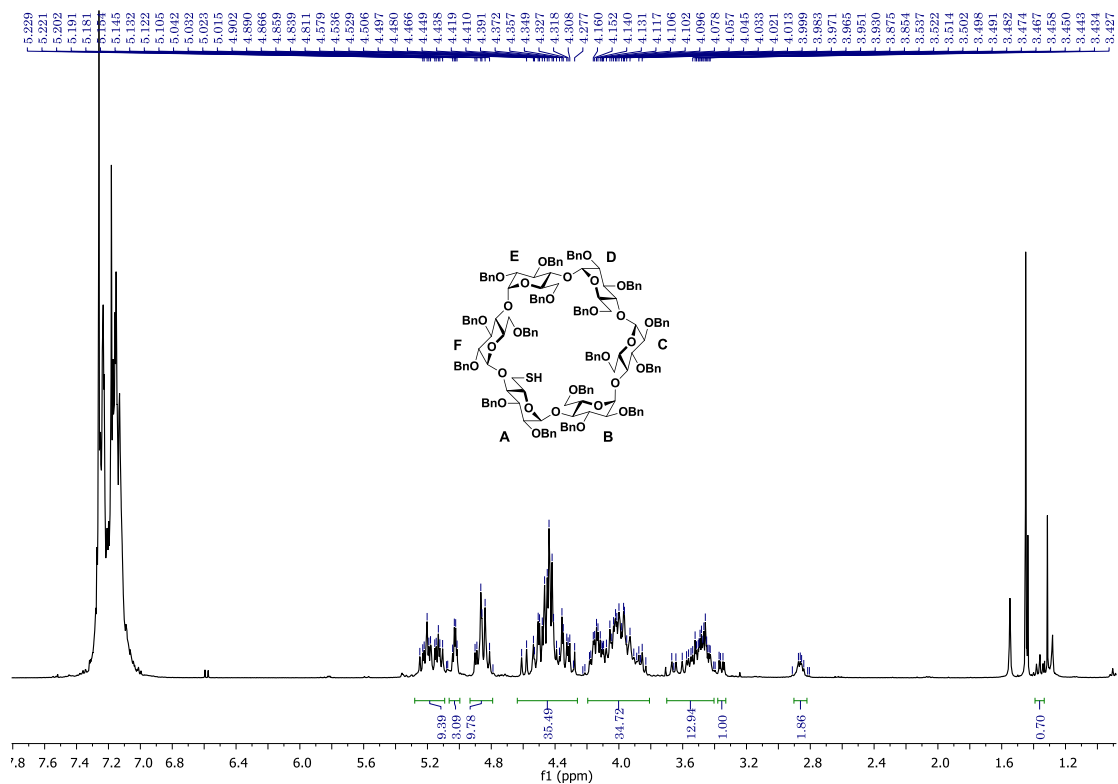
$R_f = 0.67$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.27-7.11 (m, 85H, 85×H-Ar.), 5.25 (d, 1H, <sup>2</sup>J=10.9 Hz, CHPh), 5.23 (d, 1H, <sup>2</sup>J=10.9 Hz, CHPh), 5.21 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.0 Hz, H-1), 5.18 (d, 1H, <sup>2</sup>J=10.2 Hz, CHPh), 5.15 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.6 Hz, H-1), 5.13 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.5 Hz, H-1), 5.12 (d, 1H, <sup>2</sup>J=10.6 Hz, CHPh), 5.04-5.02 (m, 3H, 2×H-1, CHPh), 4.90-4.81 (m, 8H, H-1, 7×CHPh), 4.61-4.28 (m, 22H, 22×CHPh), 4.19-3.85 (m, 23H, 6×H-3, 6×H-4, 6×H-5, 5×H-6), 3.65 (d, 1H, <sup>2</sup>J<sub>6,6'</sub>=10.7 Hz, H-6), 3.62-3.44 (m, 9H, 5×H-2, 4×H-6), 3.36 (dd, 1H, <sup>3</sup>J<sub>1,2</sub>=3.7 Hz, <sup>3</sup>J<sub>2,3</sub>=9.9 Hz, H-2), 2.88-2.84 (m, 2H, 2×H-6), 1.36 (t, 1H, <sup>3</sup>J<sub>6,SH</sub>=8.7 Hz, SH)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.56(2C), 139.55, 139.50, 139.45, 139.43, 138.61, 138.52, 138.50(2C), 138.44, 138.41(2C), 138.39, 138.33, 138.26, 138.13 (17×C-Ar<sup>quat.</sup>), 128.47-127.03 (85×C-Ar<sup>tert.</sup>), 99.10, 99.01, 99.00, 98.81, 98.64, 98.12 (6×C-1), 81.26, 81.13, 81.05(2C), 81.01, 80.84 (6×C-3), 80.70, 80.25, 80.07, 79.76, 79.60, 79.55 (6×C-4), 79.27(2C), 79.24(2C), 78.91, 78.68 (6×C-2), 75.99, 75.84, 75.74, 75.57, 75.45, 75.31, 73.65, 73.60, 73.58, 73.52, 73.50, 73.11, 73.00(2C), 72.95, 72.77(2C) (17×CH<sub>2</sub>Ph), 71.93, 71.85, 71.66, 71.64, 71.54, 71.10 (6×C-5), 69.42(2C), 69.39(2C), 69.00, 27.06 (6×C-6)

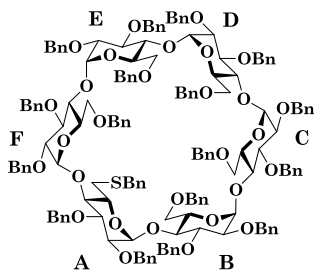
**HRMS (ESI):** Calcd. For C<sub>155</sub>H<sub>162</sub>O<sub>29</sub>SNa [M+Na]<sup>1+</sup>: 2542.0892; Found: 2542.0815 (-3.0 ppm)

EXPERIMENTAL PART





**6<sup>A</sup>-Deoxy-6<sup>A</sup>-S-Benzyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>,6<sup>F</sup>-Heptadeca  
-O-Benzyl- $\alpha$ -Cyclodextrin (**265**)**



Thiol-cyclodextrin **264** (390 mg, 0.155 mmol, 1 eq.) was dissolved in anhydrous DMF (8 mL) under nitrogen. Sodium hydride (60% in mineral oil, 37 mg, 0.93 mmol, 6 eq.) was added at 0°C. The reaction mixture was stirred for 30 min. Benzyl bromide (0.111 mL, 0.93 mmol, 6 eq.) was added and the reaction mixture was stirred at r.t. for 2 h. The reaction was quenched with water (20 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash

chromatography of the residue (CyH/EtOAc: 98/2, then 4/1) gave thiobenzyl- $\alpha$ -cyclodextrin **265** (200 mg, 50%) as a yellowish foam.

$\alpha_D = +40.0$  (c 1.0, CHCl<sub>3</sub>)

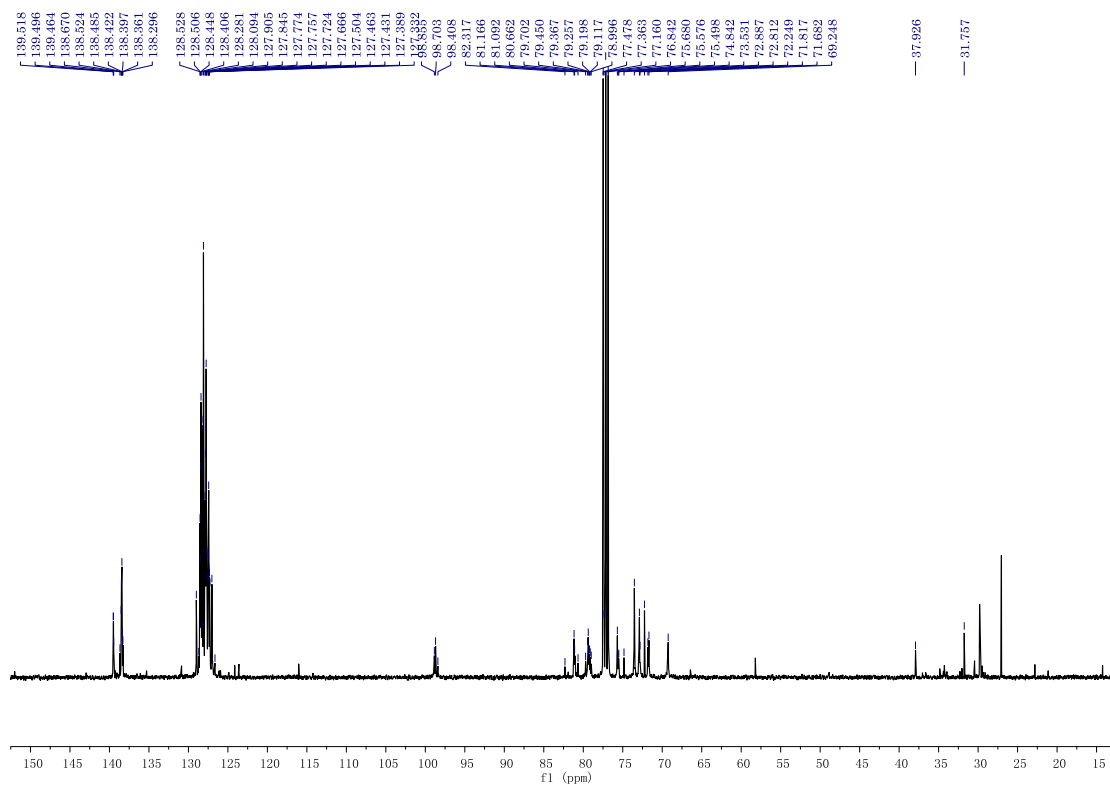
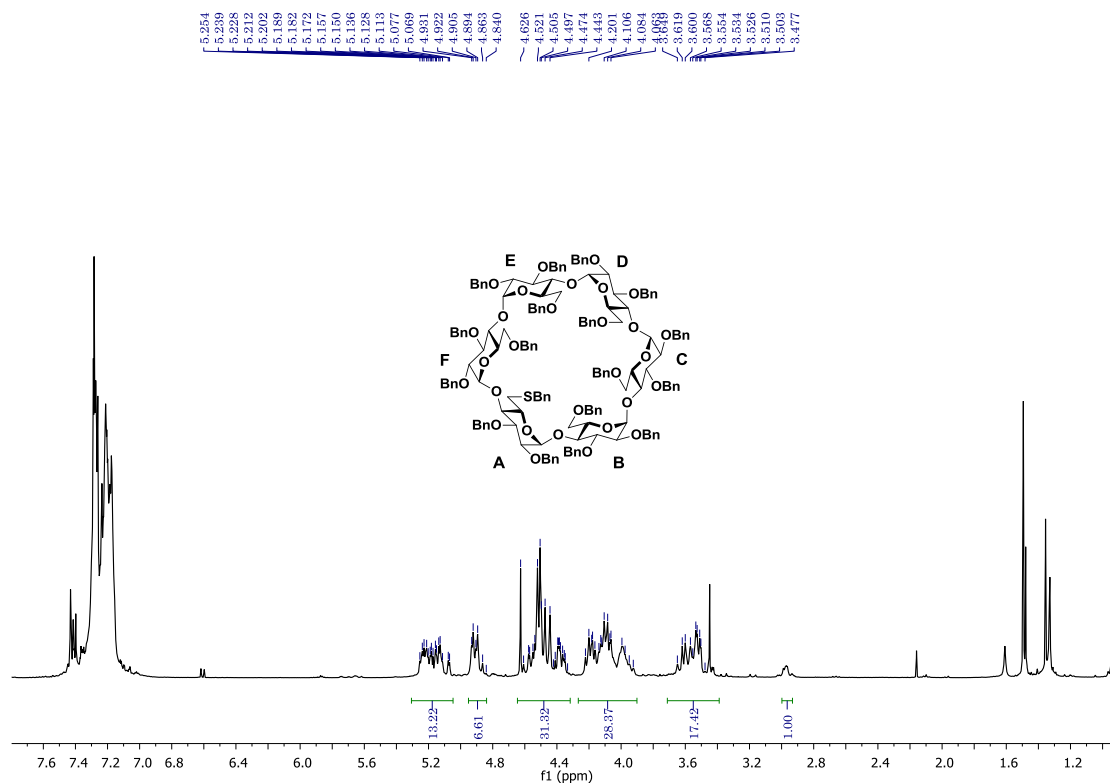
$R_f = 0.60$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.27-7.17 (m, 90H, 90×H-Ar.), 5.25-5.11 (m, 11H, 5×H-1, 6×CHPh), 5.07 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1), 4.93-4.86 (m, 6H, 6×CHPh), 4.63-4.35 (m, 22H, 22×CHPh), 4.22-3.92 (m, 23H, 6×H-3, 6×H-4, 6×H-5, 5×H-6), 3.69-3.50 (m, 12H, 5×H-2, 5×H-6, 2×SCHPh), 3.44 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, H-2), 2.99-2.96 (m, 2H, 2×H-6),

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.53, 139.52(2C), 139.50(2C), 139.46, 138.67, 138.52(2C), 138.49(3C), 138.42(4C), 138.40, 138.36, 138.30 (18×C-Ar<sup>quat.</sup>), 128.53-127.03 (90×C-Ar<sup>tert.</sup>), 98.90, 98.87, 98.86, 98.70(2C), 98.41 (6×C-1), 82.83 (C-4), 81.21, 81.17(2C), 81.09, 81.04, 80.66 (6×C-3), 79.70, 79.45(2C) (3×C-4), 79.37(3C) (2×C-4, C-2), 79.32, 79.26, 79.20, 79.12, 79.00 (5×C-2), 75.72, 75.68(3C), 75.58, 75.50, 73.54(2C), 73.53(2C), 72.95, 72.92, 72.89(2C), 72.81, 72.25(2C) (17×CH<sub>2</sub>Ph), 71.82(2C), 71.73, 71.68(3C), 69.30(2C), 69.25(3C) (5×C-6), 37.93 (SCH<sub>2</sub>Ph), 34.23 (C-6)

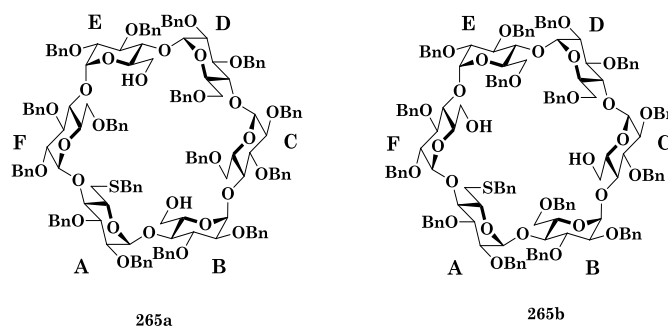
**HRMS (ESI):** Calcd. For C<sub>162</sub>H<sub>168</sub>O<sub>29</sub>SNa [M+Na]<sup>1+</sup>: 2632.1272; Found: 2632.1284 (+0.5 ppm)

EXPERIMENTAL PART

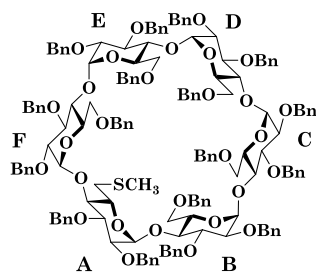


**6<sup>A</sup>-Deoxy-6<sup>A</sup>-S-Benzyl- $\alpha$ -Cyclodextrin (265) was debenzylated by DIBAL-H**

DIBAL-H (1.5 M in toluene, 1.0 mL, 1.54 mmol, 20 eq.) was added to a solution of thiobenzyl-cyclodextrin **265** (200 mg, 0.077 mmol, 1 eq.) in toluene (0.54 mL) under nitrogen at r. t. The reaction mixture was stirred at 55°C with a nitrogen balloon reflux for 30 min, until Mass spectrum indicated formation of diol as a major product, and then cooled to r.t. and poured into ice/water. Aqueous HCl (5 mL, 1 M) and EtOAc (5 mL) were added, and the solution was stirred for 1 h. The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Silica gel chromatography of the residue (CyH/EtOAc: 4/1) gave an inseparable mixture of BE-diol-cyclodextrin **265a** and CF-diol-cyclodextrin **265b** (54 mg) as yellowish foams.



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-S-Methyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>,6<sup>F</sup>-Heptadeca-  
O-Benzyl- $\alpha$ -Cyclodextrin (266)**



Thioacetate-cyclodextrin **262** (150 mg, 0.06 mmol, 1 eq.) was dissolved in anhydrous DMF (5 mL) under nitrogen. Sodium hydride (60% in mineral oil, 24 mg, 0.60 mmol, 10 eq.) was added at 70°C. The reaction mixture was stirred for 30 min. Methyl iodide (0.036 mL, 0.60 mmol, 10 eq.) was added and the reaction mixture was stirred at r.t. overnight. The reaction was quenched with water (3 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel

flash chromatography of the residue (CyH/EtOAc: 4/1) gave thiomethyl- $\alpha$ -cyclodextrin **266** (115 mg, 76%) as a yellowish foam.

$\alpha_D = +37.6$  (c 1.0, CHCl<sub>3</sub>)

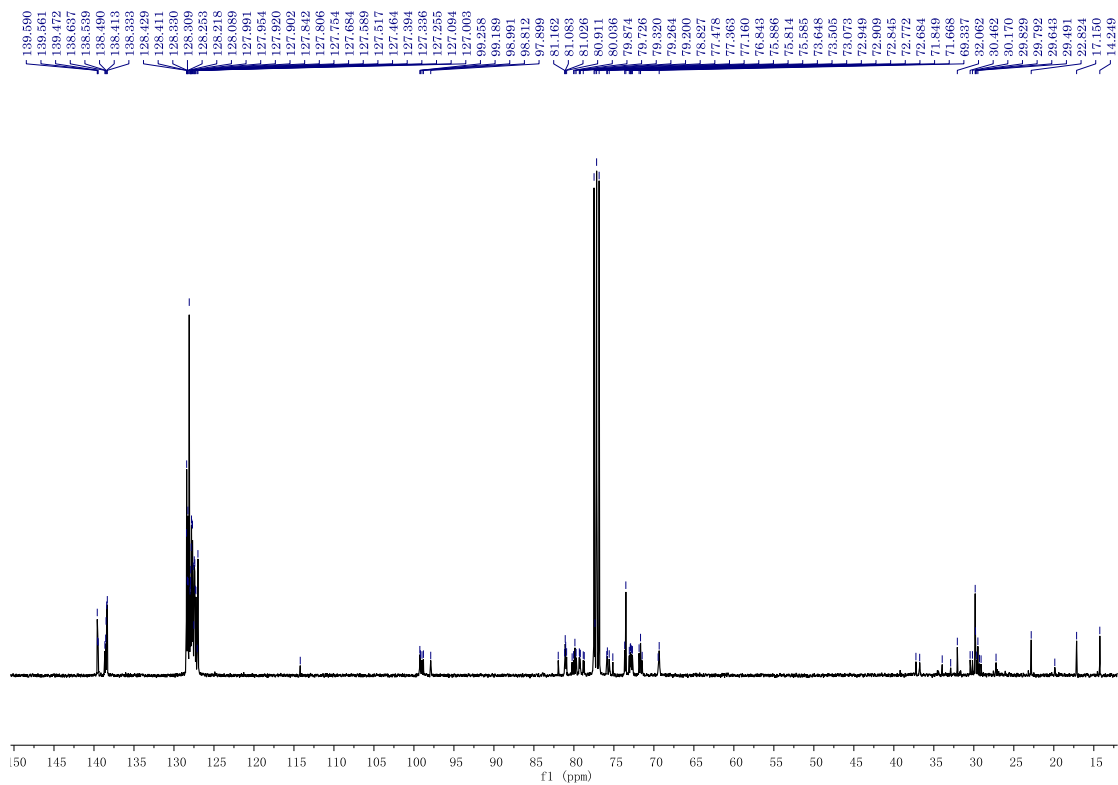
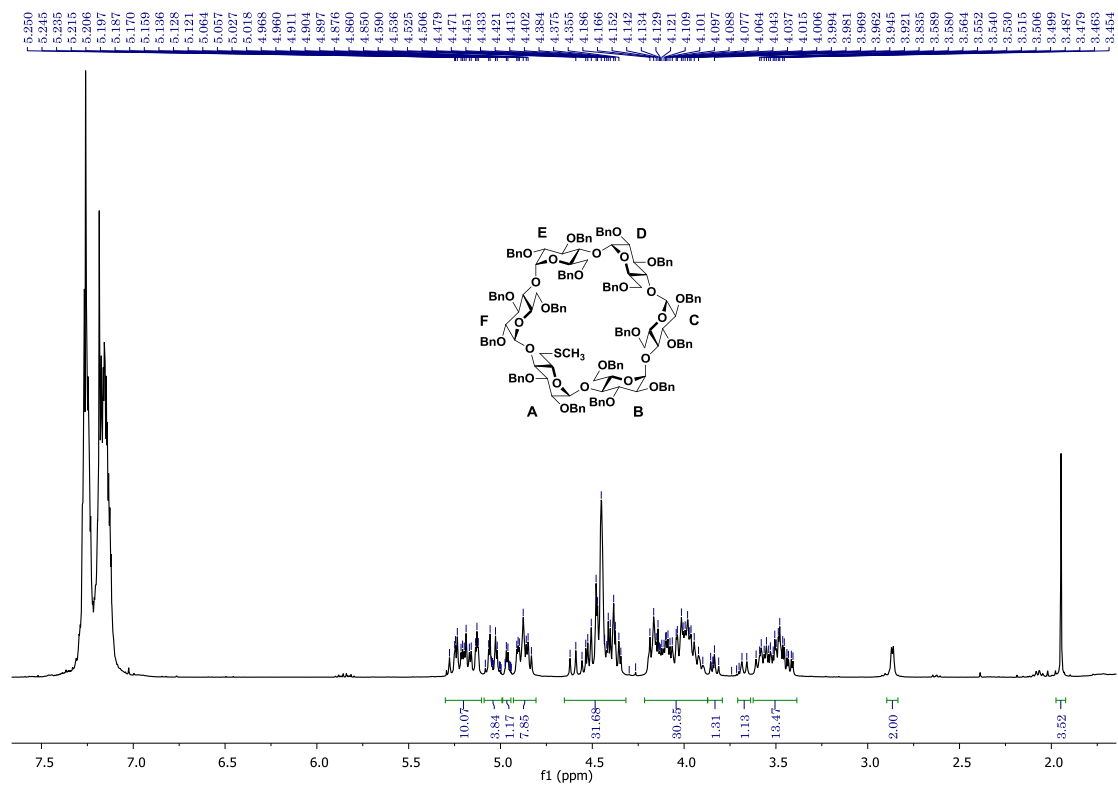
$R_f = 0.67$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.28-7.13 (m, 85H, 85×H-Ar.), 5.27 (d, 1H, <sup>2</sup>J = 11.1 Hz, CHPh), 5.24 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.9 Hz, H-1), 5.22 (d, 1H, <sup>2</sup>J = 11.4 Hz, CHPh), 5.20 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 5.19 (d, 1H, <sup>2</sup>J = 11.0 Hz, CHPh), 5.17 (d, 1H, <sup>2</sup>J = 11.4 Hz, CHPh), 5.13 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1), 5.12 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1), 5.06 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1), 5.04 (d, 1H, <sup>2</sup>J = 11.5 Hz, CHPh), 5.02 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 4.96 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1), 4.91-4.83 (m, 6H, 6×CHPh), 4.62-4.34 (m, 22H, 22×CHPh), 4.19-3.90 (m, 22H, 6×H-3, 5×H-4, 6×H-5, 5×H-6), 3.84 (t, 1H, <sup>3</sup>J<sub>2,3</sub> = <sup>3</sup>J<sub>3,4</sub> = 8.3 Hz, H-4), 3.67 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.5 Hz, H-6), 3.61-3.45 (m, 9H, 5×H-2, 4×H-6), 3.42 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.6 Hz, H-2), 2.87 (d, 2H, 2×H-6), 1.95 (s, 3H, SCH<sub>3</sub>)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.59(3C), 139.56, 139.48, 139.47, 138.64, 138.54, 138.52, 138.49(2C), 138.41(3C), 138.33(3C) (17×C-Ar<sup>quat.</sup>), 128.43-127.00 (85×C-Ar<sup>tert.</sup>), 99.26(2C), 99.19, 98.99, 98.81, 97.90 (6×C-1), 81.96 (C-4), 81.16, 81.08(2C), 81.02, 81.01, 80.91 (6×C-3), 80.22, 80.04, 79.87(2C), 79.73 (5×C-4), 79.69, 79.32, 79.26, 79.20, 78.83, 78.71 (6×C-2), 75.89, 75.81, 75.79, 75.56, 75.53, 75.13, 73.65, 73.51(4C), 73.07, 72.95, 72.91, 72.85, 72.77, 72.68 (17×CH<sub>2</sub>Ph), 71.85, 71.84, 71.67(2C), 71.64, 71.46 (6×C-5), 69.47, 69.38, 69.34(2C), 69.28, 36.77 (6×C-6), 17.15 (SCH<sub>3</sub>)

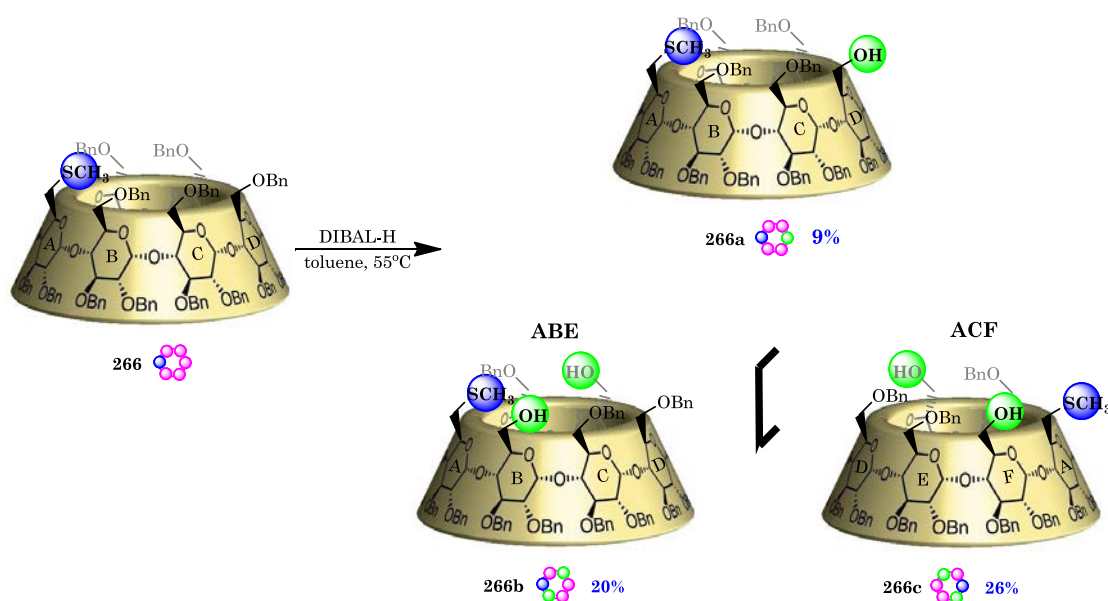
**HRMS (ESI):** Calcd. For C<sub>156</sub>H<sub>164</sub>O<sub>29</sub>SNa [M+Na]<sup>1+</sup>: 2556.0918; Found: 2556.0971 (+2.1 ppm)

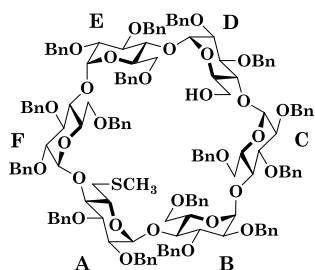
EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-S-Methyl- $\alpha$ -Cyclodextrin (266) was debenzylated by DIBAL-H**

DIBAL-H (1.5 M in toluene, 0.79 mL, 1.18 mmol, 20 eq.) was added to a solution of thiomethyl-cyclodextrin **266** (150 mg, 0.059 mmol, 1 eq.) in toluene (0.39 mL) under nitrogen at r. t.. The reaction mixture was stirred at 55°C with a nitrogen balloon reflux for 30 min, until Mass spectrum indicated formation of diol as a major product, and then cooled to r.t. and poured into ice/water. Aqueous HCl (5 mL, 1 M) and EtOAc (5 mL) were added, and the solution was stirred for 1 h. The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuum*. Silica gel chromatography of the residue (CyH/EtOAc: 4/1) gave mono-debenzylated cyclodextrin **266a** (9%), BE-diol-cyclodextrin **266b** (30 mg, 20%) and CF-diol-cyclodextrin **266c** (35 mg, 26%) as yellowish foams.



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-S-Methyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>-Hexadeca-O-Benzyl- $\alpha$ -Cyclodextrin (266a)**

Potassium carbonate (49 mg, 0.357 mmol, 3 eq.) was added to a solution of thiol-monol-cyclodextrin **263** (290 mg, 0.119 mmol, 1 eq.) in anhydrous DMF (5 mL) under nitrogen at 0°C. Methyl iodide (0.022 mL, 0.357 mmol, 3 eq.) was added, and the reaction mixture was stirred for 2 h at r.t.. Until the TLC showed the reaction finished, Water (10 mL) was added and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash

chromatography of the residue (CyH/EtOAc: 4/1) gave thiomethyl- $\alpha$ -cyclodextrin **266a** (160 mg, 55%) as a yellowish foam.

$\alpha_D = +33.2$  (c 1.0, CHCl<sub>3</sub>)

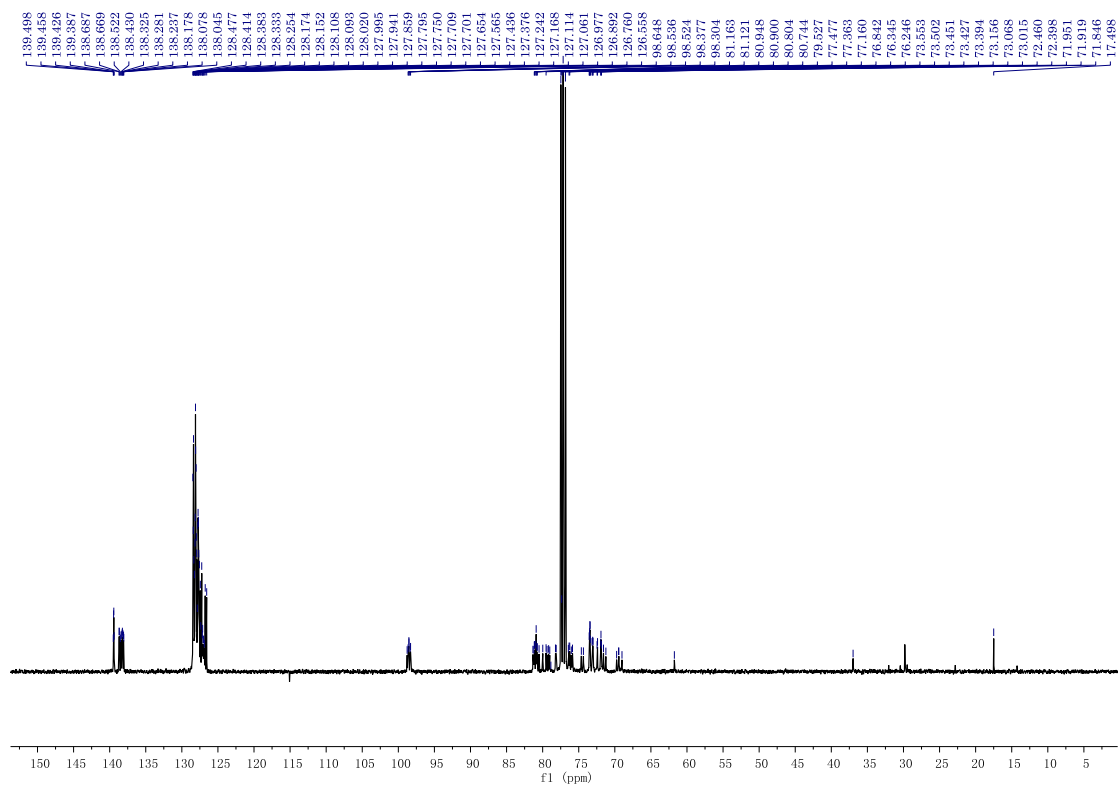
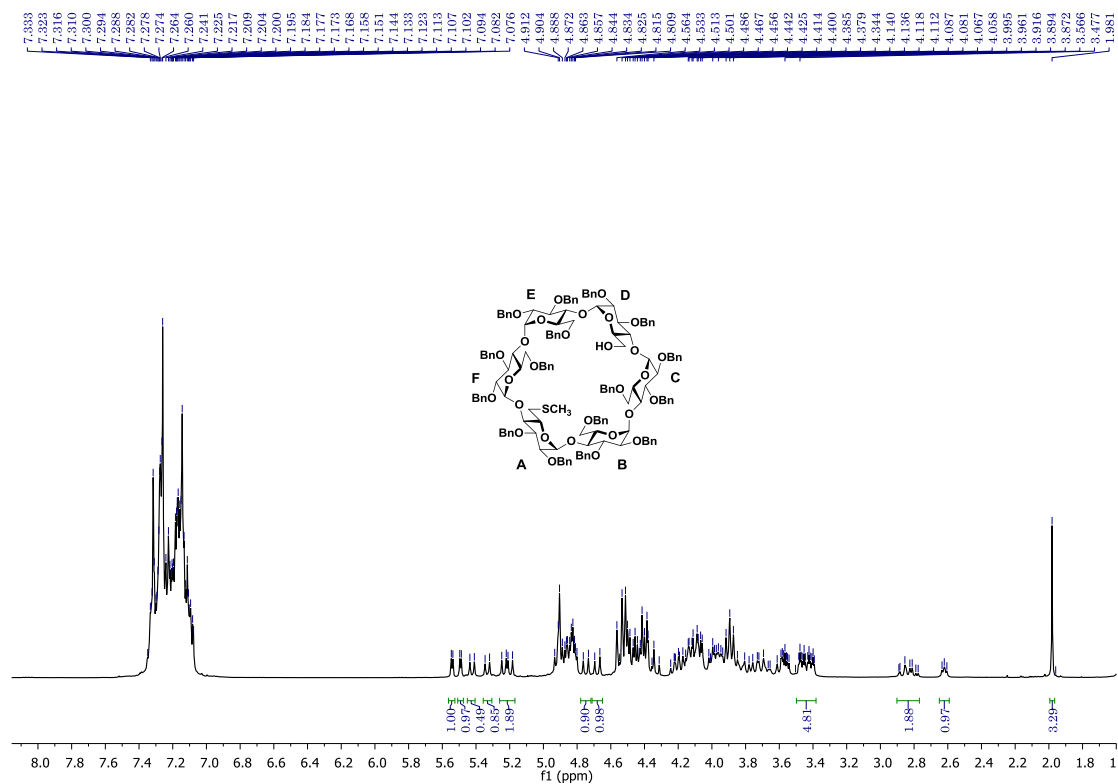
$R_f = 0.47$  (CyH/EtOAc: 4/1)

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.31-7.08 (m, 80H, 80×H-Ar.), 5.54 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 5.49 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 5.42 (d, 1H, <sup>2</sup>J = 10.5 Hz, CHPh), 5.33 (d, 1H, <sup>2</sup>J = 10.8 Hz, CHPh), 5.23 (d, 1H, <sup>2</sup>J = 10.6 Hz, CHPh), 5.19 (d, 1H, <sup>2</sup>J = 10.6 Hz, CHPh), 4.93-4.80 (m, 12H, 4×H-1, 8×CHPh), 4.75 (d, 1H, <sup>2</sup>J = 12.1 Hz, CHPh), 4.68 (d, 1H, <sup>2</sup>J = 12.1 Hz, CHPh), 4.56-4.31 (m, 18H, 18×CHPh), 4.24-4.06 (m, 10H, 6×H-3, H-5, 3×H-6), 4.02-3.65 (m, 17H, 6×H-4, 5×H-5, 6×H-6), 2.61-3.39 (m, 7H, 6×H-2, H-6), 2.89-2.77 (m, 2H, 2×H-6), 2.62 (t, 1H, <sup>2</sup>J = 5.5 Hz, OH), 1.98 (s, 3H, SCH<sub>3</sub>)

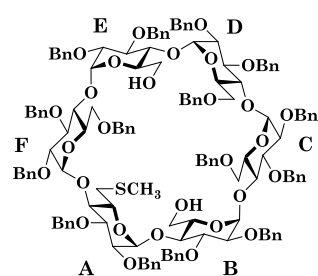
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.50, 139.46(2C), 139.43(2C), 139.39, 138.69, 138.67, 138.52, 138.43, 138.33, 138.28, 138.24, 138.18, 138.08, 138.05 (16×C-Ar<sup>quat</sup>), 128.48-126.56 (80×C-Ar<sup>tert</sup>), 98.78, 98.65, 98.54, 98.53, 98.38, 98.30 (6×C-1), 81.35, 81.21, 81.16 (3×C-4), 81.12, 80.95, 80.90(2C), 80.80, 80.74 (6×C-3), 80.50 (C-4), 79.98 (C-2), 79.53 (C-4), 79.39, 79.17, 79.02, 78.22, 78.12 (5×C-2), 76.44 (C-4), 76.35, 76.25, 76.03, 75.86, 74.64, 74.35, 73.55, 73.50, 73.45, 73.43, 73.39, 73.16, 73.07, 73.02, 72.46, 72.40 (16×CH<sub>2</sub>Ph), 71.95, 71.92(2C), 71.85, 71.57, 71.24 (6×C-5), 69.75, 69.48, 69.44, 69.00, 61.75, 36.98 (6×C-6), 17.50 (SCH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>149</sub>H<sub>158</sub>O<sub>29</sub>SNa [M+Na]<sup>1+</sup>: 2466.0484; Found: 2466.0502 (+0.7 ppm)

EXPERIMENTAL PART





**6<sup>A</sup>-Deoxy-6<sup>A</sup>-S-Methyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>F</sup>-Pentadeca-O-Benzyl- $\alpha$ -Cyclodextrin (266b)**

$\alpha_D = +53.8$  (c 0.1, CHCl<sub>3</sub>)

$R_f = 0.27$  (CyH/EtOAc: 3/1)

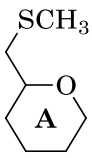
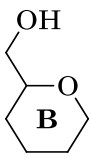
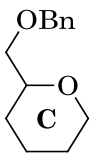
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.30-7.05 (m, 75H, 75×H-Ar.), 5.68 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.9 Hz, H-1D), 5.52 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.9 Hz, H-1A), 5.41 (t, 2H, <sup>2</sup>J = 10.4 Hz, 2×CHPh), 5.16 (t, 2H, <sup>2</sup>J = 10.4 Hz, 2×CHPh), 4.89 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh), 4.87 (d, 1H, <sup>2</sup>J = 11.1 Hz, CHPh), 4.83 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 4.81 (d, 1H, <sup>2</sup>J = 10.5 Hz, CHPh), 4.80

(d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1F), 4.77-4.73 (m, 4H, 4×CHPh), 4.72 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1C), 4.70 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1B), 4.69 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1E), 4.62-4.28 (m, 18H, 18×CHPh), 4.21-4.17 (m, 2H, H-3A, H-3D), 4.10-4.06 (m, 2H, H-3E, H-3B), 4.04-3.91 (m, 10H, H-3C, H-3F, H-5A, H-5B, H-5C, H-5D, H-5E, H-5F, H-4D, H-6F), 3.88-3.64 (m, 14H, H-4A, H-4B, H-4C, H-4E, H-4F, 2×H-6B, 2×H-6C, 2×H-6D, 2×H-6E, H-6F), 3.56 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.6 Hz, H-2D), 3.53 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.8 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.6 Hz, H-2A), 3.46 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.8 Hz, H-2F), 3.41-3.37 (m, 3H, H-2B, H-2C, H-2E), 3.06-2.96 (m, 2H, 2×H-6A), 2.10 (s, 3H, SCH<sub>3</sub>)

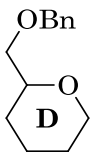
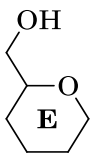
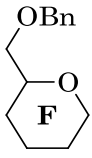
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  149.44, 139.41, 139.40(2C), 139.32, 139.28, 138.74(2C), 138.41, 138.39, 138.14(2C), 138.11, 137.97, 137.87 (15×C-Ar<sup>quat.</sup>), 128.53-126.47 (75×C-Ar<sup>tert.</sup>), 98.47, 98.35, 98.11, 97.96, 97.87, 97.64 (C-1E, C-1B, C-1D, C-1F, C-1C, C-1A), 83.77, 81.86 (C-4A, C-4C), 81.77(2C) (C-4F, C-3B), 81.66, 81.18 (C-3E, C-3D), 81.08 (C-4D), 80.78, 80.73, 80.61 (C-3A, C-3C, C-3F), 79.99, 79.89, 79.24, 79.19, 77.91(2C) (C-2E, C-2B, C-2C, C-2F, C-2D, C-2A), 76.59, 76.54, 76.16, 76.07 (4×CH<sub>2</sub>Ph), 75.01, 74.92 (C-4B, C-4E), 74.27, 74.11, 73.57(2C), 73.55, 73.50, 74.48, 73.34, 73.13 (9×CH<sub>2</sub>Ph), 72.85 (C-5A), 72.51, 72.38 (2×CH<sub>2</sub>Ph), 72.16, 72.13, 71.79, 71.48, 71.42 (C-5C, C-5B, C-5D, C-5E, C-5F), 69.95, 69.67, 69.55, 62.18, 62.07, 36.75 (C-6C, C-6D, C-6F, C-6B, C-6E, C-6A), 17.42 (SCH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>142</sub>H<sub>152</sub>O<sub>29</sub>SNa [M+Na]<sup>1+</sup>: 2376.0168; Found: 2376.0032 (-5.7 ppm)

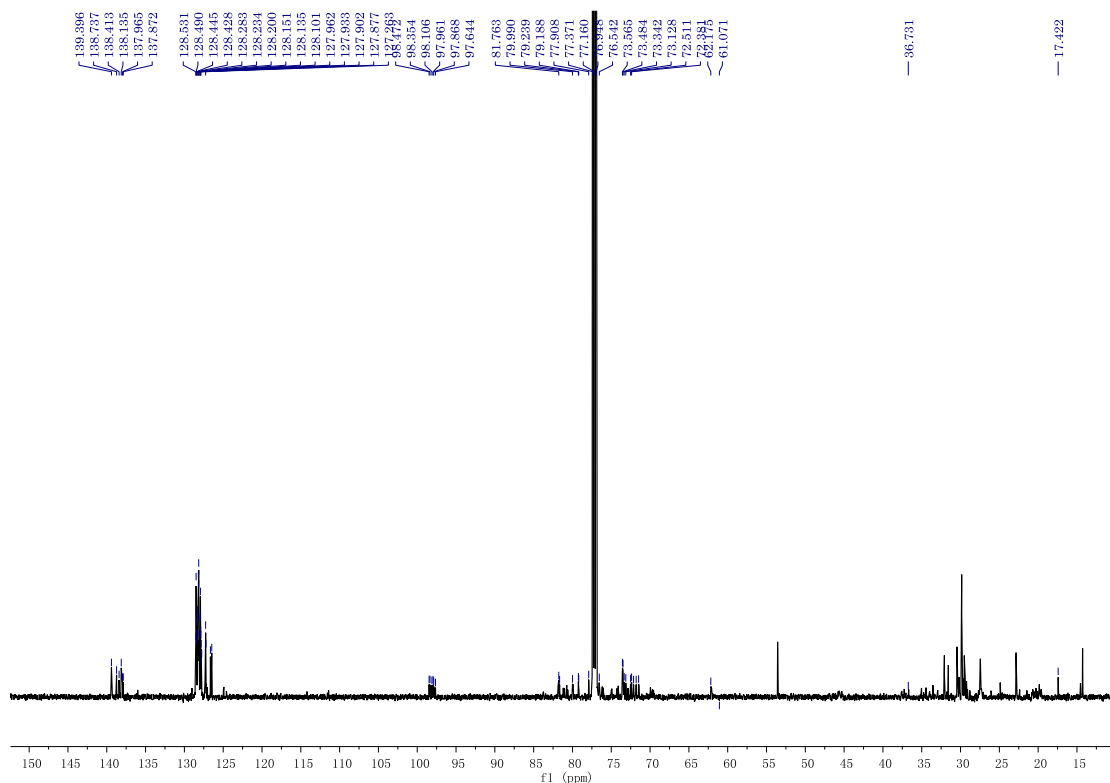
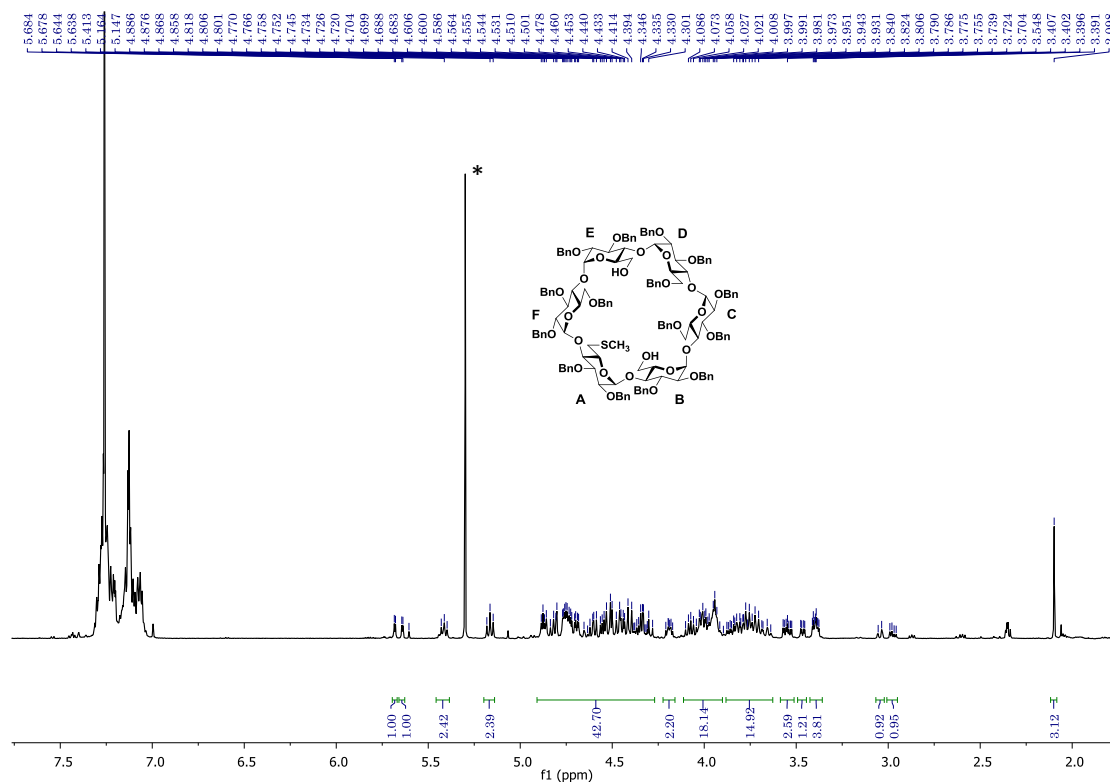
**EXPERIMENTAL PART**

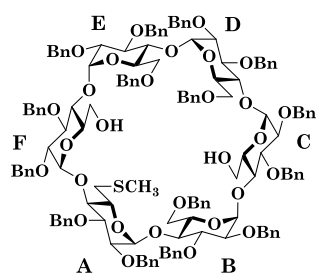
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>A</b></p>	H-1A	5.641	NOE: 3.784 ppm	H-4B
	C-1A	97.644		
	H-2A	3.536		
	C-2A	77.908		
	H-3A	4.192		
	C-3A	80.785		
	H-4A	3.819	NOE: 4.802 ppm	H-1F
	C-4A	83.756		
	H-5A	4.023		
	C-5A	72.851		
	H-6A	3.046		
		2.973		
C-6A	36.705			
 <p style="text-align: center;"><b>B</b></p>	H-1B	4.702	NOE: 3.737 ppm	H-4C
	C-1B	98.354		
	H-2B	3.398		
	C-2B	79.898		
	H-3B	4.057		
	C-3B	81.770		
	H-4B	3.784	NOE: 5.641 ppm	H-1A
	C-4B	75.013		
	H-5B	3.968		
	C-5B	72.125		
	H-6B	3.723		
		3.705		
C-6B	62.169			
 <p style="text-align: center;"><b>C</b></p>	H-1C	4.723	NOE: 3.935 ppm	H-4D
	C-1C	97.868		
	H-2C	3.403		
	C-2C	79.239		
	H-3C	4.011		
	C-3C	80.729		
	H-4C	3.737	NOE: 4.702 ppm	H-1B
	C-4C	81.859		
	H-5C	3.978		
	C-5C	72.161		
	H-6C	3.771		
		3.854		
C-6C	69.952			

**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	5.680	NOE: 3.828 ppm	H-4E
	C-1D	98.106		
	H-2D	3.560		
	C-2D	77.908		
	H-3D	4.180		
	C-3D	81.180		
	H-4D	3.935	NOE: 4.723 ppm	H-1C
	C-4D	81.085		
	H-5D	3.947		
	C-5D	71.790		
	H-6D	3.723		
		3.705		
C-6D	69.665			
	H-1E	4.685	NOE: 3.787 ppm	H-4F
	C-1E	98.472		
	H-2E	3.388		
	C-2E	79.990		
	H-3E	4.086		
	C-3E	81.656		
	H-4E	3.828	NOE: 5.680 ppm	H-1D
	C-4E	74.922		
	H-5E	3.947		
	C-5E	71.479		
	H-6E	3.684		
		3.655		
C-6E	62.063			
	H-1F	4.802	NOE: 3.819 ppm	H-4A
	C-1F	97.961		
	H-2F	3.465		
	C-2F	79.188		
	H-3F	4.007		
	C-3F	80.609		
	H-4F	3.787	NOE: 4.685 ppm	H-1E
	C-4F	81.763		
	H-5F	3.936		
	C-5F	71.418		
	H-6F	3.994		
		3.768		
C-6F	69.546			

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-S-Methyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>D</sup>,6<sup>E</sup>-Pentadeca-O-Benzyl- $\alpha$ -Cyclodextrin (266c)**

$\alpha_D = +86.1$  (c 0.1, CHCl<sub>3</sub>)

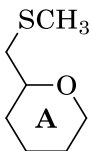
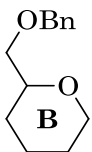
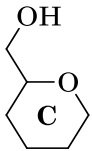
$R_f = 0.17$  (CyH/EtOAc: 3/1)

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.31-7.05 (m, 75H, 75×H-Ar.), 5.74 (d, 1H,  $^3J_{1,2} = 3.8$  Hz, H-1B), 5.69 (d, 1H,  $^3J_{1,2} = 3.8$  Hz, H-1E), 5.42 (d, 2H,  $^2J = 10.5$  Hz, 2×CHPh), 5.17 (d, 1H,  $^2J = 10.7$  Hz, CHPh), 5.17 (d, 1H,  $^2J = 10.4$  Hz, CHPh), 4.89-4.87 (m, 4H, 4×CHPh), 4.79-4.72 (m, 8H, H-1F, 7×CHPh), 4.70 (d, 1H,  $^3J_{1,2} = 3.2$  Hz, H-1D), 4.67 (d, 1H,  $^3J_{1,2} = 3.2$  Hz, H-1C), 4.65 (d, 1H,  $^2J = 12.0$  Hz, CHPh), 4.63 (d, 1H,  $^3J_{1,2} = 3.0$  Hz, H-1A), 4.55-4.30 (m, 14H, 14×CHPh), 4.21-4.17 (m, 2H, H-3B, H-3E), 4.12-4.07 (m, 2H, H-3F, H-3C), 4.03-3.89 (m, 14H, H-3D, H-3A, H-4B, H-4C, H-4E, H-4F, H-5A, H-5B, H-5C, H-5D, H-5E, H-5F, H-6B, H-6E), 3.87-3.64 (m, 10H, H-4A, H-4D, H-6B, 2×H-6C, 2×H-6D, H-6E, 2×H-6F), 3.57-3.55 (m, 2H, H-2E, H-2B), 3.47 (dd, 1H,  $^3J_{1,2} = 3.5$  Hz,  $^3J_{2,3} = 9.7$  Hz, H-2F), 3.42-3.36 (m, 3H, H-2C, H-2D, H-2A), 3.06-2.96 (m, 2H, 2×H-6A), 2.01 (s, 3H, SCH<sub>3</sub>)

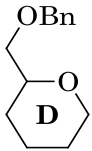
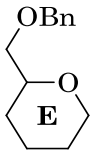
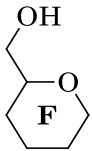
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.40, 139.38, 139.35(2C), 139.33(2C), 138.70, 138.66, 138.41, 138.38, 138.08(2C), 138.03(2C), 137.70 (15×C-Ar<sup>quat.</sup>), 128.52-126.45 (75×C-Ar<sup>tert.</sup>), 98.58, 98.47, 98.02, 97.98, 97.82, 97.58 (C-1C, C-1F, C-1B, C-1E, C-1D, C-1A), 84.59, 82.15 (C-4A, C-4D), 81.76, 81.74 (C-3F, C-3C), 81.31, 81.30 (C-4B, C-4C), 81.00, 80.90, 80.72, 80.47 (C-3B, C-3E, C-3D, C-3A), 79.98, 79.96, 79.46, 79.18, 77.87, 77.84 (C-2C, C-2F, C-2A, C-2D, C-2E, C-2B), 76.56, 76.53, 76.26, 76.23 (4×CH<sub>2</sub>Ph), 74.35 (C-4E), 74.21 (CH<sub>2</sub>Ph), 74.15 (C-4F), 74.10 (CH<sub>2</sub>Ph), 73.63, 73.58, 73.53, 73.52, 73.49, 73.14, 73.08 (7×CH<sub>2</sub>Ph), 72.70 (C-5A), 72.64, 72.50 (2×CH<sub>2</sub>Ph), 72.28, 71.92, 71.82, 71.54, 71.38 (C-5C, C-5D, C-5B, C-5E, C-5F), 70.02, 69.68, 69.60, 61.91, 61.52, 36.99 (C-6D, C-6B, C-6E, C-6C, C-6F, C-6A), 17.25 (SCH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>142</sub>H<sub>152</sub>O<sub>29</sub>SNa [M+Na]<sup>1+</sup>: 2376.0015; Found: 2376.0032 (+0.7 ppm)

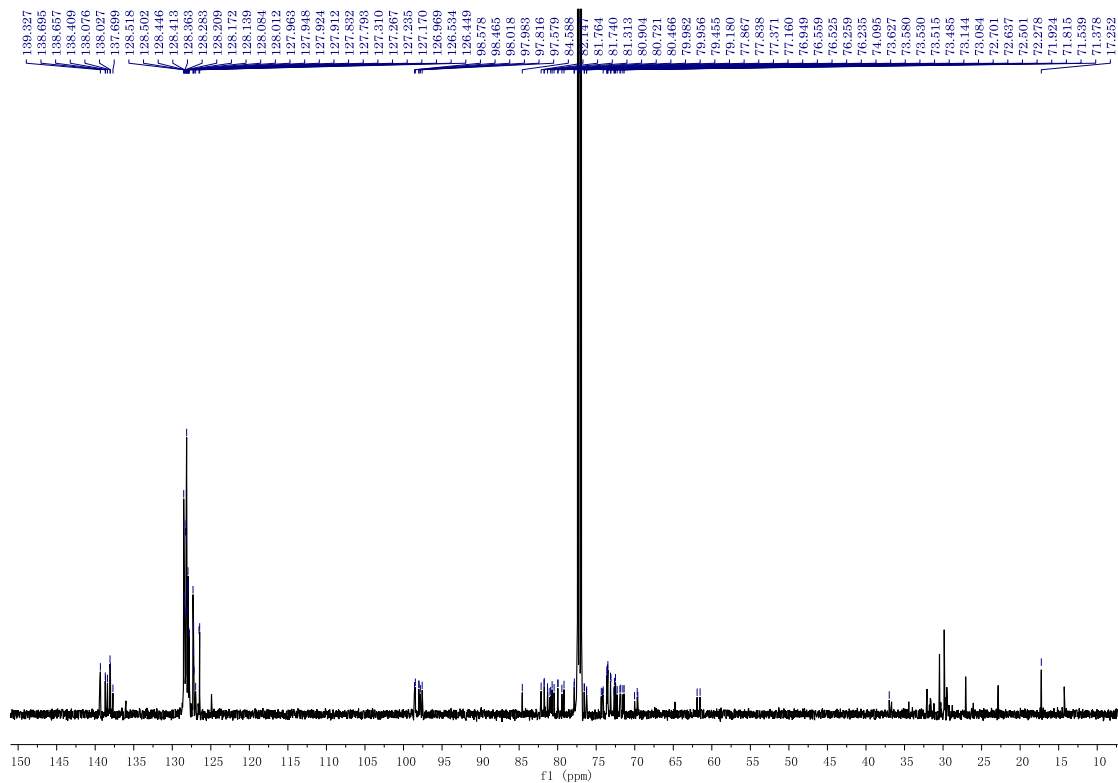
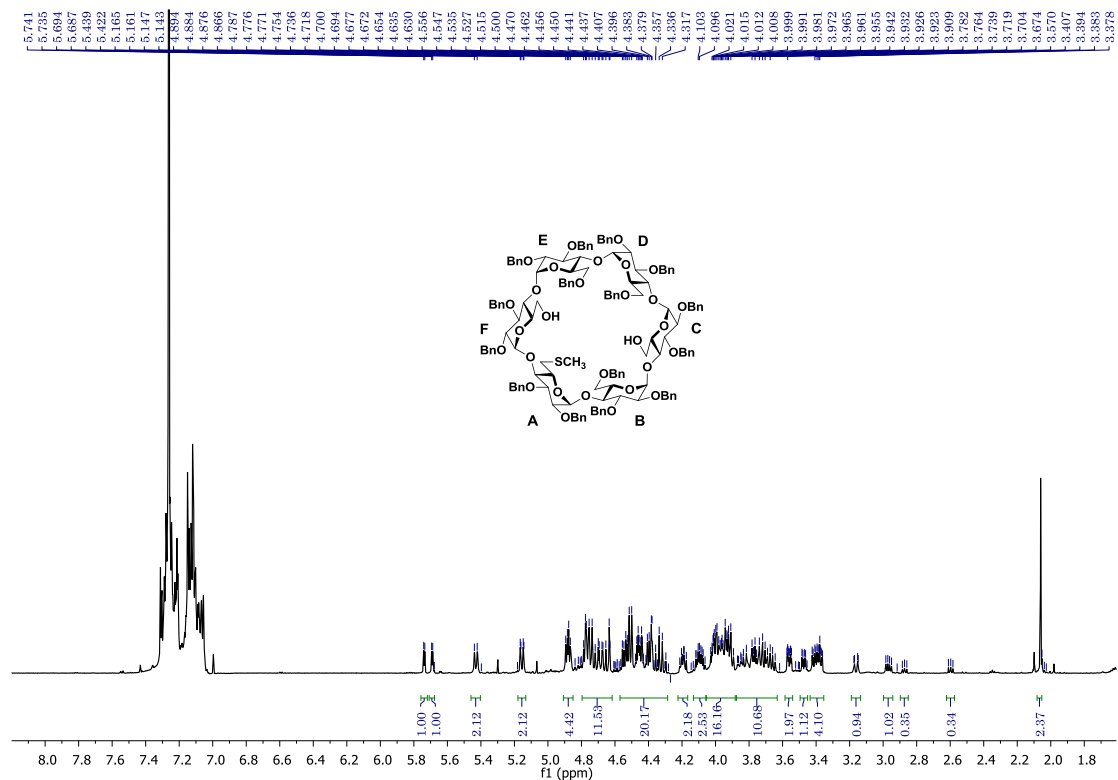
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>A</b></p>	H-1A	4.633	NOE: 3.940 ppm	H-4B
	C-1A	97.597		
	H-2A	3.371		
	C-2A	79.455		
	H-3A	4.001		
	C-3A	80.466		
	H-4A	3.707	NOE: 4.774 ppm	H-1F
	C-4A	84.588		
	H-5A	3.999		
	C-5A	72.701		
	H-6A	3.161		
		2.972		
C-6A	36.987			
 <p style="text-align: center;"><b>B</b></p>	H-1B	5.738	NOE: 3.913 ppm	H-4C
	C-1B	98.018		
	H-2B	3.558		
	C-2B	77.838		
	H-3B	4.198		
	C-3B	81.000		
	H-4B	3.940	NOE: 4.633 ppm	H-1A
	C-4B	81.313		
	H-5B	3.939		
	C-5B	71.815		
	H-6B	3.771		
		3.984		
C-6B	69.679			
 <p style="text-align: center;"><b>C</b></p>	H-1C	4.674	NOE: 3.659 ppm	H-4D
	C-1C	98.578		
	H-2C	3.411		
	C-2C	79.782		
	H-3C	4.100		
	C-3C	81.740		
	H-4C	3.913	NOE: 5.738 ppm	H-1B
	C-4C	81.295		
	H-5C	3.919		
	C-5C	72.278		
	H-6C	3.856		
		3.730		
C-6C	61.903			

**EXPERIMENTAL PART**

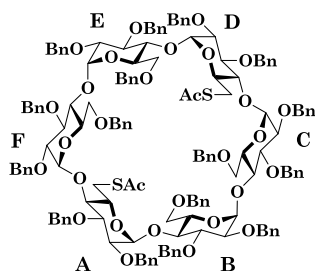
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	4.697	NOE: 3.911 ppm	H-4E
	C-1D	97.816		
	H-2D	3.383		
	C-2D	79.180		
	H-3D	4.015		
	C-3D	80.721		
	H-4D	3.659	NOE: 4.674 ppm	H-1C
	C-4D	82.147		
	H-5D	3.922		
	C-5D	71.924		
	H-6D	3.822		
		3.772		
C-6D	70.022			
	H-1E	5.691	NOE: 3.913 ppm	H-4F
	C-1E	97.983		
	H-2E	3.561		
	C-2E	77.867		
	H-3E	4.185		
	C-3E	80.904		
	H-4E	3.911	NOE: 4.697 ppm	H-1D
	C-4E	74.345		
	H-5E	3.952		
	C-5E	71.539		
	H-6E	3.727		
		4.002		
C-6E	69.597			
	H-1F	4.774	NOE: 3.707 ppm	H-4A
	C-1F	98.465		
	H-2F	3.473		
	C-2F	79.956		
	H-3F	4.105		
	C-3F	81.764		
	H-4F	3.913	NOE: 5.691 ppm	H-1E
	C-4F	74.146		
	H-5F	3.962		
	C-5F	71.378		
	H-6F	3.795		
		3.690		
C-6F	61.519			

EXPERIMENTAL PART





**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>,6<sup>D</sup>-Di-S-Acetyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>-Hexadeca-O-Benzyl- $\alpha$ -Cyclodextrin (268)**



Mesylated cyclodextrin **267** (0.99 g, 0.385 mmol, 1 eq.) was dissolved in anhydrous DMF (20 mL) under nitrogen. Potassium thioacetate (264 mg, 2.31 mmol, 6 eq.) was added at r.t.. The reaction mixture was stirred overnight at 50°C. Water (50 mL) was added and the aqueous layer was washed with EtOAc (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 5/1) gave thioacetate- $\alpha$ -cyclodextrin **268** (0.828 g,

84%) as a yellowish foam.

$\alpha_D = +38.8$  (c 1.0, CHCl<sub>3</sub>)

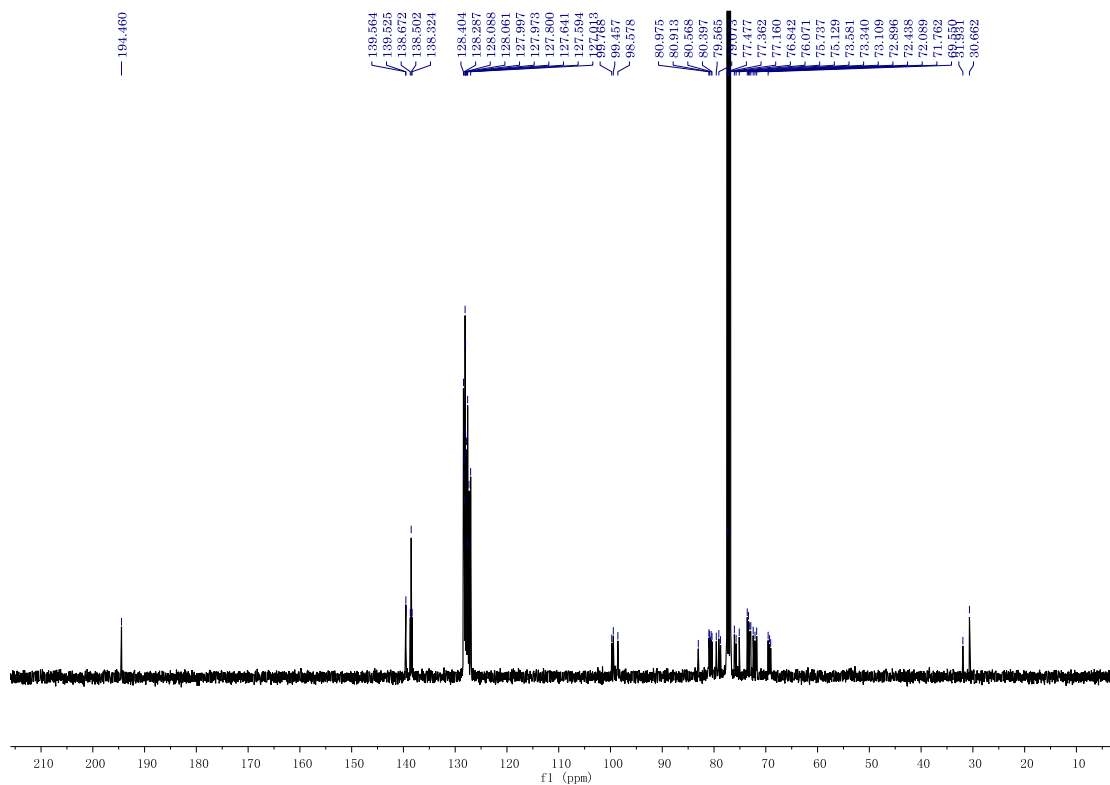
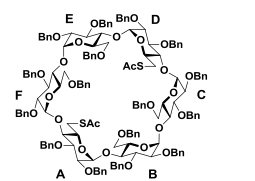
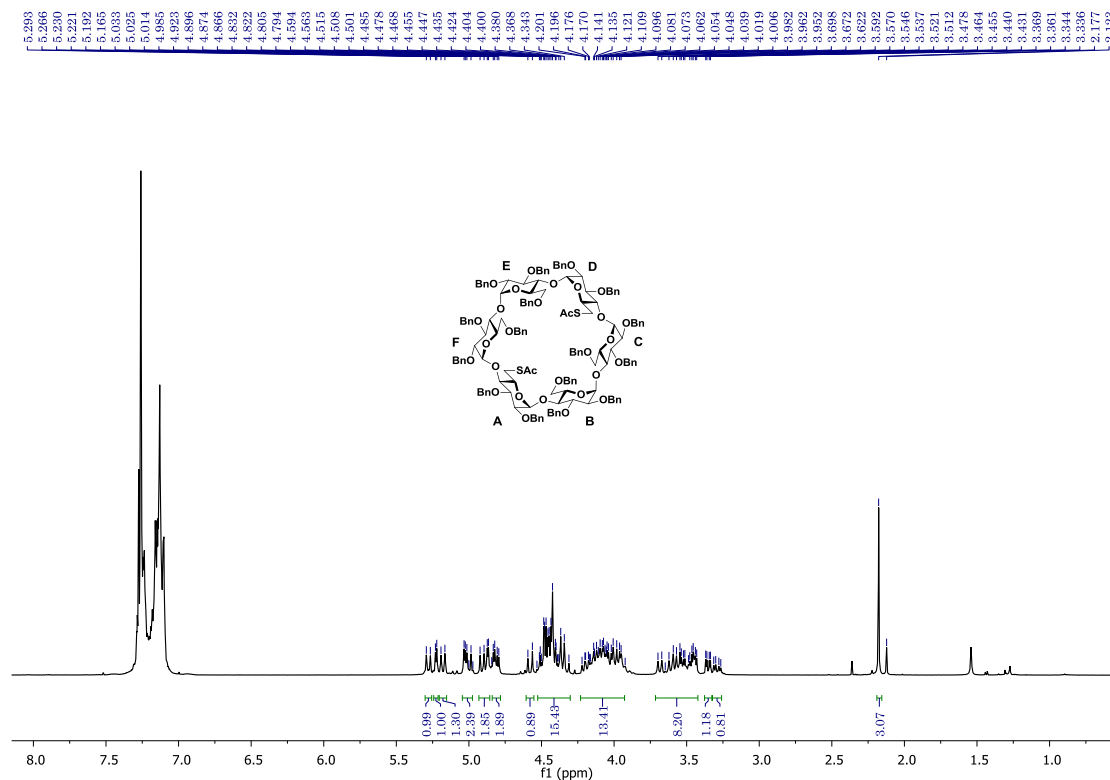
$R_f = 0.50$  (CyH/EtOAc: 3/1)

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.28-7.10 (m, 40H, 40×H-Ar.), 5.28 (d, 1H, <sup>2</sup> $J$ =11.2 Hz, CHPh), 5.23 (d, 1H, <sup>3</sup> $J_{1,2}$ =3.7 Hz, H-1), 5.18 (d, 1H, <sup>2</sup> $J$ =10.7 Hz, CHPh), 5.03 (d, 1H, <sup>3</sup> $J_{1,2}$ =3.4 Hz, H-1), 5.00 (d, 1H, <sup>2</sup> $J$ =11.5 Hz, CHPh), 4.91 (d, 1H, <sup>2</sup> $J$ =11.0 Hz, CHPh), 4.87 (d, 1H, <sup>3</sup> $J_{1,2}$ =3.2 Hz, H-1), 4.82 (d, 1H, <sup>2</sup> $J$ =11.2 Hz, CHPh), 4.81 (d, 1H, <sup>2</sup> $J$ =11.2 Hz, CHPh), 4.58 (d, 1H, <sup>2</sup> $J$ =12.0 Hz, CHPh), 4.51-4.31 (m, 9H, 9×CHPh), 4.14-3.95 (m, 10H, 3×H-3, 2×H-4, 3×H-5, 2×H-6), 3.69 (d, 1H, <sup>2</sup> $J_{6,6'}$ =10.5 Hz, H-6), 3.61 (d, 1H, <sup>2</sup> $J_{6,6'}$ =10.7 Hz, H-6), 3.59-3.43 (m, 4H, 2×H-2, H-4, H-6), 3.35 (dd, 1H, <sup>3</sup> $J_{1,2}$ =3.2 Hz, <sup>3</sup> $J_{2,3}$ =9.7 Hz, H-2), 3.29 (dd, 1H, <sup>3</sup> $J_{5,6}$ =5.3 Hz, <sup>2</sup> $J_{6,6'}$ =13.6 Hz, H-6), 2.18 (s, 3H, SC(O)CH<sub>3</sub>)

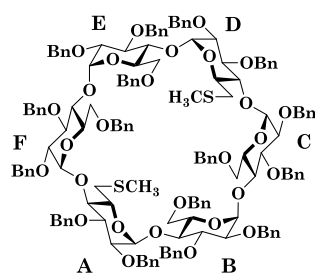
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  194.46 (SC(O)CH<sub>3</sub>),  $\delta$  139.56, 139.55, 139.53, 138.67, 138.51, 138.50(2C), 138.32 (8×C-Ar<sup>quat.</sup>), 128.40-127.01 (40×C-Ar<sup>tert.</sup>), 99.76, 99.46, 98.58 (3×C-1), 83.04 (C-4), 80.98, 80.91, 80.67 (3×C-3), 80.57, 80.40 (2×C-4), 79.57, 79.07, 78.74 (3×C-2), 76.07, 75.74, 75.13, 73.58, 73.34, 73.11, 72.90, 72.44 (8×CH<sub>2</sub>Ph), 72.09, 71.76, 69.55 (3×C-5), 69.27, 69.06, 31.93 (3×C-6), 30.66 (SC(O)CH<sub>3</sub>)

**HRMS (ESI)**: Calcd. For C<sub>152</sub>H<sub>160</sub>O<sub>30</sub>S<sub>2</sub>Na [M+Na]<sup>1+</sup>: 2552.0452; Found: 2552.0328 (-4.9 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>,6<sup>D</sup>-Di-S-Methyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>-Hexadeca-O-Benzyl- $\alpha$ -Cyclodextrin (269)**



**Method I:** The di-*O*-methylsulfonyl-cyclodextrin **267** (400 mg, 0.156 mmol, 1 eq.) was dissolved in anhydrous DMF (5 mL) under nitrogen. Sodium methanethiolate (66 mg, 0.936 mmol, 6 eq.) was added at r.t.. The reaction mixture was stirred for 1h30 at 50°C. EtOAc (20 mL) was added and the organic layer was washed with brine (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 4/1) gave

thiomethyl- $\alpha$ -cyclodextrin **269** (355 mg, 92%) as a yellowish foam.

**Method II:** The thioacetate-cyclodextrin **268** (500 mg, 0.198 mmol, 1 eq.) was dissolved in anhydrous DMF (10 mL) under nitrogen. Sodium hydride (60% in mineral oil, 119 mg, 2.97 mmol, 15 eq.) was added at 70°C. The reaction mixture was stirred for 30 min. Methyl iodide (0.185 mL, 2.97 mmol, 15 eq.) was added and the reaction mixture was stirred at r.t. overnight. The reaction was quenched with water (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 5/1) gave thiomethyl- $\alpha$ -cyclodextrin **269** (350 mg, 71%) as a yellowish foam.

$\alpha_D = +42.2$  (c 1.0, CHCl<sub>3</sub>)

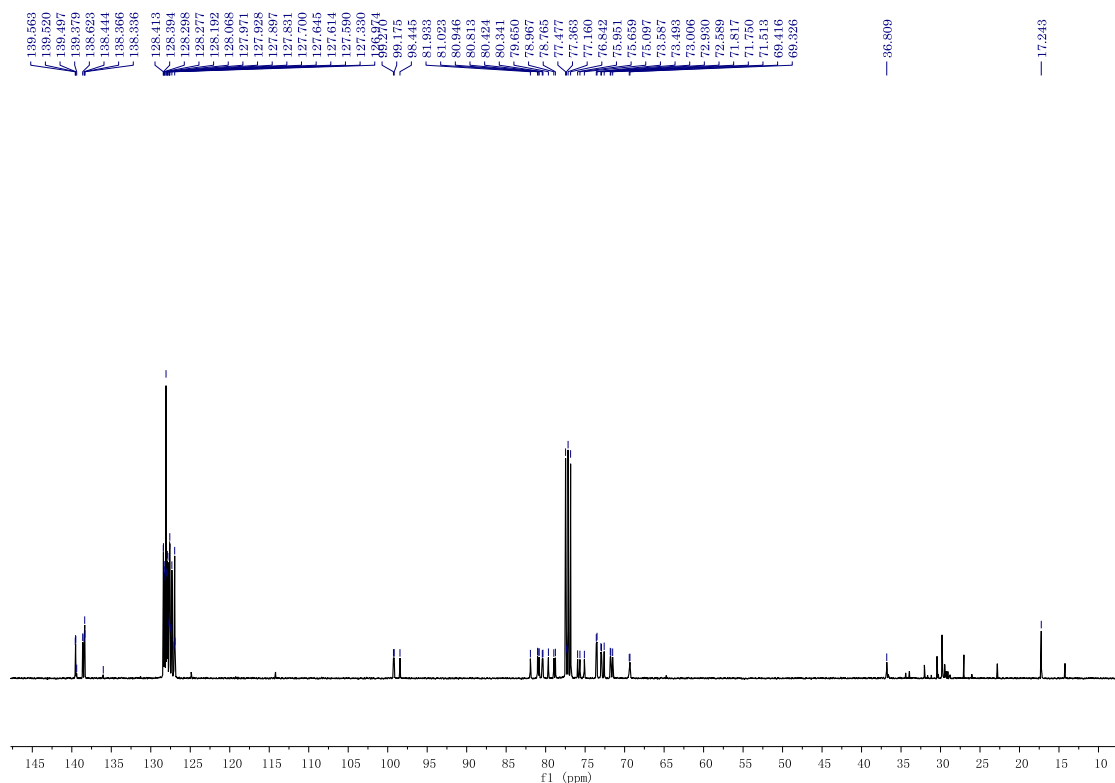
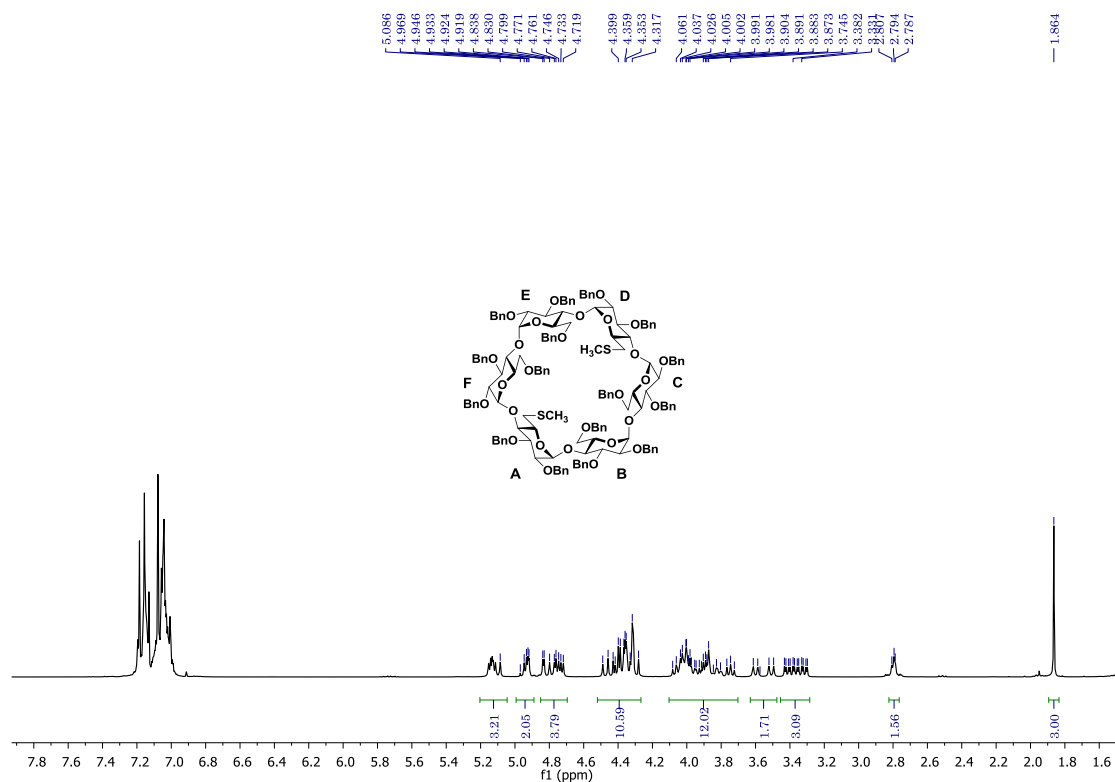
$R_f = 0.47$  (CyH/EtOAc: 3/1)

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.18-7.06 (m, 40H, 40×H-Ar.), 5.15 (d, 1H, <sup>2</sup> $J$ =10.6 Hz, CHPh), 5.14 (d, 1H, <sup>3</sup> $J_{1,2}$ =3.7 Hz, H-1), 5.11 (d, 1H, <sup>2</sup> $J$ =10.8 Hz, CHPh), 4.95 (d, 1H, <sup>2</sup> $J$ =11.1 Hz, CHPh), 4.93 (d, 1H, <sup>3</sup> $J_{1,2}$ =3.7 Hz, H-1), 4.83 (d, 1H, <sup>3</sup> $J_{1,2}$ =3.3 Hz, H-1), 4.78 (d, 1H, <sup>2</sup> $J$ =11.2 Hz, CHPh), 4.76 (d, 1H, <sup>2</sup> $J$ =11.2 Hz, CHPh), 4.74 (d, 1H, <sup>2</sup> $J$ =10.8 Hz, CHPh), 4.46 (t, 2H, <sup>2</sup> $J$ =11.5 Hz, 2×CHPh), 4.42-4.28 (m, 8H, 8×CHPh), 4.08-3.80 (m, 10H, 3×H-3, 2×H-4, 3×H-5, 2×H-6), 3.75 (t, 1H, <sup>3</sup> $J_{2,3}$ =<sup>3</sup> $J_{3,4}$ =9.0 Hz, H-4), 3.60 (d, 1H, <sup>2</sup> $J_{6,6'}$ =10.3 Hz, H-6), 3.51 (d, 1H, <sup>2</sup> $J_{6,6'}$ =11.0 Hz, H-6), 3.42 (dd, 1H, <sup>3</sup> $J_{1,2}$ =3.4 Hz, <sup>3</sup> $J_{2,3}$ =9.7 Hz, H-2), 3.37 (dd, 1H, <sup>3</sup> $J_{1,2}$ =3.4 Hz, <sup>3</sup> $J_{2,3}$ =9.7 Hz, H-2), 3.31 (dd, 1H, <sup>3</sup> $J_{1,2}$ =3.4 Hz, <sup>3</sup> $J_{2,3}$ =9.9 Hz, H-2), 2.81-2.79 (m, 2H, 2×H-6), 1.86 (s, 3H, SCH<sub>3</sub>)

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.56, 139.52, 139.50, 138.62, 138.44, 138.37, 138.33 (8×C-Ar<sup>quat.</sup>), 128.41-126.93 (40×C-Ar<sup>tert.</sup>), 99.27, 99.18, 98.45 (3×C-1), 81.93 (C-4), 81.02, 80.95, 80.81 (3×C-3), 80.42, 80.34 (2×C-4), 79.65, 78.97, 78.76 (3×C-2), 75.95, 75.66, 75.10, 73.58, 73.49, 73.00, 72.93, 72.06 (8×CH<sub>2</sub>Ph), 71.82, 71.75, 71.51 (3×C-5), 69.42, 69.33, 36.80 (3×C-6), 17.24 (SCH<sub>3</sub>)

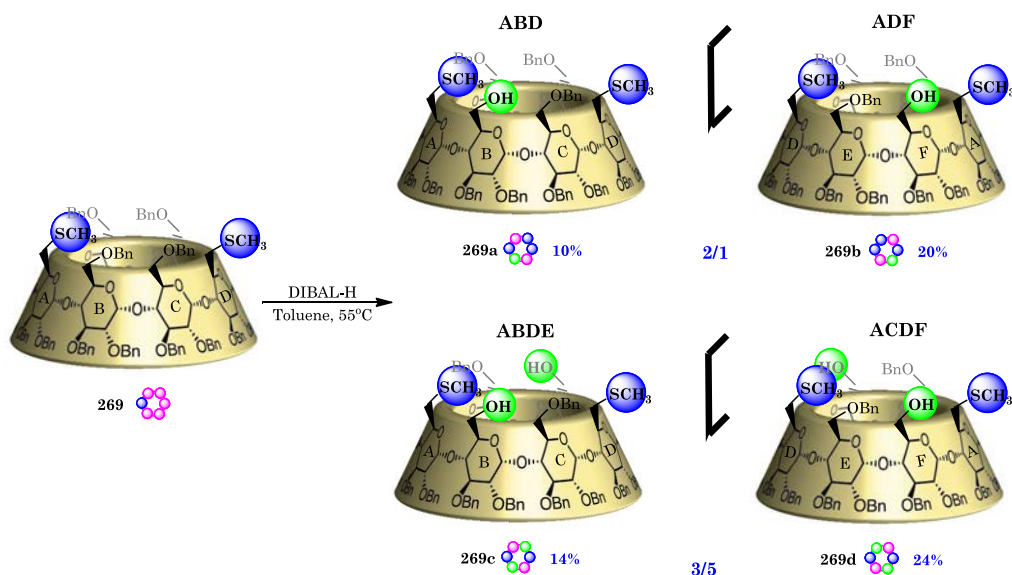
**HRMS (ESI):** Calcd. For C<sub>150</sub>H<sub>160</sub>O<sub>28</sub>S<sub>2</sub>Na [M+Na]<sup>1+</sup>: 2496.0484; Found: 2496.0430 (-2.2 ppm)

EXPERIMENTAL PART

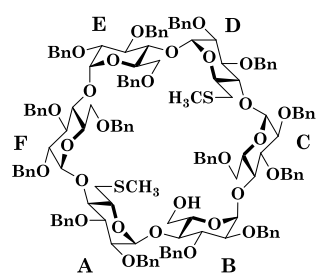


**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>,6<sup>D</sup>-Di-S-Methyl- $\alpha$ -Cyclodextrin (269)**  
was debenzylated by DIBAL-H

DIBAL-H (1.5 M in toluene, 2.1 mL, 3.23 mmol, 20 eq.) was added to a solution of cyclodextrin **269** (400 mg, 0.162 mmol, 1 eq.) in toluene (1.1 mL) under nitrogen at r. t. The reaction mixture was stirred at 55°C with a nitrogen balloon reflux for 10 min, until Mass spectrum indicated formation of diol as a major product, and then cooled to r.t. and poured into ice/water. Aqueous HCl (15 mL, 1 M) and EtOAc (15 mL) were added, and the solution was stirred for 1 h. The aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Silica gel chromatography of the residue (CyH/EtOAc: 3.5/1, then 3/1) gave two monodebenzylated cyclodextrins **269a** (40 mg, 10%) and **269b** (80 mg, 20%), two diol-cyclodextrins **269c** (53 mg, 14%) and **269d** (87 mg, 24%) as yellowish foams.



**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>,6<sup>D</sup>-Di-S-Methyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>-Pentadeca-  
O-Benzyl- $\alpha$ -Cyclodextrin (269a)**



$\alpha_D = +47.0$  (c 1.0, CHCl<sub>3</sub>)

$R_f = 0.40$  (CyH/EtOAc: 3/1)

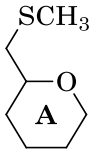
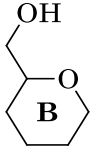
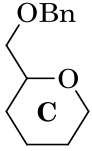
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.30-7.11 (m, 75H, 75×H-Ar.), 5.34 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, H-1A), 5.25 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1D), 5.24 (d, 1H, <sup>2</sup>J = 10.1 Hz, CHPh), 5.23 (bd, 2H, <sup>2</sup>J = 10.91.1 Hz, 2×CHPh), 5.20 (d, 1H, <sup>2</sup>J = 11.0 Hz, CHPh), 5.11 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1E), 5.02 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1F), 5.00 (d, 1H, <sup>2</sup>J = 11.6 Hz, CHPh),

4.93 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh), 4.89-4.80 (m, 7H, H-1B, 6×CHPh), 4.67-4.38 (m, 18H, 18×CHPh), 4.19-4.01 (m, 13H, H-6E, H-3A, H-3D, H-3E, H-3C, H-3F, H-5A, H-3B, H-5D, H-4C, H-6F, H-5C, H-6C), 3.97-3.89 (m, 7H, H-5F, H-5B, H-4E, H-5E, H-4F, H-4D, H-6B), 3.84-3.64 (m, 6H, H-4A, H-4B, H-6B, H-6F, H-6C, H-6E), 3.53-3.47 (m, 4H, H-2E, H-2A, H-2F, H-2D), 3.43 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, H-2C), 3.40 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.9 Hz, H-2B), 3.04-2.89 (m, 4H, 2×H-6D, 2×H-6A), 2.46 (b, 1H, OH), 2.10 (s, 3H, SCH<sub>3</sub>), 2.01 (s, 3H, SCH<sub>3</sub>)

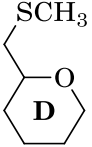
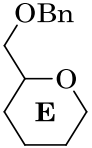
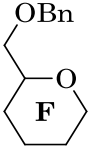
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.53, 139.50, 139.46, 139.43, 139.37, 139.32, 138.61, 138.56, 138.44, 138.39, 138.34, 138.31, 138.25(2C), 138.11 (15×C-Ar<sup>quat.</sup>), 128.45-126.88 (75×C-Ar<sup>tert.</sup>), 99.16, 98.80, 98.60, 98.28, 98.12, 98.06 (C-1C, C-1E, C-1F, C-1D, C-1B, C-1A), 82.89, 82.49 (C-4A, C-4D), 81.32, 81.16, 81.13, 80.93(2C) (C-3B, C-3C, C-3E, C-3A, C-3D), 80.90 (C-4F), 80.60 (C-3F), 80.48 (C-4C), 79.42(2C), 79.16, 79.02, 78.73, 78.60 (C-2B, C-2C, C-2F, C-2D, C-2A, C-2E), 78.42, 77.29 (C-4E, C-4B), 76.19, 76.00, 75.53, 75.50, 75.12, 75.05, 73.75, 73.51(2C), 73.21, 73.14, 73.06(2C), 72.67, 72.61 (15×CH<sub>2</sub>Ph), 72.50, 71.95, 71.90, 71.82, 71.70, 71.42 (C-5A, C-5F, C-5B, C-5E, C-5D, C-5C), 69.81, 69.42, 69.12, 61.92, 36.77, 36.74 (C-6C, C-6F, C-6E, C-6B, C-6A, C-6D), 17.39, 17.30 (2×SCH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>143</sub>H<sub>154</sub>O<sub>28</sub>S<sub>2</sub>Na [M+Na]<sup>1+</sup>: 2405.9951; Found: 2405.9960 (+0.4 ppm)

**EXPERIMENTAL PART**

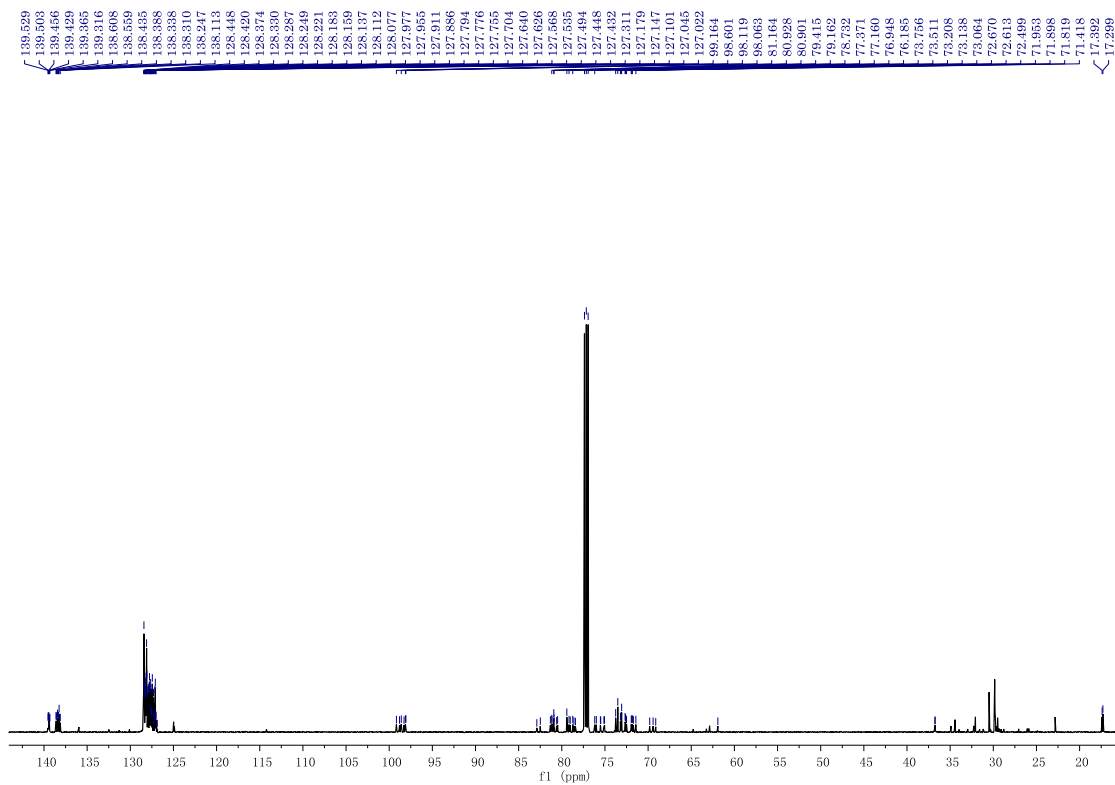
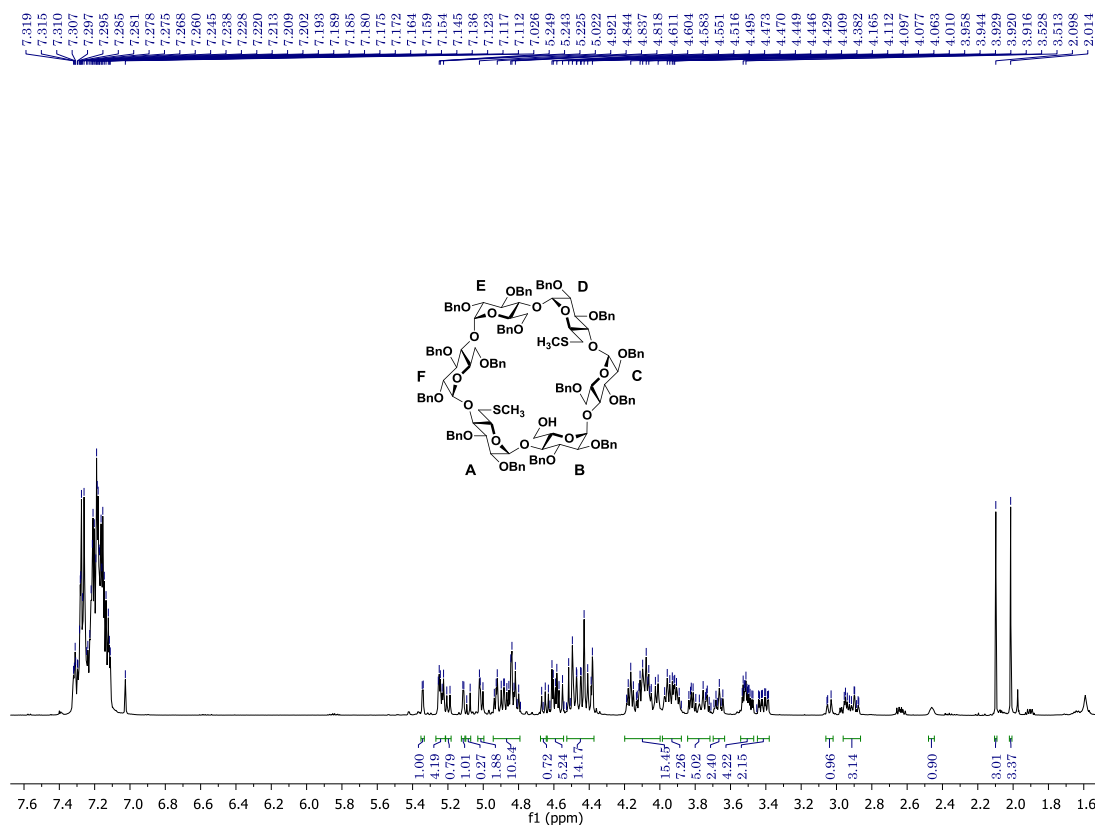
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>A</b></p>	H-1A	5.343	NOE: 3.814 ppm	H-4B
	C-1A	98.063		
	H-2A	3.518		
	C-2A	78.73		
	H-3A	4.165		
	C-3A	80.928		
	H-4A	3.825	NOE: 5.017 ppm	H-1F
	C-4A	82.892		
	H-5A	4.090		
	C-5A	72.499		
	H-6A	3.044		
		2.930		
C-6A	36.770			
 <p style="text-align: center;"><b>B</b></p>	H-1B	4.841	NOE: 4.079 ppm	H-4C
	C-1B	98.119		
	H-2B	3.395		
	C-2B	79.415		
	H-3B	4.080		
	C-3B	81.321		
	H-4B	3.814	NOE: 5.343 ppm	H-1A
	C-4B	77.29		
	H-5B	3.960		
	C-5B	71.898		
	H-6B	3.767		
		3.900		
C-6B	61.919			
 <p style="text-align: center;"><b>C</b></p>	H-1C	4.923	NOE:3.909 ppm	H-4D
	C-1C	99.164		
	H-2C	3.429		
	C-2C	79.415		
	H-3C	4.112		
	C-3C	81.164		
	H-4C	4.079	NOE: 4.841 ppm	H-1B
	C-4C	80.484		
	H-5C	4.013		
	C-5C	71.418		
	H-6C	4.103		
		3.673		
C-6C	69.814			

**EXPERIMENTAL PART**

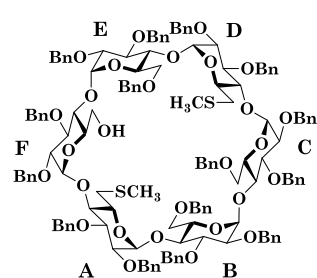
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>D</b></p>	H-1D	5.249	NOE: 3.947 ppm	H-4E
	C-1D	98.282		
	H-2D	3.483		
	C-2D	79.02		
	H-3D	4.162		
	C-3D	80.928		
	H-4D	3.909	NOE: 4.923ppm	H-1C
	C-4D	82.489		
	H-5D	4.080		
	C-5D	71.704		
	H-6D	2.963		
		2.889		
C-6D	36.77			
 <p style="text-align: center;"><b>E</b></p>	H-1E	5.112	NOE: 3.920 ppm	H-4F
	C-1E	98.800		
	H-2E	3.523		
	C-2E	78.60		
	H-3E	4.119		
	C-3E	81.133		
	H-4E	3.947	NOE: 5.249 ppm	H-1D
	C-4E	78.42		
	H-5E	3.933		
	C-5E	71.819		
	H-6E	3.651		
		4.176		
C-6E	69.166			
 <p style="text-align: center;"><b>F</b></p>	H-1F	5.017	NOE:3.825 ppm	H-4A
	C-1F	98.601		
	H-2F	3.509		
	C-2F	79.162		
	H-3F	4.096		
	C-3F	80.593		
	H-4F	3.920	NOE: 5.112 ppm	H-1E
	C-4F	80.901		
	H-5F	3.960		
	C-5F	71.953		
	H-6F	3.745		
		4.061		
C-6F	69.421			



EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>,6<sup>D</sup>-Di-S-Methyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>C</sup>,6<sup>B</sup>,6<sup>E</sup>-Pentadeca-O-Benzyl- $\alpha$ -Cyclodextrin (269b)**



$\alpha_D = +48.7$  (c 1.0, CHCl<sub>3</sub>)

$R_f = 0.27$  (CyH/EtOAc: 3/1)

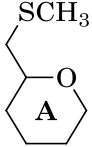
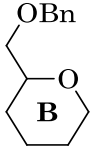
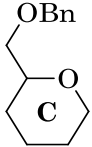
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.34-7.01 (m, 75H, 75×H-Ar.), 5.43 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, H-1E), 5.38 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1B), 5.36 (d, 1H, <sup>2</sup>J = 10.6 Hz, CHPh), 5.32 (d, 1H, <sup>2</sup>J = 10.9 Hz, CHPh), 5.14 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 5.09 (d, 1H, <sup>2</sup>J = 10.6 Hz, CHPh), 5.08 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.8 Hz, H-1C), 5.06 (d, 1H, <sup>2</sup>J = 10.2 Hz, CHPh), 5.00

(d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1F), 4.98 (d, 1H, <sup>2</sup>J = 11.6 Hz, CHPh), 4.92 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 4.89 (d, 1H, <sup>2</sup>J = 10.2 Hz, CHPh), 4.88 (d, 1H, <sup>2</sup>J = 10.2 Hz, CHPh), 4.86 (d, 1H, <sup>2</sup>J = 10.6 Hz, CHPh), 4.83 (d, 1H, <sup>2</sup>J = 10.9 Hz, CHPh), 4.82 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1A), 4.81 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 4.76 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1D), 4.68 (d, 1H, <sup>2</sup>J = 12.3 Hz, CHPh), 4.64 (d, 1H, <sup>2</sup>J = 12.3 Hz, CHPh), 4.63 (d, 1H, <sup>2</sup>J = 11.8 Hz, CHPh), 4.58-4.34 (m, 15H, 15×CHPh), 4.20-4.14 (m, 4H, H-3B, H-3E, H-3C, H-3F), 4.11-3.87 (m, 16H, H-6B, H-3A, H-5A, H-5D, H-4B, H-3D, H-6E, H-6C, H-6F, H-5E, H-5C, H-5B, H-5F, H-4F, H-4E, H-4A), 3.84-3.70 (m, 4H, H-6F, H-6E, H-4D, H-6C), 3.58-3.48 (m, 5H, H-6B, H-2E, H-2B, H-2C, H-2F), 3.42 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.9 Hz, H-2D), 3.40 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.9 Hz, H-2A), 3.06-3.01 (m, 2H, H-6D, H-6A), 2.94-2.91 (m, 2H, H-6A, H-6D), 2.69 (b, 1H, OH), 2.01 (s, 3H, SCH<sub>3</sub>), 1.98 (s, 3H, SCH<sub>3</sub>)

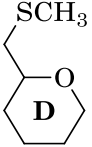
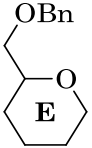
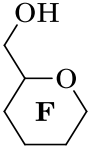
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.48, 139.46(2C), 139.41, 139.36, 139.30, 138.57, 138.53, 138.42(2C), 138.32, 138.31, 138.30, 138.12, 138.00 (15×C-Arquat.), 128.48-126.87 (75×C-Artert.), 99.21, 98.89, 98.63, 98.58, 98.05, 98.01 (C-1C, C-1B, C-1E, C-1F, C-1A, C-1D), 83.42, 82.81 (C-4D, C-4A), 81.62(2C), 81.28 (C-3F, C-3C, C-3B), 81.09, 80.94 (C-4E, C-4B), 80.73, 80.61(2C) (C-3A, C-3D, C-3E), 79.69, 79.40(2C), 79.30, 78.59, 78.06 (C-2D, C-2C, C-2F, C-2A, C-2B, C-2E), 77.91, 76.91 (C-4C, C-4F), 76.10, 76.00, 75.58, 75.65, 74.90, 74.84, 73.86, 73.58, 73.46, 73.25, 73.23, 72.86, 72.79, 72.75, 72.72 (15×CH<sub>2</sub>Ph), 72.11, 72.03, 71.99, 71.90, 71.62, 71.57 (C-5A, C-5D, C-5E, C-5F, C-5C, C-5B), 69.51, 69.48, 69.23, 61.70, 36.82(2C) (C-6C, C-6E, C-6B, C-6F, C-6A, C-6D), 17.39, 17.19 (2×SCH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>143</sub>H<sub>154</sub>O<sub>28</sub>S<sub>2</sub>Na [M+Na]<sup>1+</sup>: 2405.9955; Found: 2405.9960 (+0.2 ppm)

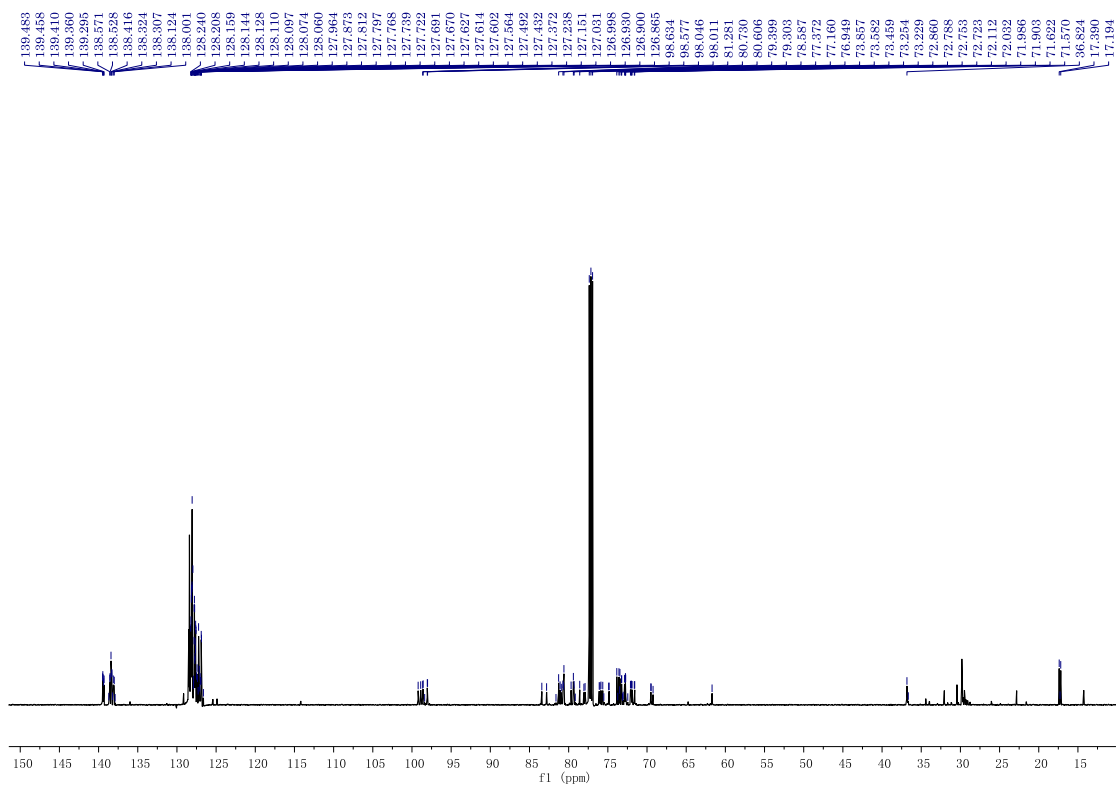
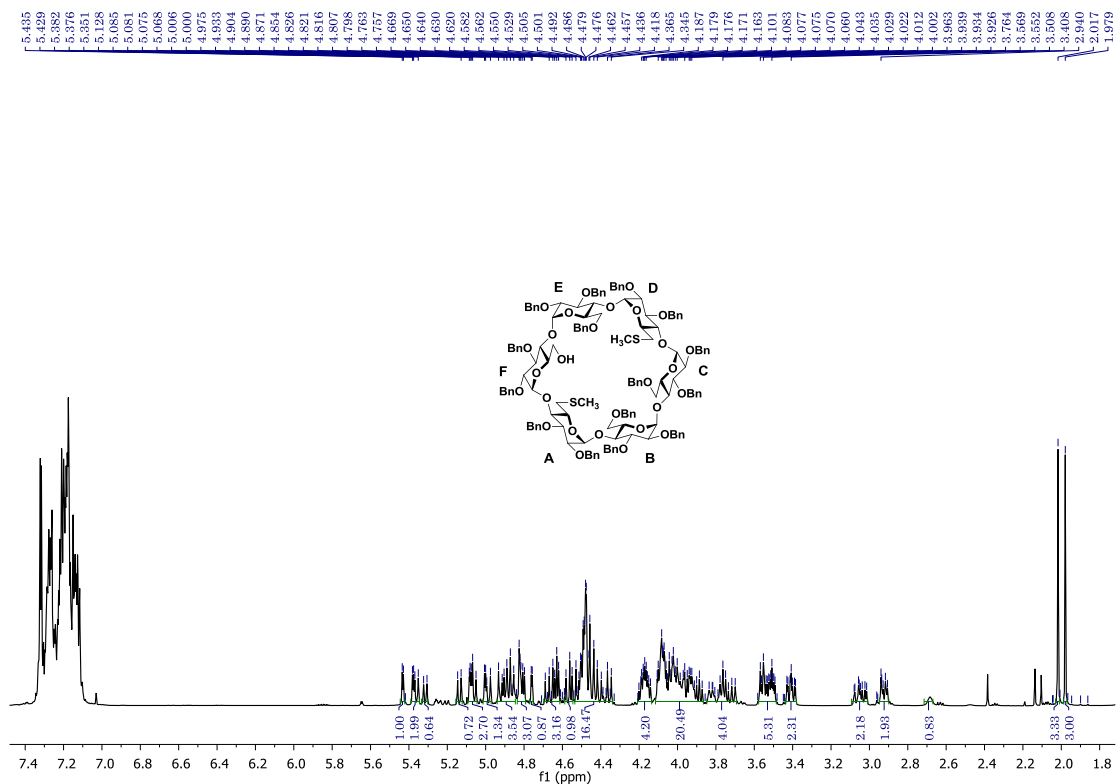
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>A</b></p>	H-1A	4.823	NOE: 4.079 ppm	H-4B
	C-1A	98.046		
	H-2A	3.395		
	C-2A	79.158		
	H-3A	4.085		
	C-3A	80.651		
	H-4A	3.885	NOE: 5.003 ppm	H-1F
	C-4A	82.181		
	H-5A	4.080		
	C-5A	72.112		
	H-6A	3.022		
		2.922		
C-6A	36.824			
 <p style="text-align: center;"><b>B</b></p>	H-1B	5.379	NOE: 4.042 ppm	H-4C
	C-1B	98.887		
	H-2B	3.541		
	C-2B	78.587		
	H-3B	4.186		
	C-3B	81.097		
	H-4B	4.079	NOE: 4.823 ppm	H-1A
	C-4B	80.730		
	H-5B	3.935		
	C-5B	71.570		
	H-6B	3.570		
		4.104		
C-6B	69.229			
 <p style="text-align: center;"><b>C</b></p>	H-1C	5.078	NOE:3.752 ppm	H-4D
	C-1C	99.212		
	H-2C	3.513		
	C-2C	79.303		
	H-3C	4.163		
	C-3C	81.281		
	H-4C	4.042	NOE: 5.379 ppm	H-1B
	C-4C	77.907		
	H-5C	3.995		
	C-5C	71.622		
	H-6C	3.712		
		4.038		
C-6C	69.506			

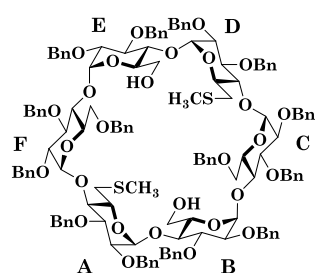
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	4.760	NOE: 3.931 ppm	H-4E
	C-1D	98.011		
	H-2D	3.418		
	C-2D	79.692		
	H-3D	4.076		
	C-3D	80.606		
	H-4D	3.752	NOE: 5.078 ppm	H-1C
	C-4D	83.427		
	H-5D	4.080		
	C-5D	72.032		
	H-6D	3.064		
		2.922		
C-6D	36.824			
	H-1E	5.431	NOE: 3.957 ppm	H-4F
	C-1E	98.634		
	H-2	3.557		
	C-2E	78.055		
	H-3E	4.176		
	C-3E	80.606		
	H-4E	3.931	NOE: 4.760 ppm	H-1D
	C-4E	80.940		
	H-5E	4.018		
	C-5E	71.986		
	H-6E	3.773		
		4.038		
C-6E	69.480			
	H-1F	5.003	NOE:3.885 ppm	H-4A
	C-1F	98.577		
	H-2F	3.501		
	C-2F	79.303		
	H-3F	4.156		
	C-3F	81.281		
	H-4F	3.957	NOE: 5.431 ppm	H-1E
	C-4F	76.914		
	H-5F	3.975		
	C-5F	71.903		
	H-6F	3.827		
		4.013		
C-6F	61.697			

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>,6<sup>D</sup>-Di-S-Methyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>C</sup>,6<sup>F</sup>-Tetradeca-O-Benzyl- $\alpha$ -Cyclodextrin (269c)**



$\alpha_D = +54.4$  (c 1.0, CHCl<sub>3</sub>)

$R_f = 0.30$  (CyH/EtOAc: 3/1)

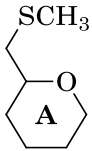
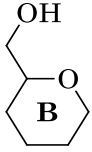
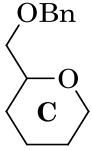
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.31-7.07 (m, 35H, 35×H-Ar.), 5.60 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1B), 5.39 (d, 1H, <sup>2</sup>J = 10.8 Hz, CHPh), 5.17 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh), 4.86 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh), 4.84 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1C), 4.83 (d, 1H, <sup>2</sup>J = 10.1 Hz, CHPh), 4.79 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh), 4.77 (d, 1H, <sup>2</sup>J = 11.4 Hz, CHPh), 4.75 (d,

1H, <sup>2</sup>J = 11.2 Hz, CHPh), 4.70 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1B), 4.61 (bd, 2H, <sup>2</sup>J = 12.1 Hz, 2×CHPh), 4.51 (d, 1H, <sup>2</sup>J = 12.5 Hz, CHPh), 4.48 (d, 1H, <sup>2</sup>J = 12.0 Hz, CHPh), 4.46 (d, 1H, <sup>2</sup>J = 11.4 Hz, CHPh), 4.34 (dd, 2H, <sup>2</sup>J = 12.3 Hz, 2×CHPh), 4.19 (dd, 1H, <sup>3</sup>J<sub>2,3</sub> = 9.1 Hz, <sup>3</sup>J<sub>3,4</sub> = 7.4 Hz, H-3A), 4.10-3.95 (m, 6H, H-3B, H-3C, H-5A, H-5B, H-5C, H-6C), 3.86-3.74 (m, 6H, H-4A, H-4B, H-4C, 2×H-6B, H-6C), 3.54 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.8 Hz, H-2A), 3.47 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.6 Hz, H-2C), 3.39 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.8 Hz, H-2B), 3.03 (m, 2H, 2×H-6A), 2.11 (s, 3H, SCH<sub>3</sub>)

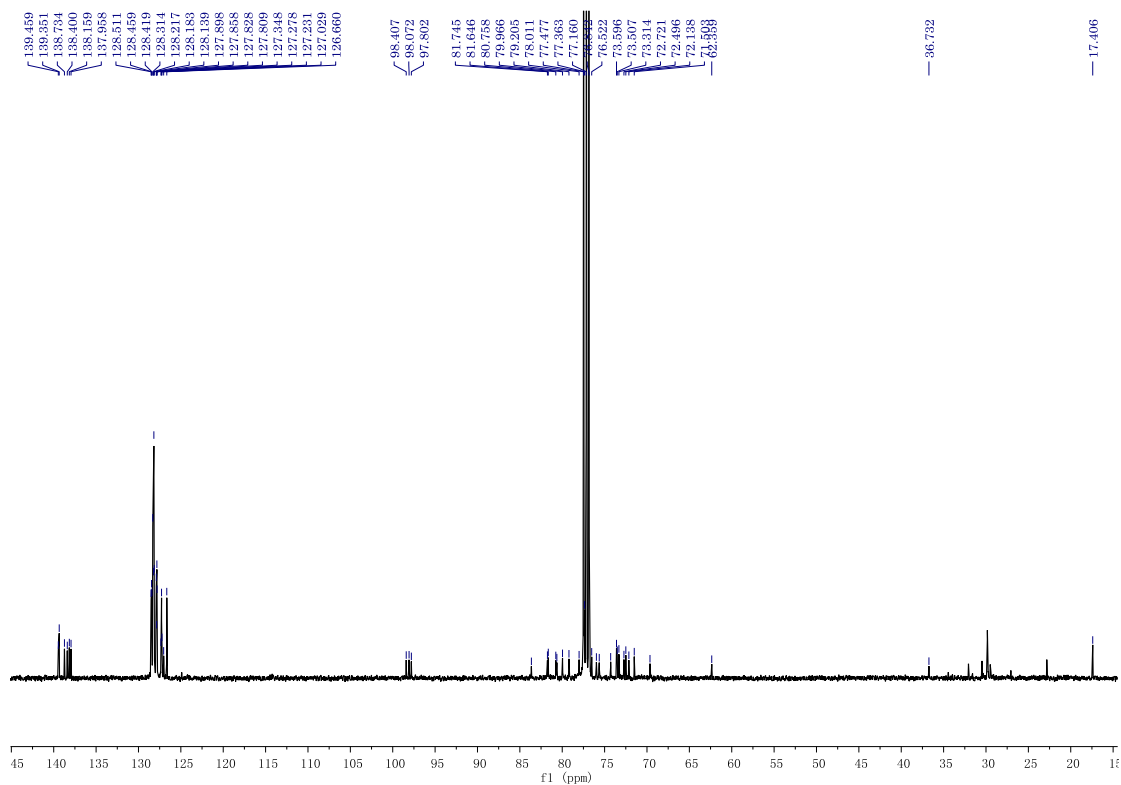
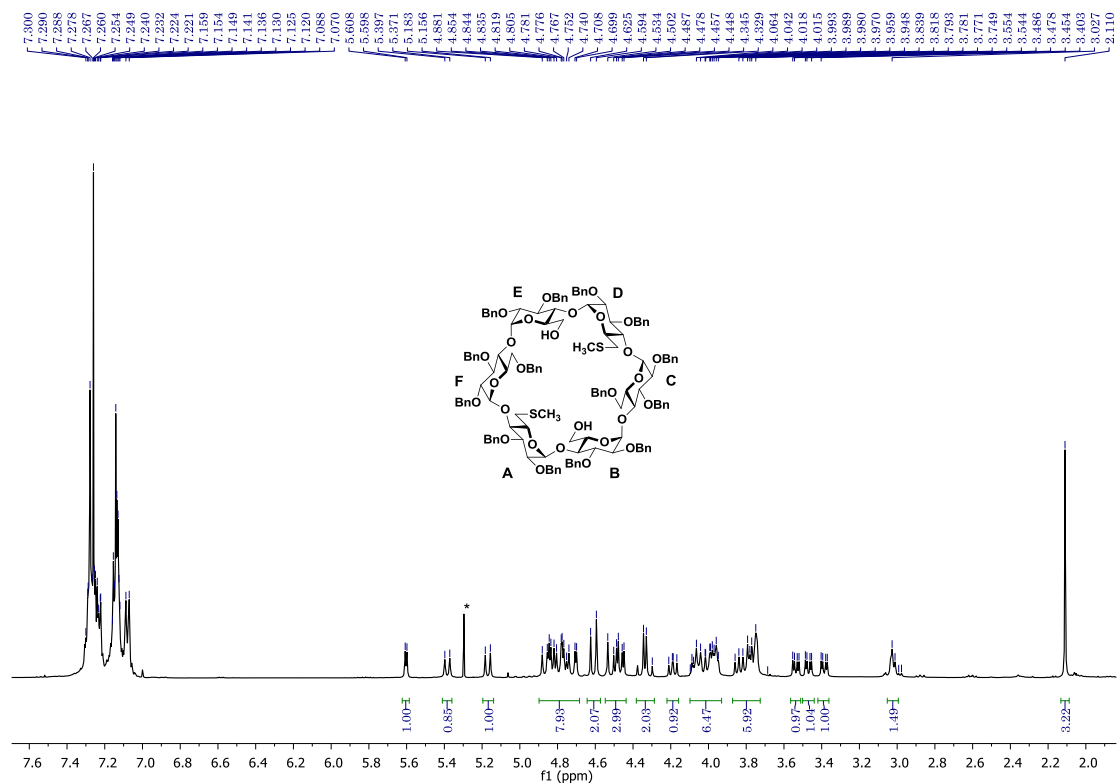
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.46, 139.35(2C), 138.73, 138.40, 138.16, 137.96 (7×C-Ar<sup>quat.</sup>), 128.51-126.66 (35×C-Ar<sup>tert.</sup>), 98.41, 98.07, 97.80 (C-1B, C-1C, C-1A), 83.64, 81.75 (C-4A, C-4C), 81.65, 80.76, 80.63 (C-3B, C-3C, C-3A), 79.97, 79.21, 78.01 (C-2B, C-2C, C-2A), 76.52, 75.97 (2×CH<sub>2</sub>Ph), 75.63 (C-4B), 74.29, 73.60, 73.51, 73.31 (4×CH<sub>2</sub>Ph), 72.72 (C-5A), 72.50 (CH<sub>2</sub>Ph), 72.14, 71.50 (C-5C, C-5B), 69.65, 62.36, 36.73 (C-6C, C-6B, C-6A), 17.41 (SCH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>136</sub>H<sub>148</sub>O<sub>28</sub>S<sub>2</sub>Na [M+Na]<sup>1+</sup>: 2315.9583; Found: 2315.9491 (-4.0 ppm)

**EXPERIMENTAL PART**

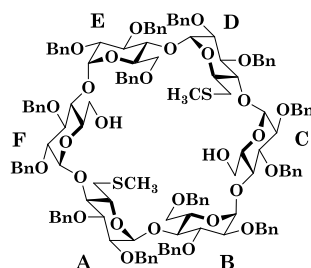
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>A</b></p>	H-1A	5.603	NOE: 3.770 ppm	H-4B
	C-1A	97.802		
	H-2A	3.535		
	C-2A	78.011		
	H-3A	4.187		
	C-3A	80.634		
	H-4A	3.839	NOE: 4.839 ppm	H-1F = H-1C
	C-4A	83.638		
	H-5A	4.059		
	C-5A	72.721		
	H-6A	3.011		
		3.011		
C-6A	36.732			
 <p style="text-align: center;"><b>B</b></p>	H-1B	4.703	NOE: 3.792 ppm	H-4C
	C-1B	98.407		
	H-2B	3.386		
	C-2B	79.966		
	H-3B	4.058		
	C-3B	81.646		
	H-4B	3.770	NOE: 5.603 ppm	H-1A
	C-4B	75.633		
	H-5B	3.954		
	C-5B	71.503		
	H-6B	3.750		
		3.750		
C-6B	62.359			
 <p style="text-align: center;"><b>C</b></p>	H-1C	4.839	NOE:3.839 ppm	H-4D =H-4A
	C-1C	98.072		
	H-2C	3.470		
	C-2C	79.205		
	H-3C	4.013		
	C-3C	80.758		
	H-4C	3.792	NOE: 4.703 ppm	H-1B
	C-4C	80.758		
	H-5C	3.972		
	C-5C	72.138		
	H-6C	3.979		
		3.770		
C-6C	69.647			

EXPERIMENTAL PART





**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>,6<sup>D</sup>-Di-S-Methyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>E</sup>-Tetradeca-  
O-Benzyl- $\alpha$ -Cyclodextrin (269d)**



$\alpha_D = +55.0$  (c 1.0, CHCl<sub>3</sub>)

$R_f = 0.17$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.32-7.09 (m, 35H, 35 $\times$ H-Ar.), 5.73 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1B), 5.44 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh), 5.16 (d, 1H, <sup>2</sup>J = 10.8 Hz, CHPh), 4.92 (d, 1H, <sup>2</sup>J = 11.3 Hz, CHPh), 4.91 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh),

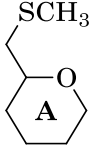
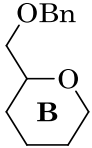
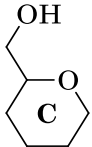
4.82 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh), 4.79 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1C), 4.76 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh), 4.75 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh),

4.66 (d, 1H, <sup>2</sup>J = 12.0 Hz, CHPh), 4.65 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1A), 4.52-4.45 (m, 4H, 4 $\times$ CHPh), 4.40 (dd, 2H, <sup>2</sup>J = 12.6 Hz, 2 $\times$ CHPh), 4.21 (dd, 1H, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, <sup>3</sup>J<sub>3,4</sub> = 7.8 Hz, H-3B), 4.15-3.91 (m, 9H, H-3C, H-3A, H-4B, H-4C, H-5A, H-5B, H-5C, H-6B, H-6C), 3.81-3.79 (m, 2H, H-6B, H-6C), 3.66 (t, 1H, <sup>3</sup>J<sub>2,3</sub> = <sup>3</sup>J<sub>3,4</sub> = 9.4 Hz, H-4A), 3.58 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.8 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.8 Hz, H-2B), 3.50 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, H-2C), 3.39 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.9 Hz, H-2A), 3.22 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 13.0 Hz, H-6A), 2.90 (dd, 1H, <sup>3</sup>J<sub>5,6</sub> = 7.7 Hz, <sup>2</sup>J<sub>6,6'</sub> = 13.3 Hz, H-6A), 2.08 (s, 3H, SCH<sub>3</sub>)

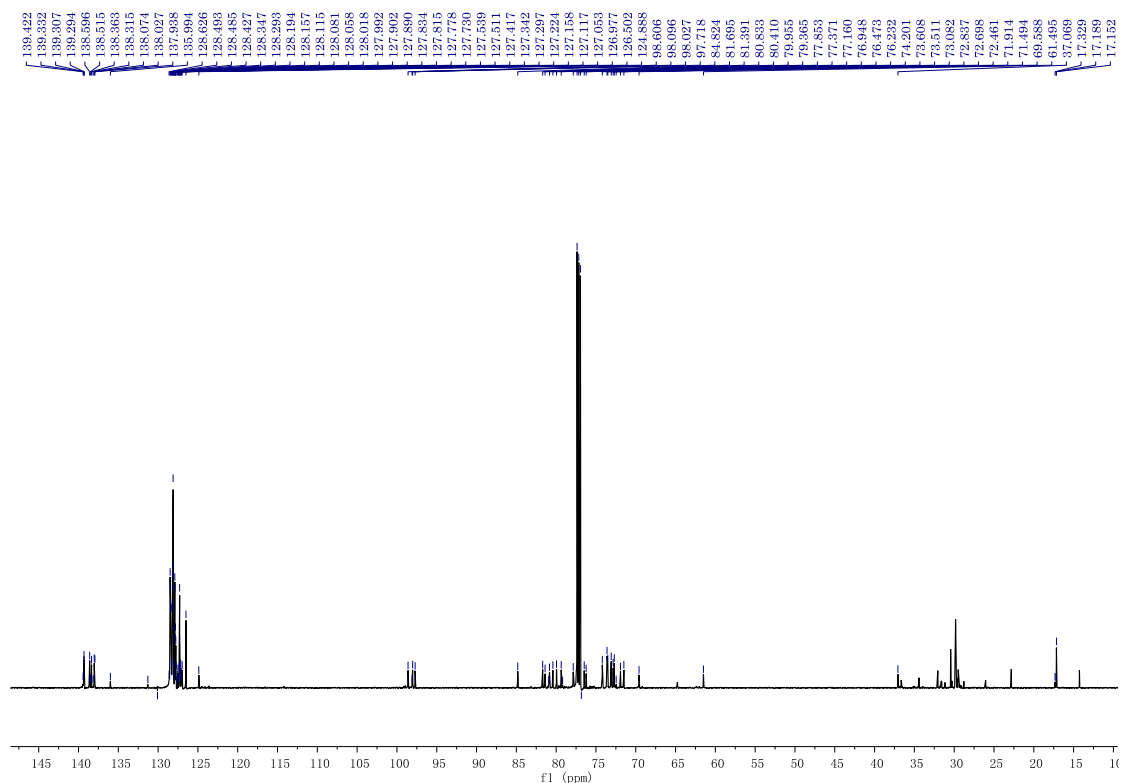
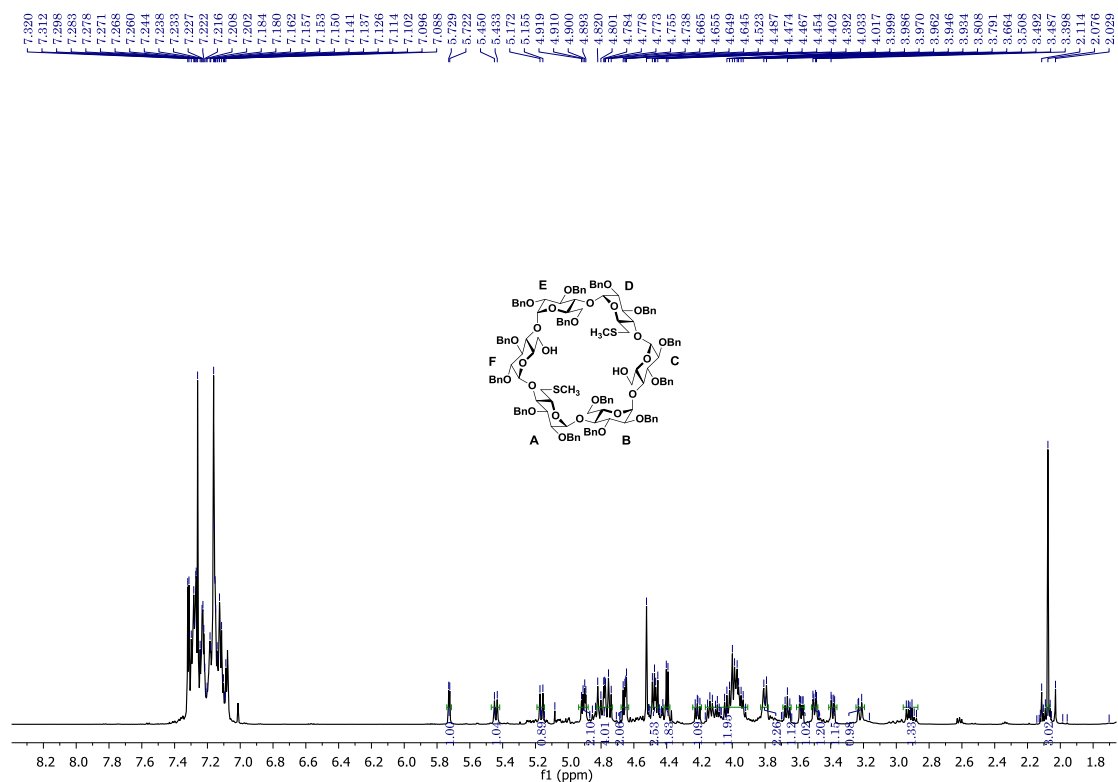
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.33, 139.31, 139.29, 138.60, 138.36, 138.03, 137.94 (7 $\times$ C-Ar<sup>quat</sup>), 128.50-126.98 (35 $\times$ C-Ar<sup>tert</sup>), 98.61, 98.03, 97.72 (C-1C, C-1A, C-1B), 84.82 (C-4A), 81.70 (C-3C), 81.39 (C-4B), 80.83, 80.41 (C-3B, C-3A), 79.96, 79.36, 77.85 (C-2C, C-2A, C-2B), 76.47, 76.23 (2 $\times$ CH<sub>2</sub>Ph), 74.20(2C) (C-4C, CH<sub>2</sub>Ph) 73.61, 73.51, 73.08 (3 $\times$ CH<sub>2</sub>Ph), 72.84 (C-5B), 72.70 (CH<sub>2</sub>Ph), 71.91, 71.49 (C-5C, C-5A), 69.59, 61.50, 37.03 (C-6B, C-6C, C-6A), 17.19 (SCH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>136</sub>H<sub>148</sub>O<sub>28</sub>S<sub>2</sub>Na [M+Na]<sup>1+</sup>: 2315.9562; Found: 2315.9491 (-3.1 ppm)

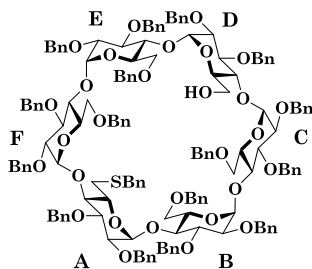
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>A</b></p>	H-1A	4.656	NOE: 3.940 ppm	H-4B
	C-1A	97.718		
	H-2A	3.389		
	C-2A	79.428		
	H-3A	4.037		
	C-3A	80.410		
	H-4A	3.666	NOE: 4.785 ppm	H-1F = H-1C
	C-4A	84.824		
	H-5A	4.007		
	C-5A	71.483		
	H-6A	3.222		
		2.938		
C-6A	37.032			
 <p style="text-align: center;"><b>B</b></p>	H-1B	5.726	NOE: 4.000 ppm	H-4C
	C-1B	98.207		
	H-2B	3.581		
	C-2B	77.849		
	H-3B	4.213		
	C-3B	80.833		
	H-4B	3.940	NOE: 4.656 ppm	H-1A
	C-4B	81.406		
	H-5B	4.005		
	C-5B	72.843		
	H-6B	3.989		
		3.804		
C-6B	69.655			
 <p style="text-align: center;"><b>C</b></p>	H-1C	4.785	NOE:3.666 ppm	H-4D =H-4A
	C-1C	98.606		
	H-2C	3.497		
	C-2C	79.949		
	H-3C	4.140		
	C-3C	80.695		
	H-4C	4.000	NOE: 5.726 ppm	H-1B
	C-4C	74.186		
	H-5C	3.979		
	C-5C	71.917		
	H-6C	3.804		
		3.975		
C-6C	61.495			

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-S-Benzyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>-Hexadeca-  
O-Benzyl- $\alpha$ -Cyclodextrin (**270**)**



Potassium carbonate (23 mg, 0.164 mmol, 2 eq.) was added to a solution of thiol-monol-cyclodextrin **263** (200 mg, 0.082 mmol, 1 eq.) in anhydrous DMF (5 mL) under nitrogen at 0°C. Benzyl bromide (0.020 mL, 0.164 mmol, 2 eq.) was added, and the reaction mixture was stirred for 2 h at r.t.. Until the TLC showed the reaction finished, Water (20 mL) was added and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated.

Silica gel flash chromatography of the residue (CyH/EtOAc: 98/2, then 4/1) gave thiobenzyl- $\alpha$ -cyclodextrin **270** (170 mg, 81%) as a yellowish foam.

$\alpha_D = +31.9$  (c 1.0, CHCl<sub>3</sub>)

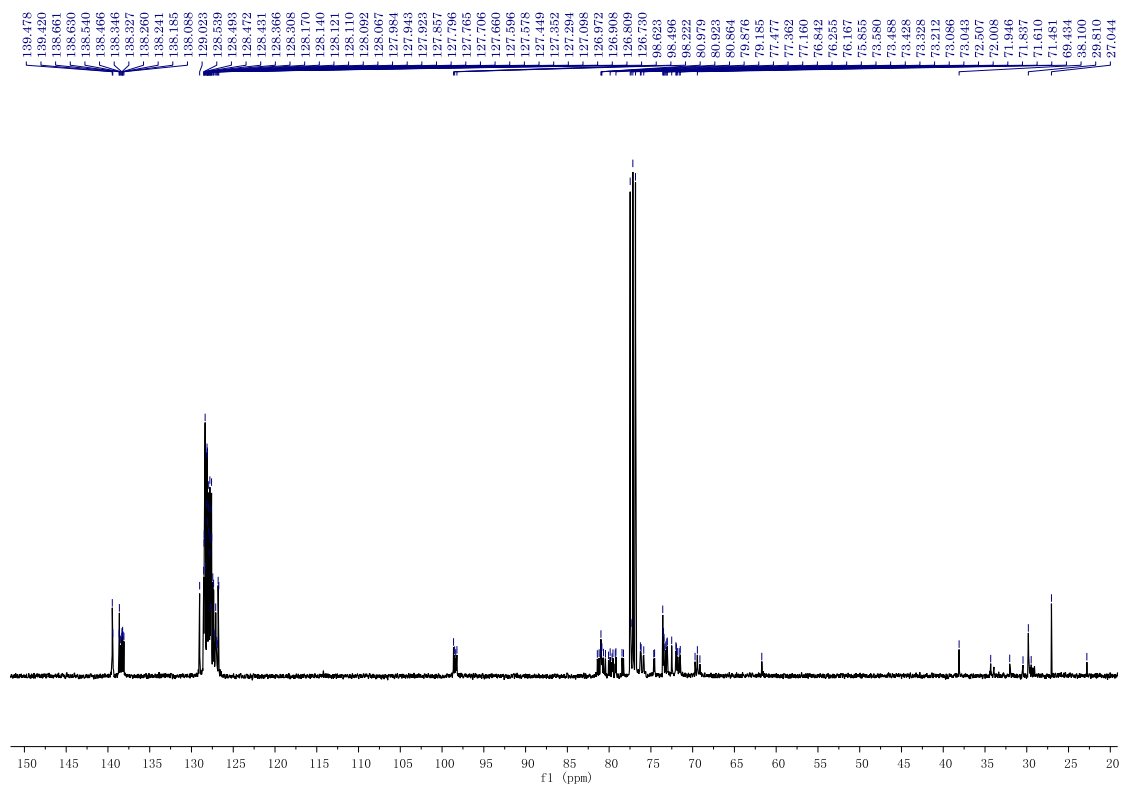
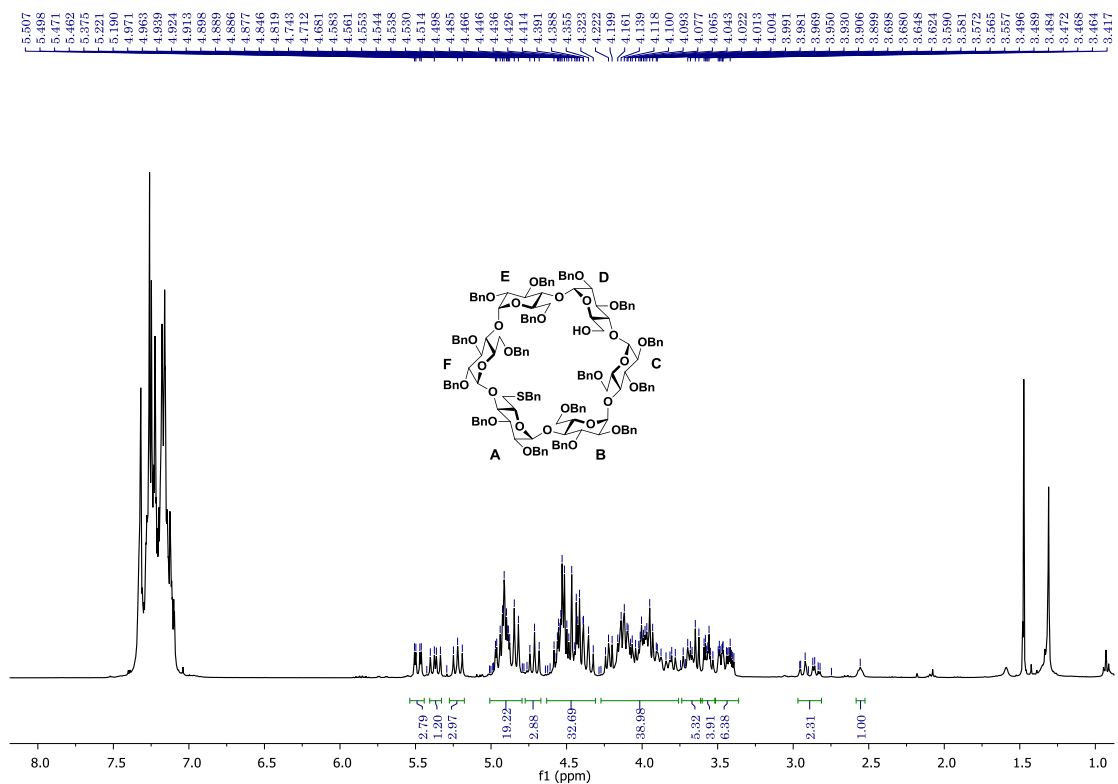
$R_f = 0.33$  (CyH/EtOAc: 4/1)

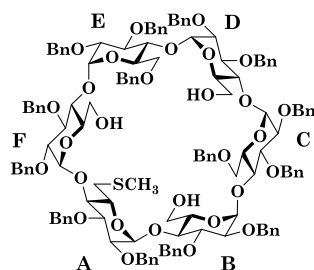
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.32-7.15 (m, 85H, 85×H-Ar.), 5.50 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 5.48 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 5.39 (d, 1H, <sup>2</sup>J = 10.6 Hz, CHPh), 5.35 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 5.24 (d, 1H, <sup>2</sup>J = 11.0 Hz, CHPh), 5.20 (d, 1H, <sup>2</sup>J = 11.0 Hz, CHPh), 4.97 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1), 4.94-4.82 (m, 11H, 3×H-1, 8×CHPh), 4.71 (d, 2H, <sup>2</sup>J = 12.0 Hz, 2×CHPh), 4.58-4.32 (m, 18H, 18×CHPh), 4.22 (dd, 1H, <sup>3</sup>J<sub>2,3</sub> = 8.1 Hz, <sup>3</sup>J<sub>3,4</sub> = 9.5 Hz, H-3), 4.16-3.78 (m, 23H, 5×H-3, 6×H-4, 6×H-5, 6×H-6), 3.73-3.53 (m, 4H, 3×H-6, SCHPh), 3.50-3.39 (m, 8H, 6×H-2, SCHPh, H-6), 2.96-2.82 (m, 2H, 2×H-6), 2.55 (t, 1H, OH)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.48(3C), 139.45, 139.42, 139.40, 138.66, 138.63(2C), 138.54, 138.47, 138.35, 138.33, 138.26, 138.24, 138.19, 138.09 (17×C-Ar<sup>quat.</sup>), 129.03-126.73 (85×C-Ar<sup>tert.</sup>), 98.63(2C), 98.50, 98.37, 98.27, 98.22 (6×C-1), 81.41, 81.20 (2×C-4), 81.05, 80.98(2C), 80.92 (4×C-3), 80.86 (C-4), 80.68, 80.44 (2×C-3), 80.07, 79.88 (2×C-4), 79.65, 79.54, 79.27, 79.19, 78.46, 78.28 (6×C-2), 76.30 (C-4), 76.26, 76.17, 75.92, 75.86, 74.66, 74.56, 73.58(2C), 73.49, 73.43, 73.33, 73.21, 73.09, 73.04, 72.51, 72.49 (16×CH<sub>2</sub>Ph), 72.04, 72.01, 71.95, 71.84, 71.61, 71.48 (6×C-5), 69.71, 69.43(2C), 69.13, 61.72 (5×C-6), 38.10 (SCH<sub>2</sub>Ph), 34.32 (C-6)

**HRMS (ESI):** Calcd. For C<sub>155</sub>H<sub>162</sub>O<sub>29</sub>SNa [M+Na]<sup>1+</sup>: 2542.0927; Found: 2542.0815 (-4.4 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-S-Methyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>C</sup>,6<sup>E</sup>-Tetradeca-O-Benzyl- $\alpha$ -Cyclodextrin (271)**

DIBAL-H (1.5 M in toluene, 0.87 mL, 1.3 mmol, 20 eq.) was added to a solution of cyclodextrin **266a** (160 mg, 0.065 mmol, 1 eq.) in toluene (0.43 mL) under nitrogen at r. t. The reaction mixture was stirred at 55°C with a nitrogen balloon reflux for 30 min, until Mass spectrum indicated formation of triol as a major product, and then cooled to r.t. and poured into ice/water. Aqueous HCl (5 mL, 1 M) and EtOAc (5 mL) were added, and the solution was stirred for 1 h. The aqueous layer was extracted

with EtOAc (3×5 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Silica gel chromatography of the residue (CyH/EtOAc: 3/1, then 2/1) gave triol-cyclodextrin **271** (89 mg, 60%) as a yellowish foam.

$\alpha_D = +42.9$  (c 1.0, CHCl<sub>3</sub>)

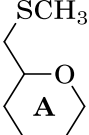
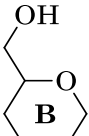
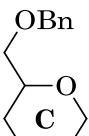
$R_f = 0.33$  (CyH/EtOAc: 2/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.31-7.13 (m, 70H, 70×H-Ar.), 5.24 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1C), 5.18 (d, 1H, <sup>2</sup>J = 10.2 Hz, CHPh), 5.17 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 5.16 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.8 Hz, H-1F), 5.14 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 5.13 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1E), 5.09 (d, 1H, <sup>2</sup>J = 10.2 Hz, CHPh), 5.07 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 5.05 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.8 Hz, H-1A), 5.03 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 4.94 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1B), 4.93 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.8 Hz, H-1D), 4.87-4.79 (m, 6H, 6×CHPh), 4.65-4.42 (m, 16H, 16×CHPh), 4.16-4.07 (m, 7H, H-3C, H-5A, H-3F, H-3A, H-3D, H-3D, H-3B), 4.03-3.81 (m, 17H, H-5C, C-5E, H-5B, H-5D, H-6C, H-6E, H-6F, H-6D, H-4C, H-4E, H-6B, H-5F, H-4A, H-4F, H-6B, H-6D, H-6F), 3.79-3.70 (m, 4H, H-4D, H-6C, H-6E, H-4B), 3.53-3.48 (m, 4H, H-2C, H-2E, H-2F, H-2A), 3.44-3.41 (m, 2H, H-2D, H-2B), 2.96 (m, 2H, 2×H-6A), 2.11 (s, 3H, SCH<sub>3</sub>)

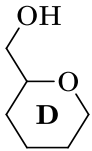
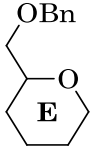
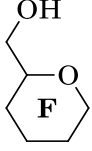
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.40, 139.36, 139.33, 139.30(2C), 139.27, 138.45, 138.39(2C), 138.31, 138.29(2C), 137.94, 137.87 (14×C-Ar<sup>quat.</sup>), 128.46-127.04 (70×C-Ar<sup>tert.</sup>), 98.64, 98.48, 98.24, 98.03, 97.98, 97.84 (C-1C, C-1E, C-1A, C-1D, C-1F, C-1B), 81.20 (C-4A), 81.14, 81.06, 80.96, 80.92, 80.79, 80.66 (C-3B, C-3D, C-3F, C-3C, C-3A, C-3E), 79.95, 79.83, 79.78 (C-4C, C-4E, C-4B), 79.38(2C) (C-4F, C-2B), 79.16, 79.05, 79.00 (C-2D, C-2A, C-2F), 78.73(2C) (C-2E, C-4D), 78.53 (C-2C), 75.73, 75.63(2C), 75.51, 75.24, 75.18, 73.75, 73.64, 73.21, 73.10(3C), 72.93, 72.90 (14×CH<sub>2</sub>Ph), 72.59, 72.49, 72.28, 72.02, 71.98, 71.92 (C-5F, C-5B, C-5D, C-5A, C-5E, C-5C), 69.62, 69.38, 62.44, 62.30(2C), 36.81 (C-6E, C-6C, C-6B, C-6D, C-6F, C-6A), 17.47 (SCH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>135</sub>H<sub>146</sub>O<sub>29</sub>SNa [M+Na]<sup>1+</sup>: 2285.9618; Found: 2285.9563 (-2.2 ppm)

**EXPERIMENTAL PART**

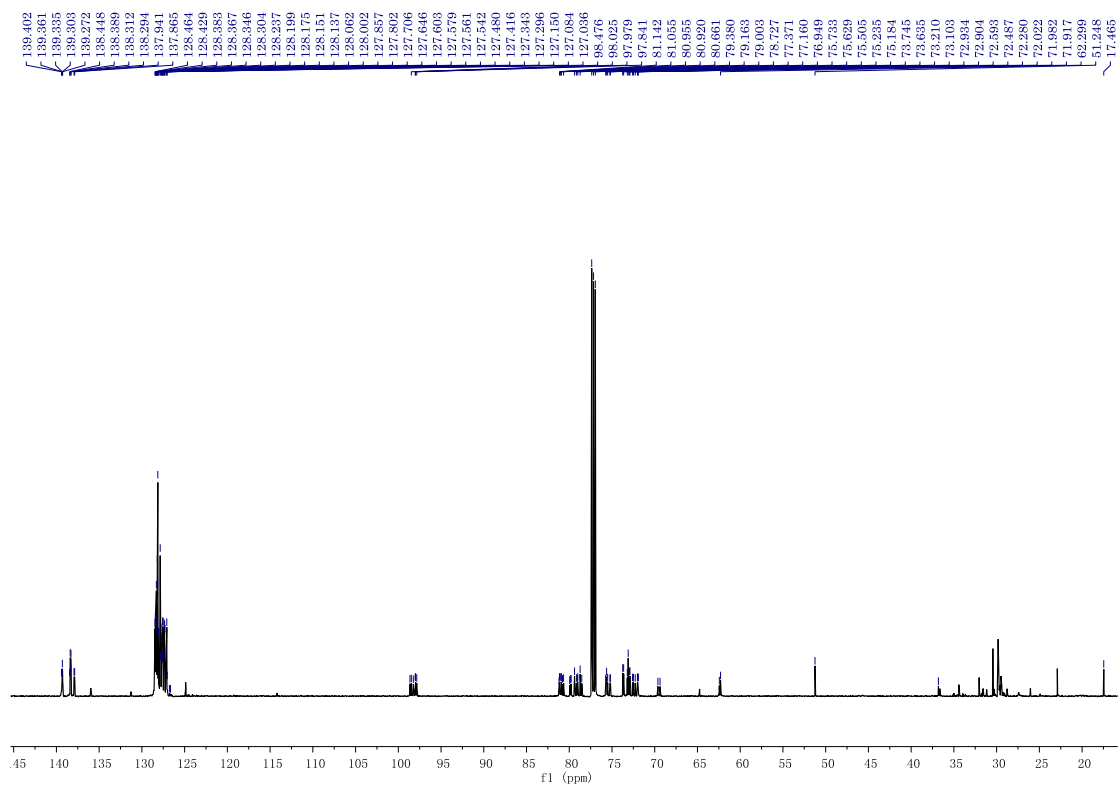
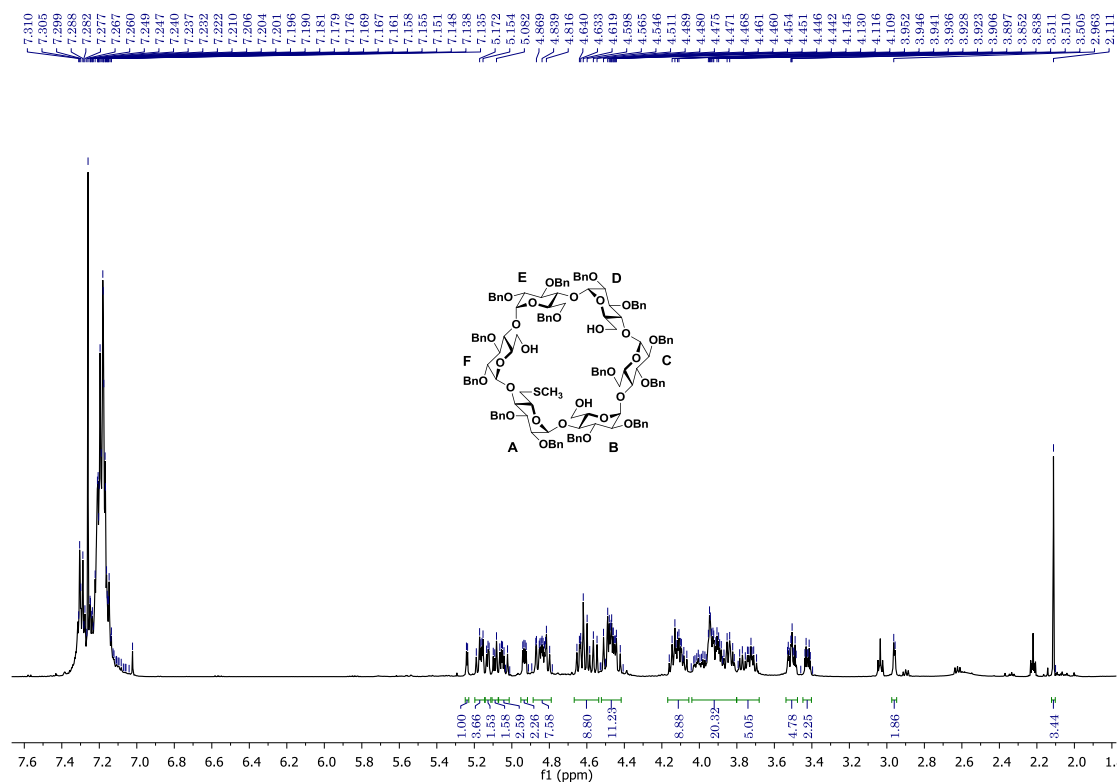
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>A</b></p>	H-1A	5.053	NOE: 3.710 ppm	H-4B
	C-1A	98.244		
	H-2A	3.495		
	C-2A	79.042		
	H-3A	4.121		
	C-3A	80.786		
	H-4A	3.844	NOE: 5.163 ppm	H-1F
	C-4A	81.190		
	H-5A	4.137		
	C-5A	72.018		
	H-6A	2.958		
		2.958		
C-6A	36.811			
 <p style="text-align: center;"><b>B</b></p>	H-1B	4.939	NOE: 3.917 ppm	H-4C
	C-1B	97.841		
	H-2B	3.422		
	C-2B	79.375		
	H-3B	4.082		
	C-3B	81.140		
	H-4B	3.710	NOE: 5.053 ppm	H-1A
	C-4B	79.780		
	H-5B	3.940		
	C-5B	72.484		
	H-6B	3.904		
		3.839		
C-6B	62.443			
 <p style="text-align: center;"><b>C</b></p>	H-1C	5.239	NOE: 3.771 ppm	H-4D
	C-1C	98.635		
	H-2C	3.521		
	C-2C	78.530		
	H-3C	4.148		
	C-3C	80.919		
	H-4C	3.917	NOE: 4.939 ppm	H-1B
	C-4C	79.942		
	H-5C	4.017		
	C-5C	71.913		
	H-6C	3.945		
		3.734		
C-6C	69.378			

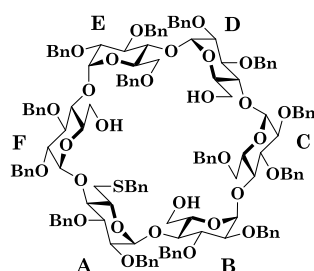
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	4.926	NOE: 3.909 ppm	H-4E
	C-1D	98.025		
	H-2D	3.427		
	C-2D	79.159		
	H-3D	4.105		
	C-3D	81.053		
	H-4D	3.771	NOE: 5.239 ppm	H-1C
	C-4D	78.722		
	H-5D	3.940		
	C-5D	72.274		
	H-6D	3.839		
		3.940		
C-6D	62.299			
	H-1E	5.125	NOE: 3.844 ppm	H-4F
	C-1E	98.476		
	H-2E	3.516		
	C-2E	78.722		
	H-3E	4.110		
	C-3E	80.659		
	H-4E	3.909	NOE: 4.926 ppm	H-1D
	C-4E	79.831		
	H-5E	3.985		
	C-5E	71.977		
	H-6E	3.727		
		3.938		
C-6E	69.624			
	H-1F	5.163	NOE: 3.884 ppm	H-4A
	C-1F	97.979		
	H-2F	3.502		
	C-2F	78.997		
	H-3F	4.128		
	C-3F	80.953		
	H-4F	3.844	NOE: 5.125 ppm	H-1E
	C-4F	79.375		
	H-5F	3.897		
	C-5F	72.588		
	H-6F	3.837		
		3.940		
C-6F	69.299			



EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-S-Benzyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>C</sup>,6<sup>E</sup>-Tetradeca-O-Benzyl- $\alpha$ -Cyclodextrin (272)**

DIBAL-H (1.5 M in toluene, 1.1 mL, 1.66 mmol, 20 eq.) was added to a solution of cyclodextrin **270** (210 mg, 0.083 mmol, 1 eq.) in toluene (0.56 mL) under nitrogen at r. t. The reaction mixture was stirred at 55°C with a nitrogen balloon reflux for 40 min, until Mass spectrum indicated formation of triol as a major product, and then cooled to r.t. and poured into ice/water. Aqueous HCl (5 mL, 1 M) and EtOAc (5 mL) were added, and the solution was stirred for 1 h. The aqueous layer was extracted

with EtOAc (3×5 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Silica gel chromatography of the residue (CyH/EtOAc: 3/1) gave triol-cyclodextrin **272** (150 mg, 74%) as a yellowish foam.

$\alpha_D = +37.0$  (c 1.0, CHCl<sub>3</sub>)

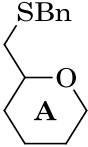
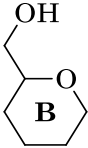
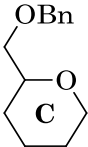
$R_f = 0.17$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.29-7.13 (m, 75H, 75×H-Ar.), 5.18 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1C), 5.15 (d, 1H, <sup>2</sup>J = 10.8 Hz, CHPh), 5.12 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1E), 5.11 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 5.09 (bd, 2H, <sup>2</sup>J = 10.7 Hz, 2×CHPh), 5.08 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1A), 5.04 (d, 2H, <sup>2</sup>J = 11.2 Hz, 2×CHPh), 4.98 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1F), 4.94 (t, 2H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1D, H-1B), 4.84-4.77 (m, 6H, 6×CHPh), 4.60-4.39 (m, 16H, 16×CHPh), 4.13-4.04 (m, 7H, H-3C, H-5A, H-3A, H-3E, H-3D, H-3F, H-3B), 3.99-3.88 (m, 9H, H-5C, H-5E, H-6E, H-4C, H-4A, H-6C, H-4E, H-5D, H-5B), 3.87-3.67 (m, 14H, H-6F, H-6D, H-5F, 2×H-6B, H-6D, H-6F, H-4F, H-4D, 2×SCHPh, H-4B, H-6C, H-6E), 3.50-3.40 (m, 6H, H-2C, H-2E, H-2A, H-2F, H-2B, H-2D), 2.89 (m, 2H, 2×H-6A)

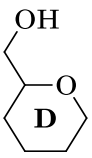
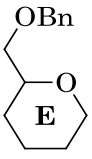
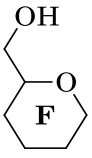
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.42, 139.39, 139.35, 139.34, 138.33, 139.27, 138.63, 138.43(2C), 138.40, 138.38, 138.36, 138.32, 138.02, 137.95 (15×C-Ar<sup>quat</sup>), 128.55-127.06 (75×C-Ar<sup>tert</sup>), 98.61, 98.45, 98.28, 97.92, 97.75, 97.71 (C-1C, C-1E, C-1A, C-1D, C-1B, C-1F), 81.35(C-4C), 81.17, 81.12, 81.08, 80.93, 80.85, 80.55 (C-3F, C-3B, C-3E, C-3D, C-3C, C-3A), 79.71, 79.61 (C-4A, C-4E), 79.36 (C-2D), 79.31(2C) (C-4B, C-2B), 79.20(2C) (C-4F, C-2F), 78.93 (C-2A), 78.86 (C-4A), 78.74, 78.62 (C-2E, C-2C), 75.65, 75.64, 75.51, 75.47, 75.41, 75.30, 73.70, 73.67, 73.18, 73.09(2C), 73.08, 73.01, 72.96 (14×CH<sub>2</sub>Ph), 72.47, 72.32(2C), 71.94, 71.93, 71.90 (C-5F, C-5D, C-5B, C-5E, C-5A, C-5C), 69.66, 69.44, 62.43, 62.34, 62.28 (C-6E, C-6C, C-6B, C-6D, C-6F), 37.64 (SCH<sub>2</sub>Ph), 33.64 (C-6A)

**HRMS (ESI):** Calcd. For C<sub>141</sub>H<sub>150</sub>O<sub>29</sub>SNa [M+Na]<sup>1+</sup>: 2361.9990; Found: 2361.9876 (-4.8 ppm)

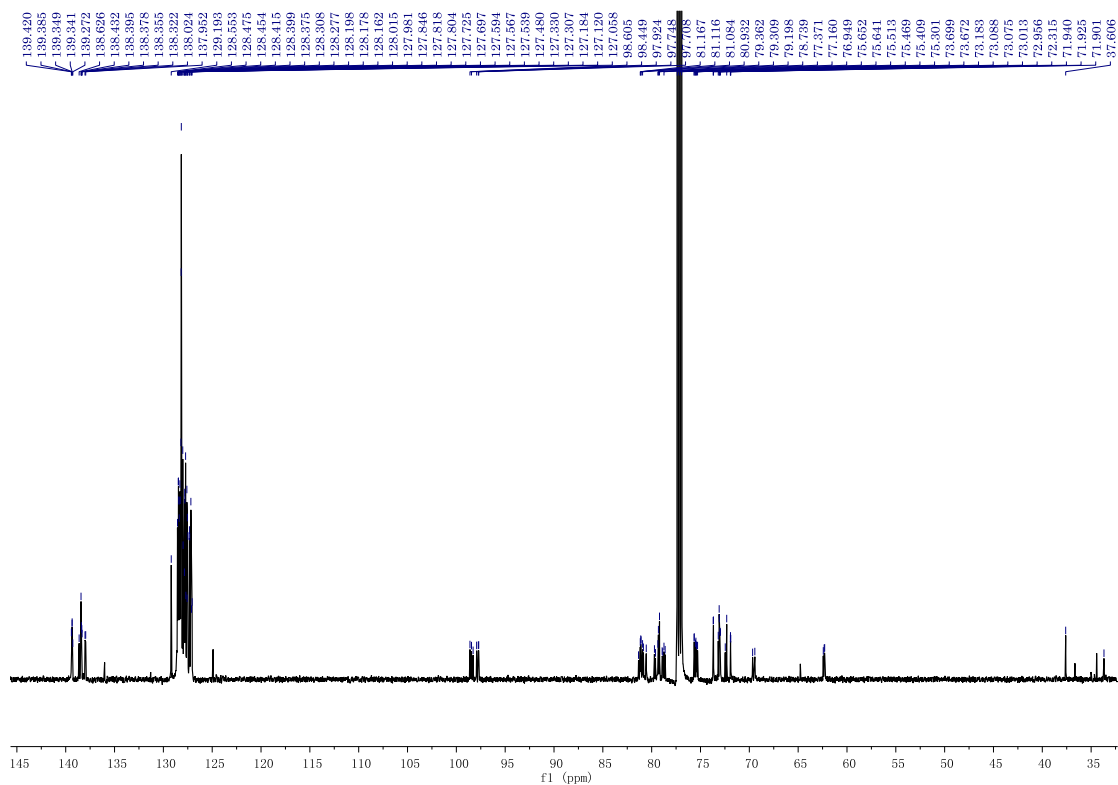
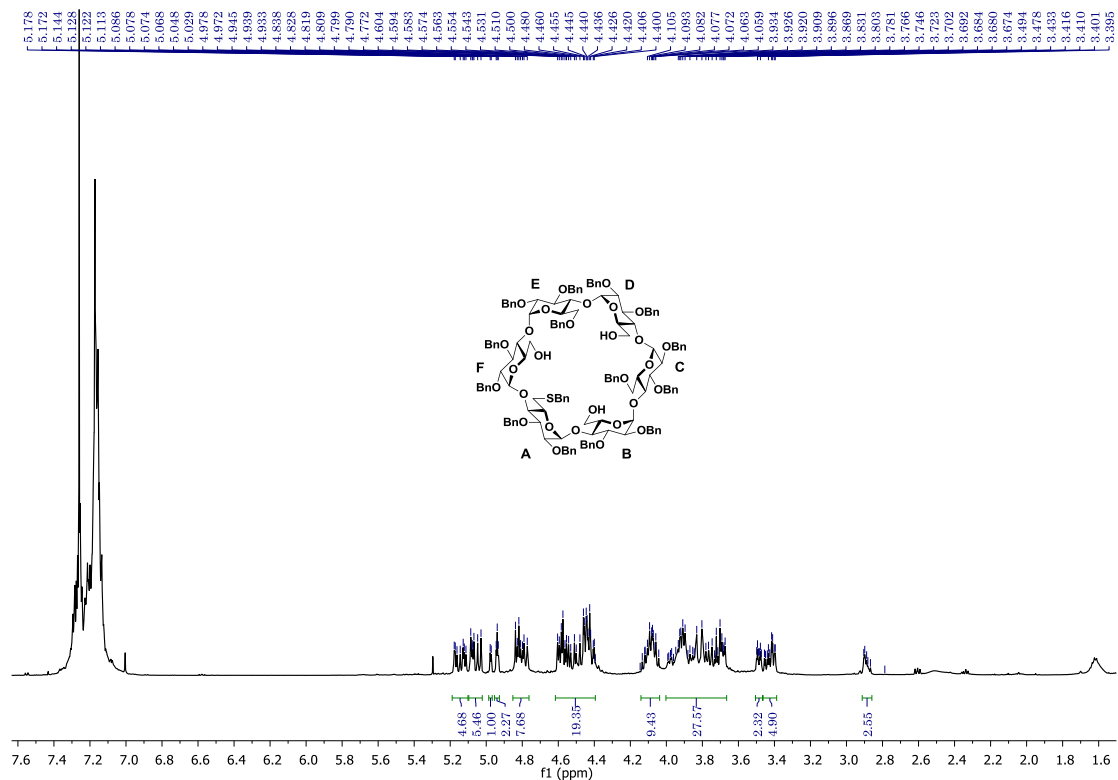
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1A	5.079	NOE: 3.698 ppm	H-4B
	C-1A	98.283		
	H-2A	3.445		
	C-2A	78.927		
	H-3A	4.089		
	C-3A	80.554		
	H-4A	3.925	NOE: 4.975 ppm	H-1F
	C-4A	79.714		
	H-5A	4.099		
	C-5A	71.925		
	H-6A	2.890		
		2.890		
C-6A	33.641			
	H-1B	4.935	NOE: 3.932 ppm	H-4C
	C-1B	97.748		
	H-2B	3.405		
	C-2B	79.309		
	H-3B	4.053		
	C-3B	81.116		
	H-4B	3.698	NOE: 5.079 ppm	H-1A
	C-4B	79.309		
	H-5B	3.905		
	C-5B	72.315		
	H-6B	3.834		
		3.834		
C-6B	62.426			
	H-1C	5.175	NOE: 3.749 ppm	H-4D
	C-1C	98.605		
	H-2C	3.494		
	C-2C	78.621		
	H-3C	4.118		
	C-3C	80.845		
	H-4C	3.932	NOE: 4.935 ppm	H-1B
	C-4C	81.345		
	H-5C	3.976		
	C-5C	71.901		
	H-6C	3.683		
		3.914		
C-6C	69.436			

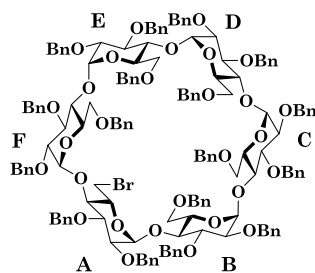
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	4.942	NOE: 3.907 ppm	H-4E
	C-1D	97.924		
	H-2D	3.402		
	C-2D	79.362		
	H-3D	4.074		
	C-3D	80.932		
	H-4D	3.749	NOE: 5.175 ppm	H-1C
	C-4D	78.861		
	H-5D	3.905		
	C-5D	72.315		
	H-6D	3.802		
		3.870		
C-6D	62.336			
	H-1E	5.124	NOE: 3.776 ppm	H-4F
	C-1E	98.449		
	H-2E	3.478		
	C-2E	78.739		
	H-3E	4.082		
	C-3E	81.084		
	H-4E	3.907	NOE: 4.942 ppm	H-1D
	C-4E	79.610		
	H-5E	3.938		
	C-5E	71.740		
	H-6E	3.679		
		3.933		
C-6E	69.622			
	H-1F	4.975	NOE: 3.925 ppm	H-4A
	C-1F	97.708		
	H-2F	3.420		
	C-2F	79.198		
	H-3F	4.068		
	C-3F	81.167		
	H-4F	3.776	NOE: 5.124 ppm	H-1E
	C-4F	79.198		
	H-5F	3.838		
	C-5F	72.465		
	H-6F	3.802		
		3.883		
C-6F	62.284			

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-Bromo-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>,6<sup>F</sup>-Heptadeca-  
O-Benzyl- $\alpha$ -Cyclodextrin (**273**)**



To a stirred mixture of triphenylphosphine (128 mg, 0.48 mmol, 3 eq.) and bromine (0.024 mL, 0.48 mmol, 3 eq.) in anhydrous DMF (10 mL), monol-cyclodextrin **107a** (400 mg, 0.16 mmol, 1 eq.) was added under nitrogen. The reaction mixture was stirred at 60°C for 1 h. The reaction was quenched with water (20 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 95/5, then 4/1) gave

bromo-cyclodextrin **273** (360 mg, 88%) as a white foam.

$\alpha_D = +34.4$  (c 1.0, CHCl<sub>3</sub>)

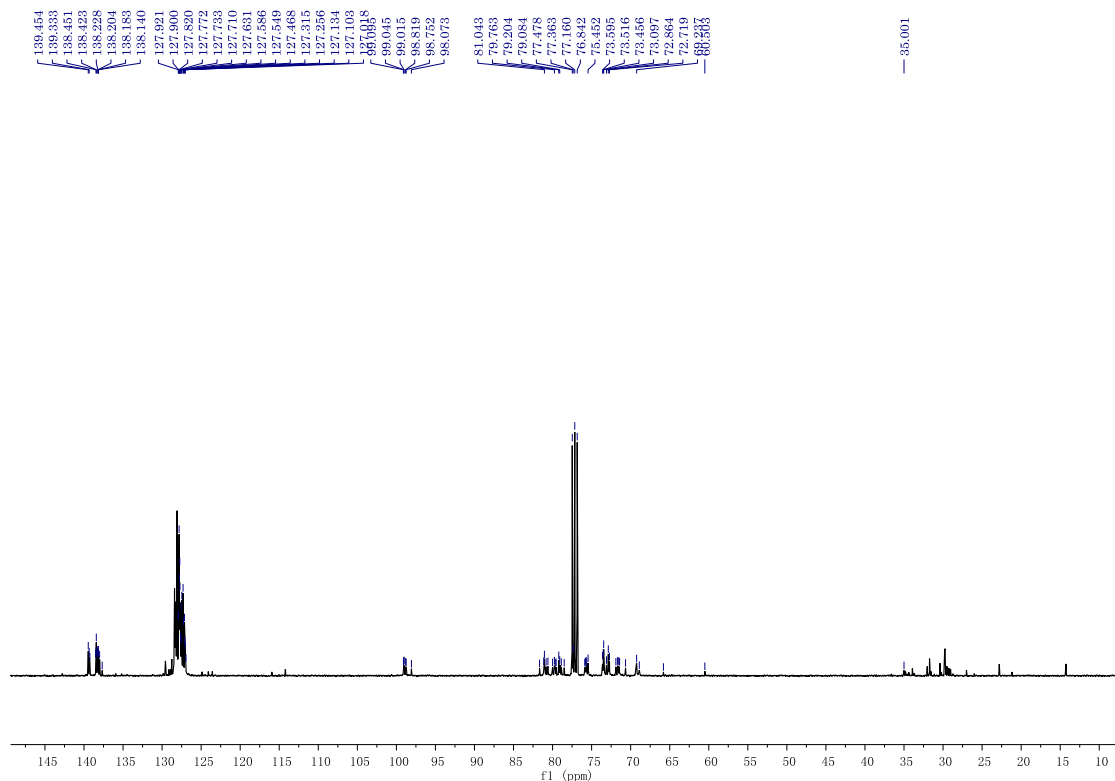
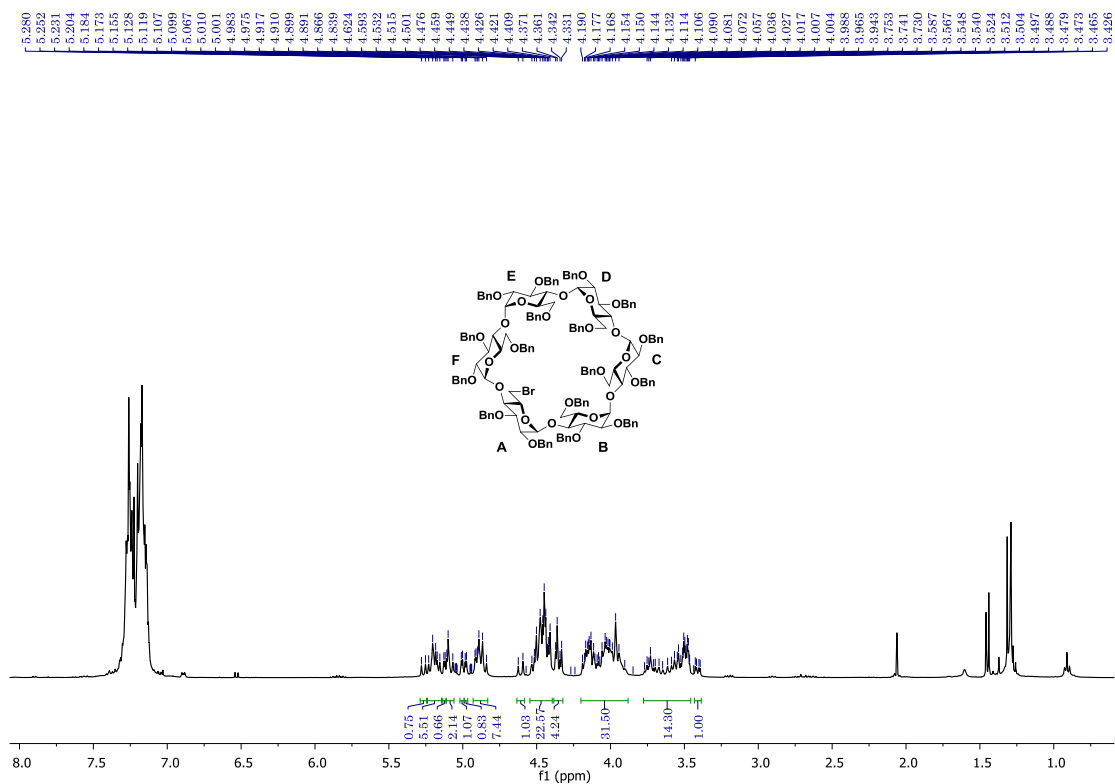
$R_f = 0.67$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.25-7.14 (m, 85H, 85×H-Ar.), 5.27 (d, 1H, <sup>2</sup>J=10.8 Hz, CHPh), 5.22 (d, 1H, <sup>2</sup>J=10.7 Hz, CHPh), 5.21 (d, 1H, <sup>2</sup>J=10.5 Hz, CHPh), 5.20 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.0 Hz, H-1), 5.19 (d, 1H, <sup>2</sup>J=10.4 Hz, CHPh), 5.18 (d, 1H, <sup>2</sup>J=11.4 Hz, CHPh), 5.13 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.5 Hz, H-1), 5.11 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.5 Hz, H-1), 5.10 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.1 Hz, H-1), 5.09 (d, 1H, <sup>2</sup>J=10.2 Hz, CHPh), 5.01 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.2 Hz, H-1), 4.98 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.5 Hz, H-1), 4.92-4.84 (m, 6H, 6×CHPh), 4.61-4.33 (m, 22H, 22×CHPh), 4.19-3.90 (m, 22H, 6×H-3, 5×H-4, 6×H-5, 5×H-6), 3.77-3.46 (m, 13H, 5×H-2, H-4, 7×H-6), 3.41 (dd, 1H, <sup>3</sup>J<sub>1,2</sub>=3.4 Hz, <sup>3</sup>J<sub>2,3</sub>=9.7 Hz, H-2)

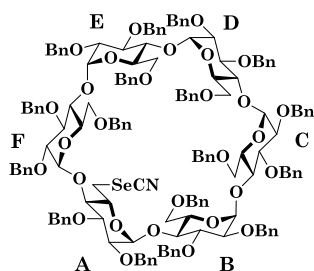
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.47, 139.45(2C), 139.33, 139.32, 139.25, 138.51, 138.45, 138.42(2C), 138.32, 138.28, 138.23, 138.20, 138.18, 138.14, 138.00 (17×C-Ar<sup>quat.</sup>), 128.45-127.01 (85×C-Ar<sup>tert.</sup>), 99.10, 99.05, 99.01, 98.82, 98.75, 98.07 (6×C-1), 81.67 (C-4), 81.13, 81.04(2C), 81.01, 80.83, 80.59 (6×C-3), 80.00, 79.79, 79.76, 79.65, 79.55 (5×C-4), 79.20(2C), 79.08, 79.05, 78.88, 78.51 (6×C-2), 75.88, 75.79, 75.69, 75.62, 75.45(2C), 73.59, 73.52, 73.46(2C), 73.43(2C), 73.10, 72.86(2C), 72.74, 72.72 (17×CH<sub>2</sub>Ph), 71.89, 71.67, 71.62, 71.50, 71.42, 70.66 (6×C-5), 69.32, 69.30, 69.24(2C), 68.89, 35.00 (6×C-6)

**HRMS (ESI):** Calcd. For C<sub>155</sub>H<sub>161</sub>O<sub>29</sub>BrNa [M+Na]<sup>1+</sup>: 2588.0188; Found: 2588.0199 (+0.4 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-Selenocyanate-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>,6<sup>F</sup>-Heptadeca-  
O-Benzyl- $\alpha$ -Cyclodextrin (274)**



Potassium selenocyanate (135 mg, 0.84 mmol, 6 eq.) was added to a solution of bromo-cyclodextrin **273** (360 mg, 0.14 mmol, 1 eq.) in DMF (15 mL). The reaction mixture was stirred at 60°C overnight. The reaction was quenched with water (30 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 4/1) gave selenocyanate-cyclodextrin **274** (290 mg, 80%) as a white foam.

$\alpha_D = +42.6$  (c 1.0, CHCl<sub>3</sub>)

$R_f = 0.49$  (CyH/EtOAc: 3/1)

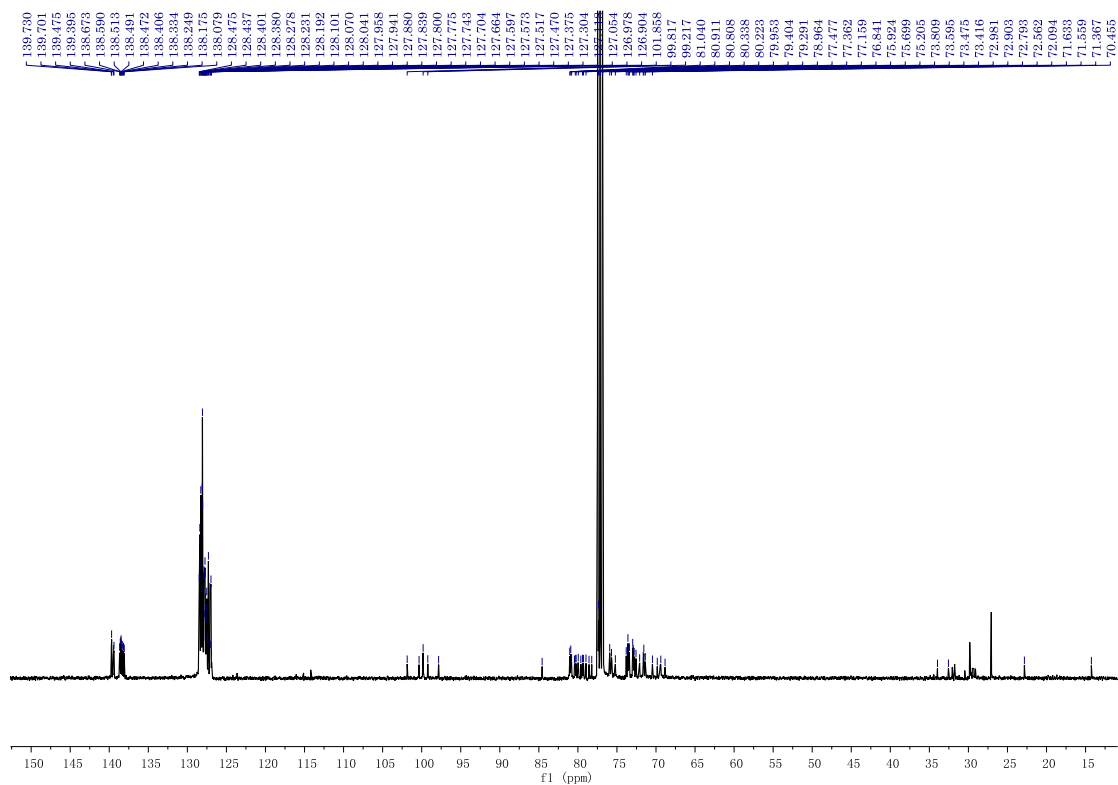
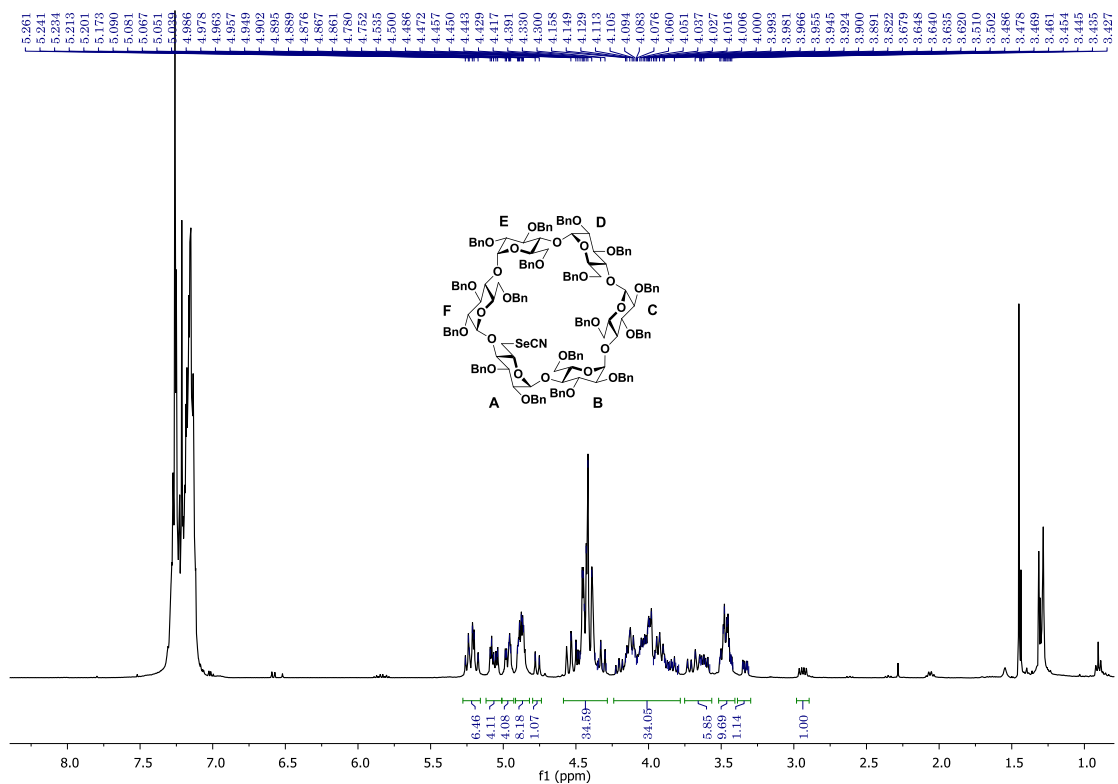
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.25-7.14 (m, 85H, 85×H-Ar.), 5.25 (d, 1H, <sup>2</sup>J=10.5 Hz, CHPh), 5.22 (d, 2H, <sup>2</sup>J=10.5 Hz, 2×CHPh), 5.20 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.4 Hz, H-1), 5.19 (d, 1H, <sup>2</sup>J=10.9 Hz, CHPh), 5.09 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.5 Hz, H-1), 5.07 (d, 1H, <sup>2</sup>J=11.7 Hz, CHPh), 5.05 (d, 1H, <sup>2</sup>J=11.2 Hz, CHPh), 4.98 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.2 Hz, H-1), 4.96 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.0 Hz, H-1), 4.95 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.2 Hz, H-1), 4.90-4.85 (m, 6H, H-1, 5×CHPh), 4.76 (d, 1H, <sup>2</sup>J=11.1 Hz, CHPh), 4.56-4.35 (m, 23H, 23×CHPh), 4.31 (d, 1H, <sup>2</sup>J=11.9 Hz, CHPh), 4.23-3.80 (m, 22H, 6×H-3, 5×H-4, 6×H-5, 5×H-6), 3.73-3.59 (m, 5H, 5×H-6), 3.51-3.43 (m, 7H, 5×H-2, H-4, H-6), 3.34 (dd, 1H, <sup>3</sup>J<sub>1,2</sub>=3.4 Hz, <sup>3</sup>J<sub>2,3</sub>=9.9 Hz, H-2), 2.94 (dd, 1H, <sup>3</sup>J<sub>5,6</sub>=6.5 Hz, <sup>2</sup>J<sub>6,6'</sub>=12.5 Hz, H-6)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.73, 139.70(2C), 139.48, 139.40, 139.38, 138.67, 138.60, 138.59, 138.51, 138.49, 138.47, 138.41, 138.33, 138.25, 138.18, 138.08 (17×C-Ar<sup>quat.</sup>), 128.48-126.97 (85×C-Ar<sup>tert.</sup>), 101.86 (SeCN), 100.34, 99.84, 99.82(2C), 99.22, 97.83 (6×C-1), 84.58 (C-4), 81.07, 81.04, 81.02 (3×C-3), 80.91(2C), 80.81 (3×C-4), 80.44, 80.34, 80.22 (3×C-3), 80.00, 79.95 (2×C-4), 79.62, 79.40, 79.29, 78.96, 78.58, 78.23 (6×C-2), 75.92(2C), 75.74, 75.70, 75.66, 75.21, 73.81, 73.60(2C), 73.58, 73.47, 73.42, 72.98, 72.90, 72.86, 72.79, 72.56 (17×CH<sub>2</sub>Ph), 72.10, 71.63, 71.56(2C), 71.37, 70.45 (6×C-5), 69.84, 69.51, 69.44, 69.38, 68.84, 32.58 (6×C-6)

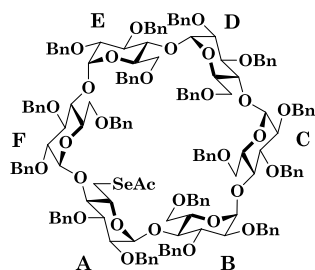
**HRMS (ESI):** Calcd. For C<sub>156</sub>H<sub>161</sub>O<sub>29</sub>NSeNa [M+Na]<sup>1+</sup>: 2615.0200; Found: 2615.0218 (+0.7 ppm)



EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-Se-Acetate-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>,6<sup>F</sup>-Heptadeca-  
O-Benzyl- $\alpha$ -Cyclodextrin (**275**)**



Lithium triethylborohydride (1 M in THF, 0.264 mL, 0.264 mmol, 2 eq.) was added to a solution of selenocyanate-cyclodextrin **274** (343 mg, 0.132 mmol, 1 eq.) in anhydrous THF (10 mL) under nitrogen at  $-78^{\circ}\text{C}$ . The reaction mixture was stirred for 15 min. Excess Acetic anhydrous (0.25 mL, 2.64 mmol, 10 eq.) was added. The reaction mixture was warmed up to r.t. gradually and stirred for another 2 h. Until the TLC showed the reaction finished, the reaction mixture was poured on ice and the aqueous phase was

extracted with EtOAc ( $3\times 30$  mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 5/1) gave selenoacetate- $\alpha$ -cyclodextrin **275** (176 mg, 51%) as a white foam.

$\alpha_{\text{D}} = +44.6$  (c 1.0,  $\text{CHCl}_3$ )

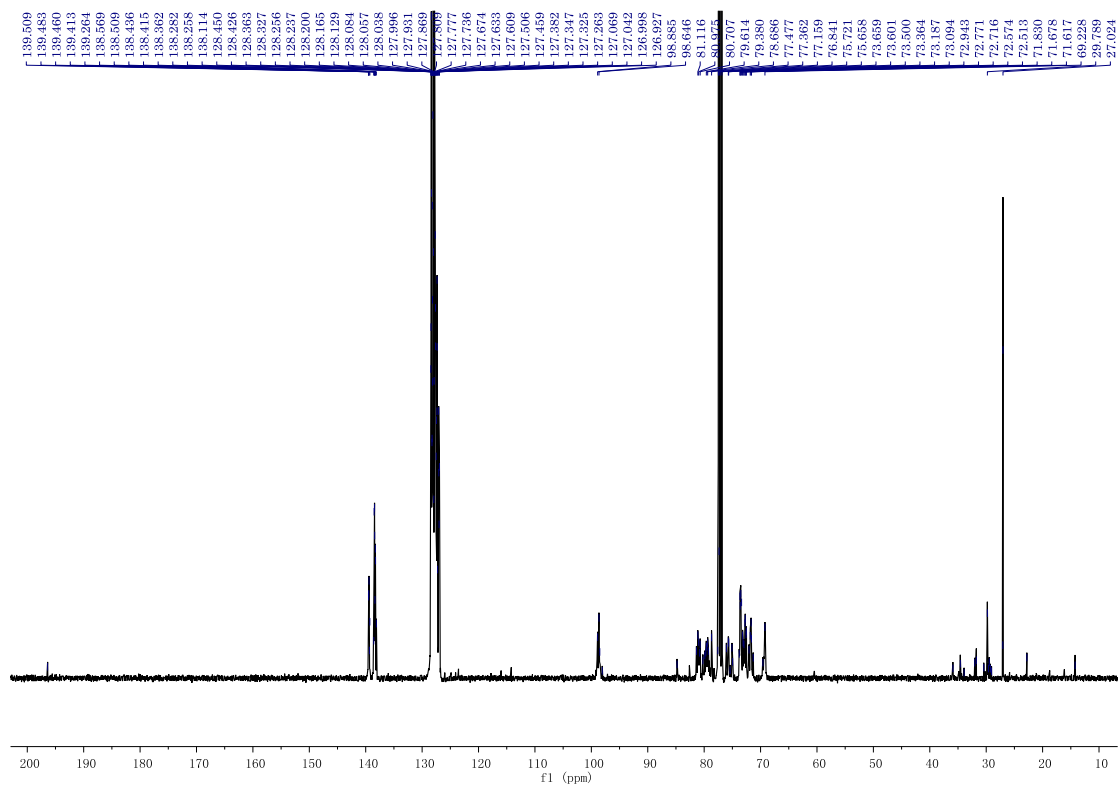
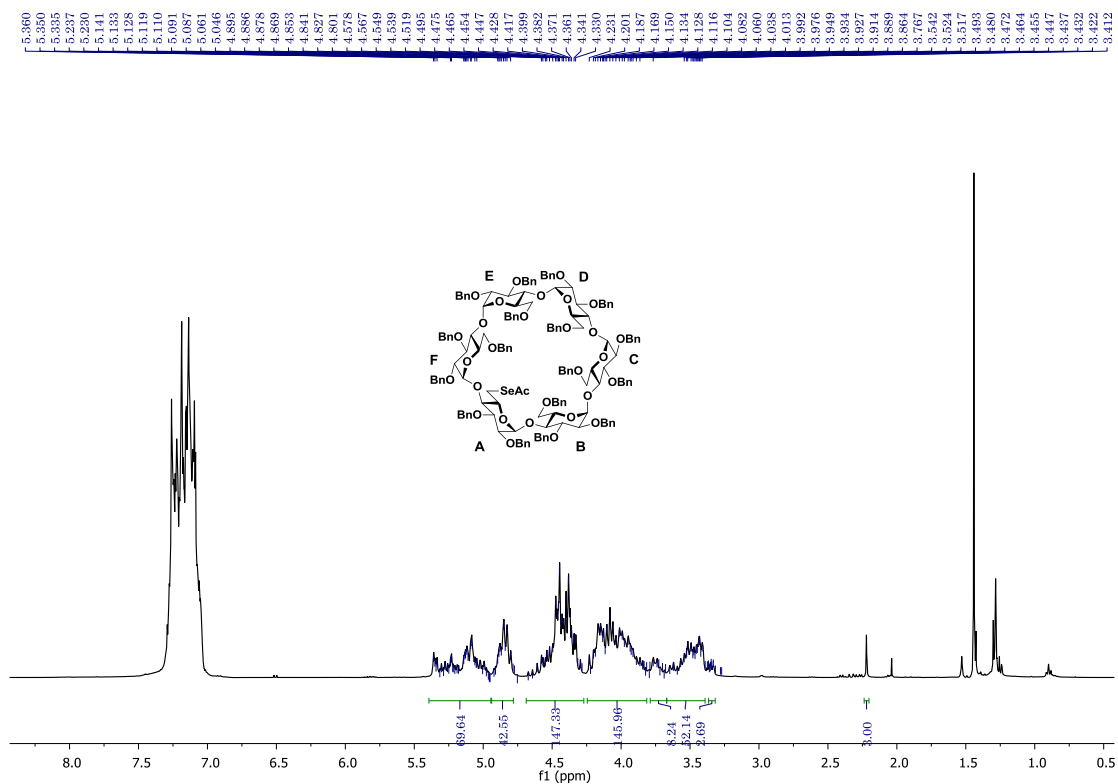
$R_f = 0.53$  (CyH/EtOAc: 4/1)

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.26-7.08 (m, 85H,  $85\times\text{H-Ar.}$ ), 5.36-4.98 (m, 11H,  $5\times\text{H-1}$ ,  $6\times\text{CHPh}$ ), 4.80-4.69 (m, 7H, H-1,  $6\times\text{CHPh}$ ), 4.57-4.19 (m, 22H,  $22\times\text{CHPh}$ ), 4.12-3.17 (m, 23H,  $6\times\text{H-3}$ ,  $6\times\text{H-4}$ ,  $6\times\text{H-5}$ ,  $5\times\text{H-6}$ ), 3.66-3.22 (m, 13H,  $7\times\text{H-6}$ ,  $6\times\text{H-2}$ ), 2.11 (s, 3H,  $\text{SeC(O)CH}_3$ )

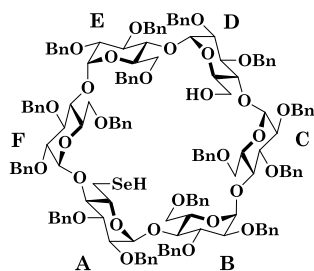
$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  196.40 ( $\text{SeC(O)CH}_3$ ), 139.51, 139.48, 139.46, 139.41, 139.40, 139.26, 138.51(2C), 138.44(2C), 138.42, 138.40, 138.36, 138.30, 138.28, 138.26, 138.12 ( $17\times\text{C-Ar}^{\text{quat.}}$ ), 128.45-126.93 ( $85\times\text{C-Ar}^{\text{tert.}}$ ), 98.89, 98.73, 98.65(2C), 98.60, 98.50 ( $6\times\text{C-1}$ ), 84.81 (C-4), 81.36, 81.13, 81.12, 81.03, 80.98, 80.71 ( $6\times\text{C-3}$ ), 80.21, 79.89, 79.70 ( $3\times\text{C-4}$ ), 79.62, 79.55, 79.38, 79.25 ( $4\times\text{C-2}$ ), 78.68(2C) (C-2, C-4), 78.61 (C-2), 77.36 (C-4), 76.11, 76.05, 75.72, 75.66, 75.08, 74.96, 73.66(2C), 73.60, 73.50(2C), 73.36(2C), 72.77, 72.72, 72.57, 72.51 ( $17\times\text{CH}_2\text{Ph}$ ), 72.05, 71.83, 71.66(2C), 71.62, 71.30 ( $6\times\text{C-5}$ ), 69.31, 69.28, 69.26, 69.23, 69.14, 35.87 ( $6\times\text{C-6}$ ), 34.57 ( $\text{SeC(O)CH}_3$ )

**HRMS (ESI):** Calcd. For  $\text{C}_{157}\text{H}_{164}\text{O}_{30}\text{SeNa}$   $[\text{M}+\text{Na}]^{1+}$ : 2632.0386; Found: 2362.0372 (-0.5 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-Selenol-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>-Hexadeca-  
O-Benzyl- $\alpha$ -Cyclodextrin (**276**)**



DIBAL-H (1.5 M in toluene, 1.0 mL, 1.54 mmol, 20 eq.) was added to a solution of cyclodextrin **275** (200 mg, 0.077 mmol, 1 eq.) in toluene (0.54 mL) under nitrogen at r. t. The reaction mixture was stirred at 55°C with a nitrogen balloon reflux for 10 min, until mass spectrometry indicated that the formation of selenol-alcohol-cyclodextrin was the major product, and then cooled to r.t. and poured into ice/water. Aqueous HCl (5 mL, 1 M) and EtOAc (5 mL) were added, and the solution was stirred for 1

h. The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Silica gel chromatography of the residue (CyH/EtOAc: 5/1) gave cyclodextrin **276** (100 mg, 52%) as a white foam.

$\alpha_D = +37.9$  (c 1.0, CHCl<sub>3</sub>)

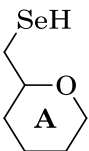
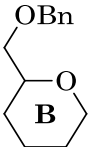
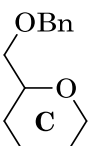
$R_f = 0.40$  (CyH/EtOAc: 3/1)

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.31-7.13 (m, 80H, 80×H-Ar.), 5.55 (d, 1H,  $^3J_{1,2} = 3.8$  Hz, H-1F), 5.54 (d, 1H,  $^3J_{1,2} = 3.7$  Hz, H-1C), 5.44 (d, 1H,  $^2J = 10.8$  Hz, CHPh), 5.37 (d, 1H,  $^2J = 10.8$  Hz, CHPh), 5.27 (d, 1H,  $^2J = 10.8$  Hz, CHPh), 5.24 (d, 1H,  $^2J = 10.8$  Hz, CHPh), 4.97 (d, 1H,  $^2J = 10.8$  Hz, CHPh), 4.95 (d, 1H,  $^3J_{1,2} = 3.3$  Hz, H-1E), 4.94 (d, 2H,  $^2J = 10.7$  Hz, 2×CHPh), 4.93 (d, 1H,  $^2J = 10.3$  Hz, CHPh), 4.92 (d, 1H,  $^3J_{1,2} = 3.2$  Hz, H-1B), 4.91 (d, 1H,  $^2J = 11.0$  Hz, CHPh), 4.87-4.85 (m, 4H, H-1D, 3×CHPh), 4.80 (d, 1H,  $^2J = 12.2$  Hz, CHPh), 4.78 (d, 1H,  $^3J_{1,2} = 3.1$  Hz, H-1A), 4.72 (d, 1H,  $^2J = 12.2$  Hz, CHPh), 4.64-4.36 (m, 18H, 18×CHPh), 4.27 (t, 1H,  $^3J_{2,3} = 9.5$  Hz,  $^3J_{3,4} = 8.3$  Hz, H-3F), 4.24 (t, 1H,  $^3J_{2,3} = 9.5$  Hz,  $^3J_{3,4} = 8.1$  Hz, H-3C), 4.19-3.87 (m, 21H, H-3A, H-3B, H-3D, H-3E, H-4A, H-4B, H-4C, H-4D, H-4E, H-4F, H-5A, H-5B, H-5C, H-5D, H-5E, H-5F, H-6B, H-6C, H-6D, H-6E, H-6F), 3.82 (d, 1H,  $^2J_{6,6'} = 10.4$  Hz, H-6C), 3.79 (d, 1H,  $^2J_{6,6'} = 10.5$  Hz, H-6F), 3.72-3.66 (m, 3H, H-6B, H-6D, H-6E), 3.63-3.60 (m, 2H, H-2F, H-2C), 3.52-3.49 (m, 2H, H-2B, H-2E), 3.45 (dd, 1H,  $^3J_{1,2} = 3.0$  Hz,  $^3J_{2,3} = 9.7$  Hz, H-2D), 3.41 (dd, 1H,  $^3J_{1,2} = 3.2$  Hz,  $^3J_{2,3} = 9.6$  Hz, H-2F), 3.00 (m, 1H, H-6A), 2.87 (m, 1H, H-6A)

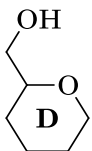
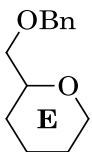
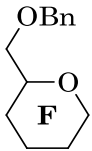
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.41, 139.40, 139.37, 139.35, 139.33(2C), 138.60(2C), 138.48, 138.28, 138.26, 138.19, 138.18, 138.14, 138.00, 137.89 (16×C-Ar<sup>quat</sup>), 128.50-126.61 (80×C-Ar<sup>tert</sup>), 98.79, 98.57, 98.49, 98.47, 98.37, 98.15 (C-1F, C-1B, C-1D, C-1A, C-1C, C-1E), 80.36 (C-4B), 81.30, 81.06 (C-3D, C-3F), 80.94 (C-4E), 80.88(2C), 80.83, 80.74 (C-3B, C-3E, C-3C, C-3A), 80.73, 80.37 (C-4C, C-4F), 79.96 (C-2A), 79.77 (C-4A), 79.53, 79.09, 79.03, 78.14, 78.11 (C-2D, C-2E, C-2B, C-2C, C-2F), 76.31, 76.25 (2×CH<sub>2</sub>Ph), 76.19 (C-4D), 75.96, 75.81, 74.62, 74.44, 73.58, 73.55, 73.46, 73.42, 73.39, 73.18, 73.08, 73.06, 72.50, 72.46 (14×CH<sub>2</sub>Ph), 71.99, 71.96, 71.93, 71.81, 71.54, 70.00 (C-5F, C-5C, C-5B, C-5E, C-5D, C-5A), 69.64, 69.61, 69.25, 69.24, 61.70, 20.68 (C-6C, C-6F, C-6B, C-6E, C-6D, C-6A)

**HRMS (ESI):** Calcd. For C<sub>148</sub>H<sub>156</sub>O<sub>29</sub>SeNa [M+Na]<sup>1+</sup>: 2499.9698; Found: 2499.9796 (+3.9 ppm)

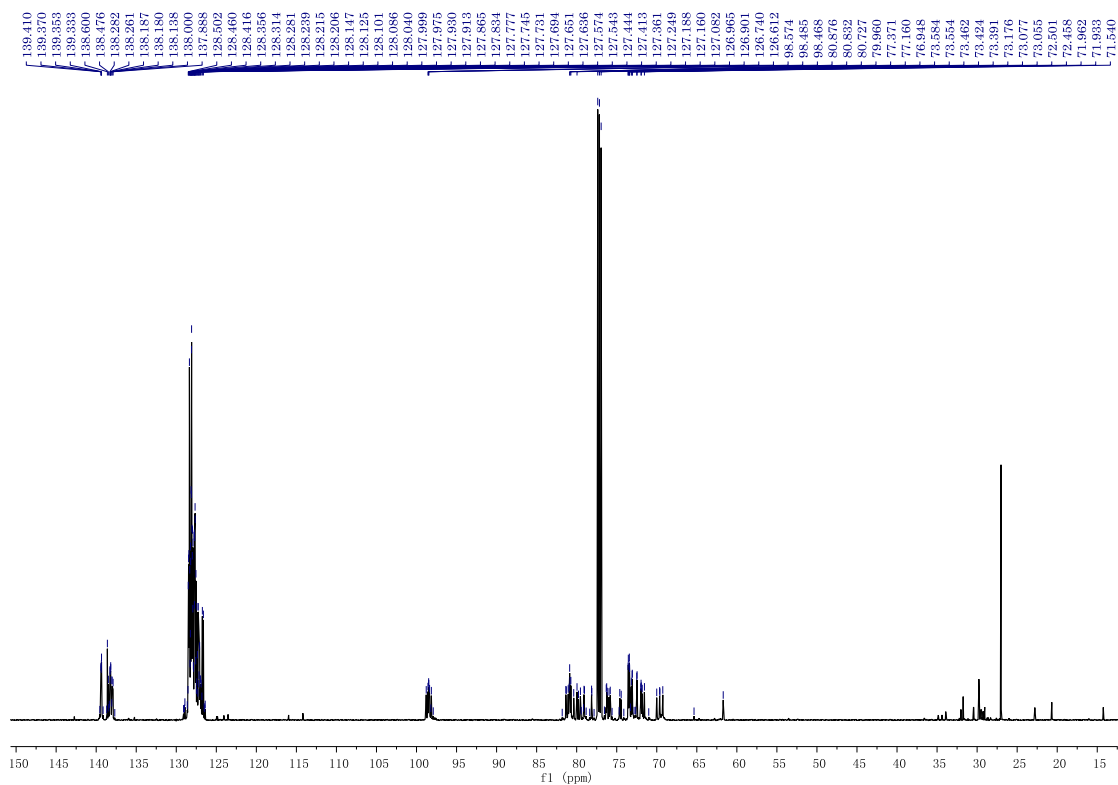
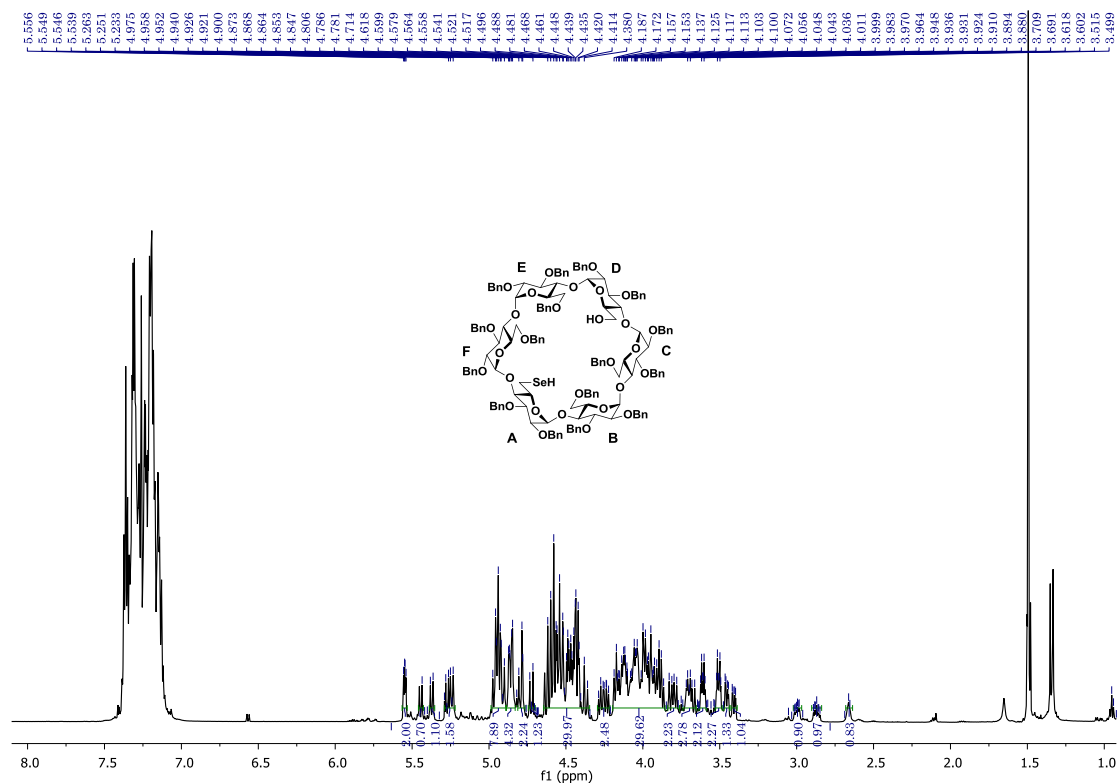
**EXPERIMENTAL PART**

	<b>Attribution</b>	<b>Signal (ppm)</b>	<b>Correlation(ppm)</b>	<b>Attribution</b>
 <p style="text-align: center;"><b>A</b></p>	H-1A	4.783	NOE: 3.913 ppm	H-4B
	C-1A	98.47		
	H-2A	3.408		
	C-2A	79.96		
	H-3A	4.123		
	C-3A	80.74		
	H-4A	3.880	NOE: 5.552 ppm	H-1F
	C-4A	79.77		
	H-5A	4.073		
	C-5A	70.00		
	H-6A	2.993		
		2.873		
	C-6A	20.68		
 <p style="text-align: center;"><b>B</b></p>	H-1B	4.923	NOE: 3.960 ppm	H-4C
	C-1B	98.57		
	H-2B	3.449		
	C-2B	79.03		
	H-3B	4.113		
	C-3B	80.88		
	H-4B	3.913	NOE: 4.783 ppm	H-1A
	C-4B	81.36		
	H-5B	3.933		
	C-5B	71.93		
	H-6B	3.709		
		4.049		
	C-6B	69.25		
 <p style="text-align: center;"><b>C</b></p>	H-1C	5.543	NOE: 3.948 ppm	H-4D
	C-1C	98.37		
	H-2C	3.602		
	C-2C	78.14		
	H-3C	4.232		
	C-3C	80.83		
	H-4C	3.960	NOE: 4.923 ppm	H-1B
	C-4C	80.73		
	H-5C	4.043		
	C-5C	71.96		
	H-6C	3.983		
		3.821		
	C-6C	69.64		

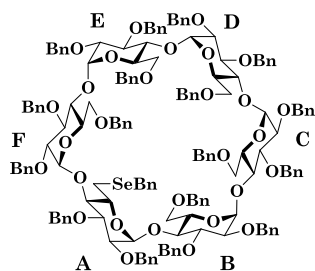
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	4.850	NOE: 3.985 ppm	H-4E
	C-1D	98.49		
	H-2D	3.454		
	C-2D	79.53		
	H-3D	4.170		
	C-3D	81.30		
	H-4D	3.948	NOE: 5.543 ppm	H-1C
	C-4D	76.19		
	H-5D	4.002		
	C-5D	71.54		
	H-6D	3.715		
		3.916		
C-6D	61.70			
	H-1E	4.955	NOE: 4.137 ppm	H-4F
	C-1E	98.15		
	H-2E	3.515		
	C-2E	79.09		
	H-3E	4.103		
	C-3E	80.88		
	H-4E	3.985	NOE: 4.850 ppm	H-1D
	C-4E	80.94		
	H-5E	3.985		
	C-5E	71.81		
	H-6E	3.686		
		4.049		
C-6E	69.24			
	H-1F	5.552	NOE: 3.880 ppm	H-4A
	C-1F	98.79		
	H-2F	3.618		
	C-2F	78.11		
	H-3F	4.267		
	C-3F	81.06		
	H-4F	4.137	NOE: 4.955 ppm	H-1E
	C-4F	80.37		
	H-5F	3.885		
	C-5F	71.99		
	H-6F	3.789		
		4.179		
C-6F	69.61			

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-Se-Benzyl-2<sup>A-F</sup>,3<sup>A-F</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>,6<sup>F</sup>-Heptadeca-  
O-Benzyl- $\alpha$ -Cyclodextrin (**277**)**



Sodium hydride (60% in mineral oil, 0.053 mg, 1.32 mmol, 6 eq.) was added to a solution of selenoacetate-cyclodextrin **275** (550 mg, 0.22 mmol, 1 eq.) in anhydrous DMF (10 mL) under nitrogen. The reaction mixture was stirred for 30 min at 75°C. Benzyl bromide (0.157 mL, 1.32 mmol, 6 eq.) was added, and the reaction mixture was stirred for another 5 h at r.t.. Until the TLC showed the reaction finished, Water (30 mL) was added and the aqueous phase was extracted with EtOAc (3×30 mL). The

combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 98/2, then 5/1) gave selenobenzyl- $\alpha$ -cyclodextrin **277** (379 mg, 69%) as a white foam.

$\alpha_D = +39.7$  (c 1.0, CHCl<sub>3</sub>)

$R_f = 0.67$  (CyH/EtOAc: 3/1)

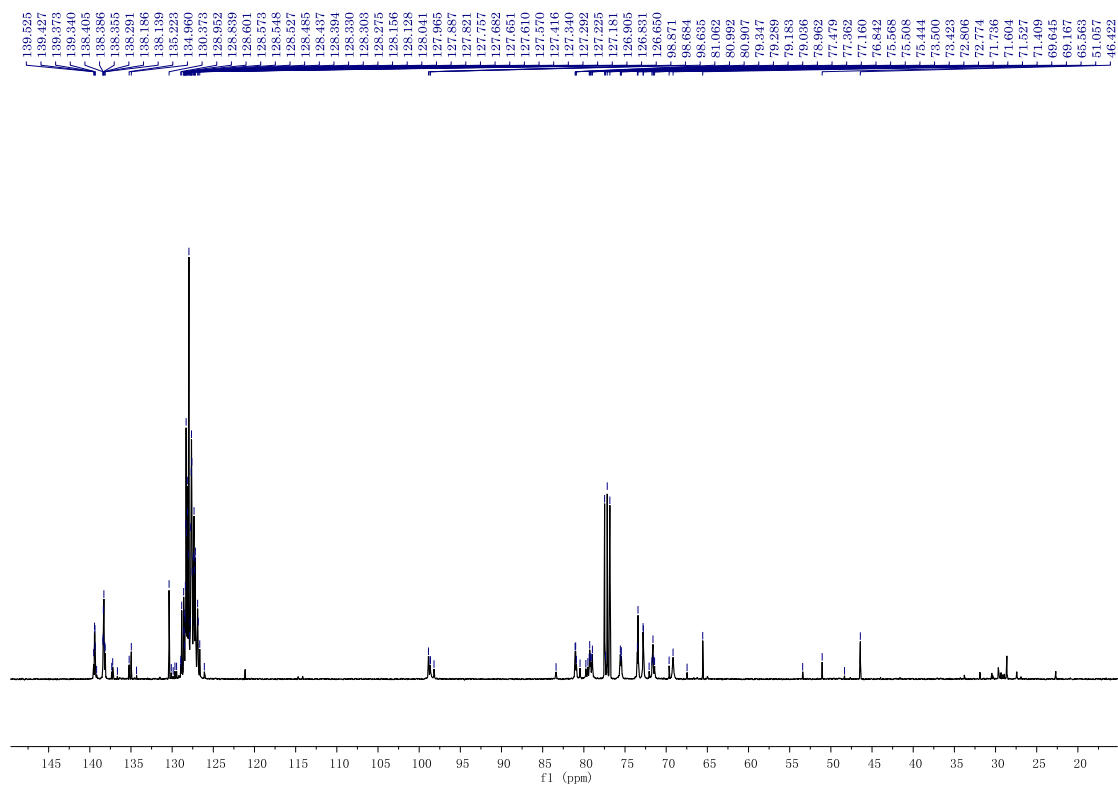
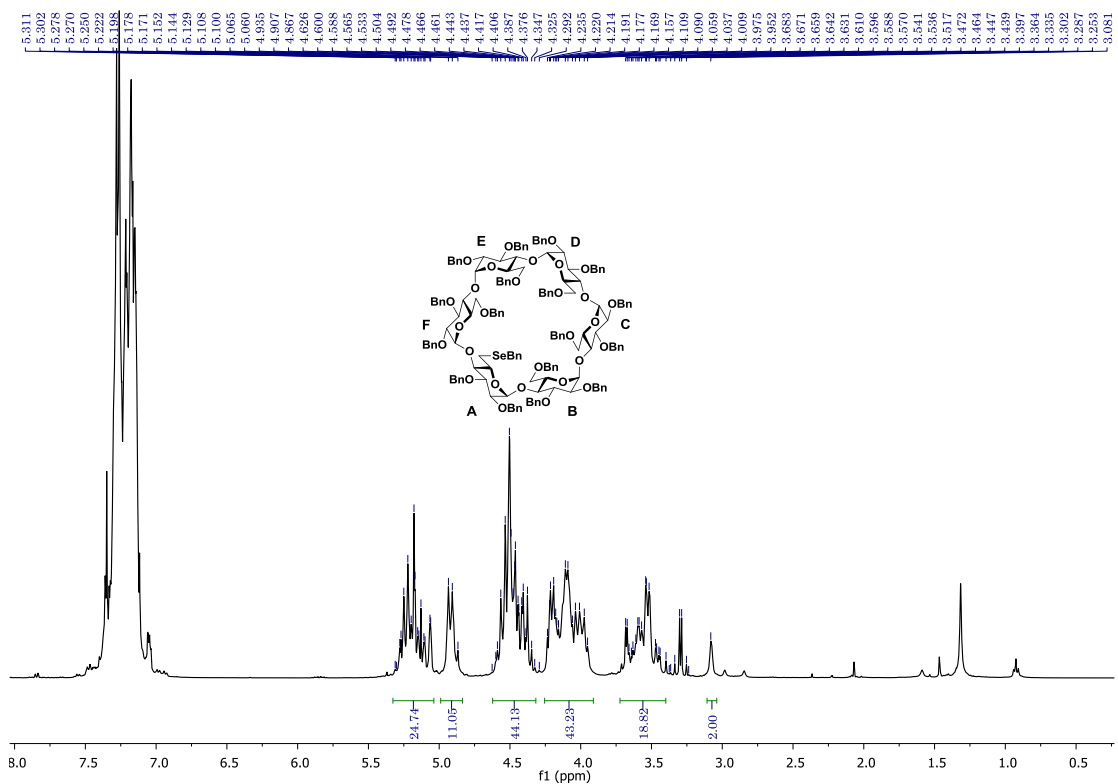
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.32-7.14 (m, 90H, 90×H-Ar.), 5.28-5.06 (m, 12H, 6×H-1, 6×CHPh), 4.94-4.90 (m, 6H, 6×CHPh), 4.59-4.35 (m, 22H, 22×CHPh), 4.24-3.95 (m, 23H, 6×H-3, 6×H-4, 6×H-5, 5×H-6), 3.68-3.44 (m, 13H, 6×H-2, 5×H-6, 2×SeCHPh), 3.08 (m, 2H, 2×H-6)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  138.53, 139.43(2C), 139.37(2C), 139.34, 138.41, 138.39, 138.36(3C), 138.34(2C), 138.29(3C), 138.19, 138.14 (18×C-Ar<sup>quat.</sup>), 128.60-126.66 (90×C-Ar<sup>tert.</sup>), 98.87(2C), 98.82, 98.68, 98.64, 98.20 (6×C-1), 83.38 (C-4), 81.06(2C), 80.99(2C), 80.91, 80.46 (6×C-3), 79.75, 79.51, 79.35, 79.29(2C) (5×C-4), 79.26(2C) (C-4, C-2), 79.18, 79.04, 78.96(2C) (4×C-2), 75.63, 75.57(2C), 75.51, 75.44(2C), 73.50, 73.42 (2C), 72.83(2C), 72.81(2C), 72.77(2C), 72.74(2C) (17×CH<sub>2</sub>Ph), 71.74, 71.60(3C), 71.53, 71.41 (6×C-5), 69.24, 69.22, 69.17(2C), 69.10 (5×C-6), 28.64 (SeCH<sub>2</sub>Ph), 27.42 (C-6)

**HRMS (ESI):** Calcd. For C<sub>162</sub>H<sub>168</sub>O<sub>29</sub>SeNa [M+Na]<sup>1+</sup>: 2680.0716; Found: 2680.0736 (+0.7 ppm)

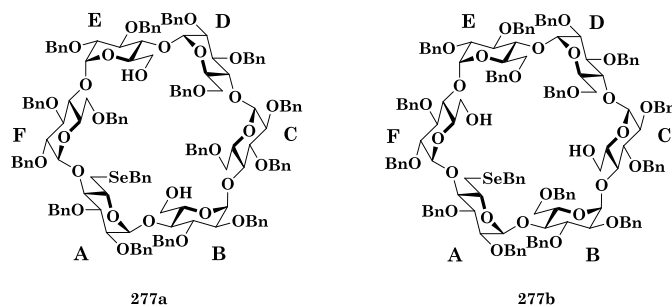


EXPERIMENTAL PART

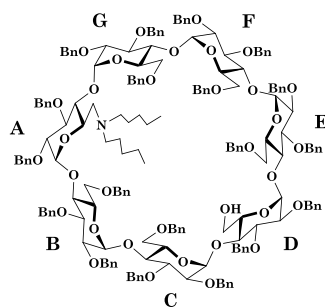


**6<sup>A</sup>-Deoxy-6<sup>A</sup>-Se-Benzyl- $\alpha$ -Cyclodextrin (277) was debenzylated by DIBAL-H**

DIBAL-H (1.5 M in toluene, 1.9 mL, 2.86 mmol, 20 eq.) was added to a solution of selenobenzyl-cyclodextrin **277** (379 mg, 0.143 mmol, 1 eq.) in toluene (0.9 mL) under nitrogen at r. t. The reaction mixture was stirred at 55°C with a nitrogen balloon reflux for 45 min, until Mass spectrum indicated formation of diol as a major product, and then cooled to r.t. and poured into ice/water. Aqueous HCl (5 mL, 1 M) and EtOAc (5 mL) were added, and the solution was stirred for 1 h. The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuum*. Silica gel chromatography of the residue (CyH/EtOAc: 4/1) gave an inseparable mixture (80 mg) of BE-diol-cyclodextrin **277a** and CF-diol-cyclodextrin **277b** as white foams.



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-N-Dipentyl-Amino-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>,6<sup>G</sup>-Nonadeca-O-Benzyl-β-cyclodextrin (281)**



To a solution of amino-alcohol **158-M** (250 mg, 0.09 mmol, 1 eq.) in dichloromethane (10 mL), valeraldehyde (0.04 mL, 0.36 mmol, 4 eq.), NaBH(OAc)<sub>3</sub> (115 mg, 0.54 mmol, 6 eq.), AcOH (0.01 mL, 0.18 mmol, 2 eq.) were added. The reaction mixture was stirred for 2 h, then sat. NaHCO<sub>3</sub> (10 mL) was added and the aqueous layers were extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc: 4/1) afforded

cyclodextrin **281** (200 g, 70%) as a white foam.

$\alpha_D = +37.6$  (c 1.0, CHCl<sub>3</sub>)

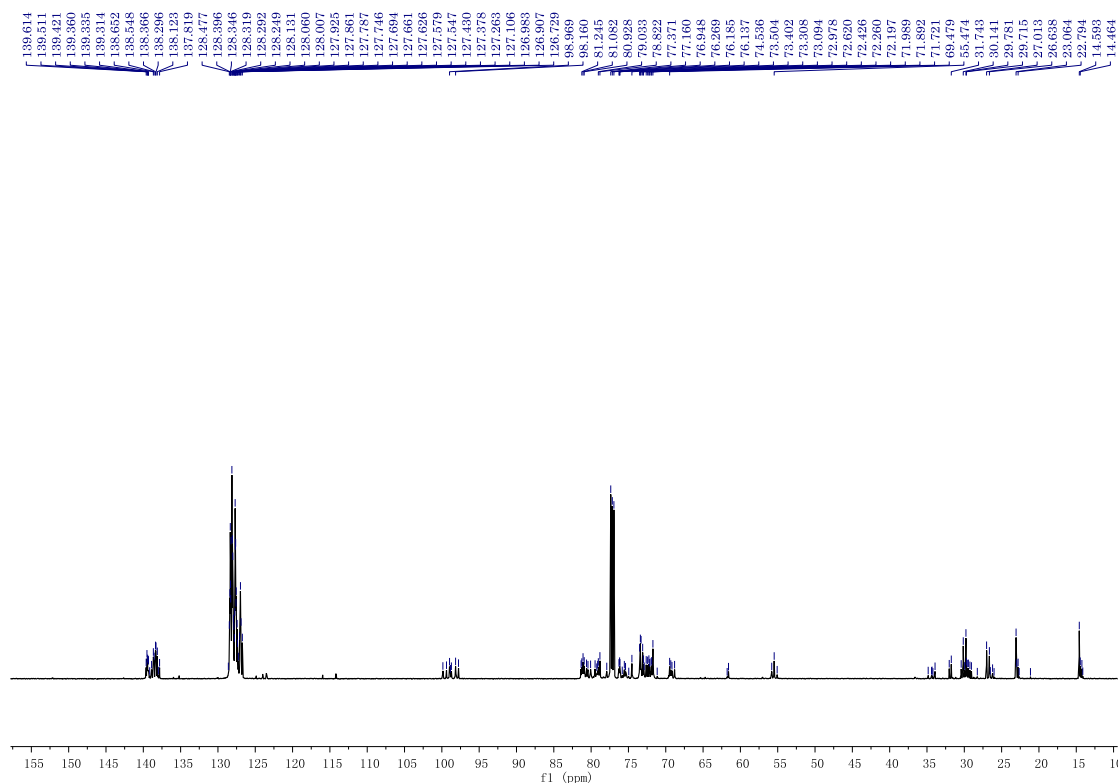
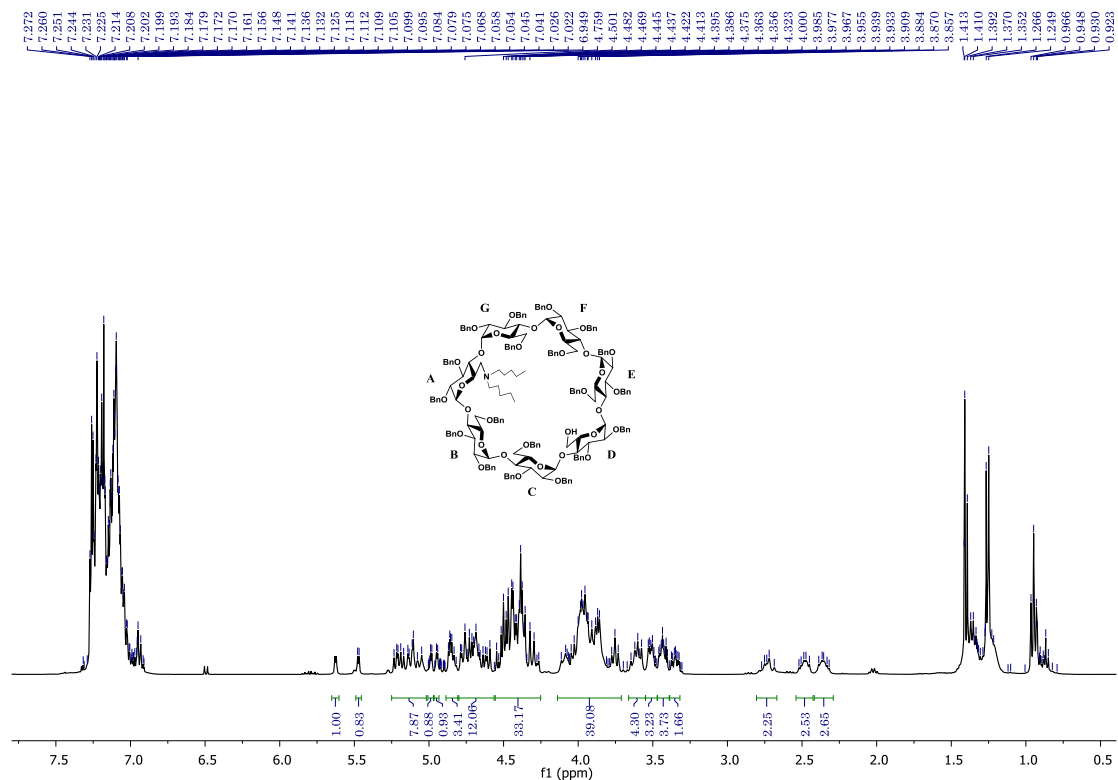
$R_f = 0.57$  (CyH/EtOAc: 2/1)

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400MHz):  $\delta$  7.27-7.02 (m, 95H, 95×H-Ar), 5.63 (d, 1H,  $^3J_{1,2} = 3.7$  Hz, H-1), 5.47 (d, 1H,  $^3J_{1,2} = 3.7$  Hz, H-1), 5.23 (d, 1H,  $^2J = 10.6$  Hz, CHPh), 5.21 (d, 1H,  $^2J = 10.7$  Hz, CHPh), 5.15 (d, 1H,  $^2J = 11.1$  Hz, CHPh), 5.13 (d, 1H,  $^2J = 11.1$  Hz, CHPh), 5.11 (d, 1H,  $^3J_{1,2} = 3.3$  Hz, H-1), 5.06 (d, 1H,  $^2J = 10.6$  Hz, CHPh), 4.98 (d, 1H,  $^3J_{1,2} = 3.7$  Hz, H-1), 4.95 (d, 1H,  $^3J_{1,2} = 3.4$  Hz, H-1), 4.86 (d, 1H,  $^3J_{1,2} = 3.7$  Hz, H-1), 4.85 (d, 1H,  $^3J_{1,2} = 3.7$  Hz, H-1), 4.83 (d, 1H,  $^2J = 11.0$  Hz, CHPh), 4.79-4.66 (m, 8H, 8×CHPh), 4.63 (d, 1H,  $^2J = 10.6$  Hz, CHPh), 4.60 (d, 1H,  $^2J = 11.9$  Hz, CHPh), 4.55-4.30 (m, 23H, 22×CHPh, H-6), 4.11-3.86 (m, 24H, 7×H-3, 7×H-5, 5×H-4, 5×H-6), 3.78-3.73 (m, 3H, H-4, 2×H-6), 3.65-3.57 (m, 4H, 4×H-6), 3.53-3.40 (m, 6H, 5×H-2, H-6), 3.36 (dd, 1H,  $^3J_{1,2} = 3.3$  Hz,  $^3J_{2,3} = 9.7$  Hz, H-2), 3.34 (dd, 1H,  $^3J_{1,2} = 3.1$  Hz,  $^3J_{2,3} = 9.7$  Hz, H-2), 2.77-2.68 (m, 2H, 2×H-6), 2.49 (m, 2H, N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 2.36 (m, 2H, N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 1.41-1.38 (m, 4H, 2×N-CH<sub>2</sub>-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>3</sub>), 1.37-1.33 (m, 4H, 2×N-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 1.27-1.24 (m, 4H, 2×N-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 0.95 (t, 6H, 2×N-(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>)

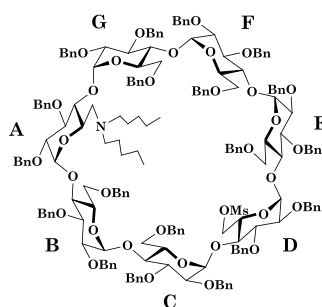
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.61, 139.51(2C), 139.42, 139.36, 139.33, 139.31, 138.89, 138.65, 138.55, 138.37(2C), 138.30(2C), 138.26, 138.12(2C), 137.82 (19×C-Ar<sup>quat.</sup>), 128.48-126.73 (95×C-Ar<sup>tert.</sup>), 99.80, 99.38, 98.97, 98.72, 98.16, 98.13, 97.77 (7×C-1), 81.35 (C-3), 81.24, 81.20 (2×C-4), 81.08(3C) (2×C-3, C-4), 80.93, 80.87, 80.61, 80.42 (4×C-3), 80.07 (C-4), 79.47 (2C) (2×C-2), 79.24 (C-4), 79.13, 79.03, 78.82(2C) (4×C-2), 77.90 (C-4), 77.12 (C-2), 76.27, 76.19, 76.14, 75.55, 75.39 (5×CH<sub>2</sub>Ph), 75.33 (C-4), 74.54(2C), 73.50, 73.49, 73.40(2C), 73.31(2C), 73.09(2C), 72.98, 72.62, 72.43, 72.26 (14×CH<sub>2</sub>Ph), 72.20, 71.99, 71.89, 71.72(3C), 71.68 (7×C-5), 69.48, 69.44, 69.33, 69.17, 68.82, 61.60, 55.81 (7×C-6), 54.49(2C) (2×N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 30.13(2C) (2×N-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 26.64(2C) (2×N-CH<sub>2</sub>-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>3</sub>), 23.07(2C) (2×N-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 14.60(2C) (2×N-(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>185</sub>H<sub>206</sub>NO<sub>34</sub> [M+H]<sup>1+</sup>: 2985.4541; Found: 2985.4416 (-4.2 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-N-Dipentyl-Amino-6<sup>D</sup>-O-Methanesulfonyl-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>,6<sup>G</sup>-Nonadeca-O-Benzyl-β-cyclodextrin (281a)**



To a solution of cyclodextrin **281** (4.0 g, 1.34 mmol, 1 eq.) in pyridine (30 mL) were added DMAP (327 mg, 2.68 mmol, 2 eq.) and MsCl (416  $\mu$ L, 5.36 mmol, 4 eq.) at r.t. The reaction mixture was stirred for 2 h under nitrogen, then the solvent was reduced to dryness. The crude was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and washed with water (30 mL), then the aqueous layers were extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 $\times$ 30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel

flash chromatography (CyH/EtOAc 5/1) afforded cyclodextrin **281a** (4.1 g, 97%) as a white foam.

$\alpha_D = +44.8$  (c 1.0, CHCl<sub>3</sub>)

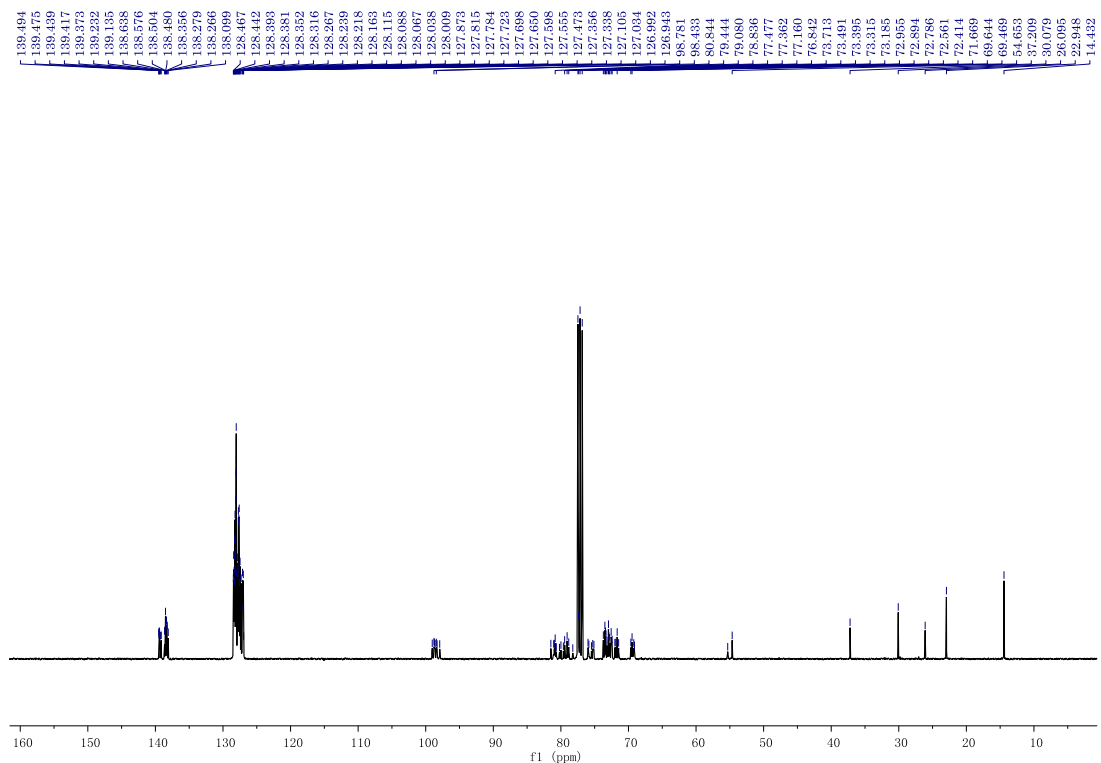
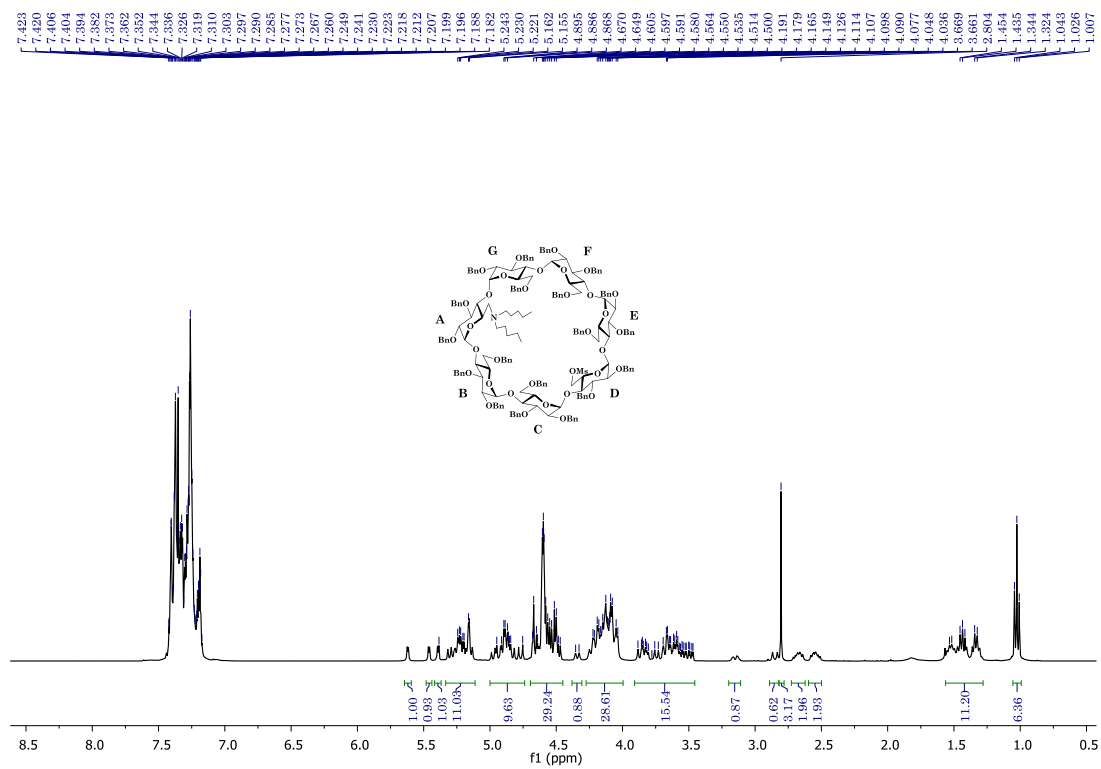
$R_f = 0.51$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.42-7.18 (m, 95H, 95 $\times$ H-Ar), 5.62 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1), 5.46 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1), 5.39 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 5.31 (d, 1H, <sup>2</sup>J = 10.5 Hz, CHPh), 5.27-5.22 (m, 4H, 2 $\times$ CHPh, 2 $\times$ H-1), 5.20 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.9 Hz, H-1), 5.18-5.13 (m, 3H, H-1, 2 $\times$ CHPh), 4.99-4.82 (m, 8H, 8 $\times$ CHPh), 4.76 (d, 1H, <sup>2</sup>J = 12.4 Hz, CHPh), 4.68-4.47 (m, 25H, 23 $\times$ CHPh, 2 $\times$ H-6), 4.34 (bd, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.5 Hz, H-6), 4.25-4.04 (m, 23H, 7 $\times$ H-3, 7 $\times$ H-5, 6 $\times$ H-4, 3 $\times$ H-6), 3.88-3.81 (m, 4H, H-4, 3 $\times$ H-6), 3.74 (bd, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.8 Hz, H-6), 3.69-3.56 (m, 7H, 5 $\times$ H-2, 2 $\times$ H-6), 3.53 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.3 Hz, H-2), 3.49 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, H-2), 3.15 (m, 1H, H-6), 2.85 (bd, 1H, <sup>2</sup>J = 13.9 Hz, H-6), 2.80 (s, 3H, S-CH<sub>3</sub>), 2.67 (m, 2H, N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 2.55 (m, 2H, N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 1.57-1.50 (m, 4H, 2 $\times$ N-CH<sub>2</sub>-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>3</sub>), 1.47-1.40 (m, 4H, 2 $\times$ N-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 1.36-1.30 (m, 4H, 2 $\times$ N-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 1.03 (t, 6H, 2 $\times$ N-(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>)

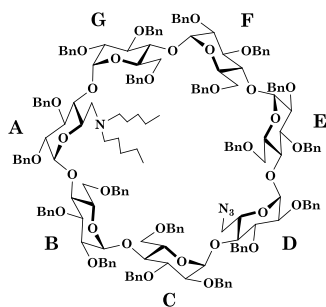
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.49, 139.47, 139.43, 139.42, 139.37, 139.23, 139.13, 138.64, 138.57, 138.50(3C), 138.48, 138.36, 138.35, 138.34, 138.28, 138.27, 138.10 (19 $\times$ C-Ar<sup>quat.</sup>), 128.47-126.94 (95 $\times$ C-Ar<sup>tert.</sup>), 99.03, 98.78, 98.72, 98.61, 98.43, 98.32, 97.93 (7 $\times$ C-1), 81.48, 81.06, 80.97, 80.87, 80.84(2C), 80.68 (7 $\times$ C-3), 80.21, 79.99, 79.63, 79.44(2C), 79.41(6 $\times$ C-4), 79.08(2C), 79.06(2C), 78.84, 78.80, 78.24 (7 $\times$ C-2), 77.36(2C) (C-4, C-5), 75.99, 75.94, 75.86, 75.47, 75.28, 75.22, 75.11, 73.71, 73.50, 73.49, 73.40, 73.31, 73.19, 72.96(2C), 72.89, 72.79, 72.56, 72.41 (19 $\times$ CH<sub>2</sub>Ph), 72.01, 71.87, 71.67(2C), 71.45, 69.64 (6 $\times$ C-5), 69.47(2C), 69.43, 69.24, 69.21, 69.11, 55.31 (7 $\times$ C-6). 54.65(2C) (2 $\times$ N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 37.21 (S-CH<sub>3</sub>), 30.08(2C) (2 $\times$ N-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 26.10(2C) (2 $\times$ N-CH<sub>2</sub>-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>3</sub>), 22.95(2C) (2 $\times$ N-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 14.43(2C) (2 $\times$ N-(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>186</sub>H<sub>208</sub>NNaO<sub>36</sub>S [M+Na+H]<sup>2+</sup>: 1543.2062; Found: 1543.2042 (-1.3 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>-N-Dipentyl-Amino-6<sup>D</sup>-Azido-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>,6<sup>G</sup>-Nonadeca-O-Benzyl-β-cyclodextrin (282)**



To a solution of previously formed mono-mesylated cyclodextrin **281a** (3.656 g, 1.193 mmol, 1 eq.) in DMF (50 mL) were added NaN<sub>3</sub> (388 mg, 5.965 mmol, 5 eq.) at r.t. The reaction mixture was stirred for 3 h at 80°C under nitrogen, then the solvent was reduced to dryness. The crude was dissolved in EtOAc (30 mL) and washed with water (30 mL). Then the aqueous layers were extracted with EtOAc (3×30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash

chromatography (CyH/EtOAc: 5/1) afforded β-cyclodextrin **282** (2.348 g, 65%) as a white foam.

$\alpha_D = +37.8$  (c 1.0, CHCl<sub>3</sub>)

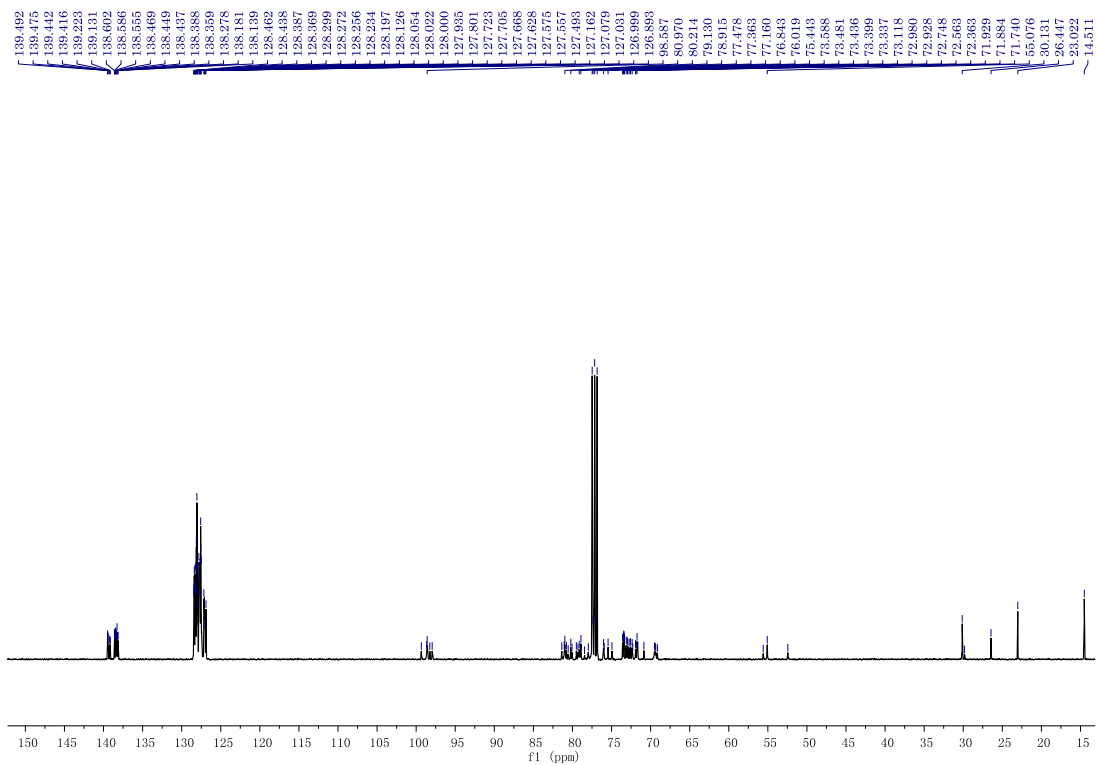
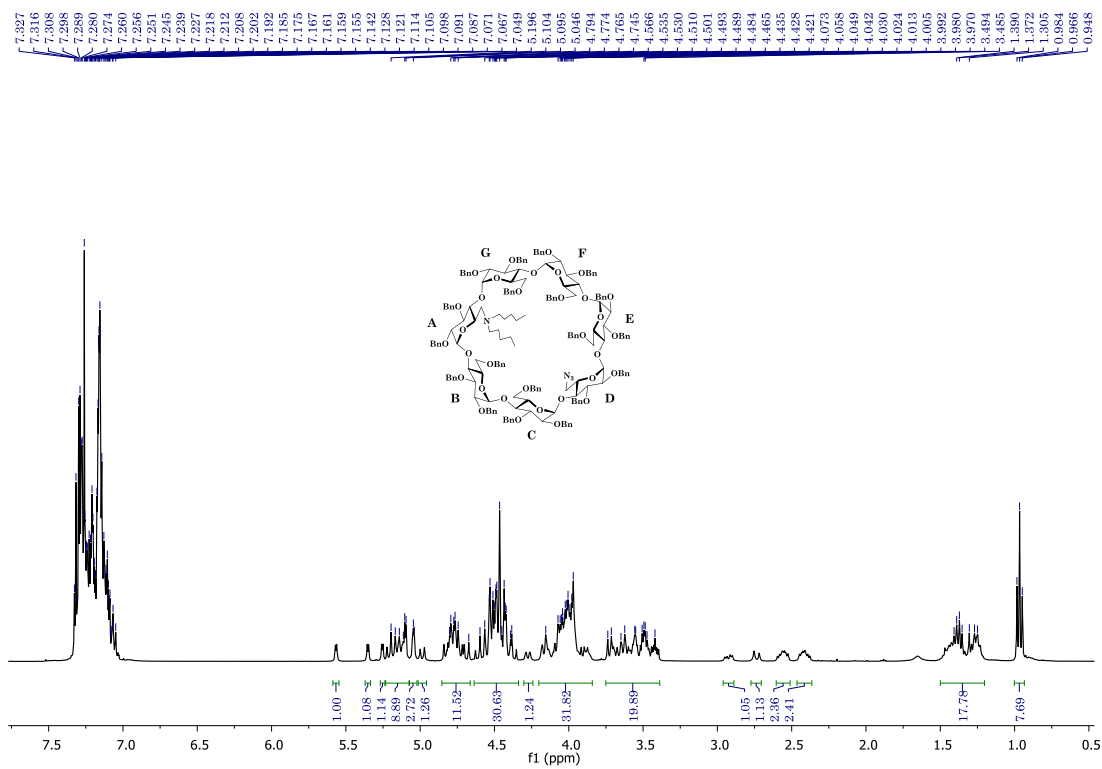
$R_f = 0.44$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.32-7.04 (m, 95H, 95×H-Ar), 5.57 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1), 5.35 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1), 5.25 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1), 5.22-5.04 (m, 8H, 4×CHPh, 4×H-1), 4.99 (d, 1H, <sup>2</sup>J = 11.3 Hz, CHPh), 5.84-5.67 (m, 9H, 9×CHPh), 4.62-4.35 (m, 24H, 24×CHPh), 4.27 (bd, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.2 Hz, H-6), 4.18-3.87 (m, 26H, 7×H-3, 6×H-4, 7×H-5, 4×H-6), 3.74-3.40 (m, 15H, 7×H-2,H-4, 7×H-6), 2.92 (dd, <sup>3</sup>J<sub>5,6</sub> = 5.9 Hz, <sup>2</sup>J<sub>6,6'</sub> = 13.3 Hz, H-6), 2.74 (bd, 1H, <sup>2</sup>J<sub>6,6'</sub> = 13.4 Hz, H-6), 2.59-2.38 (m, 4H, 2×N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 1.47-1.25 (m, 12H, 2×N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 0.96 (t, 6H, 2×N-(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.49, 139.48, 139.46, 139.44, 139.42, 139.22, 139.13, 138.60, 138.59, 138.55, 138.47, 138.45, 138.44, 138.39, 138.36, 138.28(2C), 138.18, 138.14 (19×C-Ar<sup>quat.</sup>), 128.46-126.89 (95×C-Ar<sup>tert.</sup>), 99.34, 98.65, 98.59(2C), 98.54, 98.25, 97.95 (7×C-1), 81.36, 81.06, 80.99, 80.97(2C), 80.77, 80.56 (7×C-3), 80.21(2C), 80.07, (3×C-4), 79.50(2C) (C-2, C-4), 79.30, 79.13, 78.98, 78.94 (4×C-2), 78.92(2C) (C-2, C-4), 78.46 (C-4), 78.02 (C-2), 77.97 (C-4), 76.02, 76.00(2C), 75.94, 74.94, 74.91, 73.59, 73.48, 73.44, 73.40, 73.34, 73.14, 73.12, 72.98, 72.93, 72.75, 72.56, 72.36(19×CH<sub>2</sub>Ph), 72.28, 71.93, 71.88, 71.74(2C), 71.63, 70.86 (7×C-5), 69.55, 69.49, 69.42, 69.35, 69.13, 55.59 (6×C-6), 55.08(2C) (2×N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 52.44 (C-6), 30.13(2C) (2×N-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 26.45(2C) (2×N-CH<sub>2</sub>-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>3</sub>), 23.02(2C) (2×N-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 14.51(2C) (2×N-(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>)

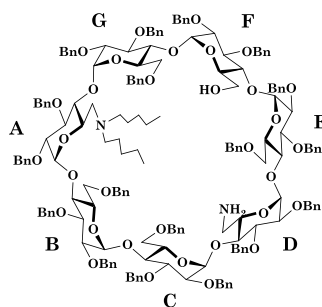
**HRMS (ESI):** Calcd. For C<sub>185</sub>H<sub>205</sub>N<sub>4</sub>O<sub>33</sub>Na [M+Na+H]<sup>2+</sup>: 1516.7210; Found: 1516.7186 (-1.5 ppm)

EXPERIMENTAL PART





**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>-*N*-Dipentyl-Amino-6<sup>D</sup>-Amine-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>G</sup>-Octadeca-  
O-Benzyl-β-cyclodextrin (283)**



DIBAL-H (1.5 M in toluene, 4.43 mL, 6.640mmol, 40 eq.) was slowly added to a solution of azido-β-cyclodextrin **282** (500 mg, 0.166 mmol, 1 eq.) in toluene (2.21 mL) under nitrogen at r.t. The reaction mixture was stirred under nitrogen reflux at 55 °C. The formation of the amino-alcohol as the major product was monitored by MS (1h10min). Heating was stopped, and the reaction mixture was poured into ice/water slowly. Aqueous HCl (10 mL) and EtOAc (10 mL) were added, and the solution was

stirred for 1 h. Then the aqueous layers were extracted with EtOAc (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc 3/1 then DCM/MeOH: 98.5/1.5) afforded β-cyclodextrin **283** (260 mg, 56%) as a white foam.

$\alpha_D = +32.0$  (c 1.0, CHCl<sub>3</sub>)

$R_f = 0.35$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.37-7.21 (m, 90H, 90×H-Ar), 5.75 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1E), 5.64 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, H-1B), 5.46 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1G), 5.43 (d, 1H, <sup>2</sup>J = 10.1 Hz, CHPh), 5.41 (d, 1H, <sup>2</sup>J = 10.9 Hz, CHPh), 5.40 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh), 5.38 (d, 1H, <sup>2</sup>J = 10.5 Hz, CHPh), 5.31 (d, 1H, <sup>2</sup>J = 10.1 Hz, CHPh), 5.12 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1F), 5.10 (d, 1H, <sup>2</sup>J = 11.1 Hz, CHPh), 5.03 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 2.7 Hz, H-1A), 4.95 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 4.94 (d, 1H, <sup>2</sup>J = 11.4 Hz, CHPh), 4.93 (d, 1H, <sup>2</sup>J = 10.6 Hz, CHPh), 4.92 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1C), 4.91 (d, 1H, <sup>2</sup>J = 10.3 Hz, CHPh), 4.91 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, H-1D), 4.88 (d, 1H, <sup>2</sup>J = 12.8 Hz, CHPh), 4.86 (d, 1H, <sup>2</sup>J = 11.8 Hz, CHPh), 4.84 (d, 1H, <sup>2</sup>J = 12.5 Hz, CHPh), 4.79 (d, 1H, <sup>2</sup>J = 11.5 Hz, CHPh), 4.75 (d, 1H, <sup>2</sup>J = 12.0 Hz, 2×CHPh), 4.71 (d, 1H, <sup>2</sup>J = 11.9 Hz, CHPh), 4.70 (d, 1H, <sup>2</sup>J = 12.3 Hz, CHPh), 4.66 (d, 1H, <sup>2</sup>J = 10.9 Hz, CHPh), 4.65 (d, 1H, <sup>2</sup>J = 12.4 Hz, CHPh), 4.64 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 4.61-4.37 (m, 16H, 15×CHPh, H-6G), 4.20-4.04 (m, 20H, H-3A, H-3B, H-3C, H-3D, H-3E, H-3F, H-3G, H-4A, H-4B, H-4C, H-4E, H-4F, H-4G, H-5C, H-5E, H-5G, H-6B, H-6C, H-6E, H-6F), 3.94-3.86 (m, 4H, H-5A, H-5B, H-5D, H-5F), 3.80 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.9 Hz, H-6F), 3.75 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.5 Hz, H-6E), 3.71 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.5 Hz, H-6C), 3.67 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 11.2 Hz, H-6G), 3.66-3.56 (m, 6H, H-2B, H-2C, H-2E, H-2F, H-2G, H-6B), 3.50-3.40 (m, 3H, H-2A, H-2D, H-4D), 3.27 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.9 Hz, H-6D), 3.15 (dd, <sup>3</sup>J<sub>5,6</sub> = 4.8 Hz, <sup>2</sup>J<sub>6,6'</sub> = 11.7 Hz, H-6A), 2.72-2.45 (m, 6H, H-6A, H-6D, 2×N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 1.47-1.26 (m, 12H, 2×N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 0.98-0.96 (t, 6H, 2×N-(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>)

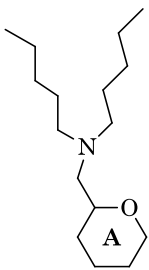
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.68, 139.63, 139.56, 139.47, 139.32, 138.98, 138.93, 138.65, 138.63, 138.43, 138.41, 138.38, 138.37, 138.35, 138.34, 138.16, 137.99, 137.83 (18×C-Ar<sup>quat.</sup>), 128.40-126.78 (90×C-Ar<sup>tert.</sup>), 99.12, 99.07, 98.57, 98.01, 97.35, 97.09, 96.92 (C-1C, C-1A, C-1F, C-1G, C-1B, C-1E, C-1D), 82.24, 82.01 (C-4D, C-4F), 81.52, 80.99, 80.90, 80.77(2C) (C-3F, C-3B, C-3D, C-3G, C-3C), 80.71(2C) (C-4C, C-4G), 80.22, 80.16 (C-3E, C-3A), 80.08(2C) (C-4B, C-4A), 79.61 (C-2D), 79.56(2C) (C-2C, C-4E), 79.37, 79.00, 78.82, 78.75, 78.05 (C-2F, C-2A, C-2G, C-2B, C-2E), 76.25, 76.14, 76.01, 75.84, 75.79, 74.81, 74.76, 73.58, 73.35, 73.30, 73.21, 73.10, 73.03, 72.92, 72.77, 72.67, 72.63, 72.60 (18×CH<sub>2</sub>Ph), 72.25, 72.06(2C), 71.66, 71.56, 71.29, 70.80 (C-5D, C-5F, C-5G, C-5B, C-5A, C-5C, C-5E), 69.38, 69.32, 69.01, 68.79, 59.88, 54.89 (C-6B, C-6C, C-6G, C-6E, C-6F, C-6A), 54.08(2C) (2×N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 43.16 (C-6D),

**EXPERIMENTAL PART**

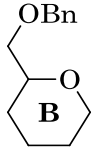
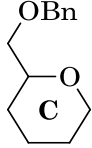
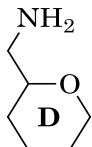
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29.99(2C) (2×N-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 25.73(2C) (2×N-CH<sub>2</sub>-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>3</sub>), 22.85(2C) (2×N-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 14.35(2C) (2×N-(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>)

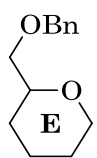
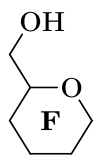
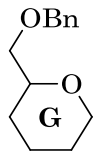
**HRMS (ESI):** Calcd. For C<sub>178</sub>H<sub>202</sub>N<sub>2</sub>O<sub>33</sub> [M+H+H]<sup>2+</sup>: 1447.7162; Found: 1447.7089 (-5.0 ppm)

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1A	5.031	NOE:4.050	H-4B
	C-1A	99.07		
	H-2A	3.440		
	C-2A	79.00		
	H-3A	4.166		
	C-3A	80.16		
	H-4A	4.131		
	C-4A	80.08		
	H-5A	3.930		
	C-5A	71.56		
	H-6A	3.156		
		2.700		
	C-6A	54.077		

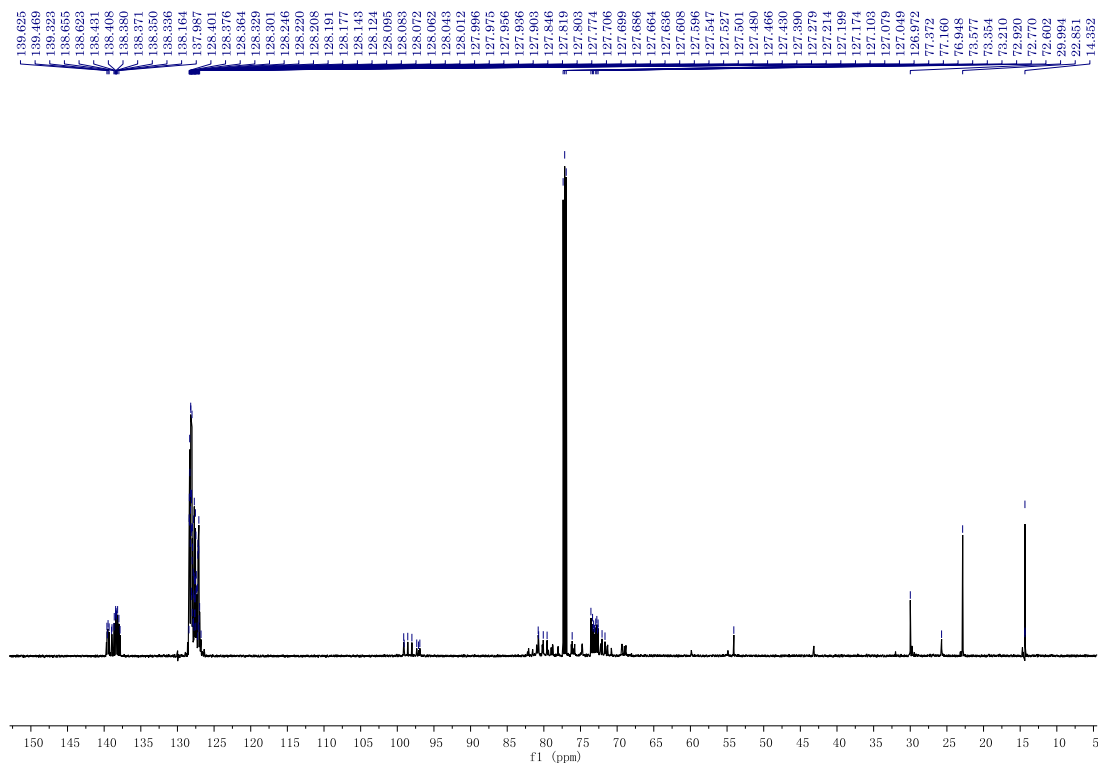
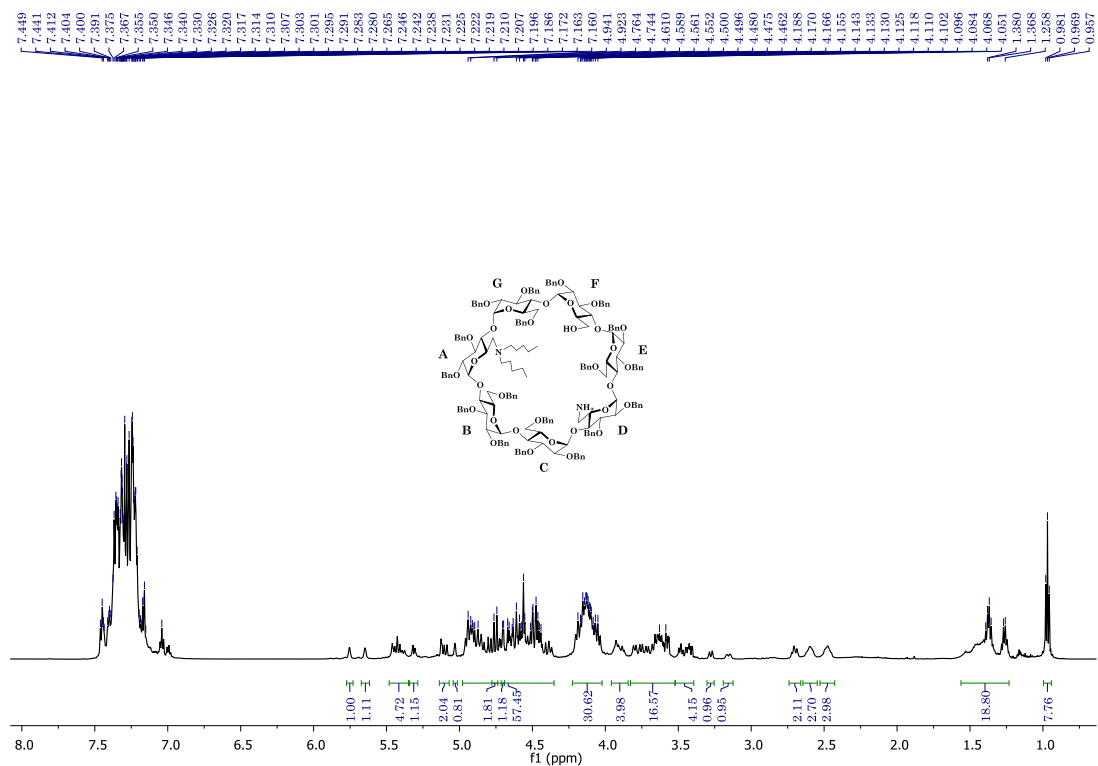
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>B</b></p>	H-1B	5.648	NOE: 4.121	H-4C
	C-1B	97.35		
	H-2B	3.634		
	C-2B	78.75		
	H-3B	4.164		
	C-3B	80.99		
	H-4B	4.050		
	C-4B	80.08		
	H-5B	3.916		
	C-5B	71.66		
	H-6B	3.620		
		4.112		
C-6B	69.383			
 <p style="text-align: center;"><b>C</b></p>	H-1C	4.921	NOE: 3.481	H-4D
	C-1C	99.12		
	H-2C	3.573		
	C-2C	79.56		
	H-3C	4.108		
	C-3C	80.77		
	H-4C	4.121		
	C-4C	81.71		
	H-5C	4.075		
	C-5C	71.29		
	H-6C	3.712		
		4.081		
C-6C	69.318			
 <p style="text-align: center;"><b>D</b></p>	H-1D	4.908	NOE: 4.198	H-4E
	C-1D	96.92		
	H-2D	3.411		
	C-2D	79.61		
	H-3D	4.065		
	C-3D	80.90		
	H-4D	3.481		
	C-4D	82.24		
	H-5D	3.890		
	C-5D	72.25		
	H-6D	3.277		
		2.710		
C-6D	43.159			

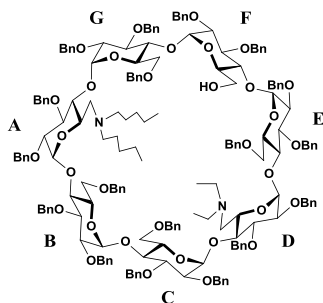
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1E	5.753	NOE: 4.107	H-4F
	C-1E	97.09		
	H-2E	3.647		
	C-2E	78.05		
	H-3E	4.150		
	C-3E	80.22		
	H-4E	4.198		
	C-4E	79.56		
	H-5E	4.143		
	C-5E	70.80		
	H-6E	3.754		
		4.139		
C-6E	68.791			
	H-1F	5.123	NOE: 4.145	H-4G
	C-1F	98.57		
	H-2F	3.573		
	C-2F	79.37		
	H-3F	4.187		
	C-3F	81.52		
	H-4F	4.107		
	C-4F	82.01		
	H-5F	3.912		
	C-5F	72.06		
	H-6F	3.800		
		4.108		
C-6F	59.870			
	H-1G	5.461	NOE: 4.131	H-4A
	C-1G	98.01		
	H-2G	3.608		
	C-2G	78.82		
	H-3G	4.113		
	C-3G	80.77		
	H-4G	4.145		
	C-4G	80.71		
	H-5G	4.045		
	C-5G	72.06		
	H-6G	4.374		
		3.666		
C-6G	69.01			

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>-*N*-Dipentyl-Amino-6<sup>D</sup>-*N*-Diethyl-Amino-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>G</sup>-  
Octadeca-*O*-Benzyl-β-cyclodextrin (**285**)**



Acetaldehyde (0.039 mL, 0.692 mmol, 4 eq.) was added to a solution of amino-alcohol-cyclodextrin **283** (500 mg, 0.173 mmol, 1 eq.) in MeCN (30mL) under nitrogen at r.t. The mixture was stirred for 1 h, then NaBH(OAc)<sub>3</sub> (147 mg, 0.692 mmol, 4 eq.) and AcOH (0.020 mL, 0.346 mmol, 2 eq.) were added and the mixture was stirred for another 1 h. Then sat. NaHCO<sub>3</sub> (30 mL) was added and the aqueous layers were extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography

(CyH/EtOAc: 4/1) afforded β-cyclodextrin **285** (378 mg, 74%) as a white foam.

$\alpha_D = +35.5$  (c 1.0, CHCl<sub>3</sub>)

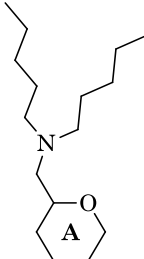
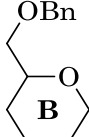
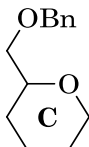
$R_f = 0.54$  (CyH/EtOAc: 2/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.13-6.89 (m, 90H, 90×H-Ar), 5.39 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1E), 5.34 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1B), 5.15 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1G), 5.09 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 5.07 (d, 1H, <sup>2</sup>J = 11.1 Hz, CHPh), 5.04 (d, 1H, <sup>2</sup>J = 11.1 Hz, CHPh), 4.99 (d, 1H, <sup>2</sup>J = 10.9 Hz, CHPh), 4.96 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1F), 4.86 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1C), 4.82 (d, 1H, <sup>2</sup>J = 10.9 Hz, CHPh), 4.77 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 2.7 Hz, H-1A), 4.66-4.12 (m, 31H, 31×CHPh, H-1D), 4.02 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.7 Hz, H-6G), 3.96 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.2 Hz, H-6C), 3.93-3.72 (m, 21H, H-3A, H-3B, H-3C, H-3D, H-3E, H-3F, H-3G, H-4A, H-4B, H-4C, H-4E, H-4F, H-4G, H-5C, H-5D, H-5E, H-5F, H-5G, H-6B, H-6E, H-6F), 3.64-3.60 (m, 2H, H-5A, H-5B), 3.53-3.50 (m, 2H, H-6E, H-6F), 3.41 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.0 Hz, H-6C), 3.38 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 11.0 Hz, H-6G), 3.36 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, <sup>3</sup>J<sub>2,3'</sub> = 9.1 Hz, H-2E), 3.33-3.28 (m, 6H, H-2B, H-2C, H-2F, H-2G, H-4D, H-6B), 3.16-3.14 (m, 2H, H-2A, H-2D), 2.97 (dd, <sup>3</sup>J<sub>5,6</sub> = 4.6 Hz, <sup>2</sup>J<sub>6,6'</sub> = 13.7 Hz, H-6A), 2.74 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 13.4 Hz, H-6D), 2.43-2.18 (m, 10H, H-6A, H-6D, 2×N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>, 2×N-CH<sub>2</sub>-CH<sub>3</sub>), 1.20-0.93 (m, 12H, 2×N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 0.75 (t, 6H, 2×N-CH<sub>2</sub>-CH<sub>3</sub>), 0.65 (t, 6H, 2×N-(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>)

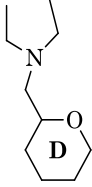
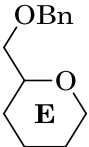
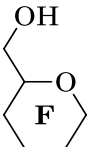
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.72, 139.64(2C), 139.57, 139.34, 139.14, 139.00, 138.75, 138.68, 138.53, 138.51(2C), 138.47, 138.37, 138.35, 138.33, 138.21, 138.03 (18×C-Ar<sup>quat.</sup>), 128.45-126.83 (90×C-Ar<sup>tert.</sup>), 99.07, 98.90, 98.84, 97.97, 97.60, 97.23, 97.19 (C-1A, C-1C, C-1F, C-1G, C-1B, C-1D, C-1E), 82.66 (C-4D), 81.76, 81.70, 81.08, 80.94(2C), 80.84(2C) (C-3F, C-3C, C-3E, C-3G, C-3A, C-3D, C-3B), 80.73, 80.67, 80.01, 79.85, (C-4F, C-4A, C-4E, C-4B), 79.80 (C-2D), 79.52(2C) (C-2C, C-4G), 79.20(2C), 78.93, 78.84, 78.27 (C-2B, C-2F, C-2A, C-2G, C-2E), 76.23, 76.10, 75.90, 75.79, 75.64 (5×CH<sub>2</sub>Ph), 75.23 (C-4C), 74.83, 74.70, 73.58, 73.53, 73.43, 73.33 (6×CH<sub>2</sub>Ph), 73.26(2C) (C-5A, C-5D), 73.08, 72.98, 72.96, 72.74, 72.68, 72.57, 72.53 (7×CH<sub>2</sub>Ph), 71.99, 71.72, 71.59, 71.54, 71.19 (C-5G, C-5E, C-5B, C-5C, C-5F), 69.41, 69.20(2C), 68.94, 68.68, 54.78, 54.62 (C-6B, C-6E, C-6C, C-6G, C-6F, C-6A, C-6D), 53.87(2C) (2×N-CH<sub>2</sub>-CH<sub>3</sub>), 47.91(2C) (2×N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 29.84(4C) (2×N-CH<sub>2</sub>-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>3</sub>, 2×N-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 22.86(2C) (2×N-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 14.33(2C) (2×N-(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>), 11.05(2C) (2×N-CH<sub>2</sub>-CH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>182</sub>H<sub>210</sub>N<sub>2</sub>O<sub>33</sub> [M+H+H]<sup>2+</sup>: 1475.7487; Found: 1475.7402 (-5.7ppm)

**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1A	4.770	NOE:2.760	H-4B
	C-1A	99.066		
	H-2A	3.156		
	C-2A	78.916		
	H-3A	3.866		
	C-3A	80.937		
	H-4A	3.927		
	C-4A	80.627		
	H-5A	3.617		
	C-5A	73.260		
	H-6A	2.962		
		2.414		
C-6A	54.771			
	H-1B	5.342	NOE: 3.871	H-4C
	C-1B	97.582		
	H-2B	3.314		
	C-2B	79.199		
	H-3B	3.867		
	C-3B	80.842		
	H-4B	3.760		
	C-4B	79.848		
	H-5B	3.636		
	C-5B	71.585		
	H-6B	3.310		
		3.783		
C-6B	69.395			
	H-1C	4.864	NOE: 3.320	H-4D
	C-1C	98.897		
	H-2C	3.291		
	C-2C	79.518		
	H-3C	3.833		
	C-3C	81.702		
	H-4C	3.871		
	C-4C	75.235		
	H-5C	3.859		
	C-5C	71.542		
	H-6C	3.415		
		3.959		
C-6C	69.183			

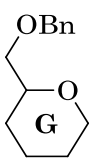
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	4.660	NOE: 3.908	H-4E
	C-1D	97.204		
	H-2D	3.149		
	C-2D	79.802		
	H-3D	3.806		
	C-3D	80.842		
	H-4D	3.320		
	C-4D	82.661		
	H-5D	3.733		
	C-5D	73.260		
	H-6D	2.741		
		2.251		
C-6D	54.606			
	H-1E	5.391	NOE: 3.801	H-4F
	C-1E	97.161		
	H-2E	3.356		
	C-2E	78.271		
	H-3E	3.868		
	C-3E	81.083		
	H-4E	3.908		
	C-4E	80.014		
	H-5E	3.846		
	C-5E	71.721		
	H-6E	3.516		
		3.857		
C-6E	69.183			
	H-1F	4.958	NOE: 3.846	H-4G
	C-1F	98.835		
	H-2F	3.307		
	C-2F	79.199		
	H-3F	3.899		
	C-3F	81.702		
	H-4F	3.801		
	C-4F	80.734		
	H-5F	3.903		
	C-5F	71.192		
	H-6F	3.508		
		3.806		
C-6F	60.647			

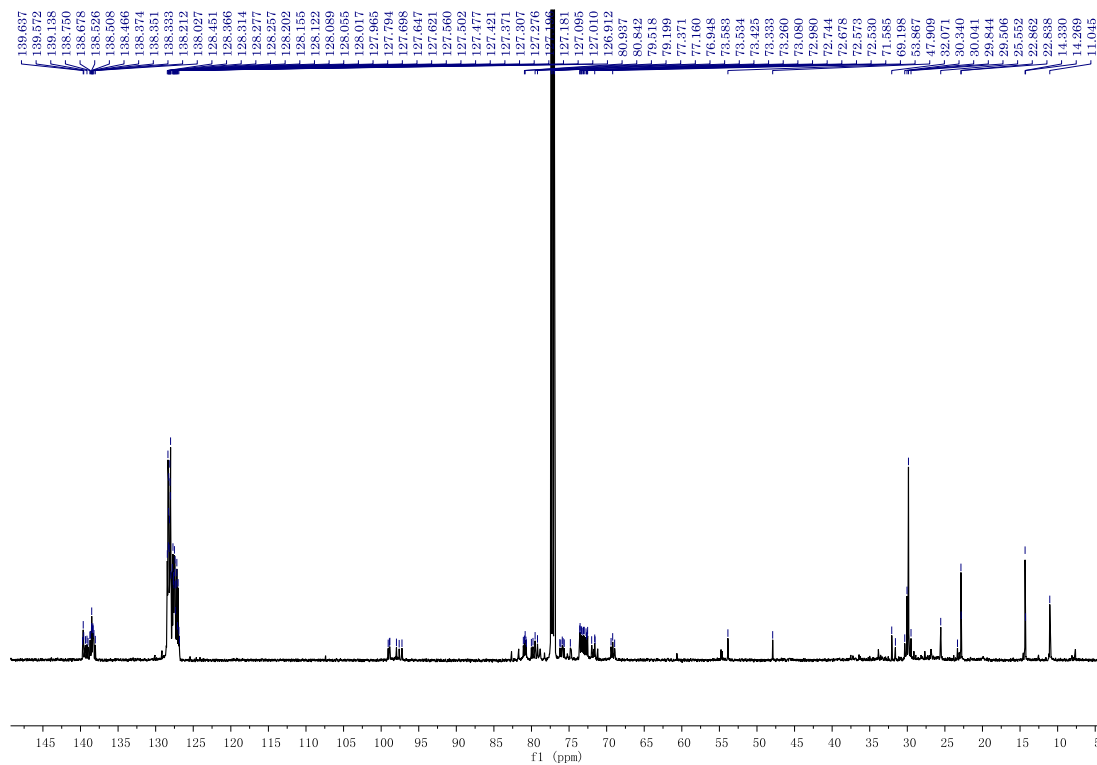
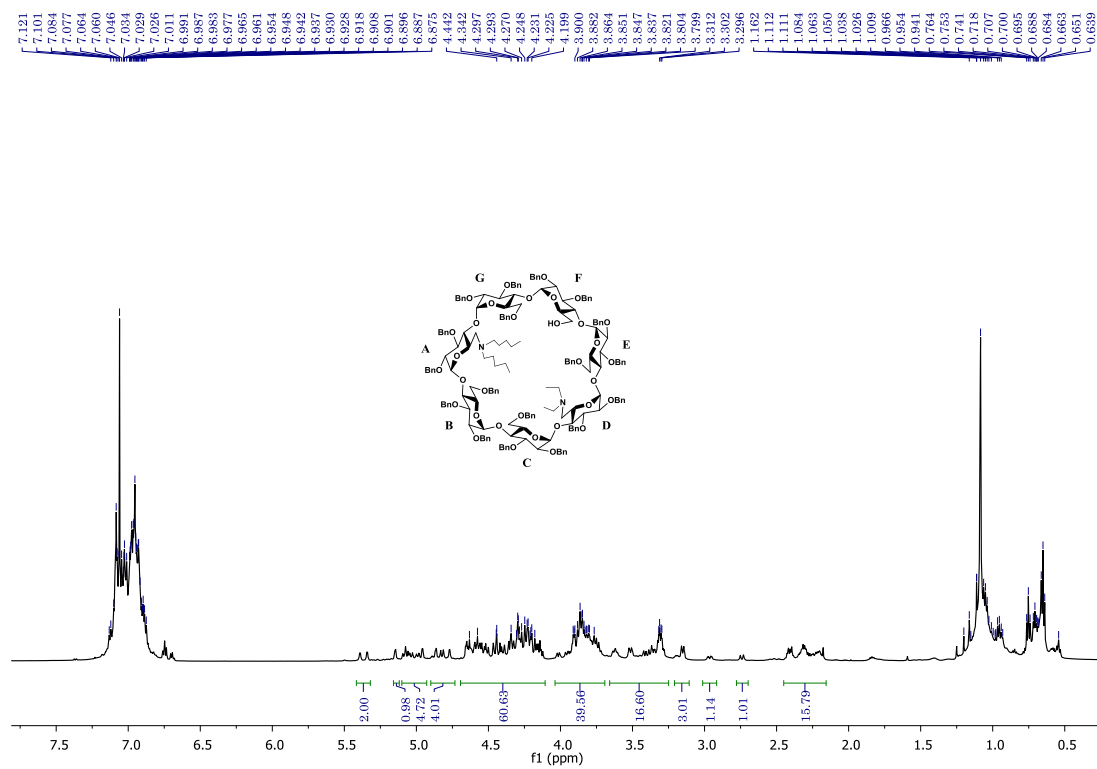


**EXPERIMENTAL PART**

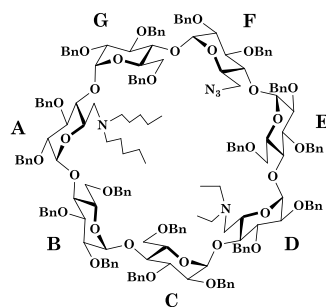
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	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1G	5.147	NOE: 3.921	H-4A
	C-1G	97.954		
	H-2G	3.317		
	C-2G	78.839		
	H-3G	3.774		
	C-3G	80.973		
	H-4G	3.846		
	C-4G	79.518		
	H-5G	3.764		
	C-5G	71.992		
	H-6G	4.014		
		3.379		
	C-6G	68.942		

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>D</sup>,6<sup>F</sup>-Trideoxy-6<sup>A</sup>-*N*-Dipentyl-Amino-6<sup>D</sup>-*N*-Diethyl-Amino-6<sup>F</sup>-Azido-2-*A*-G,3-*A*-G,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>G</sup>-Octadeca-*O*-Benzyl-β-cyclodextrin (286)**



DMAP (30 mg, 0.246 mmol, 2 eq.) was added to a solution of dipentyl-diethyl-alcohol-β-cyclodextrin **285** (363 mg, 0.123 mmol, 1 eq.) in pyridine (5 mL) at r.t.. Then MsCl (38 μL, 0.492 mmol, 4 eq.) was added. The reaction mixture was stirred at r.t. for 2 h under nitrogen. TLC (CyH/EtOAc: 2/1) showed that the reaction was finished. The solvent was removed in vacuo. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), washed with water (5 mL). The aqueous layers were extracted by CH<sub>2</sub>Cl<sub>2</sub> (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. After dried in vacuum, β-cyclodextrin (240 mg, 64%) was obtained as a white foam.

Sodium azide (67 mg, 1.035 mmol, 5 eq.) was added to a solution of dipentyl-diethyl-mesylated-cyclodextrin (628 mg, 0.207 mmol, 1 eq.) in DMF (10 mL) at r.t.. The reaction mixture was stirred at 80°C for 3 h under nitrogen. TLC (CyH/EtOAc: 2/1) showed that the reaction was finished, then the heating was stopped and the solvent was removed in vacuum. The residue was dissolved in EtOAc (20 mL), washed with water (10 mL). The aqueous layers were extracted by EtOAc (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc: 4/1) afforded β-cyclodextrin **286** (440 mg, 71%) as a white foam.

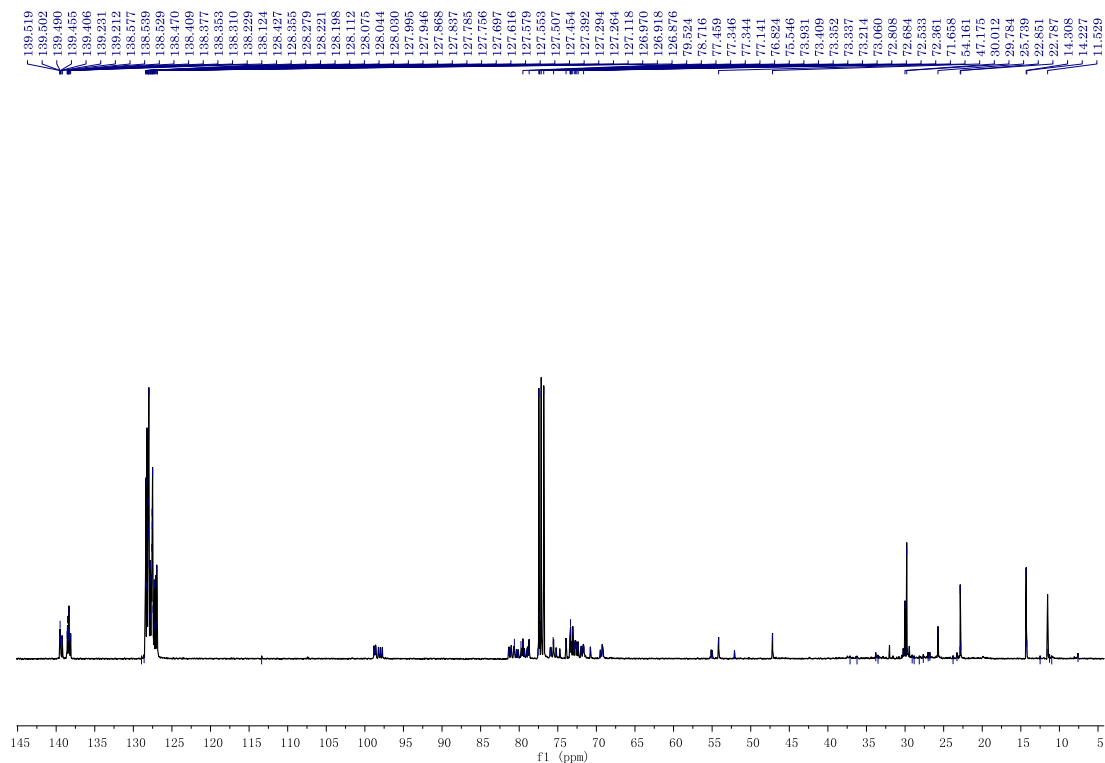
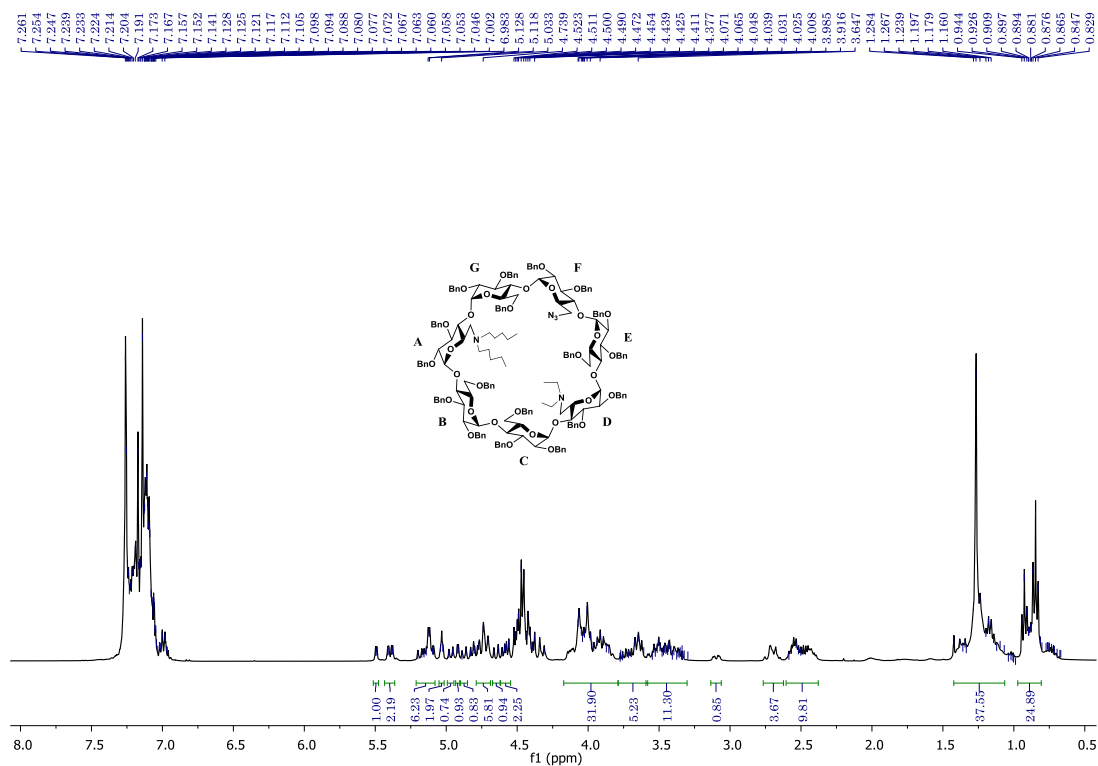
$\alpha_D^{20} = +22.9$  (c 1.0, CHCl<sub>3</sub>)

$R_f = 0.54$  (CyH/EtOAc: 2/1)

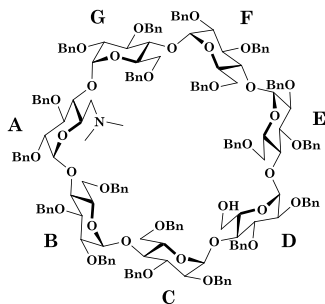
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.25-7.00 (m, 90H, 90×H-Ar), 5.49 (d, 1H,  $^3J_{1,2} = 3.8$  Hz, H-1), 5.41 (d, 1H,  $^3J_{1,2} = 3.5$  Hz, H-1), 5.38 (d, 1H,  $^3J_{1,2} = 3.4$  Hz, H-1), 5.18 (d, 1H,  $^2J = 10.9$  Hz, CHPh), 5.16 (d, 1H,  $^2J = 11.4$  Hz, CHPh), 5.13 (d, 1H,  $^2J = 12.3$  Hz, CHPh), 5.12 (d, 1H,  $^3J_{1,2} = 4.0$  Hz, H-1), 5.10 (d, 1H,  $^2J = 10.9$  Hz, CHPh), 5.04 (d, 1H,  $^3J_{1,2} = 3.2$  Hz, H-1), 5.03 (d, 1H,  $^3J_{1,2} = 3.4$  Hz, H-1), 4.97 (d, 1H,  $^2J = 11.4$  Hz, CHPh), 4.92 (d, 1H,  $^3J_{1,2} = 3.4$  Hz, H-1), 4.87 (d, 1H,  $^2J = 11.1$  Hz, CHPh), 4.81 (d, 1H,  $^2J = 10.9$  Hz, CHPh), 4.79 (d, 1H,  $^2J = 11.1$  Hz, CHPh), 4.77-4.70 (m, 6H, 6×CHPh), 4.66-4.31 (m, 24H, 22×CHPh, 2×H-6), 4.14-3.83 (m, 22H, 7×H-3, 4×H-4, 7×H-5, 4×H-6), 3.77-3.62 (m, 5H, 3×H-4, 2×H-6), 3.55-3.38 (m, 8H, 6×H-2, 2×H-6), 3.35 (dd, 1H,  $^3J_{1,2} = 3.0$  Hz,  $^3J_{2,3} = 9.8$  Hz, H-2), 3.10 (dd,  $^3J_{5,6} = 4.7$  Hz,  $^2J_{6,7} = 14.2$  Hz, H-6), 2.76-2.65 (m, 3H, 3×H-6), 2.58-2.39 (m, 8H, 2×N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>, 2×N-CH<sub>2</sub>-CH<sub>3</sub>), 1.42-1.14 (m, 12H, 2×N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 0.93 (t, 6H, 2×N-CH<sub>2</sub>-CH<sub>3</sub>), 0.85 (t, 6H, 2×N-(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>)

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.51, 139.50, 139.49, 139.45, 139.41, 139.23, 139.21, 138.58, 138.54, 138.53, 138.47, 138.41, 138.38, 138.35(2C), 138.31, 138.23, 138.12 (18×C-Ar<sup>quat.</sup>), 128.42-126.88 (90×C-Ar<sup>tert.</sup>), 98.82, 98.74, 98.63, 98.58, 98.23, 97.98, 97.73 (7×C-1), 81.36, 81.27, 81.07, 81.02, 80.73, 80.68, 80.63 (7×C-3), 79.77 (C-4), 79.71 (C-2), 79.52(2C) (2×C-4), 79.32, 78.99, 78.93, 78.86, 78.72(2C) (6×C-2) 77.34(2C) (2×C-4), 75.98, 75.85, 75.61, 75.55, 75.21, 74.74, 73.93(2C), 73.41, 73.35, 73.34, 73.21, 73.06(2C) (14×CH<sub>2</sub>Ph), 72.96 (C-5), 72.81, 72.68, 72.53, 72.36 (4×CH<sub>2</sub>Ph), 72.01, 71.93, 71.72, 71.66, 71.59, 70.77 (6×C-5), 69.48, 69.25(2C), 69.14, 55.12, 54.98 (6×C-6), 54.18(2C) (2×N-CH<sub>2</sub>-CH<sub>3</sub>), 52.10 (C-6), 47.20(2C) (2×N-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>), 29.79(4C) (2×N-CH<sub>2</sub>-CH<sub>2</sub>-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>3</sub>, 2×N-(CH<sub>2</sub>)<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 22.85(2C) (2×N-(CH<sub>2</sub>)<sub>3</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 14.31(2C) (2×N-(CH<sub>2</sub>)<sub>4</sub>-CH<sub>3</sub>), 11.28(2C) (2×N-CH<sub>2</sub>-CH<sub>3</sub>)

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-*N*-Dimethyl-Amino-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>,6<sup>G</sup>-Nonadeca-*O*-Benzyl-β-cyclodextrin (288)**



To a solution of **158-M** (3.0 g, 1.05 mmol, 1 eq.) in DCM (50 mL), formaldehyde (0.32 mL, 4.20 mmol, 4 eq. 37% in H<sub>2</sub>O), NaBH(OAc)<sub>3</sub> (1.33 g, 6.30 mmol, 6 eq.), AcOH (0.12 mL, 2.10 mmol, 2 eq.) were added. The reaction mixture was stirred for 2 h, then the sat. NaHCO<sub>3</sub> (30 mL) was added and the aqueous layers were extracted with DCM (3×30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc: 4/1) afforded cyclodextrin **288** (2.0 g, 65%) as a white foam.

$\alpha_D = +39.4$  (c 1.0, CHCl<sub>3</sub>)

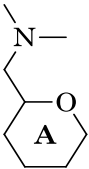
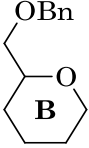
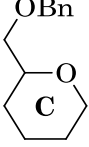
$R_f = 0.43$  (CyH/EtOAc: 2/1)

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 600MHz):  $\delta$  7.33-7.08 (m, 95H, 95×H-Ar), 5.59 (d, 1H,  $^3J_{1,2} = 3.5$  Hz, H-1C), 5.57 (d, 1H,  $^3J_{1,2} = 3.7$  Hz, H-1G), 5.29 (d, 1H,  $^2J = 10.6$  Hz, CHPh), 5.27 (d, 1H,  $^2J = 10.7$  Hz, CHPh), 5.19 (d, 1H,  $^2J = 10.9$  Hz, CHPh), 5.18 (d, 1H,  $^2J = 11.2$  Hz, CHPh), 5.16 (d, 1H,  $^3J_{1,2} = 3.7$  Hz, H-1F), 5.15 (d, 1H,  $^2J = 10.7$  Hz, CHPh), 4.99 (d, 1H,  $^3J_{1,2} = 3.4$  Hz, H-1E), 4.94 (d, 1H,  $^3J_{1,2} = 3.4$  Hz, H-1B), 4.92 (d, 1H,  $^3J_{1,2} = 3.3$  Hz, H-1D), 4.86-4.68 (m, 12H, H-1A, 11×CHPh), 4.56-4.35 (m, 22H, 22×CHPh), 4.12-3.85 (m, 25H, H-6B, H-6G, H-3G, H-6E, H-3D, H-3C, H-3F, H-3E, H-3A, H-4G, H-6C, H-5A, H-3B, H-4E, H-6F, H-4D, H-6D, H-4F, H-4C, H-4B, 6×H-5), 3.76 (d, 1H,  $^2J_{6,6'} = 9.4$  Hz, H-6C), 3.72-3.63 (m, 5H, H-4A, H-6B, H-6G, H-6D, H-6F), 3.58-3.55 (m, 2H, H-2C, H-2G), 3.64 (d, 1H,  $^2J_{6,6'} = 9.8$  Hz, H-6E), 3.49-3.45 (m, 3H, H-2E, H-2B, H-2F), 3.43 (dd, 1H,  $^3J_{1,2} = 3.5$  Hz,  $^3J_{2,3} = 9.7$  Hz, H-2D), 3.37 (dd, 1H,  $^3J_{1,2} = 3.7$  Hz,  $^3J_{2,3} = 9.7$  Hz, H-2A), 2.64 (dd,  $^3J_{5,6} = 7.0$  Hz,  $^2J_{6,6'} = 13.6$  Hz, H-6A), 2.47 (d, 1H,  $^2J_{6,6'} = 12.9$  Hz, H-6A), 2.12 (s, 6H, 2×N-CH<sub>3</sub>)

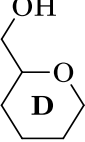
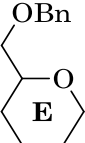
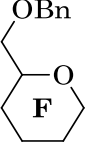
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.58, 139.55(2C), 139.49, 139.37, 139.12, 139.07, 138.70, 138.67, 138.65, 138.44, 138.38(2C), 138.34, 138.32, 138.29, 138.24, 138.07, 138.05 (19×C-Ar<sup>quat.</sup>), 128.48-126.85 (95×C-Ar<sup>tert.</sup>), 99.28, 98.90, 98.81, 98.47, 98.44, 98.00, 97.46 (C-1E, C-1F, C-1D, C-1A, C-1B, C-1G, C-1C), 81.54, 81.22, 81.17, 80.97 (C-3G, C-3D, C-3C, C-3A), 80.93(2C) (C-3E, C-4C), 80.88(2C) (C-3F, C-4B), 80.43, 79.88 (C-4E, C-4F), 79.74, 79.53 (C-2A, C-2D), 79.02 (C-4G), 78.97, 78.83(2C), 78.77 (C-2F, C-2E, C-2B, C-2G), 78.40 (C-4A), 77.37 (C-2C), 76.28, 76.23, 76.18, 75.43(2C), 74.64, 74.61 (7×CH<sub>2</sub>Ph), 74.23 (C-4D), 73.48(2C), 73.45, 73.37, 73.35(2C), 73.15, 73.04, 72.90, 72.71, 72.55, 72.44 (12×CH<sub>2</sub>Ph), 71.87, 71.82, 71.75(3C), 71.55, 70.76 (7×C-5), 69.59, 69.49, 69.16, 69.06, 68.75, 61.64, 60.73 (C-6C, C-6F, C-6B, C-6G, C-6E, C-6D, C-6A), 46.78(2C) (2×N-CH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>177</sub>H<sub>190</sub>NO<sub>34</sub> [M+H]<sup>1+</sup>: 2873.3180; Found: 2873.3164 (-0.6 ppm)

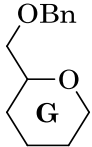
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>A</b></p>	H-1A	4.855	NOE: 3.845	H-4B
	C-1A	98.473		
	H-2A	3.370		
	C-2A	79.737		
	H-3A	4.006		
	C-3A	80.969		
	H-4A	3.704	NOE: 5.566	H-1G
	C-4A	78.410		
	H-5A	3.993		
	C-5A			
	H-6A	2.635		
		2.472		
	C-6A	60.734		
 <p style="text-align: center;"><b>B</b></p>	H-1B	4.936	NOE: 3.891	H-4C
	C-1B	98.442		
	H-2B	3.469		
	C-2B	78.827		
	H-3B	3.976		
	C-3B	80.748		
	H-4B	3.845	NOE: 4.855	H-1A
	C-4B	80.878		
	H-5B			
	C-5B			
	H-6B	3.668		
		4.115		
	C-6B	69.157		
 <p style="text-align: center;"><b>C</b></p>	H-1C	5.594	NOE: 3.926	H-4D
	C-1C	97.464		
	H-2C	3.573		
	C-2C	77.365		
	H-3C	4.064		
	C-3C	81.165		
	H-4C	3.891	NOE: 4.936	H-1B
	C-4C	80.929		
	H-5C			
	C-5C			
	H-6C	3.756		
		4.001		
	C-6C	69.591		

**EXPERIMENTAL PART**

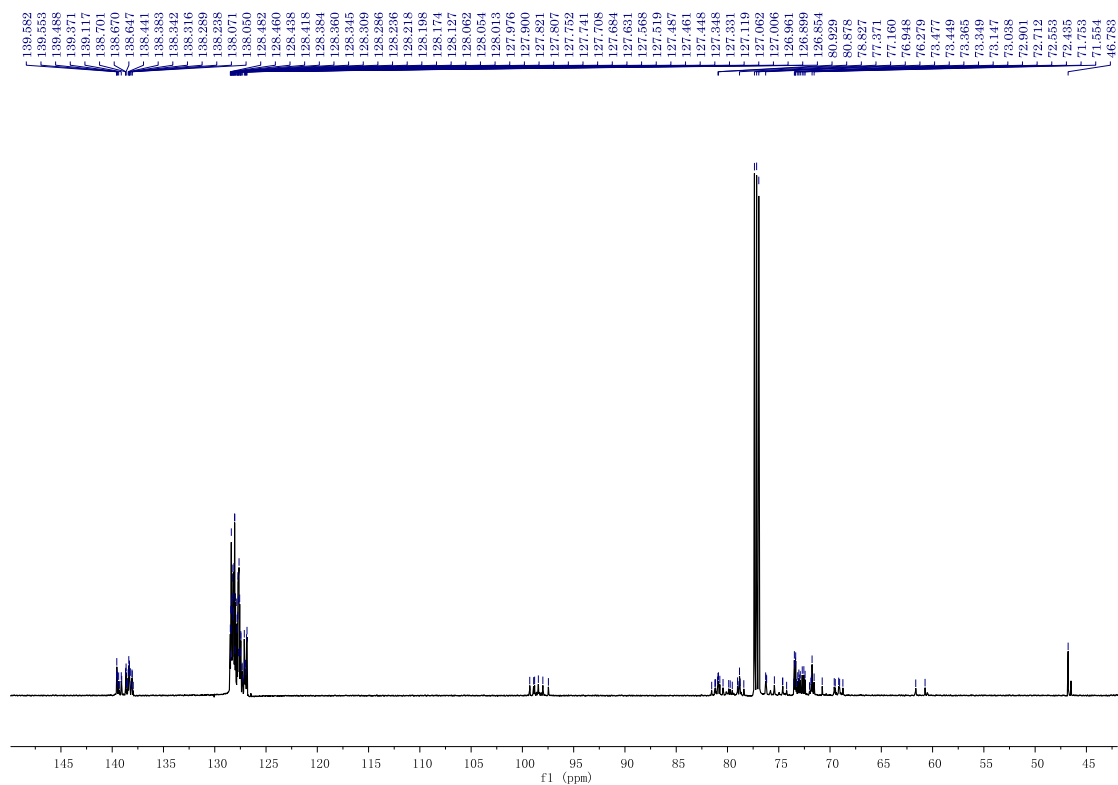
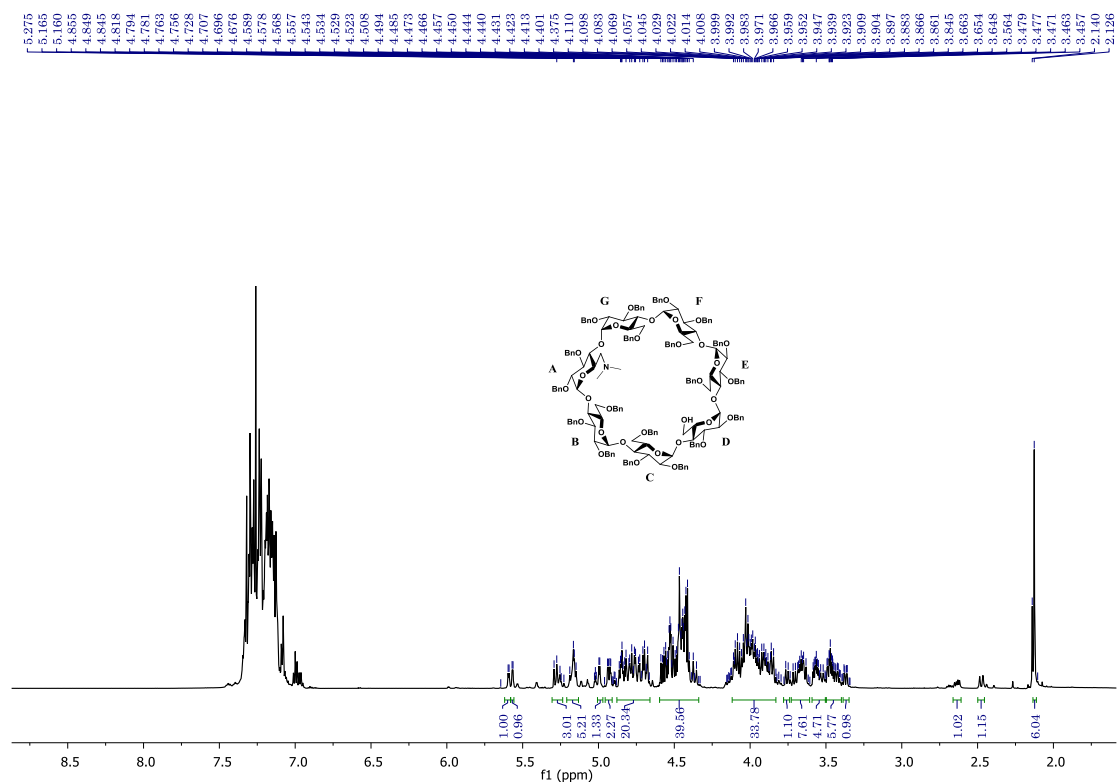
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	4.922	NOE: 3.970	H-4E
	C-1D	98.902		
	H-2D	3.429		
	C-2D	79.533		
	H-3D	4.082		
	C-3D	81.288		
	H-4D	3.926	NOE: 5.594	H-1C
	C-4D	74.233		
	H-5D			
	C-5D			
	H-6D	3.658		
		3.918		
C-6D	61.644			
	H-1E	4.994	NOE: 3.898	H-4F
	C-1E	99.282		
	H-2E	3.482		
	C-2E	78.827		
	H-3E	4.022		
	C-3E	80.929		
	H-4E	3.970	NOE: 4.922	H-1D
	C-4E	80.434		
	H-5E	3.857		
	C-5E			
	H-6E	3.528		
		4.091		
C-6E	68.748			
	H-1F	5.165	NOE: 4.019	H-4G
	C-1F	98.902		
	H-2F	3.457		
	C-2F	78.971		
	H-3F	4.025		
	C-3F	80.878		
	H-4F	3.898	NOE: 4.994	H-1E
	C-4F	79.882		
	H-5F			
	C-5F			
	H-6F	3.639		
		3.964		
C-6F	69.492			

**EXPERIMENTAL PART**

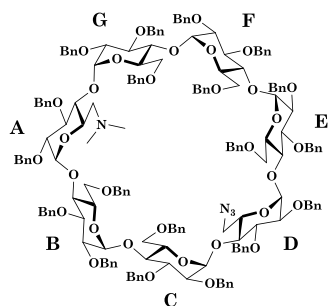
	<b>Attribution</b>	<b>Signal (ppm)</b>	<b>Correlation(ppm)</b>	<b>Attribution</b>
	H-1G	5.566	NOE: 3.704	H-4A
	C-1G	98.005		
	H-2G	3.560		
	C-2G	78.767		
	H-3G	4.092		
	C-3G	81.542		
	H-4G	4.019	NOE: 5.165	H-1F
	C-4G	79.019		
	H-5G			
	C-5G			
	H-6G	3.668		
		4.115		
	C-6G	69.064		



EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>-*N*-Dimethyl-Amino-6<sup>D</sup>-Azido-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>,6<sup>G</sup>-Nonadeca-*O*-Benzyl- $\beta$ -cyclodextrin (**289**)**



To a solution of cyclodextrin **288** (2.1 g, 0.731 mmol, 1 eq.) in dichloromethane (50 mL) at r.t., methanesulfonyl chloride (114  $\mu$ L, 1.462 mmol, 2 eq.) and Et<sub>3</sub>N (203  $\mu$ L, 1.462 mmol, 2 eq.) were added. The reaction mixture was stirred at r.t. for 2 h under nitrogen. Water (30 mL) was added and the aqueous layers were extracted by dichloromethane (3 $\times$ 30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc: 3/1, then 2/1) afforded mesylated cyclodextrin (1.8 mg, 83%) as a white foam.

To a solution of previously formed mesylated cyclodextrin (1.8 g, 0.610 mmol, 1 eq.) in DMF (20 mL) were added NaN<sub>3</sub> (159 mg, 2.440 mmol, 4 eq.) at r.t. The reaction mixture was stirred for 5 h at 80°C under nitrogen, then the solvent was reduced to dryness. The crude was dissolved in EtOAc (20 mL) and washed with water (20 mL). Then the aqueous layers were extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc: 4/1) afforded cyclodextrin **289** (1.37 g, 78%) as a white foam.

$\alpha_D = +48.4$  (c 1.0, CHCl<sub>3</sub>)

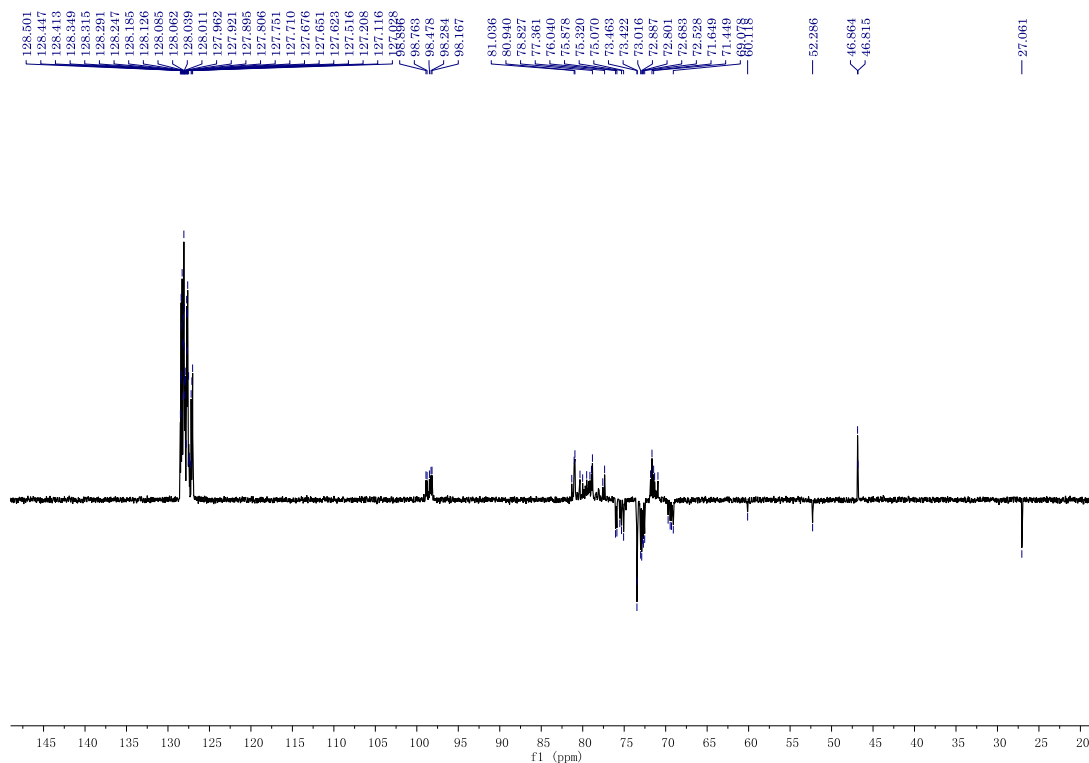
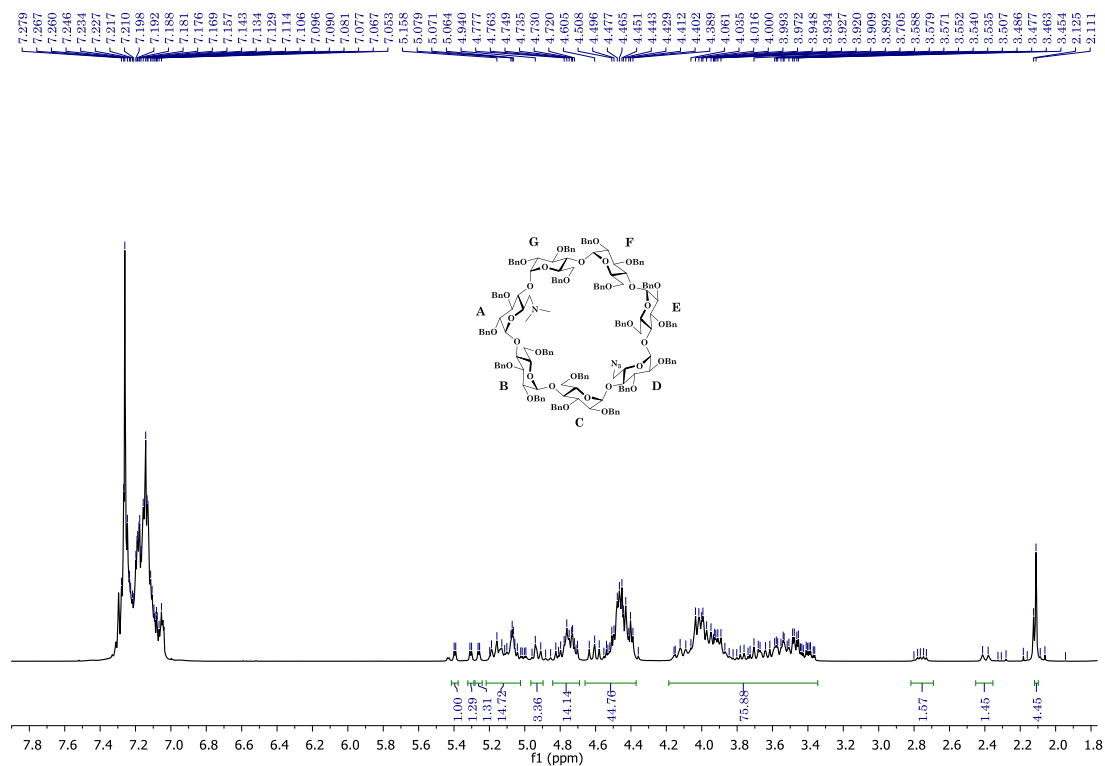
$R_f = 0.26$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz):  $\delta$  7.29-7.04 (m, 95H, H-Ar), 5.39 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 5.30 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1), 5.26 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1), 5.19-5.04 (m, 10H, 3 $\times$ H-1, 7 $\times$ CHPh), 4.94 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1), 4.92 (d, 1H, <sup>2</sup>J = 11.7 Hz, CHPh), 4.82-4.70 (m, 6H, 6 $\times$ CHPh), 4.62 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh), 4.59 (d, 1H, <sup>2</sup>J = 10.3 Hz, CHPh), 4.51-4.43 (m, 22H, 22 $\times$ CHPh), 4.16-3.87 (m, 24H, 7 $\times$ H-3, 5 $\times$ H-4, 7 $\times$ H-5, 5 $\times$ H-6), 3.77 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 9.3 Hz, H-6), 3.74-3.36 (m, 13H, 7 $\times$ H-2, 2 $\times$ H-4, 4 $\times$ H-6), 2.75 (dd, 1H, <sup>3</sup>J<sub>5,6</sub> = 6.0 Hz, <sup>2</sup>J<sub>6,6'</sub> = 12.9 Hz, H-6), 2.39 (dd, 1H, <sup>2</sup>J<sub>6,6'</sub> = 12.0 Hz, H-6), 2.11 (s, 6H, 2 $\times$ N-CH<sub>3</sub>)

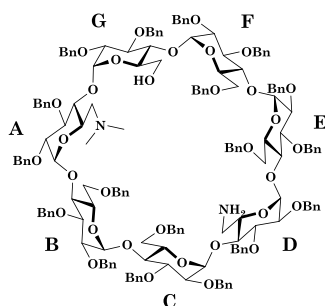
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.50, 139.49, 139.46, 139.44, 139.42, 139.23, 139.15, 138.61, 138.60(2C), 138.53, 138.47, 138.43, 138.42, 138.37(2C), 138.34, 138.16(2C) (19 $\times$ C-Ar<sup>quat.</sup>), 128.49-127.03 (95 $\times$ C-Ar<sup>tert.</sup>), 98.91, 98.76, 98.48, 98.39, 98.35, 98.28, 98.17 (7 $\times$ C-1), 81.32 (C-4), 81.03(2C), 80.94(2C), 80.92 (5 $\times$ C-3), 80.41 (C-4), 80.33, 80.01 (2 $\times$ C-3), 79.71, 79.62, 79.52 (3 $\times$ C-4), 79.46, 79.24, 79.13, 78.904, 78.84, 78.83, 78.11 (7 $\times$ C-2), 78.05, 77.36 (2 $\times$ C-4), 76.04, 76.00, 75.88, 75.55, 75.35, 75.32, 75.06, 73.48, 73.46(2C), 73.42, 73.41, 73.07, 73.02, 72.99, 72.89, 72.80, 72.68, 72.53 (19 $\times$ CH<sub>2</sub>Ph), 71.87, 71.82, 71.65(2C), 71.45, 71.33, 70.93 (7 $\times$ C-5), 69.70, 69.46, 69.29, 69.07, 69.05, 60.07, 52.19 (7 $\times$ C-6), 46.87(2C) (2 $\times$ N-CH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>177</sub>H<sub>189</sub>N<sub>4</sub>O<sub>33</sub>, [M+H]<sup>1+</sup>: 2898.3204; Found: 2898.3229 (+0.9 ppm)

EXPERIMENTAL PART



**6A,6D-Dideoxy-6A-N-Dimethyl-Amino-6D-Amino-2A-G,3A-G,6B,6C,6E,6F-  
Octadeca-O-Benzyl-β-cyclodextrin (290)**



DIBAL-H (1.5 M in toluene, 2.77 mL, 4.15 mmol, 50 eq.) was slowly added to a solution of azido-β-cyclodextrin (0.24 g, 0.083 mmol, 1 eq.) in toluene (1.38 mL) under nitrogen at r.t. The reaction mixture was stirred under nitrogen reflux at 55 °C. The formation of the amino-monol as the major product was monitored by mass spectrometry (40 min). Heating was stopped, and the reaction mixture was poured into ice/water slowly. Aqueous HCl (20 mL) and EtOAc (20 mL) were added, and the solution was stirred for 1 h. Then

the aqueous layers were extracted with EtOAc (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/AcOEt: 3/1, then DCM/MeOH: 97/3) gave β-cyclodextrin **290** (163 mg, 68%) as a white foam.

$\alpha_D = +43.3$  (c 1.0, CHCl<sub>3</sub>)

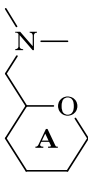
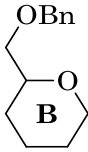
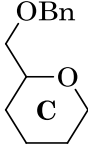
$R_f = 0.18$  (DCM/MeOH: 95/5)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.42-7.19 (m, 90H, H-Ar), 5.80 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.0 Hz, H-1E), 5.71 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.0 Hz, H-1F), 5.46 (d, 1H, <sup>2</sup>J=11.5 Hz, CHPh), 5.42 (d, 1H, <sup>2</sup>J=11.7 Hz, CHPh), 5.34 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.1 Hz, H-1C), 5.32 (d, 1H, <sup>2</sup>J=11.3 Hz, CHPh), 5.16 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.4 Hz, H-1G), 5.13 (d, 1H, <sup>2</sup>J=11.4 Hz, CHPh), 5.03 (d, 1H, <sup>3</sup>J<sub>1,2</sub>=3.4 Hz, H-1A), 4.98-4.42 (m, 34H, H-1D, H-1B, 32×CHPh), 4.36 (bd, 1H, <sup>2</sup>J<sub>6,6'}</sub>=10.0 Hz, H-6C), 4.25-3.93 (m, 24H, H-3A, H-3B, H-3C, H-3D, H-3E, H-3F, H-3G, H-4A, H-4B, H-4D, H-4E, H-4F, H-4G, H-5A, H-5B, H-5C, H-5D, H-5E, H-5F, H-5G, H-6B, H-6E, H-6F, H-6G), 3.83-3.59 (m, 10H, H-2B, H-2C, H-2E, H-2F, H-2G, H-6B, H-6C, H-6E, H-6F, H-6G), 3.56-3.45 (m, 3H, H-2A, H-2D, H-4C), 3.22 (bd, 1H, <sup>2</sup>J<sub>6,6'}</sub>=10.8 Hz, H-6D), 3.02 (dd, 1H, <sup>3</sup>J<sub>5,6}</sub>=6.3 Hz, <sup>2</sup>J<sub>6,6'}</sub>=12.7 Hz, H-6A), 2.73 (dd, 1H, <sup>3</sup>J<sub>5,6}</sub>=8.4 Hz, <sup>2</sup>J<sub>6,6'}</sub>=12.2 Hz, H-6D), 2.36 (bd, 1H, <sup>2</sup>J<sub>6,6'}</sub>=12.6 Hz, H-6A), 2.21 (s, 6H, 2×NCH<sub>3</sub>)

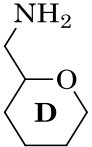
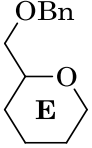
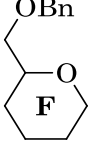
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.64, 139.60, 139.41, 139.24, 138.94, 138.74, 138.71, 138.40(3C), 138.34, 138.32, 138.27, 138.19(2C), 138.17, 137.95, 137.86 (18×C-Ar<sup>quat.</sup>), 128.38-126.95 (90×C-Ar<sup>tert.</sup>), 99.08, 98.97, 98.72, 98.49, 97.39, 96.78, 96.59 (C-1B, C-1A, C-1C, C-1G, C-1F, C-1E, C-1D), 82.42 (C-4C), 82.11 (C-3G), 81.44, 81.23 (C-4F, C-4D), 80.87(3C), 80.79(2C), 80.77, 80.62 (C-4E, C-4F, 5×C-3), 80.47, 80.00 (C-4B, C-4A), 79.84 (C-3E), 79.65, 79.53, 79.41, 79.29, 78.94, 78.79, 77.98 (C-2B, C-2D, C-2A, C-2G, C-2C, C-2F, C-2E), 76.21, 76.05(2C), 75.88, 75.84 (5×CH<sub>2</sub>Ph), 74.67(2C) (C-4G, CH<sub>2</sub>Ph), 74.58, 73.55(2C), 73.26, 73.18, 73.14, 73.10, 72.94, 72.89, 72.78, 72.66(2C) (12×CH<sub>2</sub>Ph), 72.34, 71.92, 71.72, 71.68, 71.48, 71.19, 70.65 (7×C-5), 69.34, 69.12, 68.82, 68.71, 60.42, 59.15 (C-6B, C-6F, C-6E, C-6C, C-6G, C-6A), 46.64(2C) (2×NCH<sub>3</sub>), 43.00 (C-6D)

**HRMS (ESI):** Calcd. For C<sub>170</sub>H<sub>185</sub>N<sub>2</sub>O<sub>33</sub> [M+H]<sup>1+</sup>: 2783.2799; Found: 2782.2854 (+2.0 ppm)

**EXPERIMENTAL PART**

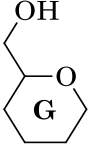
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>A</b></p>	H-1A	5.025	NOE: 4.033	H-4B
	C-1A	98.081		
	H-2A	3.440		
	C-2A	79.53		
	H-3A	4.134		
	C-3A			
	H-4A	4.162		
	C-4A	79.99		
	H-5A	3.914		
	C-5A			
	H-6A	3.023		
		2.365		
	C-6A	59.139		
 <p style="text-align: center;"><b>B</b></p>	H-1B	4.949	NOE: 3.480	H-4C
	C-1B	98.957		
	H-2B	3.575		
	C-2B	79.65		
	H-3B	4.130		
	C-3B			
	H-4B	4.033		
	C-4B	80.47		
	H-5B			
	C-5B			
	H-6B	3.716		
		4.042		
	C-6B	69.12		
 <p style="text-align: center;"><b>C</b></p>	H-1C	5.336	NOE: 3.979	H-4D
	C-1C	98.713		
	H-2C	3.615		
	C-2C	78.94		
	H-3C	4.144		
	C-3C			
	H-4C	3.480		
	C-4C	82.42		
	H-5C	4.014		
	C-5C			
	H-6C	4.333		
		3.692		
	C-6C	68.696		

**EXPERIMENTAL PART**

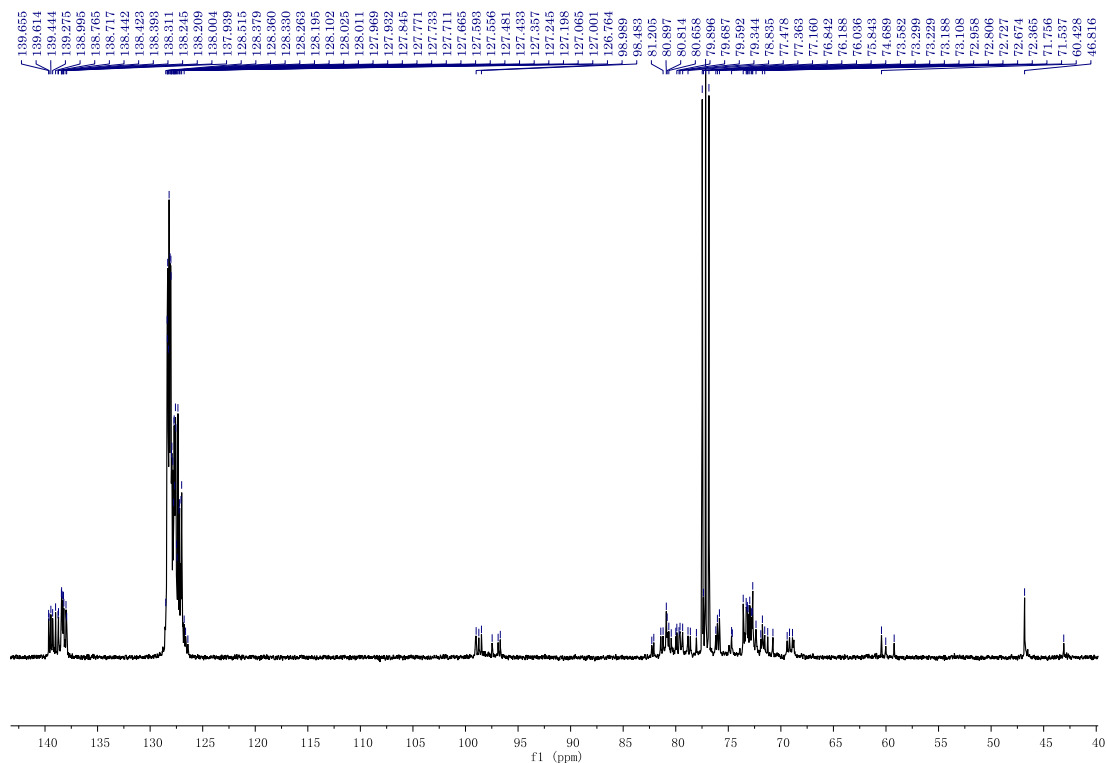
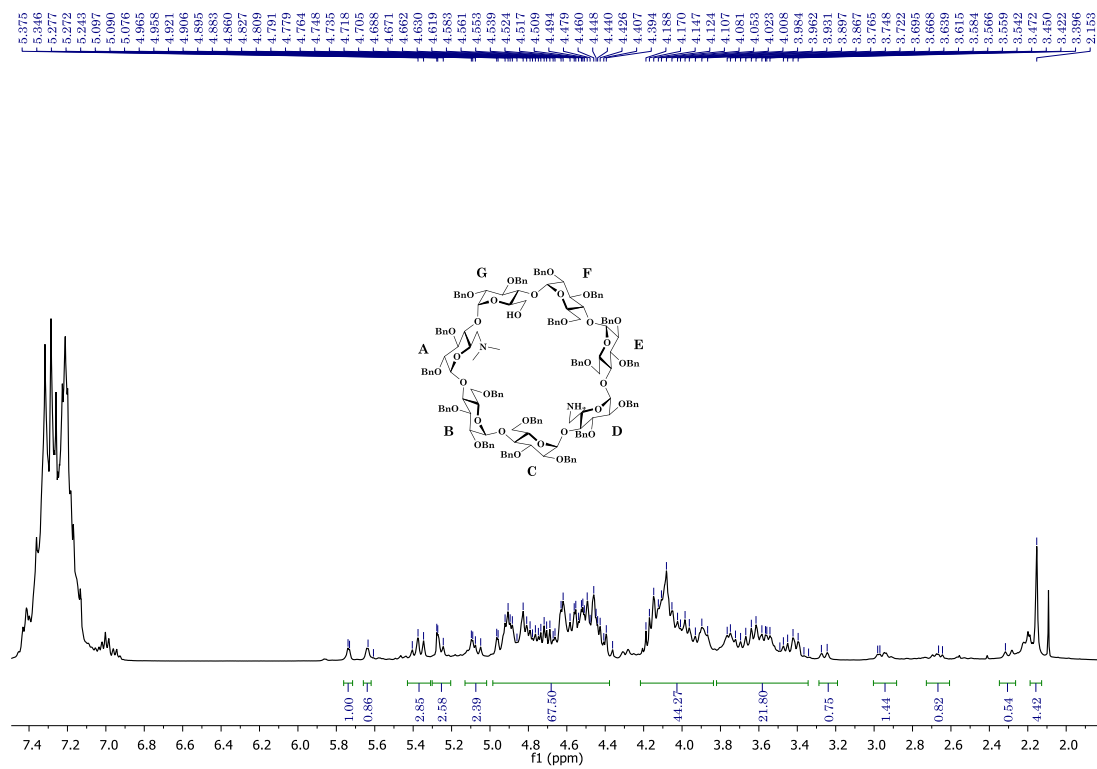
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	4.974	NOE: 4.174	H-4E
	C-1D	96.578		
	H-2D	3.444		
	C-2D	79.53		
	H-3D	4.084		
	C-3D			
	H-4D	3.979		
	C-4D	81.23		
	H-5D	3.916		
	C-5D			
	H-6D	3.323		
		2.734		
	C-6D	43.069		
	H-1E	5.799	NOE: 4.139	H-4F
	C-1E	96.768		
	H-2E	3.671		
	C-2E	77.98		
	H-3E	4.180		
	C-3E	79.84		
	H-4E	4.174		
	C-4E			
	H-5E			
	C-5E			
	H-6E	3.775		
		4.141		
	C-6E	68.82		
	H-1F	5.707	NOE: 4.137	H-4G
	C-1F	97.372		
	H-2F	3.653		
	C-2F	78.79		
	H-3F	4.176		
	C-3F			
	H-4F	4.139		
	C-4F	81.45		
	H-5F	3.911		
	C-5F	69.12		
	H-6F	4.102		
		3.659		
	C-6F	69.12		

**EXPERIMENTAL PART**

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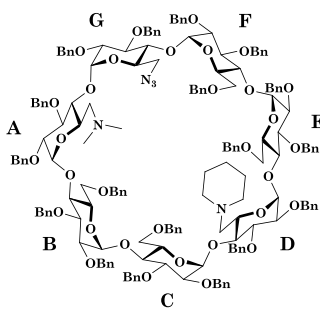
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1G	5.155	NOE: 4.162	H-4A
	C-1G	98.496		
	H-2G	3.599		
	C-2G	79.29		
	H-3G	4.209		
	C-3G	82.11		
	H-4G	4.137		
	C-4G	74.66		
	H-5G	4.125		
	C-5G			
	H-6G	3.822		
		4.132		
	C-6G	60.42		

EXPERIMENTAL PART





**6<sup>A</sup>,6<sup>D</sup>,6<sup>G</sup>-Trideoxy-6<sup>A</sup>-*N*-Dimethyl-Amino-6<sup>D</sup>-*N*-Piperidine-6<sup>G</sup>-Azido-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>-Octadeca-*O*-Benzyl- $\beta$ -cyclodextrin (**292**)**



To a solution of **290** (886 mg, 0.319 mmol, 1 eq.) in DCM (20 mL), glutaraldehyde (0.058 mL, 0.383 mmol, 1.2 eq. 50% in H<sub>2</sub>O), NaBH(OAc)<sub>3</sub> (406 mg, 0.914 mmol, 6 eq.), AcOH (0.018 mL, 0.319 mmol, 1 eq.) were added. The reaction mixture was stirred for 2 h, then sat. NaHCO<sub>3</sub> (30 mL) was added and the aqueous layers were extracted with DCM (3×30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc: 4/1) afforded cyclodextrin

**291** (486 mg, 53%) as a white foam.

DMAP (21 mg, 0.171 mmol, 1 eq.) was added to a solution of  $\beta$ -cyclodextrin **291** (486 mg, 0.171 mmol, 1 eq.) in pyridine (10 mL) at r.t.. Then methanesulfonyl chloride (53  $\mu$ L, 0.684 mmol, 4 eq.) was added. The reaction mixture was stirred at r.t. for 1 h under nitrogen. Water (20 mL) was added and the aqueous layers were extracted by EtOAc (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc: 1/1, then MeOH/DCM: 97/3) afforded mesylated cyclodextrin (430 mg, 86%) as a white foam

Sodium azide (38 mg, 0.588 mmol, 4 eq.) was added to a solution of mesylated  $\beta$ -cyclodextrin (430 mg, 0.147 mmol, 1 eq.) in DMF (10 mL) at r.t.. The reaction mixture was stirred at 80°C overnight under nitrogen. TLC (CyH/EtOAc: 2/1) showed that the reaction was finished, then the heating was stopped and the solvent was removed in vacuum. The residue was dissolved in EtOAc (20 mL), washed with water (10 mL). The aqueous layers were extracted by EtOAc (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc: 3/1, then 2/1) afforded azido- $\beta$ -cyclodextrin **292** (320 mg, 76%) as a white foam.

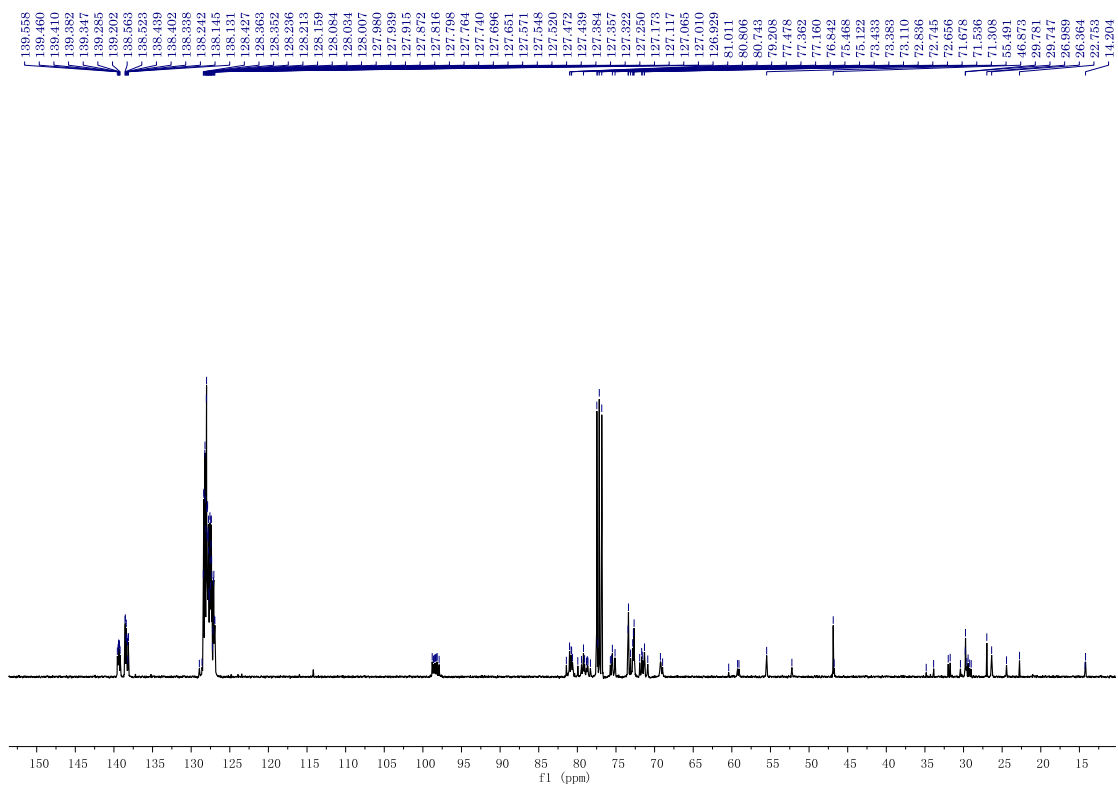
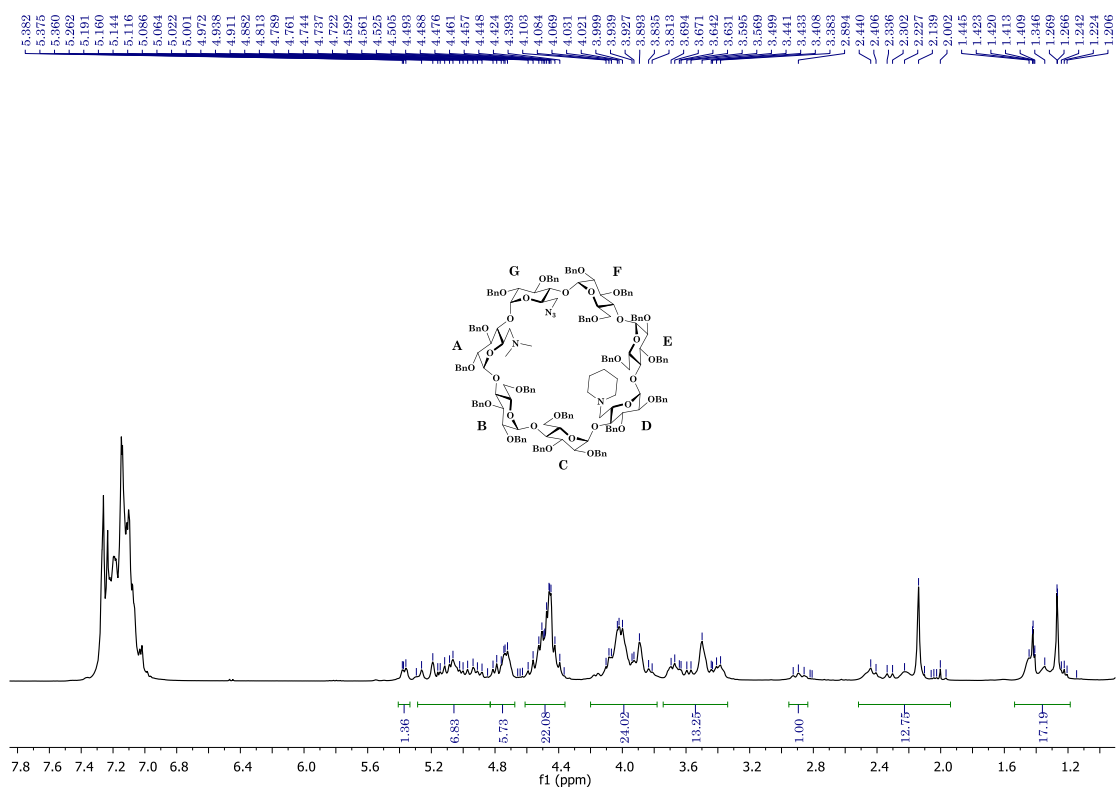
$\alpha_D = +49.2$  (c 1.0, CHCl<sub>3</sub>)

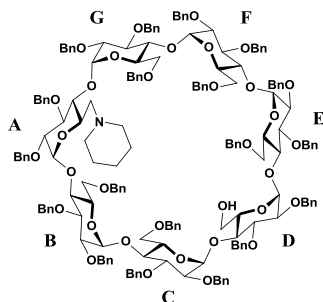
$R_f = 0.18$  (DCM/MeOH: 95/5)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.27-7.08 (m, 90H, H-Ar), 5.38 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1), 5.36 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1), 5.26 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1), 5.19-4.72 (m, 16H, 4×H-1, 12×CHPh), 4.59-4.39 (m, 24H, 24×CHPh), 4.18-3.81 (m, 24h, 7×H-3, 6×H-4, 7×H-5, 4×H-6), 3.69-3.38 (m, 14H, 7×H-2, H-4, 6×H-6), 2.92-2.84 (m, 2H, 2×H-6), 2.44-1.97 (m, 12H, 2×H-6, 4×CH<sub>ortho</sub>, 2×CH<sub>3</sub>), 1.44-1.27 (m, 6H, 4×CH<sub>meta</sub>, 2×CH<sub>para</sub>)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.56, 139.46, 139.41, 139.38, 139.35, 139.28, 139.20, 138.56(2C), 138.52(2C), 138.44, 138.40(2C), 138.34, 138.24, 138.14, 138.13 (18×C-Ar<sub>quat</sub>), 128.43-126.93 (90×C-Ar<sub>tert</sub>), 98.79, 98.63, 98.48, 98.37, 98.21, 98.15, 97.90 (7×C-1), 81.42 (C-4), 81.01(2C), 80.81(2C), 80.74(2C), 80.63 (7×C-3), 80.57, 79.94 (2×C-4), 79.47, 79.33 (2×C-2), 79.21(2C) (2×C-4), 79.07, 78.82, 78.71, 78.63, 78.31 (5×C-2), 77.53, 77.35 (2×C-4), 75.72, 75.56, 75.47(2C), 75.12(2C), 73.43(2C), 73.38(4C), 73.11, 72.84, 72.74(2C), 72.66(2C) (18×CH<sub>2</sub>Ph), 71.93, 71.68(2C), 71.54, 71.31(2C), 70.89 (7×C-5), 69.29, 69.25, 69.18, 68.97, 59.20, 59.07 (6×C-6), 55.49(2C) (2×CH<sub>2</sub><sub>ortho</sub>), 52.22 (C-6), 46.87(2C) (2×CH<sub>3</sub>), 26.36(2C) (2×CH<sub>2</sub><sub>meta</sub>), 24.41 (CH<sub>2</sub><sub>para</sub>)

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-N-Piperidine -2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>,6<sup>G</sup>-Nonadeca-O-Benzyl-β-cyclodextrin (295)**


To a solution of **158-M** (1.114 g, 0.319 mmol, 1 eq.) in DCM (25 mL), glutaraldehyde (0.071 mL, 0.469 mmol, 1.2 eq. 50% in H<sub>2</sub>O), NaBH(OAc)<sub>3</sub> (497 mg, 2.346 mmol, 6 eq.), AcOH (0.022 mL, 0.391 mmol, 1 eq.) were added. The reaction mixture was stirred for 2 h, then sat. NaHCO<sub>3</sub> (30 mL) was added and the aqueous layers were extracted with DCM (3×30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc: 4/1) afforded cyclodextrin **295** (714 mg, 63%) as a white foam.

$\alpha_D = +41.6$  (c 1.0, CHCl<sub>3</sub>)

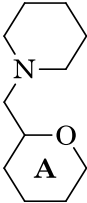
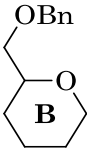
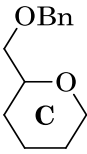
$R_f = 0.57$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600MHz):  $\delta$  7.40-7.18 (m, 95H, H-Ar), 5.60 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1G), 5.54 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1C), 5.44 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1F), 5.34 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 5.32 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 5.26 (d, 1H, <sup>2</sup>J = 11.3 Hz, CHPh), 5.17 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1E), 5.14 (d, 1H, <sup>2</sup>J = 10.8 Hz, CHPh), 5.06 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1B), 5.03 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 5.01 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1D), 4.99 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1A), 4.91 (d, 1H, <sup>2</sup>J = 11.4 Hz, CHPh), 4.90 (d, 1H, <sup>2</sup>J = 11.3 Hz, CHPh), 4.89 (d, 1H, <sup>2</sup>J = 10.9 Hz, CHPh), 4.86 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 4.84 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 4.83 (d, 1H, <sup>2</sup>J = 11.4 Hz, CHPh), 4.80 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 4.79 (d, 1H, <sup>2</sup>J = 11.8 Hz, CHPh), 4.73 (d, 1H, <sup>2</sup>J = 12.3 Hz, CHPh), 4.64-4.46 (m, 24H, 24×CHPh), 4.26 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 11.2 Hz, H-6B), 4.22-3.88 (m, 25H, H-3A, H-3B, H-3C, H-3D, H-3E, H-3F, H-3G, H-4A, H-4B, H-4C, H-4D, H-4E, H-4F, H-4G, H-5A, H-5B, H-5C, H-5D, H-5E, H-5F, H-5G, H-6C, H-6D, H-6E, H-6G), 3.85 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 11.0 Hz, H-6C), 3.76 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.1 Hz, H-6G), 3.72 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.4 Hz, H-6F), 3.70 (d, 2H, <sup>2</sup>J<sub>6,6'</sub> = 10.7 Hz, H-6B, H-6F), 3.66-3.55 (m, 6H, H-2G, H-2C, H-2F, H-2E, H-2B, H-6E), 3.50 (dd, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, H-2D), 3.45 (dd, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.8 Hz, H-2A), 2.88 (dd, 1H, <sup>3</sup>J<sub>5,6</sub> = 7.2 Hz, <sup>2</sup>J<sub>6,6'</sub> = 13.8 Hz, H-6A), 2.55-2.30 (m, 5H, H-6A, 4×CH<sub>ortho</sub>), 1.41-1.33 (m, 6H, 4×CH<sub>meta</sub>, 2×CH<sub>para</sub>)

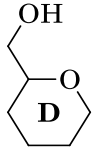
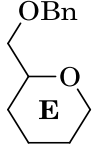
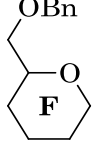
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.51, 139.49, 139.48, 139.44, 139.35, 139.24, 138.99, 138.63, 138.55(2C), 138.50, 138.49, 138.33, 138.27(2C), 138.26(2C), 138.10, 137.88 (19×C-Ar<sup>quat.</sup>), 128.46-126.87 (95×C-Ar<sup>tert.</sup>), 99.14, 99.06, 98.73, 98.70, 98.34, 98.12, 98.11 (C-1E, C-1B, C-1A, C-1D, C-1F, C-1C, C-1G), 81.47, 81.26, 80.97(2C), 80.82 (C-3G, C-3C, C-3D, C-3B, C-3E), 80.75 (C-4B), 80.63(2C) (C-3F, C-3A), 80.37, 80.25, 79.80, 79.70 (C-4E, C-4F, C-4C, C-4A), 79.63, 79.38, 78.94(2C), 78.84, 78.82 (C-2A, C-2D, C-2C, C-2F, C-2E, C-2B), 77.44 (C-4G), 77.36 (C-2G), 76.17, 76.05, 75.97 (3×CH<sub>2</sub>Ph), 75.77 (C-4D), 75.09, 75.04, 74.68, 73.52(2C), 73.41, 73.40, 73.35, 73.33, 73.12, 72.88, 72.77(2C), 72.72, 72.48, 72.42 (16×CH<sub>2</sub>Ph), 72.00, 71.87, 71.79, 71.75, 71.57, 71.19, 71.08 (C-5C, C-5E, C-5A, C-5B, C-5F, C-5G, C-5D), 69.57, 69.16, 69.14, 69.13, 68.79, 61.50, 59.63 (C-6C, C-6B, C-6F, C-6G, C-6E, C-6D, C-6A), 55.54(2C) (2×CH<sub>2</sub><sub>ortho</sub>), 26.20(2C) (2×CH<sub>2</sub><sub>meta</sub>), 24.43 (CH<sub>2</sub><sub>para</sub>)

**HRMS (ESI):** Calcd. For C<sub>180</sub>H<sub>194</sub>NO<sub>34</sub> [M+H]<sup>1+</sup>: 2913.3352; Found: 2913.3477 (+4.3)

**EXPERIMENTAL PART**

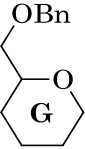
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1A	4.991	NOE:3.976	H-4B
	C-1A	98.732		
	H-2A	3.456		
	C-2A	79.629		
	H-3A	4.089		
	C-3A	80.632		
	H-4A	3.906		
	C-4A	79.699		
	H-5A	4.048		
	C-5A	71.785		
	H-6A	2.876		
		2.541		
C-6A	59.634			
	H-1B	5.059	NOE: 3.895	H-4C
	C-1B	99.060		
	H-2B	3.566		
	C-2B	78.818		
	H-3B	4.074		
	C-3B	80.974		
	H-4B	3.976		
	C-4B	80.748		
	H-5B	3.980		
	C-5B	71.749		
	H-6B	4.263		
		3.686		
C-6B	69.146			
	H-1C	5.540	NOE: 4.017	H-4D
	C-1C	98.118		
	H-2C	3.646		
	C-2C	78.936		
	H-3C	4.155		
	C-3C	80.255		
	H-4C	3.895		
	C-4C	79.800		
	H-5C	4.117		
	C-5C	71.996		
	H-6C	3.850		
		3.979		
C-6C	69.568			

**EXPERIMENTAL PART**

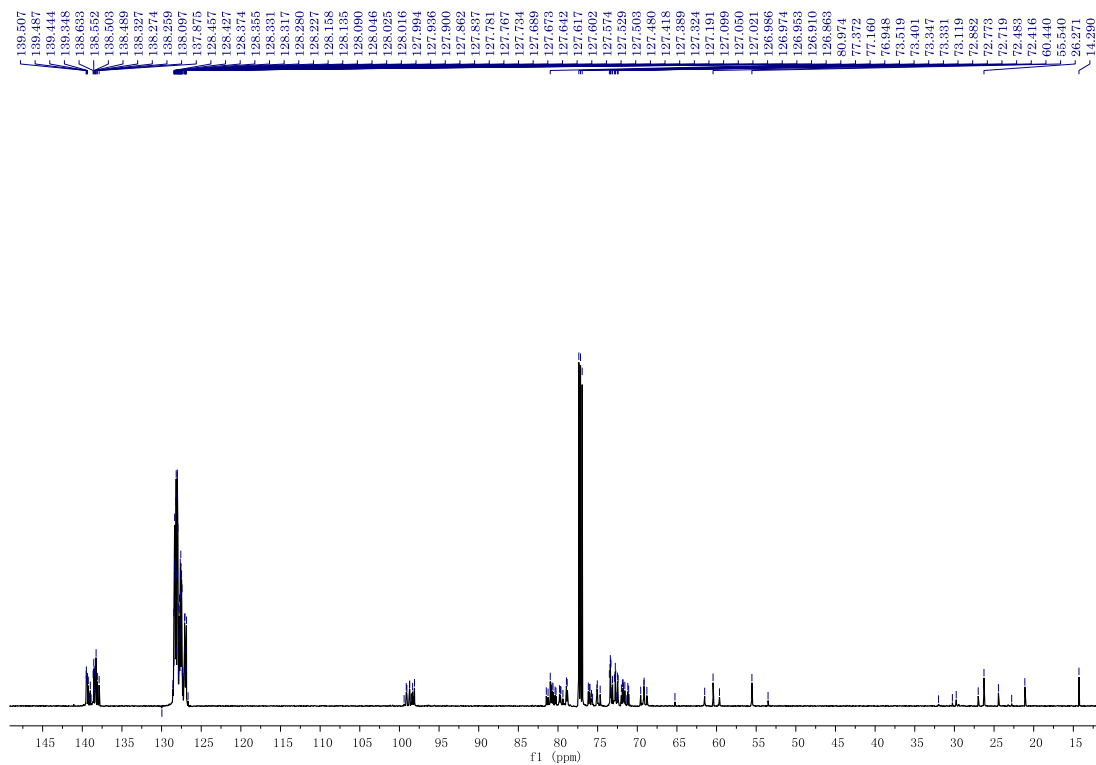
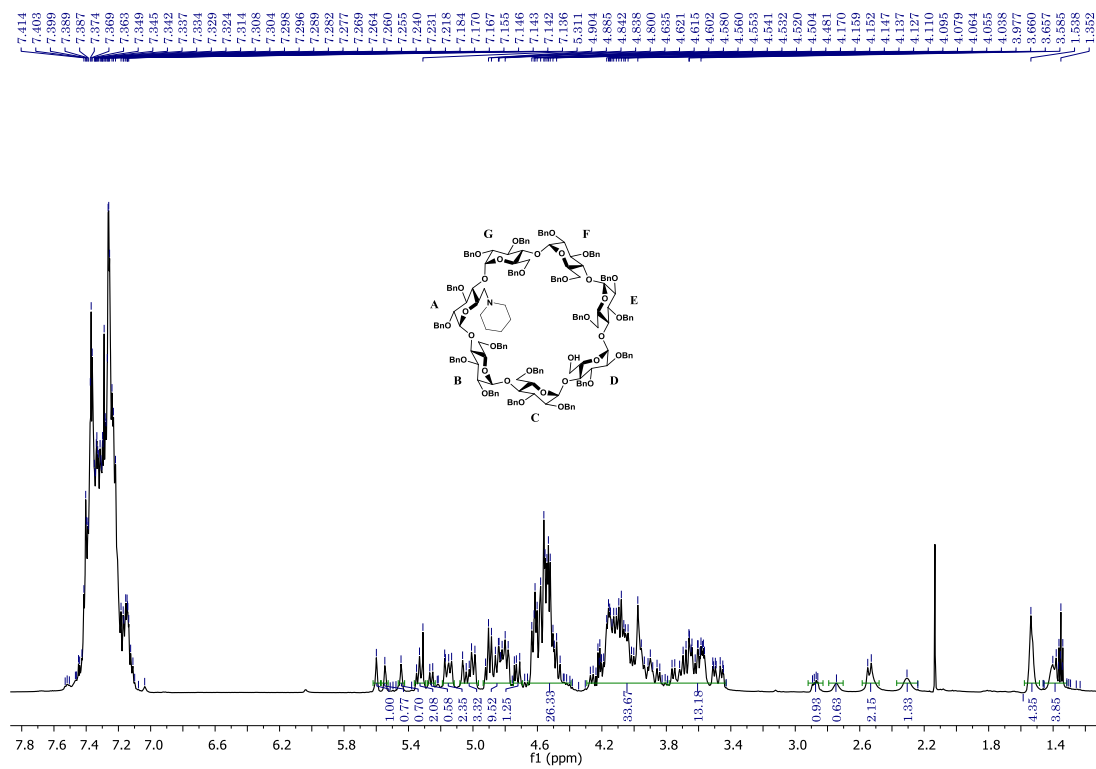
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	5.013	NOE: 4.088	H-4E
	C-1D	98.699		
	H-2D	3.500		
	C-2D	79.381		
	H-3D	4.149		
	C-3D	80.974		
	H-4D	4.017		
	C-4D	75.781		
	H-5D	4.044		
	C-5D	71.077		
	H-6D	4.057		
		3.717		
C-6D	61.497			
	H-1E	5.174	NOE: 4.084	H-4F
	C-1E	99.140		
	H-2E	3.574		
	C-2E	78.841		
	H-3E	4.120		
	C-3E	80.822		
	H-4E	4.088		
	C-4E	80.369		
	H-5E	3.959		
	C-5E	71.870		
	H-6E	3.618		
		4.170		
C-6E	68.786			
	H-1F	5.441	NOE: 4.164	H-4G
	C-1F	98.337		
	H-2F	3.597		
	C-2F	78.936		
	H-3F	4.127		
	C-3F	80.632		
	H-4F	4.084		
	C-4F	80.253		
	H-5F	3.943		
	C-5F	71.566		
	H-6F	3.670		
		4.097		
C-6F	69.146			

**EXPERIMENTAL PART**

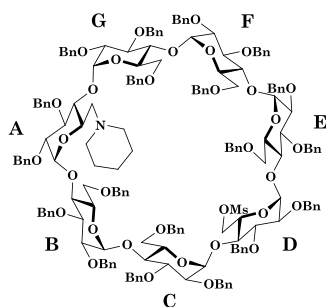
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	<b>Attribution</b>	<b>Signal (ppm)</b>	<b>Correlation(ppm)</b>	<b>Attribution</b>
	H-1G	5.596	NOE: 3.906	H-4A
	C-1G	98.101		
	H-2G	3.651		
	C-2G	77.362		
	H-3G	4.199		
	C-3G	80.475		
	H-4G	4.164		
	C-4G	77.426		
	H-5G	4.168		
	C-5G	71.187		
	H-6G	3.756		
		4.172		
	C-6G	69.146		

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-N-Piperidine-6<sup>D</sup>-O-Methanesulfonyl-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>,6<sup>G</sup>-  
Nonadeca-O-Benzyl-β-cyclodextrin (295a)**



To a solution of cyclodextrin **295** (1.7 g, 0.583 mmol, 1 eq.) in dichloromethane (20 mL) were added Et<sub>3</sub>N (810 μL, 5.83 mmol, 10 eq.) and MsCl (543 μL, 5.83 mmol, 10 eq.) at r.t. The reaction mixture was stirred for 2 h under nitrogen. Water (20 mL) were added and the aqueous phase was washed with CH<sub>2</sub>Cl<sub>2</sub> (3×30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc 3/1) afforded mesylated cyclodextrin **295a** (1.6 g, 91%) as a white foam.

$\alpha_D = +43.2$  (c 1.0, CHCl<sub>3</sub>)

$R_f = 0.36$  (CyH/EtOAc: 2/1)

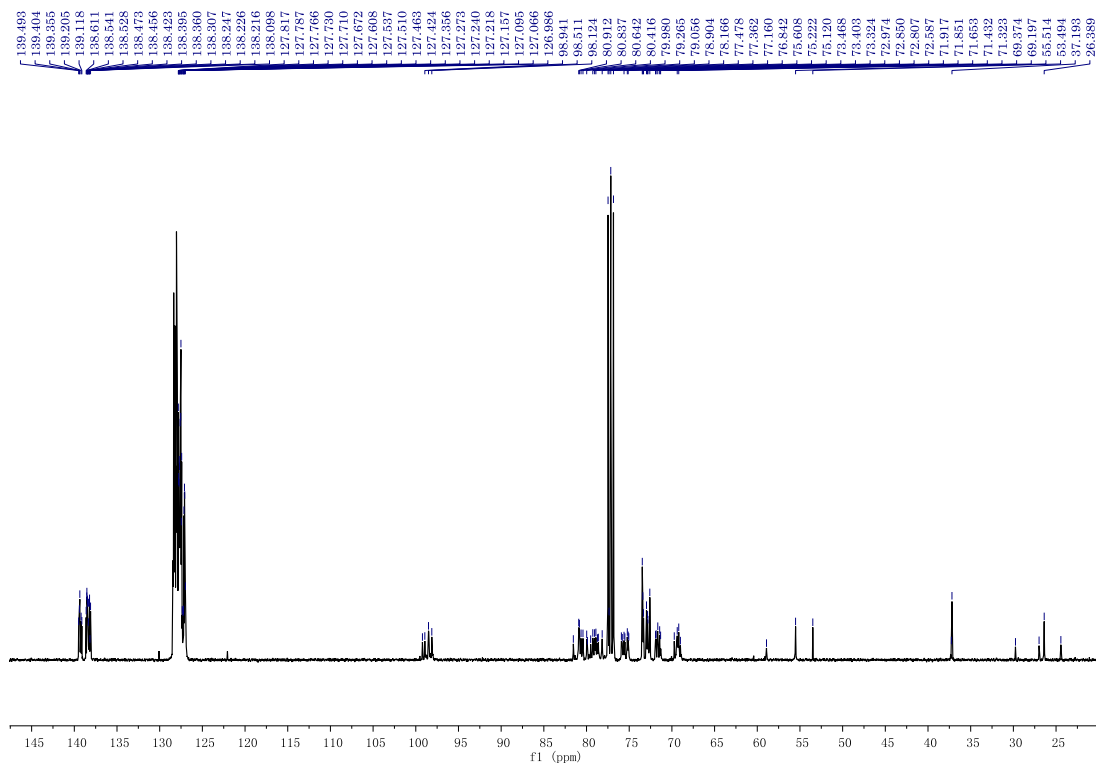
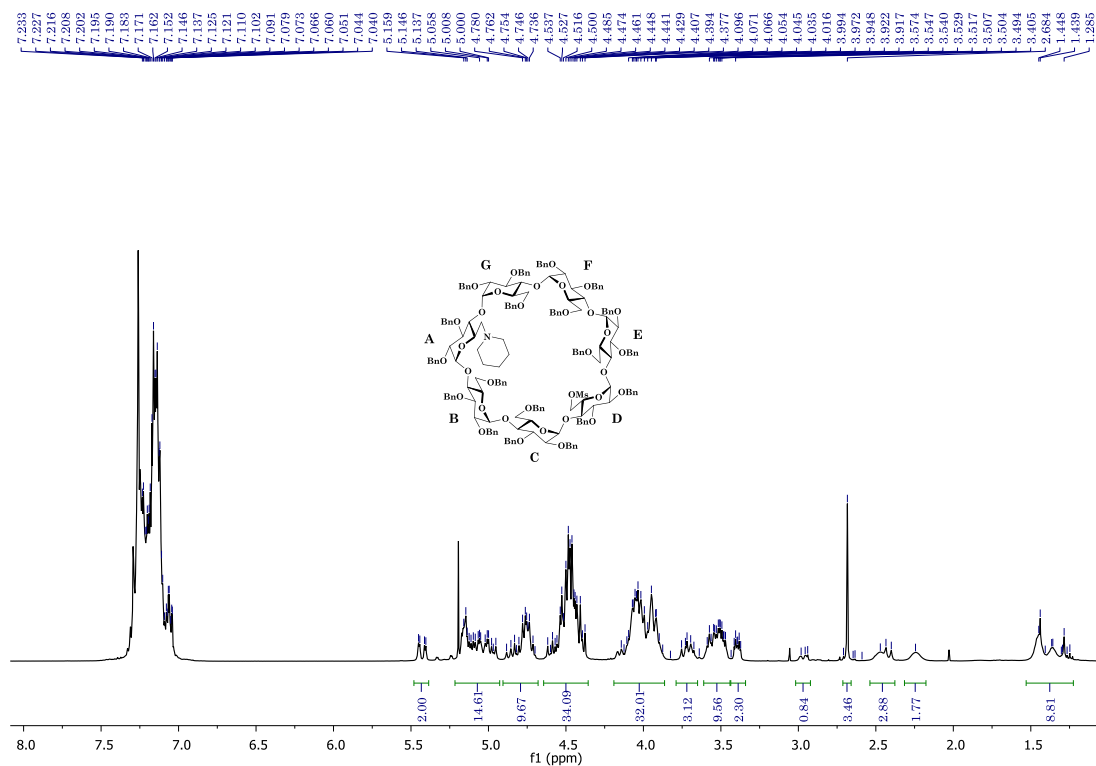
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400MHz):  $\delta$  7.29-7.04 (m, 95H, H-Ar), 5.45 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1), 5.41 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1), 5.17-4.95 (m, 12H, 5×H-1, 7×CHPh), 4.87 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 4.82 (d, 1H, <sup>2</sup>J = 11.4 Hz, CHPh), 4.78-4.71 (m, 5H, 5×CHPh), 4.62-4.38 (m, 26H, 24×CHPh, 2×H-6), 4.17-3.90 (m, 26H, 7×H-3, 6×H-4, 7×H-5, 6×H-6), 3.75-3.67 (m, 3H, H-4, 2×H-6), 3.59-3.46 (m, 7H, 5×H-2, 2×H-6), 3.41-3.37 (m, 2H, 2×H-2), 2.97 (dd, 1H, <sup>3</sup>J<sub>5,6</sub> = 4.5 Hz, <sup>2</sup>J<sub>6,6'</sub> = 12.4 Hz, H-6), 2.68 (s, 3H, S-CH<sub>3</sub>), 2.51-2.24 (m, 5H, H-6, 4×CH<sup>ortho</sup>), 1.46-1.32 (m, 6H, 4×CH<sup>meta</sup>, 2×CH<sup>para</sup>)

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.49, 139.40, 139.37, 139.35(2C), 139.21, 139.12, 138.61, 138.54, 138.53, 138.47, 138.46, 138.42, 138.40, 138.30, 138.25, 138.23, 138.22, 138.10 (19×C-Ar<sup>quat.</sup>), 128.43-126.99 (95×C-Ar<sup>tert.</sup>), 99.22, 98.94, 98.51, 98.48, 98.45, 98.12, 98.09 (7×C-1), 81.54, 80.91(2C) (3×C-4), 80.84(2C) (C-4, C-3), 80.64, 80.42(2C), 79.98, 79.90, 79.51(6×C-3), 79.27, 79.23, 79.06, 79.01, 78.90, 78.72, 78.61 (7×C-2), 78.12(2C), 77.36, 76.91 (4×C-4), 75.92, 75.81, 75.61, 75.50, 75.22, 75.12, 75.05, 73.49, 73.47(2C), 73.40(2C), 73.32, 72.97, 72.85, 72.81, 72.59(2C), 72.56 (19×CH<sub>2</sub>Ph), 71.92, 71.85, 71.69, 71.66, 71.43(2C), 71.32 (7×C-5), 69.72, 69.46, 69.38, 69.29, 69.20, 69.00, 58.92 (7×C-6), 55.51(2C) (2×CH<sub>2</sub><sup>ortho</sup>), 37.26 (S-CH<sub>3</sub>), 26.39(2C) (2×CH<sub>2</sub><sup>meta</sup>), 24.44 (CH<sub>2</sub><sup>para</sup>)

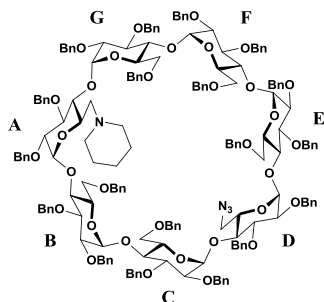
**HRMS (ESI):** Calcd. For C<sub>181</sub>H<sub>196</sub>NSO<sub>36</sub> [M+H]<sup>1+</sup>: 2991.3468; Found: 2991.3252 (-7.2 ppm)



EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>-N-Piperidine-6<sup>D</sup>-Azido-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>,6<sup>G</sup>-Nonadeca-O-Benzyl-β-cyclodextrin (296)**



To a solution of previously formed mesylated cyclodextrin (110 mg, 0.037 mmol, 1 eq.) in DMF (4 mL) were added NaN<sub>3</sub> (12 mg, 0.185 mmol, 5 eq.) at r.t. The reaction mixture was stirred for 5 h at 80 °C under nitrogen, then the solvent was reduced to dryness. The crude was dissolved in EtOAc (10 mL) and washed with water (10 mL). Then the aqueous layers were extracted with EtOAc (3×30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc: 5/1) afforded β-cyclodextrin **296**

(100 mg, 92%) as a white foam.

$\alpha_D = +49.0$  (c 1.0, CHCl<sub>3</sub>)

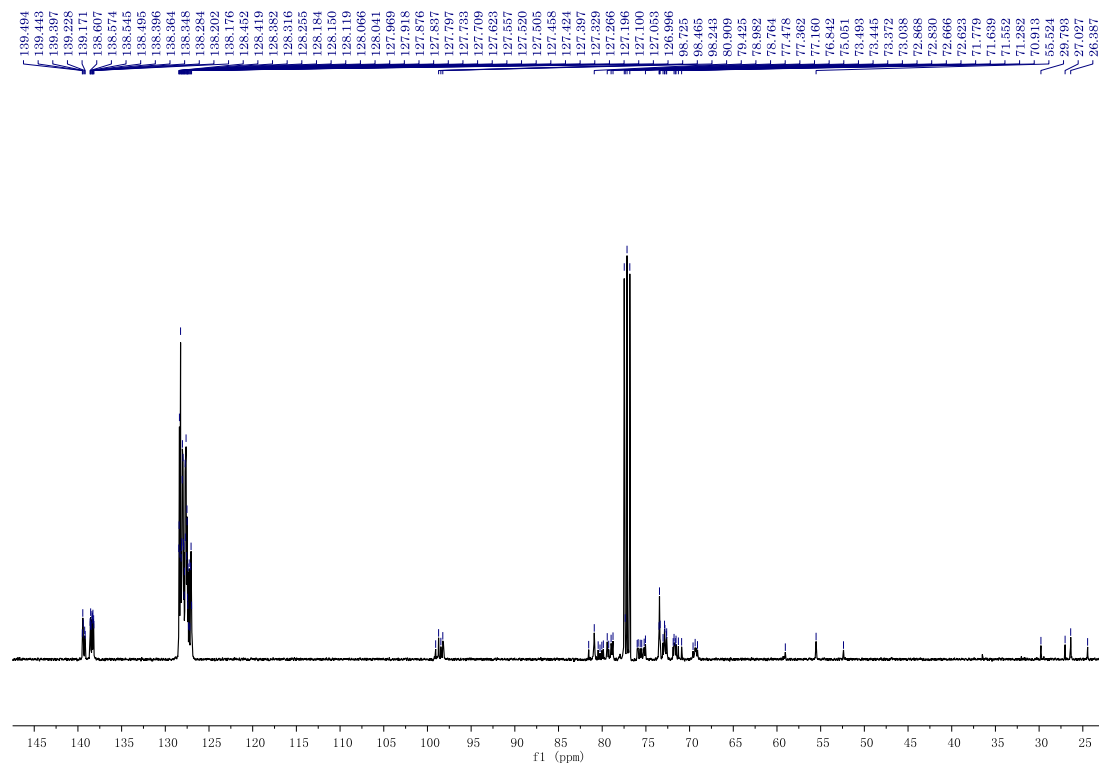
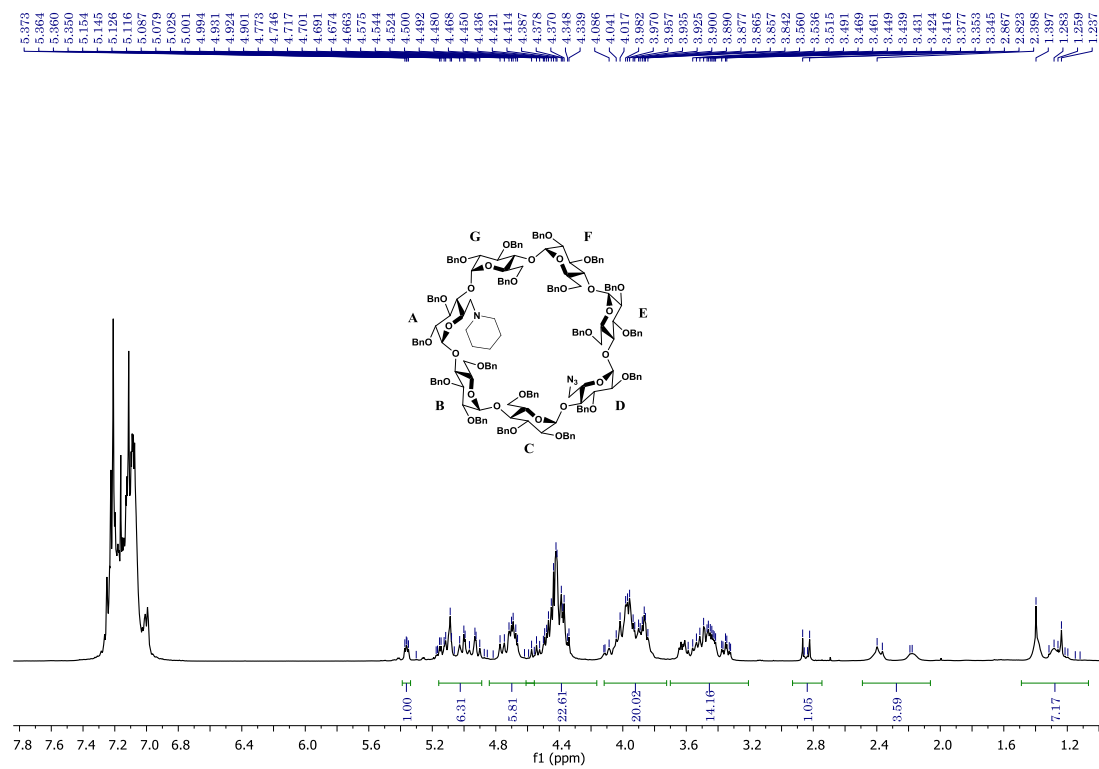
$R_f = 0.42$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz):  $\delta$  7.25-7.07 (m, 95H, H-Ar), 5.37 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1), 5.35 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1), 5.15 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1), 5.12-5.07 (m, 5H, 2×H-1, 3×CHPh), 5.03-4.90 (m, 5H, 2×H-1, 3×CHPh), 4.77-4.66 (m, 6H, 6×CHPh), 4.58-4.34 (m, 26H, 26×CHPh), 4.11-3.85 (m, 25H, 7×H-3, 6×H-4, 7×H-5, 5×H-6), 3.64-3.41 (m, 13H, 5×H-2, H-4, 7×H-6), 3.37 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.6 Hz, H-2), 3.33 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.5 Hz, H-2), 2.85 (dd, 1H, H-6), 2.40-2.18 (m, 5H, H-6, 4×CH<sub>ortho</sub>), 1.40-1.27 (m, 6H, 4×CH<sub>meta</sub>, 2×CH<sub>para</sub>)

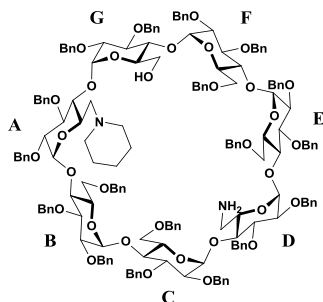
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.49, 139.44(2C), 139.40, 139.39, 139.23, 139.17, 138.60, 138.57, 138.55(2C), 138.50, 138.40, 138.36, 138.35, 138.28(2C), 138.20, 138.18 (19×C-Ar<sup>quat.</sup>), 128.45-126.99 (95×C-Ar<sup>tert.</sup>), 99.06, 98.73(2C), 98.46, 98.24, 98.21, 98.17 (7×C-1), 81.55, 80.95 (2×C-4), 80.91(2C) (C-4, C-3), 80.88, 80.86, 80.46, 80.25, 80.04, 79.87 (6×C-3), 79.48 (C-4), 79.43(2C) (2×C-2), 79.26 (C-4), 79.01, 78.98, 78.92, 78.76, 77.95 (5×C-2), 77.36, 77.01 (2×C-4), 76.00, 75.89, 75.65, 75.48, 75.20, 75.05, 73.49, 73.44(3C), 73.42(2C), 73.37, 73.04, 72.87, 72.83, 72.67, 72.62, 72.60 (19×CH<sub>2</sub>Ph), 71.88, 71.78, 71.76, 71.64, 71.55, 71.28, 70.91 (7×C-5), 69.60, 69.36, 69.29, 69.22, 69.09, 59.04 (6×C-6), 55.52(2C) (2×CH<sub>2</sub><sub>ortho</sub>), 52.39 (C-6), 26.39(2C) (2×CH<sub>2</sub><sub>meta</sub>), 24.45 (CH<sub>2</sub><sub>para</sub>)

**HRMS (ESI):** Calcd. For C<sub>180</sub>H<sub>193</sub>N<sub>4</sub>O<sub>33</sub> [M+H]<sup>1+</sup>: 2938.3395; Found: 2938.3542 (+5.0 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>-*N*-Piperidine-6<sup>D</sup>-Amino-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>-Octadeca-*O*-Benzyl- $\beta$ -cyclodextrin (**297**)**



DIBAL-H (1.5 M in toluene, 25.7 mL, 39.1 mmol, 50 eq.) was slowly added to a solution of cyclodextrin **296** (2.3 g, 0.782 mmol, 1 eq.) in toluene (13.4 mL) under nitrogen at r.t. The reaction mixture was stirred under nitrogen reflux at 55 °C. The formation of the amino-monol as the major product was monitored by MS (1h). Heating was stopped, and the reaction mixture was poured into ice/water slowly. Aqueous HCl (100 mL) and EtOAc (100 mL) were added, and the solution was stirred for

1 h. Then the aqueous layers were extracted with EtOAc (3×100 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated to give an unseparated mixture of amino-, amino-monol- and amino-diol- $\beta$ -cyclodextrin (2.0 g) as a white foam.

A solution of Boc<sub>2</sub>O (464 mg, 2.124 mmol, 3 eq.) in absolute ethanol (5 mL) was added to a solution of the mixed  $\beta$ -cyclodextrins (2.0 g, 0.708 mmol, 1 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (10.0 mL) at r.t. The reaction mixture was stirred for 2 h, the solvent was evaporated under reduced pressure. Silica gel flash chromatography of the residue (CyH/AcOEt 4:1) gave the Boc protected amino-monol- $\beta$ -cyclodextrin (650 mg) as a white foam.

The Boc protected cyclodextrin (650 mg, 0.23 mmol, 1 eq.) was dissolved in dichloromethane (10 mL) and TFA (1.5 mL) was added at 0 °C for 2 h. Dichloromethane (10 mL) and saturated aqueous solution of NaHCO<sub>3</sub> (10 mL) were added at the same temperature and the solution was stirred during 1 h. Then the layers were separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/AcOEt: 3/1, then DCM/MeOH: 97/3) afforded cyclodextrin **297** (558 mg, 25% in 3 steps) as a white foam.

$\alpha_D = +42.4$  (c 1.0, CHCl<sub>3</sub>)

$R_f = 0.18$  (DCM/MeOH: 95/5)

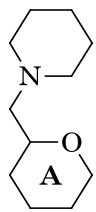
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.44-7.15 (m, 90H, H-Ar), 5.82 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1E), 5.70 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1F), 5.44-5.35 (m, 5H, H-1C, 4×CHPh), 5.14-5.11 (m, 2H, H-1G, CHPh), 5.01-4.91 (m, 6H, H-1A, H-1D, 4×CHPh), 4.87-4.81 (m, 6H, H-1B, 5×CHPh), 4.77-4.39 (m, 22H, 22×CHPh), 4.32 (bd, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.5 Hz, H-6C), 4.23-4.00 (m, 20H, H-3A, H-3B, H-3C, H-3D, H-3E, H-3F, H-3G, H-4A, H-4B, H-4D, H-4E, H-4F, H-4G, H-5B, H-5C, H-5E, H-5G, H-6E, H-6F, H-6G), 3.92-3.87 (m, 3H, H-5A, H-5D, H-5F), 3.80-3.75 (m, 2H, H-6E, H-6G), 3.70-3.55 (m, 8H, H-2B, H-2C, H-2E, H-2F, H-2G, H-6B, H-6C, H-6F), 3.46-3.42 (m, 3H, H-2A, H-2D, H-4C), 3.31 (bd, <sup>2</sup>J<sub>6,6'</sub> = 10.8 Hz, H-6D), 3.06 (m, 1H, H-6A), 2.71-2.29 (m, 6H, H-6A, H-6D, 4×CH<sub>ortho</sub>), 1.55-1.37 (m, 6H, 4×CH<sub>meta</sub>, 2×CH<sub>para</sub>)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.67(2C), 139.61, 139.49(2C), 139.28, 138.98, 138.87(2C), 138.45(2C), 138.41, 138.38, 138.33, 138.28, 138.20, 138.03, 137.89 (18×C-Ar<sub>quat.</sub>), 128.41-126.97 (90×C-Ar<sub>tert.</sub>), 99.19, 99.17, 98.60, 98.42, 97.52, 96.76, 96.67 (C-1B, C-1A, C-1G, C-1C, C-1F, C-1E, C-1D), 82.83, 82.18, 81.46, (C-4C-C-4E, C-4D), 81.34 (C-3C), 81.23 (C-4G), 80.91(2C), 80.85, 80.77(2C) (C-3E, C-3F, C-3B, C-3A, C-3D), 80.18, 80.05 (C-4B, C-4F), 79.92 (C-3G), 79.74, 79.63, 79.47, 78.68, 78.02 (C-2G, C-2A, C-2B, C-2D, C-2F, C-2C, C-2E), 76.42,

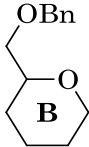
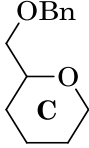
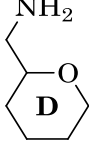
**EXPERIMENTAL PART**

76.24, 76.18, 76.05, 75.93 (5×CH<sub>2</sub>Ph), 74.76 (C-4A), 74.60(2C), 73.61, 73.34, 73.20, 73.16, 73.10, 72.99, 72.94, 72.85, 72.71, 72.68, 72.57 (13×CH<sub>2</sub>Ph), 72.42, 71.75(3C), 71.48, 71.30, 70.79, (C-5A, C-5F, C-5C, C-5B,C-5E, C-5D, C-5G), 69.35, 69.27, 68.92, 68.81, 59.90, 58.54 (C-6F, C-6B, C-6E, C-6C, C-6G, C-6A), 55.44(2C) (2×CH<sub>2</sub><sup>ortho</sup>), 43.12 (C-6D), 26.36(2C) (2×CH<sub>2</sub><sup>meta</sup>), 24.40 (CH<sub>2</sub><sup>para</sup>)

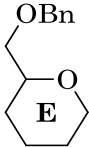
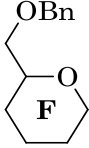
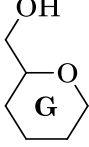
**HRMS (ESI):** Calcd. For C<sub>173</sub>H<sub>189</sub>N<sub>2</sub>O<sub>33</sub> [M+H]<sup>1+</sup>: 2822.3029; Found: 2822.3167 (+4.9 ppm)

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1A	5.007	NOE: 4.007	H-4B
	C-1A	99.176		
	H-2A	3.422		
	C-2A	79.631		
	H-3A	4.103		
	C-3A	80.771		
	H-4A	4.118		
	C-4A	74.765		
	H-5A	3.904		
	C-5A	72.423		
	H-6A	3.064		
		2.311		
	C-6A	58.552		

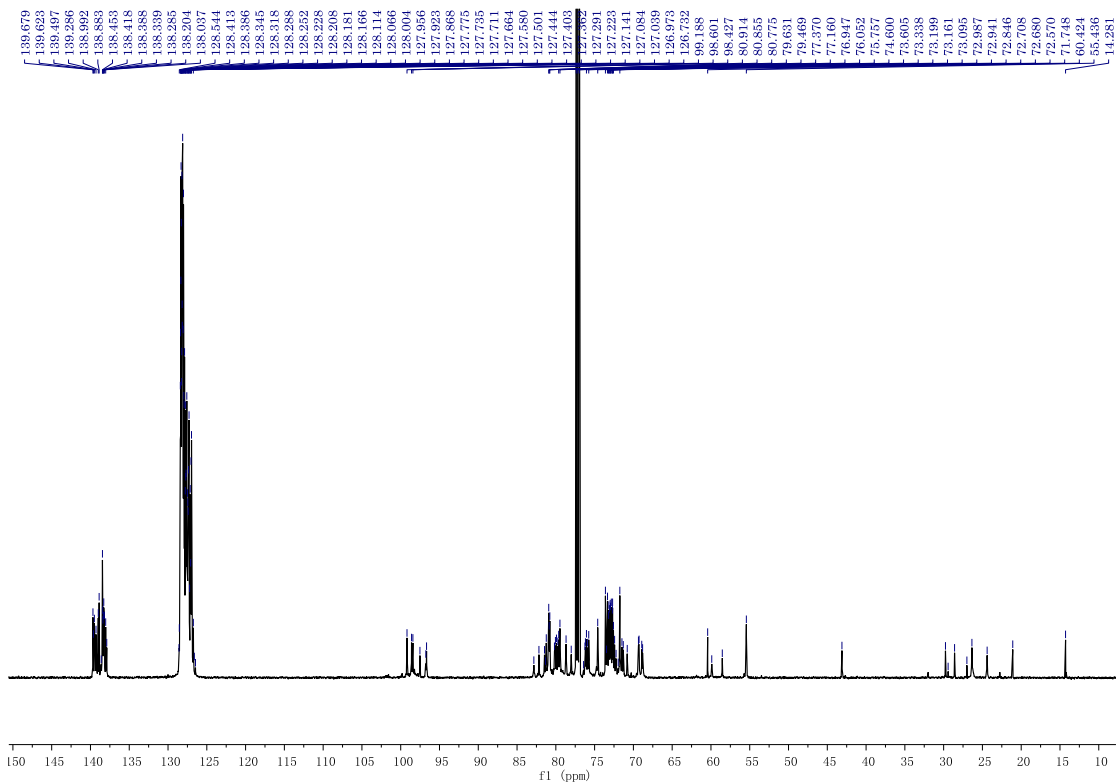
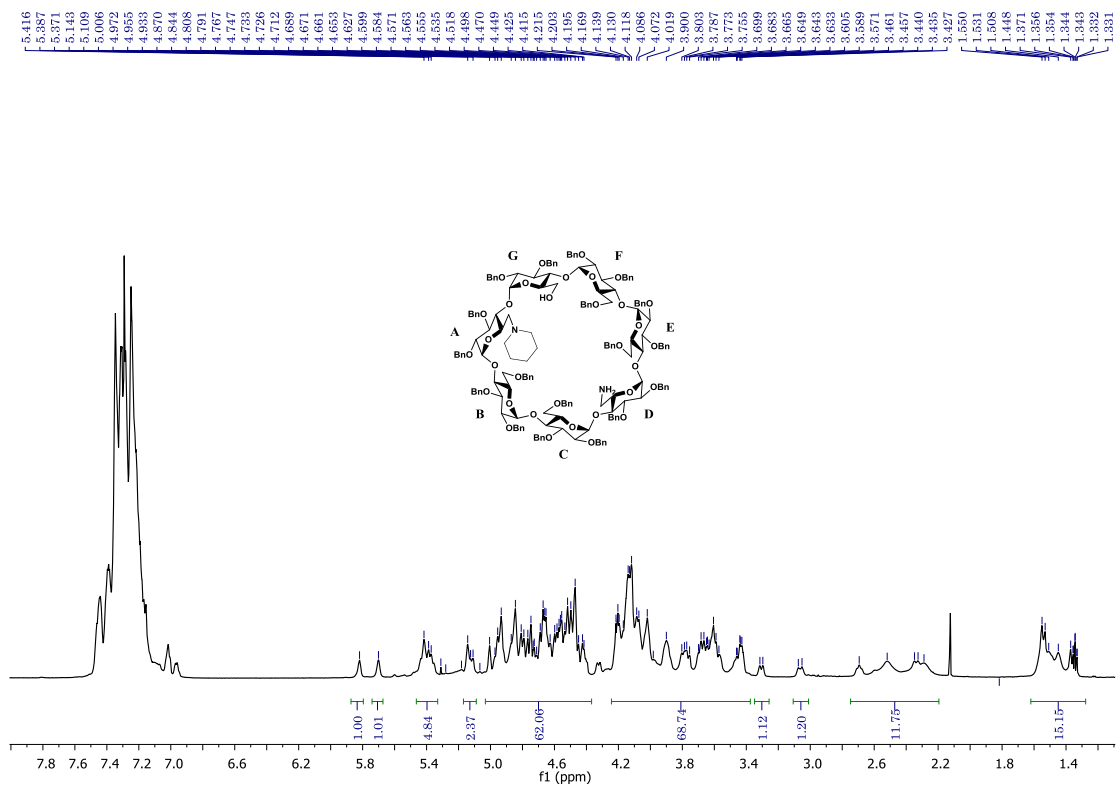
**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1B	4.852	NOE: 3.429	H-4C
	C-1B	99.190		
	H-2B	3.564		
	C-2B	79.460		
	H-3B	4.109		
	C-3B	80.850		
	H-4B	4.007		
	C-4B	80.183		
	H-5B	4.117		
	C-5B	71.306		
	H-6B	3.693		
		4.028		
C-6B	69.275			
	H-1C	5.426	NOE: 4.124	H-4D
	C-1C	98.423		
	H-2C	3.610		
	C-2C	78.717		
	H-3C	4.124		
	C-3C	81.346		
	H-4C	3.429		
	C-4C	82.830		
	H-5C	4.014		
	C-5C	71.753		
	H-6C	4.320		
		3.666		
C-6C	68.822			
	H-1D	4.935	NOE: 4.205	H-4E
	C-1D	96.673		
	H-2D	3.435		
	C-2D	79.468		
	H-3D	4.058		
	C-3D	80.771		
	H-4D	4.124		
	C-4D	81.462		
	H-5D	3.890		
	C-5D	71.753		
	H-6D	3.305		
		2.690		
C-6D	43.153			

**EXPERIMENTAL PART**

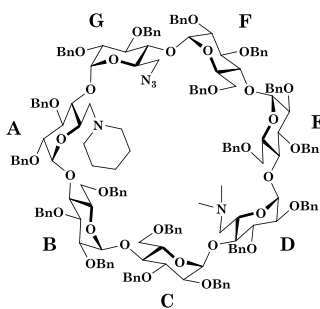
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1E	5.819	NOE: 4.137	H-4F
	C-1E	96.761		
	H-2E	3.658		
	C-2E	78.008		
	H-3E	4.156		
	C-3E	80.914		
	H-4E	4.205		
	C-4E	82.176		
	H-5E	4.180		
	C-5E	71.482		
	H-6E	3.760		
		4.130		
C-6E	68.926			
	H-1F	5.700	NOE: 4.105	H-4G
	C-1F	97.522		
	H-2F	3.633		
	C-2F	78.717		
	H-3F	4.143		
	C-3F	80.915		
	H-4F	4.137		
	C-4F	80.059		
	H-5F	3.880		
	C-5F	71.753		
	H-6F	3.600		
		4.084		
C-6F	69.354			
	H-1G	5.150	NOE: 4.118	H-4A
	C-1G	98.604		
	H-2G	3.597		
	C-2G	79.752		
	H-3G	4.203		
	C-3G	79.925		
	H-4G	4.105		
	C-4G	81.227		
	H-5G	4.203		
	C-5G	70.791		
	H-6G	3.798		
		4.113		
C-6G	59.874			

EXPERIMENTAL PART





**6A,6D,6G-Trideoxy-6A-N-Piperidine-6D-N-Dimethyl-Amino-6G-Azido-2A-G,3A-G,6B,6C,6E,6F-Octadeca-O-Benzyl- $\beta$ -cyclodextrin (298)**



Formaldehyde (0.060 mL, 0.792 mmol, 4 eq.), NaBH(OAc)<sub>3</sub> (252 mg, 1.188 mmol, 6 eq.) and AcOH (0.011 mL, 0.198 mmol, 1 eq.) were added to a solution of cyclodextrin **297** (558 mg, 0.198 mmol, 1 eq.) in DCM (10 mL) under nitrogen at r.t. The mixture was stirred for 1 h. Then sat. NaHCO<sub>3</sub> (20 mL) was added and the aqueous layers were extracted with DCM (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was dried *in vacuo* to give

cyclodextrin (540 mg, 96%) as a white foam.

DMAP (23 mg, 0.191 mmol, 1 eq.) was added to the methylated cyclodextrin (540 mg, 0.191 mmol, 1 eq.) in DCM (10 mL) at r.t.. Then MsCl (148  $\mu$ L, 1.91 mmol, 10 eq.) and Et<sub>3</sub>N (266  $\mu$ L, 1.91 mmol, 10 eq.) were added. The reaction mixture was stirred at r.t. for 2 h. Water (10 mL) was added and the aqueous layers were extracted by DCM (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was dried *in vacuo* to give mesylated cyclodextrin (540 mg, 96%) as a white foam.

Sodium azide (60 mg, 0.915 mmol, 5 eq.) was added to a solution of mesylated cyclodextrin (540 mg, 0.183 mmol, 1 eq.) in DMF (10 mL) at r.t.. The reaction mixture was stirred at 80°C under nitrogen overnight. TLC showed that the reaction finished, then the heating was stopped and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (20 mL), washed with water (10 mL). The aqueous layers were extracted by EtOAc (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography (CyH/EtOAc: 4/1) afforded cyclodextrin **298** (500 mg, 95%) as a white foam.

$\alpha_D = +49.9$  (c 1.0, CHCl<sub>3</sub>)

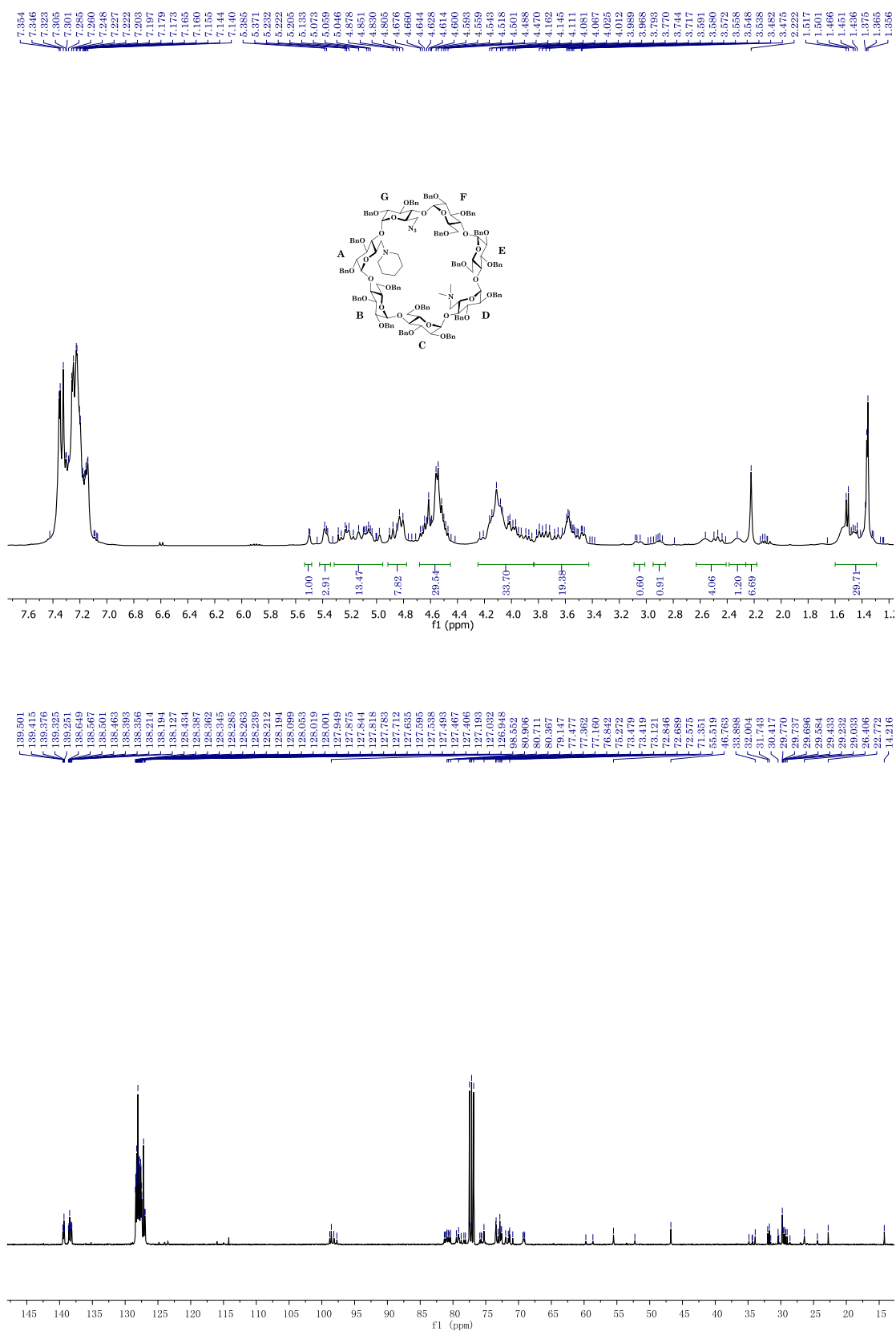
$R_f = 0.29$  (CyH/EtOAc: 2/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.35-7.14 (m, 90H, H-Ar), 5.50 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1), 5.38 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1), 5.37 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1), 5.36 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1), 5.28-4.98 (m, 8H, 2×H-1, 6×CHPh), 4.90-4.80 (m, 6H, 4×CHPh), 4.67-4.50 (m, 24H, 24×CHPh), 4.24-3.85 (m, 24H, 7×H-3, 6×H-4, 7×H-5, 4×H-6), 3.81-3.65 (m, 4H, 4×H-6), 3.62-3.45 (m, 8H, 7×H-2, 2×H-6), 3.06 (dd, 1H, <sup>3</sup>J<sub>5,6</sub> = 5.2 Hz, <sup>2</sup>J<sub>6,6'</sub> = 14.2 Hz, H-6), 2.93-2.88 (m, 1H, H-6), 2.56-2.33 (m, 6H, 2×H-6, 4×CH<sup>ortho</sup>), 2.22 (s, 6H, 2×S-CH<sub>3</sub>), 1.55-1.40 (m, 6H, 4×CH<sup>meta</sup>, 2×CH<sup>para</sup>)

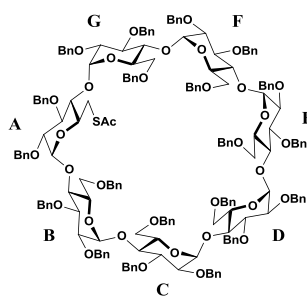
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.50, 139.49, 139.41, 139.38, 139.33(2C), 139.25, 138.65, 138.57, 138.50, 138.47, 138.46(2C), 138.39, 138.36, 138.21, 138.19, 138.13 (18×C-Ar<sup>quat.</sup>), 128.41-126.97 (90×C-Ar<sup>tert.</sup>), 98.79, 98.55(3C), 98.17, 98.01, 97.71 (7×C-1), 81.31 (C-4), 81.16, 81.02, 80.93, 80.91, 80.71, 80.66, 80.55 (7×C-3), 80.37(2C) (2×C-4), 79.51, 79.48 (2×C-2), 79.20, 79.15 (2×C-4), 79.07, 78.75, 78.33, 78.09 (4×C-2), 77.56, 77.36 (2×C-4), 75.90, 75.71, 75.60, 75.27(2C), 75.23, 73.48(2C), 73.45(2C), 73.42(2C), 73.12, 72.85(2C), 72.69, 72.67, 72.58 (18×CH<sub>2</sub>Ph), 71.97, 71.93, 71.56, 71.42, 71.35(2C), 70.87 (7×C-5), 69.33, 69.22, 69.16, 69.07, 59.73, 58.66 (6×C-6), 55.52(2C) (2×CH<sub>2</sub><sup>ortho</sup>), 52.26 (C-6), 46.76(2C) (2×S-CH<sub>3</sub>), 26.40(2C) (2×CH<sub>2</sub><sup>meta</sup>), 24.42 (CH<sub>2</sub><sup>para</sup>)

**HRMS (ESI):** Calcd. For C<sub>175</sub>H<sub>192</sub>N<sub>5</sub>O<sub>32</sub> [M+H]<sup>1+</sup>: 2875.3301; Found: 2875.3545 (+8.2 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-S-Acetyl-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>,6<sup>F</sup>,6<sup>G</sup>-Icosa-  
O-Benzyl-β-Cyclodextrin (300)**



The *O*-methylsulfonyl-cyclodextrin **300a** (0.5 g, 0.166 mmol, 1 eq.) was dissolved in anhydrous DMF (10 mL) under nitrogen. Potassium thioacetate (57 mg, 0.498 mmol, 3 eq.) was added at r.t.. The reaction mixture was stirred overnight at 50 °C. EtOAc (200 mL) was added and the organic layer was washed with brine (3×200 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 4/1) gave thioacetate-β-cyclodextrin **300** (480

g, 97%) as a yellowish foam.

$\alpha_D = +50.0$  (c 1.0, CHCl<sub>3</sub>)

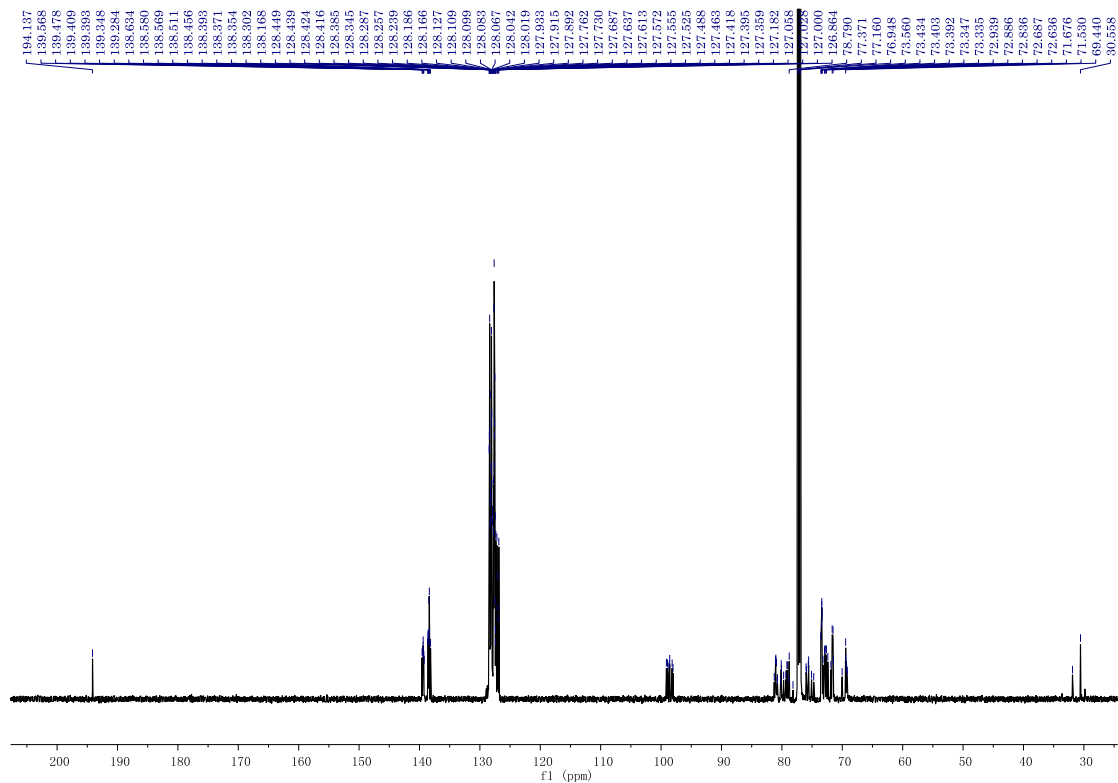
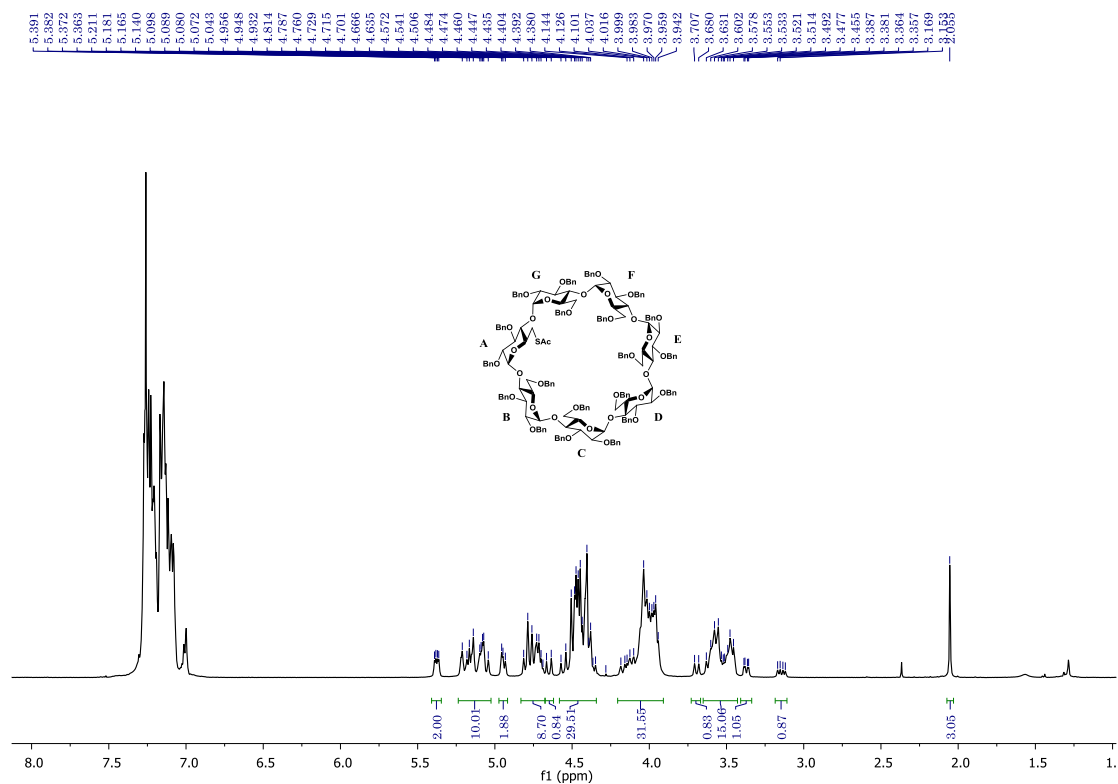
$R_f = 0.46$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.25-7.14 (m, 100H, 100×H-Ar.), 5.39 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, H-1), 5.37 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 5.22 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 5.18-5.07 (m, 8H, 3×H-1, 5×CHPh), 5.06 (d, 1H, <sup>2</sup>J = 11.6 Hz, CHPh), 4.95 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1), 4.94 (d, 1H, <sup>2</sup>J = 10.2 Hz, CHPh), 4.81-4.69 (m, 6H, 6×CHPh), 4.65 (d, 1H, <sup>2</sup>J = 12.0 Hz, CHPh), 4.55 (d, 1H, <sup>2</sup>J = 12.2 Hz, CHPh), 4.54-4.38 (m, 25H, 25×CHPh), 4.18-3.94 (m, 26H, 7×H-3, 6×H-4, 7×H-5, 6×H-6), 3.69 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.8 Hz, H-6), 3.63-3.46 (m, 13H, 6×H-2, H-4, 6×H-6), 3.37 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, H-2), 3.14 (dd, 1H, <sup>3</sup>J<sub>5,6</sub> = 6.6 Hz, <sup>2</sup>J<sub>6,6'</sub> = 13.0 Hz, H-6), 2.06 (s, 3H, SC(O)CH<sub>3</sub>)

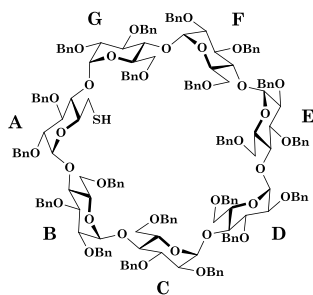
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  194.14 (SC(O)CH<sub>3</sub>), 139.57, 139.48, 139.41, 139.40, 139.35, 139.28, 139.21, 138.63, 138.58, 138.57, 138.51, 138.46(3C), 138.39, 138.37(2C), 138.35, 138.30, 138.17 (20×C-Ar<sup>quat.</sup>), 128.45-126.86 (100×C-Ar<sup>tert.</sup>), 99.11, 98.94, 98.82, 98.63, 98.57, 98.17, 98.03 (7×C-1), 81.27, 81.06, 81.00(2C), 80.99, 80.89, 80.79 (7×C-3), 80.72, 80.27, 80.11, 80.06, 79.36 (5×C-4), 79.20, 79.13(2C), 78.90, 78.83(2C), 78.20 (7×C-2), 77.35, 77.17 (2×C-4), 75.99, 75.93, 75.63, 75.60, 75.57, 75.09, 74.73, 73.56, 73.43, 73.40, 73.39, 73.35, 73.34, 73.19, 72.94, 72.89, 72.84, 72.69, 72.64, 72.40 (20×CH<sub>2</sub>Ph), 71.88, 71.68(2C), 71.53(2C), 71.49, 70.02 (7×C-5), 69.44(2C), 69.41, 69.31, 69.26, 69.17, 31.89 (7×C-6), 30.56 (SC(O)CH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>184</sub>H<sub>192</sub>O<sub>35</sub>SNa [M+Na]<sup>1+</sup>: 3016.2851; Found: 3016.2857 (+0.2 ppm); Calcd. For C<sub>184</sub>H<sub>192</sub>O<sub>35</sub>SNa<sub>2</sub> [M+Na+Na]<sup>2+</sup>: 1519.6388; Found: 1519.6375 (-0.8 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>-Deoxy-6<sup>A</sup>-Thiol-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>E</sup>,6<sup>F</sup>,6<sup>G</sup>-Icosa-  
O-Benzyl- $\beta$ -Cyclodextrin (**300b**)**



DIBAL-H (1.5 M in toluene, 11.6 mL, 17.4 mmol, 20 eq.) was added to a solution of thioacetate-cyclodextrin **300** (2.6 g, 0.87 mmol, 1 eq.) in toluene (5.8 mL) under nitrogen at r. t. The reaction mixture was stirred at 55 °C with a nitrogen balloon reflux for 35 min, until mass spectrum indicated the formation of thiol-monol as a major product, and then cooled to r.t. and poured into ice/water. Aqueous HCl (20 mL, 1 M) and EtOAc (20 mL) were added, and the solution was stirred for 1 h. The aqueous layer was extracted with EtOAc

(3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Silica gel chromatography of the residue (CyH/EtOAc: 5/1) gave the thiol-cyclodextrin **300b** (200 mg, 7.7%) and an inseparable mixture of AD, AE-cyclodextrins **300-M** (1.8 g, 72%, AE/AD=2/1) as yellowish foams.

$\alpha_D +44.3$  (c 1.0, CHCl<sub>3</sub>)

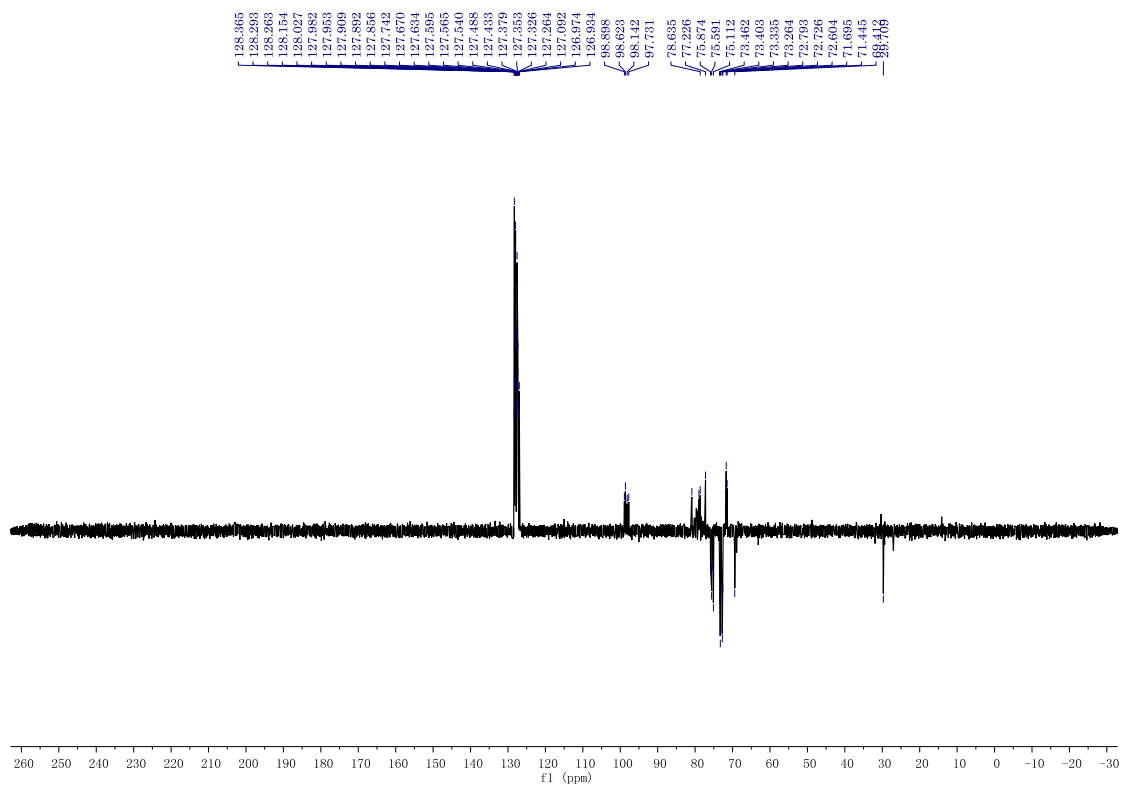
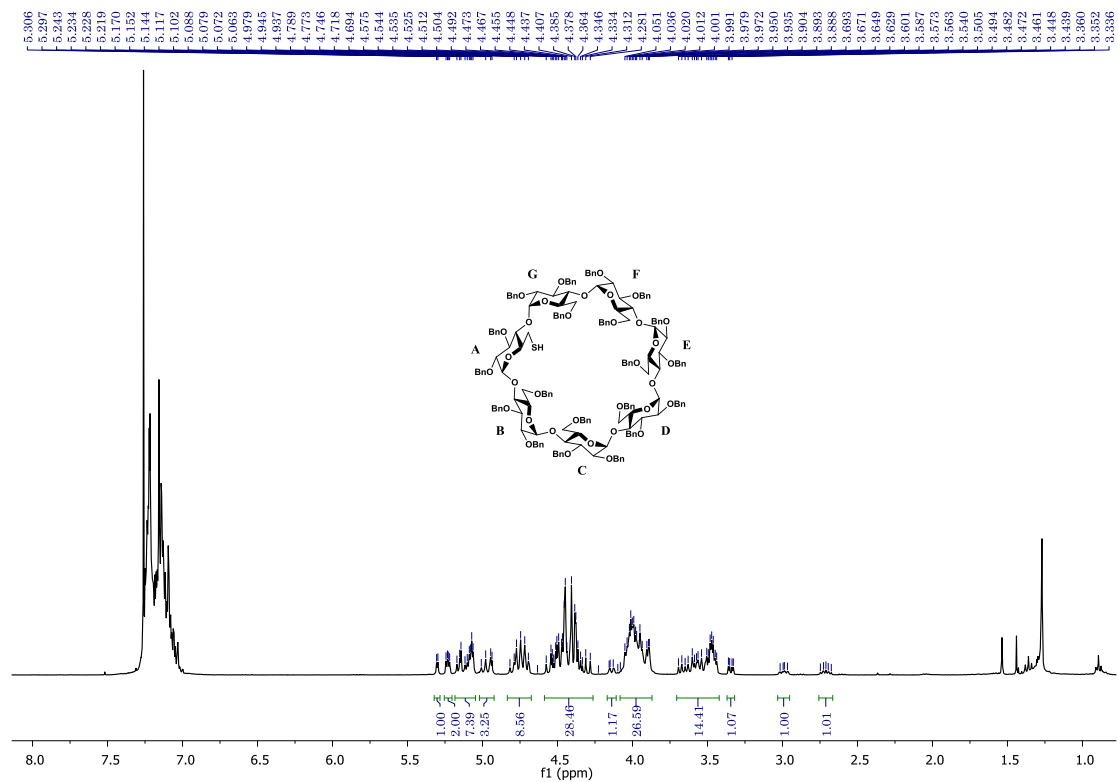
$R_f = 0.60$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.25-7.03 (m, 100H, 100×H-Ar.), 5.30 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1), 5.24 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.9 Hz, H-1), 5.22 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.9 Hz, H-1), 5.16 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 5.15 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1), 5.12-5.06 (m, 5H, 2×H-1, 3×CHPh), 4.99 (d, 1H, <sup>2</sup>J = 11.7 Hz, CHPh), 4.96 (d, 1H, <sup>2</sup>J = 11.5 Hz, CHPh), 4.94 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.9 Hz, H-1), 4.82-4.69 (m, 8H, 8×CHPh), 4.57-4.28 (m, 26H, 26×CHPh), 4.14 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.8 Hz, H-6), 4.05-3.89 (m, 25H, 7×H-3, 6×H-4, 7×H-5, 5×H-6), 3.63-3.46 (m, 13H, 6×H-2, H-4, 6×H-6), 3.43 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, <sup>3</sup>J<sub>2,3</sub> = 10.1 Hz, H-2), 2.92 (m, 1H, H-6), 2.71 (m, 1H, H-6), 1.35 (t, 1H, <sup>3</sup>J<sub>SH,6</sub> = 6.7 Hz, SH)

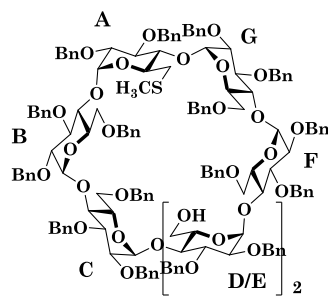
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.45, 139.44, 139.40, 139.38(2C), 139.28, 139.22, 138.58, 138.56, 138.51, 138.49, 138.45, 138.43, 138.37, 138.36(2C), 138.33(2C), 138.26, 138.07 (20×C-Ar<sup>quat.</sup>), 128.49-127.00 (100×C-Ar<sup>tert.</sup>), 99.02, 98.76, 98.74, 98.66, 98.41, 98.27, 97.84 (7×C-1), 81.24, 81.09, 81.06, 80.99, 80.97, 80.96, 80.80 (7×C-3), 80.21, 79.84, 79.77, 79.56, 79.30 (5×C-4), 71.15, 79.06, 79.03, 79.02, 78.92, 78.72(2C) (7×C-2), 78.07, 78.00 (2×C-4), 76.01, 75.74(2C), 75.77, 75.46, 75.25(2C), 73.58, 73.52, 73.45(2C), 73.38(3C), 72.92(2C), 72.84(2C), 72.72, 72.69 (20×CH<sub>2</sub>Ph), 71.81, 71.79, 71.76, 71.62, 71.56, 71.55, 71.50 (7×C-5), 69.52, 69.47, 69.46, 69.42, 69.36, 69.01, 27.13 (7×C-6)

**HRMS (ESI):** Calcd. For C<sub>182</sub>H<sub>190</sub>O<sub>34</sub>SNa [M+Na]<sup>1+</sup>: 2974.2638; Found: 2974.2751 (+3.8 ppm);

EXPERIMENTAL PART



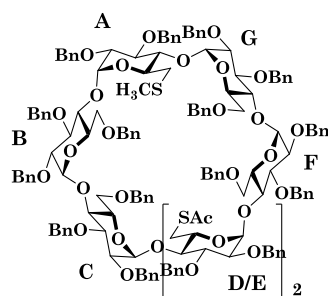
**6<sup>A</sup>-Deoxy-6<sup>A</sup>-S-Methyl-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D/E</sup>,6<sup>F</sup>,6<sup>G</sup>-Nonadeca-O-Benzyl-β-Cyclodextrin (301-M)**



Potassium carbonate (362 mg, 2.62 mmol, 5 eq.) was added to a solution of cyclodextrins **300-M** (1.5 g, 0.524 mmol, 1 eq.) in anhydrous DMF (20 mL) under nitrogen at 0 °C. MeI (0.160 mL, 2.62 mmol, 5 eq.) was added, and the reaction mixture was stirred for 1h30. Until TLC showed the reaction finished, water (20 mL) was added and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash

chromatography of the residue (CyH/EtOAc: 4/1) gave β-cyclodextrins **301-M** (1.29 g, 86%) as yellowish foams.

**6<sup>A</sup>,6<sup>D/E</sup>-Dideoxy-6<sup>A</sup>-S-Methyl-6<sup>D/E</sup>-S-Acetyl-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>D/E</sup>,6<sup>F</sup>,6<sup>G</sup>-Nonadeca-O-Benzyl-β-Cyclodextrin (302-M)**



Triethylamine (0.125 mL, 0.896 mmol, 2 eq.) followed by methanesulfonyl chloride (0.070 mL, 0.896 mmol, 2 eq.) was added to a solution of cyclodextrins **301-M** (1.29 g, 0.448 mmol, 1 eq.) in DCM (20 mL) under nitrogen at r. t. The reaction mixture was stirred at r.t. for 1h30 min. Water (20 mL) was added, and the aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, concentrated *in vacuum* and dried in oil pump to give

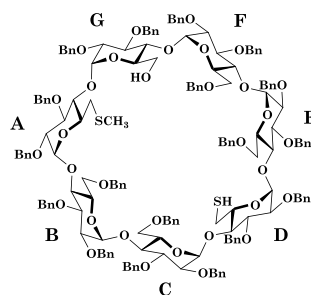
the mesylated-cyclodextrins (1.3 g) as yellowish foams.

The formed mesylated-cyclodextrins (0.60 g, 0.203 mmol, 1 eq.) was dissolved in anhydrous DMF (10 mL) under nitrogen. Potassium thioacetate (70 mg, 0.609 mmol, 3 eq.) was added at r.t.. The reaction mixture was stirred overnight at 50°C. EtOAc (20 mL) was added and the organic layer was washed with brine (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 5/1) gave thioacetate-β-cyclodextrin **302-M** (0.526 g, 88%) as yellowish foams.

### The mixture of $\beta$ -Cyclodextrins (**302-M**) underwent the action of DIBAL-H

DIBAL-H (1.5 M in toluene, 26.1 mL, 38.6 mmol, 20 eq.) was added to a solution of cyclodextrin **302-M** (5.7 g, 2.342 mmol, 1 eq.) in toluene (12.5 mL) under nitrogen at r. t. The reaction mixture was stirred at 55°C with a nitrogen balloon reflux for 20 min, until Mass spectrum indicated formation of monol as a major product, and then cooled to r.t. and poured into ice/water. Aqueous HCl (70 mL, 1 M) and EtOAc (70 mL) were added, and the solution was stirred for 1 h. The aqueous layer was extracted with EtOAc (3×70 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuum*. Silica gel chromatography (40-60  $\mu$ m) of the residue (CyH/EtOAc: 4/1) gave **301a** (1.0 g, 18%) and cyclodextrin **301b** (1.828 g, 34%) as yellowish foams.

#### 6A,6D-Dideoxy-6A-S-Methyl-6D-Thiol-2A-G,3A-G,6B,6C,6E, 6F-Octadeca-O-Benzyl- $\beta$ -Cyclodextrin (**301a**)



$$\alpha_D = +51.5 \text{ (c 1.0, CHCl}_3\text{)}$$

$$R_f = 0.33 \text{ (CyH/EtOAc: 3/1)}$$

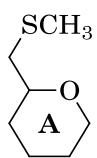
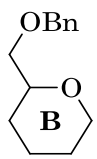
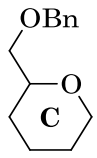
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.34-7.09 (m, 90H, 90×H-Ar), 5.43 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1F), 5.39 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1C), 5.27 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 5.20 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh), 5.19 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1B), 5.08 (d, 1H, <sup>2</sup>J = 10.4 Hz, CHPh), 5.05 (d, 1H, <sup>2</sup>J = 11.1 Hz, CHPh), 5.00 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1G), 4.97 (d, 1H, <sup>2</sup>J = 10.1 Hz, CHPh), 4.94 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1A), 4.90 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1E), 4.84 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1D), 4.81 (d, 1H, <sup>2</sup>J = 11.3 Hz, CHPh), 4.76-4.62 (m, 8H, 8×CHPh), 4.59-4.34 (m, 22H, 22×CHPh), 4.23 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 10.4 Hz, H-6B), 4.09-3.84 (m, 22H, H-3A, H-3B, H-3C, H-3D, H-3E, H-3F, H-3G, H-4B, H-4C, H-4E, H-4G, H-5A, H-5B, H-5C, H-5D, H-5E, H-5F, H-5G, H-6E, H-6G, H-6C, H-6F), 3.77-3.61 (m, 7H, H-6G, H-4F, H-6F, H-4D, H-6C, H-6B, H-4A), 3.57-3.45 (m, 6H, H-6E, H-2F, H-2C, H-2G, H-2B, H-2E), 3.40 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.3 Hz, H-2A), 3.36 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.3 Hz, H-2D), 3.14 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 11.8 Hz, H-6A), 3.04-2.74 (m, 3H, H-6A, 2×H-6D), 2.01 (s, 3H, SCH<sub>3</sub>)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.47, 139.45, 139.43, 139.25, 139.22, 139.15, 139.00, 138.70, 138.62, 138.46, 138.41, 138.40, 138.35, 138.34, 138.30, 138.21, 137.98, 137.90 (18×C-Ar<sup>quat.</sup>), 128.52-126.93 (90×C-Ar<sup>tert.</sup>), 99.20, 99.11, 98.81, 98.31, 98.28, 98.11, 97.91 (C-1G, C-1E, C-1B, C-1D, C-1C, C-1A, C-1F), 83.29 (C-4A), 81.23, 81.15, 80.95, 80.92 (C-3C, C-3A, C-3B, C-3D), 80.69(2C) (C-4E, C-3E), 80.63 (C-4C), 80.32 (C-3G), 80.25 (C-4D), 79.79(2C) (C-2D, C-3F), 79.37, 79.21, 78.98 (C-2A, C-2E, C-2B), 78.92 (C-4F), 78.67 (C-2G), 78.32 (C-4B), 77.98, 77.91 (C-2F, C-2C), 76.31, 76.30, 75.96 (3×CH<sub>2</sub>Ph), 75.35 (C-4G), 75.12, 75.01, 74.77, 74.74, 73.59, 73.56(3C), 73.43, 73.16, 73.08, 72.83, 72.66(3C) (15×CH<sub>2</sub>Ph), 72.06, 71.95, 71.93, 71.79, 71.74, 71.65, 71.45 (C-5F, C-5A, C-5G, C-5B, C-5C, C-5E, C-5D), 69.72, 69.64, 69.26, 68.97, 61.45, 36.72, 27.05 (C-6F, C-6C, C-6B, C-6E, C-6G, C-6A, C-6D), 17.21 (SCH<sub>3</sub>)

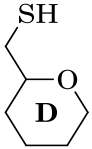
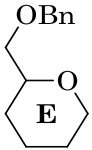
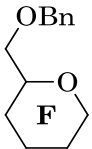
**HRMS (ESI):** Calcd. For C<sub>169</sub>H<sub>180</sub>O<sub>32</sub>S<sub>2</sub>Na [M+Na]<sup>1+</sup>: 2824.1614; Found: 2824.1741 (+4.5 ppm)



**EXPERIMENTAL PART**

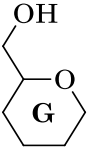
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1A	4.943	NOE: 3.974 ppm	H-4B
	C-1A	98.106		
	H-2A	3.404		
	C-2A	79.370		
	H-3A	3.969		
	C-3A	81.145		
	H-4A	3.632	NOE: 4.986 ppm	H-1G
	C-4A	82.294		
	H-5A	4.029		
	C-5A	71.954		
	H-6A	2.814		
		3.139		
	C-6A	36.720		
	H-1B	5.188	NOE: 3.994 ppm	H-4C
	C-1B	98.807		
	H-2B	3.479		
	C-2B	79.981		
	H-3B	4.009		
	C-3B	80.947		
	H-4B	3.974	NOE: 4.943 ppm	H-1A
	C-4B	78.321		
	H-5B	3.882		
	C-5B	71.792		
	H-6B	4.223		
		3.636		
	C-6B	69.260		
	H-1C	5.388	NOE: 3.747 ppm	H-4D
	C-1C	98.277		
	H-2C	3.540		
	C-2C	77.910		
	H-3C	4.046		
	C-3C	81.226		
	H-4C	3.994	NOE: 5.188 ppm	H-1B
	C-4C	80.630		
	H-5C	3.980		
	C-5C	71.743		
	H-6C	3.705		
		4.017		
	C-6C	69.644		

**EXPERIMENTAL PART**

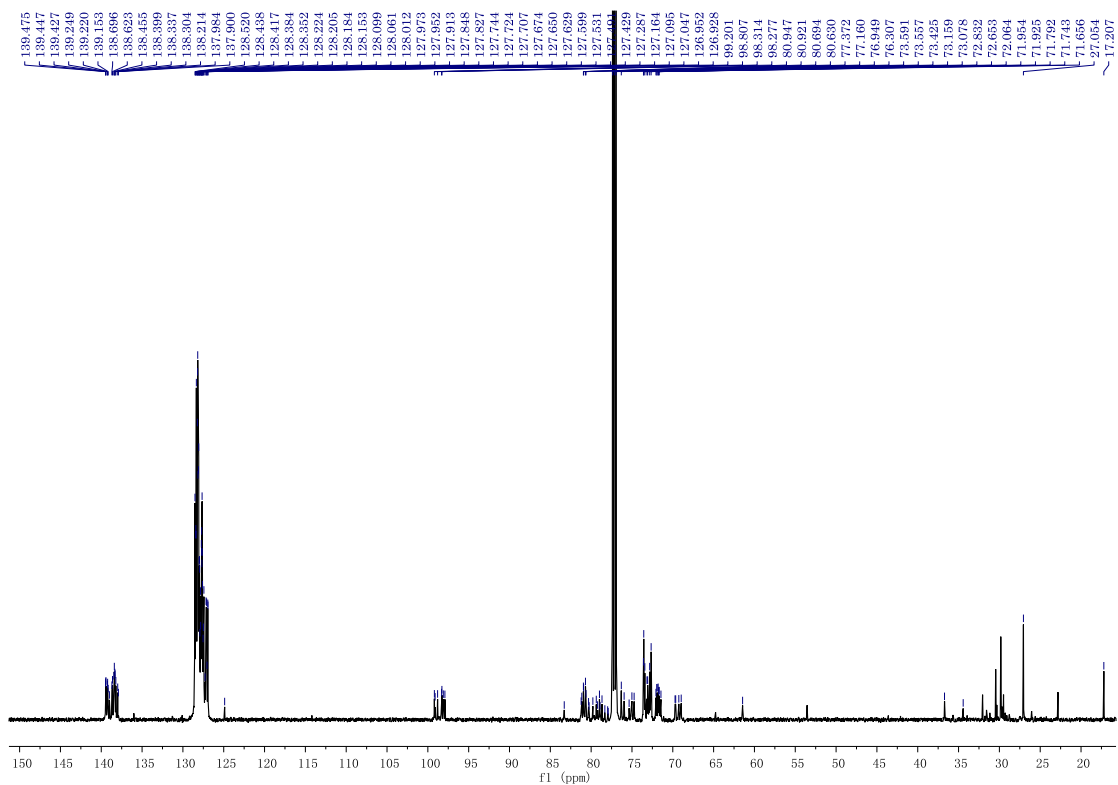
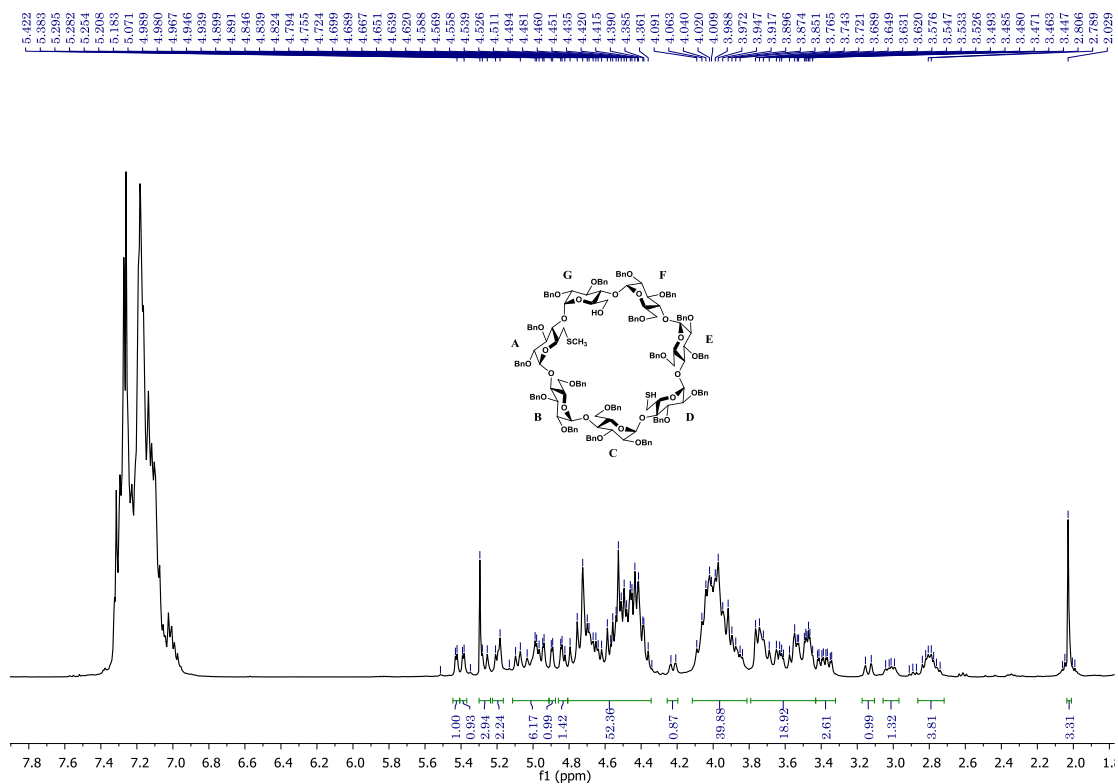
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	4.844	NOE: 3.914 ppm	H-4E
	C-1D	98.314		
	H-2D	3.357		
	C-2D	79.789		
	H-3D	3.976		
	C-3D	80.921		
	H-4D	3.747	NOE: 5.388 ppm	H-1C
	C-4D	80.250		
	H-5D	4.062		
	C-5D	71.451		
	H-6D	3.004		
		2.762		
C-6D	27.054			
	H-1E	4.896	NOE: 3.749 ppm	H-4F
	C-1E	99.112		
	H-2E	3.463		
	C-2E	79.208		
	H-3E	3.960		
	C-3E	80.694		
	H-4E	3.914	NOE: 4.844 ppm	H-1D
	C-4E	80.694		
	H-5E	3.924		
	C-5E	71.656		
	H-6E	3.565		
		4.082		
C-6E	68.971			
	H-1F	5.427	NOE: 3.948 ppm	H-4G
	C-1F	97.910		
	H-2F	3.542		
	C-2F	77.979		
	H-3F	4.029		
	C-3F	79.789		
	H-4F	3.749	NOE: 4.896 ppm	H-1E
	C-4F	78.918		
	H-5F	4.027		
	C-5F	72.064		
	H-6F	3.857		
		3.749		
C-6F	69.723			

**EXPERIMENTAL PART**

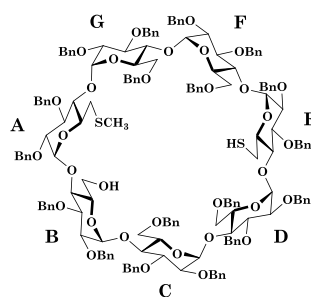
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	<b>Attribution</b>	<b>Signal (ppm)</b>	<b>Correlation(ppm)</b>	<b>Attribution</b>	
	H-1G	4.986	NOE: 3.632 ppm	H-4A	
	C-1G	99.201			
	H-2G	3.481			
	C-2G	78.670			
	H-3G	4.039			
	C-3G	80.317			
	H-4G	3.948	NOE: 5.427 ppm	H-1F	
	C-4G	75.350			
	H-5G	3.982			
	C-5G	71.925			
	H-6G		3.749		
			4.034		
	C-6G	61.450			

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>E</sup>-Dideoxy-6<sup>A</sup>-S-Methyl-6<sup>E</sup>-Thiol-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>C</sup>,6<sup>D</sup>,6<sup>F</sup>,6<sup>G</sup>-Octadeca-  
O-Benzyl- $\beta$ -Cyclodextrin (301b)**



$\alpha_D = +38.8$  (c 1.0, CHCl<sub>3</sub>)

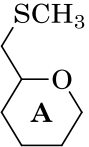
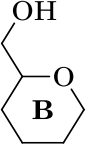
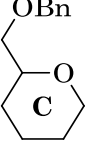
$R_f = 0.43$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$  7.34-7.09 (m, 90H, 90×H-Ar), 5.26 (t, 2H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1D, H-1C), 5.23 (d, 1H, <sup>2</sup>J = 10.0 Hz, CHPh), 5.22 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1G), 5.20 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1A), 5.16 (d, 1H, <sup>2</sup>J = 10.5 Hz, CHPh), 5.13 (d, 1H, <sup>2</sup>J = 10.8 Hz, CHPh), 5.05 (d, 1H, <sup>2</sup>J = 11.3 Hz, CHPh), 5.04 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1F), 4.96 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1E), 4.91 (t, 2H, <sup>2</sup>J = 11.3 Hz, 2×CHPh), 4.86 (d, 1H, <sup>2</sup>J = 12.0 Hz, CHPh), 4.85 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1B), 4.81-4.71 (m, 7H, 7×CHPh), 4.60-4.40 (m, 20H, 20×CHPh), 4.36 (d, 1H, <sup>2</sup>J = 11.8 Hz, CHPh), 4.29 (d, 1H, <sup>2</sup>J = 12.0 Hz, CHPh), 4.11-3.83 (m, 23H, H-3A, H-3B, H-3C, H-3D, H-3E, H-3F, H-3G, H-4C, H-4D, H-4F, H-4G, H-5A, H-5B, H-5C, H-5D, H-5E, H-5F, H-5G, H-6F, H-6C, H-6G, H-6B, H-6D), 3.80-3.64 (m, 6H, H-4B, H-4E, H-4A, H-6B, H-6G, H-6C), 3.57-3.50 (m, 6H, H-6F, H-2D, H-2G, H-6D, H-2C, H-2A), 3.46 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.8 Hz, H-2F), 3.38 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.5 Hz, H-2E), 3.33 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.5 Hz, H-2B), 3.07 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 12.3 Hz, H-6A), 3.03-2.76 (m, 3H, H-6A, 2×H-6E), 2.01 (s, 3H, SCH<sub>3</sub>)

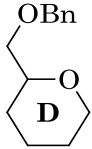
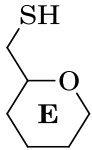
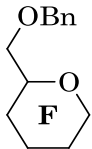
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$  139.45, 139.42, 139.38, 139.28, 139.25, 139.21, 139.12, 138.60, 138.55, 138.48(2C), 138.39, 138.34(2C), 138.30, 138.20, 138.10, 138.07 (18×C-Ar<sup>quat.</sup>), 128.49-127.09 (90×C-Ar<sup>tert.</sup>), 99.12, 98.64, 98.59, 98.38, 98.31, 98.13, 97.90 (C-1F, C-1G, C-1D, C-1C, C-1B, C-1E, C-1A), 81.03, 80.94(2C), 80.88, 80.85 (C-3F, C-3C, C-3D, C-3A, C-3E), 80.82 (C-4A), 80.41, 80.40 (C-3G, C-3B), 80.23, 79.91, 79.83(2C) (C-4C, C-4G, C-4E, C-4F), 79.42, 79.11, 78.89, 78.63, 78.54, 78.36, 78.32 (C-2E, C-2B, C-2F, C-2A, C-2C, C-2G, C-2D), 77.96, 77.90 (C-4D, C-4B), 76.07, 76.01, 75.50(2C), 75.31, 75.26, 74.92, 73.54, 73.48, 73.47, 73.39, 73.07, 73.01, 72.94, 72.92, 72.80, 72.71, 72.68 (18×CH<sub>2</sub>Ph), 72.25, 72.06, 71.80, 71.62(2C), 71.55, 71.52 (C-5A, C-5B, C-5F, C-5D, C-5G, C-5C, C-5E), 69.47, 69.40, 69.05, 68.71, 61.92, 36.87, 27.12 (C-6C, C-6G, C-6F, C-6D, C-6B, C-6A, C-6E), 17.28 (SCH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>169</sub>H<sub>180</sub>O<sub>32</sub>S<sub>2</sub>Na [M+Na]<sup>1+</sup>: 2824.1748; Found: 2824.1741 (-0.3 ppm);

**EXPERIMENTAL PART**

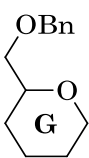
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>A</b></p>	H-1A	5.198	NOE: 3.772 ppm	H-4B
	C-1A	97.898		
	H-2A	3.502		
	C-2A	78.628		
	H-3A	4.021		
	C-3A	80.881		
	H-4A	3.697	NOE: 5.220 ppm	H-1G
	C-4A	80.820		
	H-5A	4.096		
	C-5A	72.245		
	H-6A	3.068		
		2.787		
C-6A	36.868			
 <p style="text-align: center;"><b>B</b></p>	H-1B	4.849	NOE: 3.985 ppm	H-4C
	C-1B	98.305		
	H-2B	3.330		
	C-2B	79.112		
	H-3B	3.990		
	C-3B	80.415		
	H-4B	3.772	NOE: 5.198 ppm	H-1A
	C-4B	77.904		
	H-5B	3.978		
	C-5B	72.058		
	H-6B	3.700		
		3.997		
C-6B	61.921			
 <p style="text-align: center;"><b>C</b></p>	H-1C	5.254	NOE: 4.023 ppm	H-4D
	C-1C	98.381		
	H-2C	3.507		
	C-2C	78.524		
	H-3C	3.993		
	C-3C	80.936		
	H-4C	3.985	NOE: 4.849 ppm	H-1B
	C-4C	80.231		
	H-5C	3.836		
	C-5C	71.553		
	H-6C	3.667		
		4.054		
C-6C	69.466			

**EXPERIMENTAL PART**

	<b>Attribution</b>	<b>Signal (ppm)</b>	<b>Correlation(ppm)</b>	<b>Attribution</b>
	H-1D	5.260	NOE: 3.749 ppm	H-4E
	C-1D	98.593		
	H-2D	3.524		
	C-2D	78.321		
	H-3D	4.035		
	C-3D	80.936		
	H-4D	4.023	NOE: 5.254 ppm	H-1C
	C-4D	77.964		
	H-5D	3.935		
	C-5D	71.618		
	H-6D	3.989		
		3.511		
	C-6D	68.714		
	H-1E	4.963	NOE: 3.930 ppm	H-4F
	C-1E	98.130		
	H-2E	3.377		
	C-2E	79.416		
	H-3E	4.003		
	C-3E	80.847		
	H-4E	3.749	NOE: 4.023 ppm	H-1D
	C-4E	79.825		
	H-5E	4.006		
	C-5E	71.518		
	H-6E	2.997		
		2.759		
	C-6E	27.115		
	H-1F	5.038	NOE: 3.947 ppm	H-4G
	C-1F	99.123		
	H-2F	3.462		
	C-2F	78.887		
	H-3F	3.991		
	C-3F	81.034		
	H-4F	3.930	NOE: 4.963 ppm	H-1E
	C-4F	79.825		
	H-5F	3.910		
	C-5F	71.804		
	H-6F	3.562		
		4.064		
	C-6F	69.052		

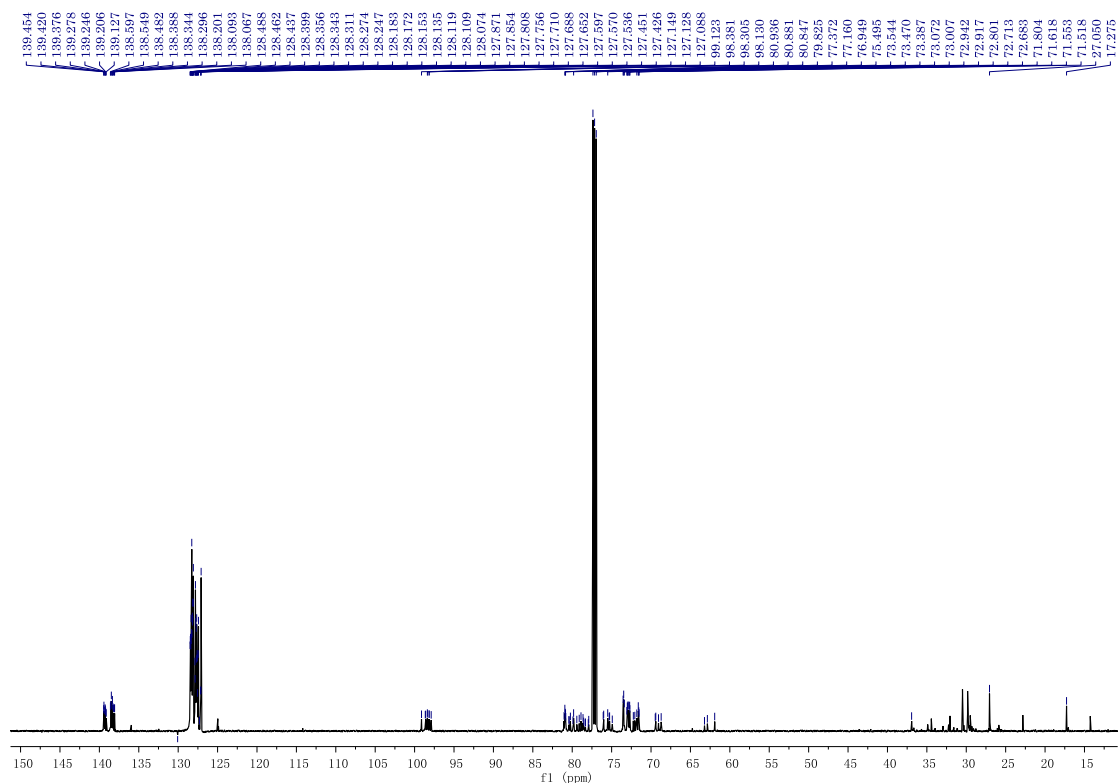
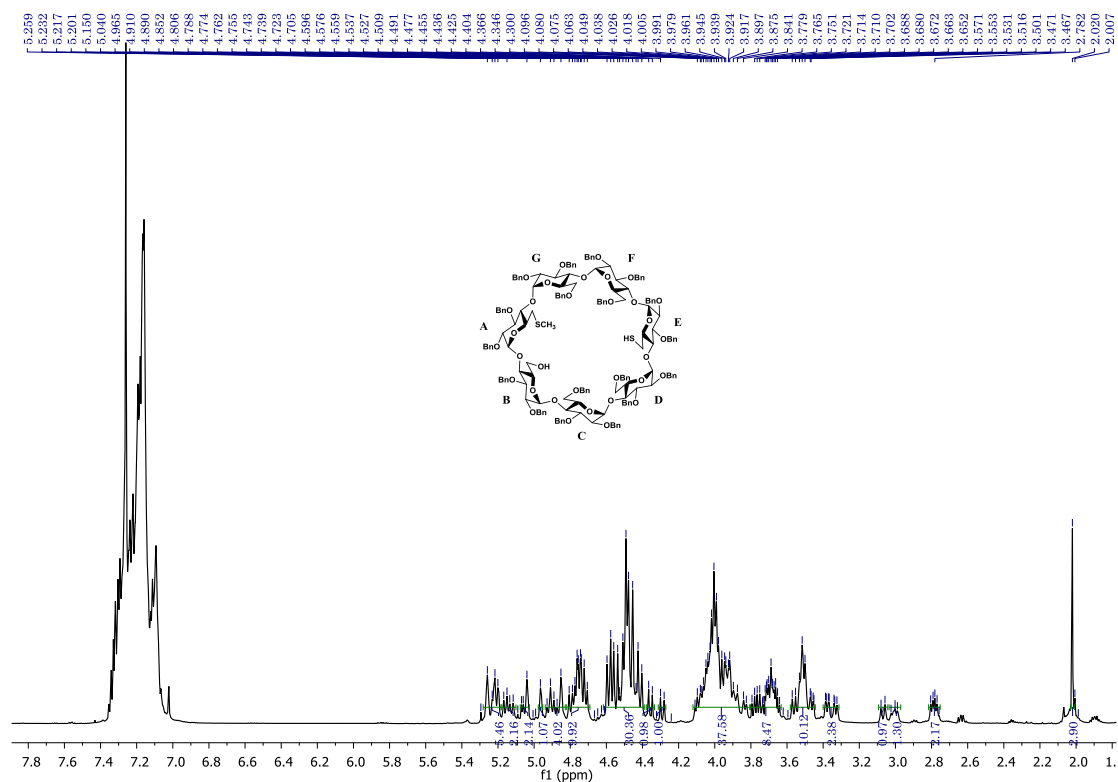
**EXPERIMENTAL PART**

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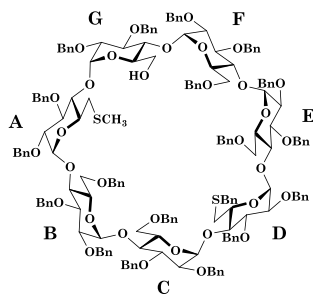
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution	
	H-1G	5.220	NOE: 3.697 ppm	H-4A	
	C-1G	98.643			
	H-2G	3.521			
	C-2G	78.357			
	H-3G	3.999			
	C-3G	80.415			
	H-4G	3.947	NOE: 5.038 ppm	H-1F	
	C-4G	79.908			
	H-5G	4.012			
	C-5G	71.618			
	H-6G		3.674		
			4.032		
	C-6G	79.396			



EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>D</sup>-Dideoxy-6<sup>A</sup>-S-Methyl-6<sup>D</sup>-S-Benzyl-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,  
6<sup>F</sup>-Octadeca-O-Benzyl-β-Cyclodextrin (302a)**



Potassium carbonate (337 mg, 2.44 mmol, 5 eq.) was added to a solution of thiol-monol-cyclodextrin **301a** (1.37 g, 0.488 mmol, 1 eq.) in anhydrous DMF (30 mL) under nitrogen at 0°C. Benzyl bromide (0.29 mL, 2.44 mmol, 5 eq.) was added, and the reaction mixture was stirred for 2h at r.t.. Until the TLC showed the reaction finished, Water (30 mL) was added and the aqueous phase was extracted with EtOAc (3×30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash

chromatography of the residue (CyH/EtOAc: 5/1, then 4/1) gave β-cyclodextrin **302a** (946 mg, 78%) as a yellowish foam.

$\alpha_D = +43.8$  (c 1.0, CHCl<sub>3</sub>)

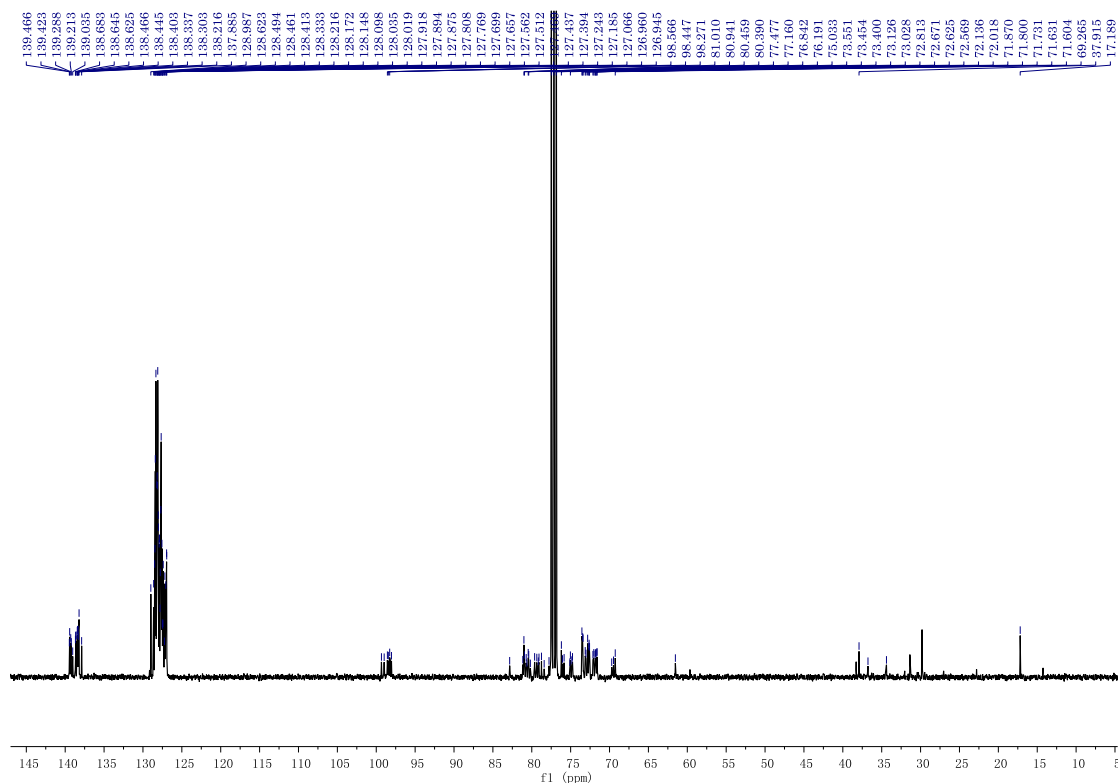
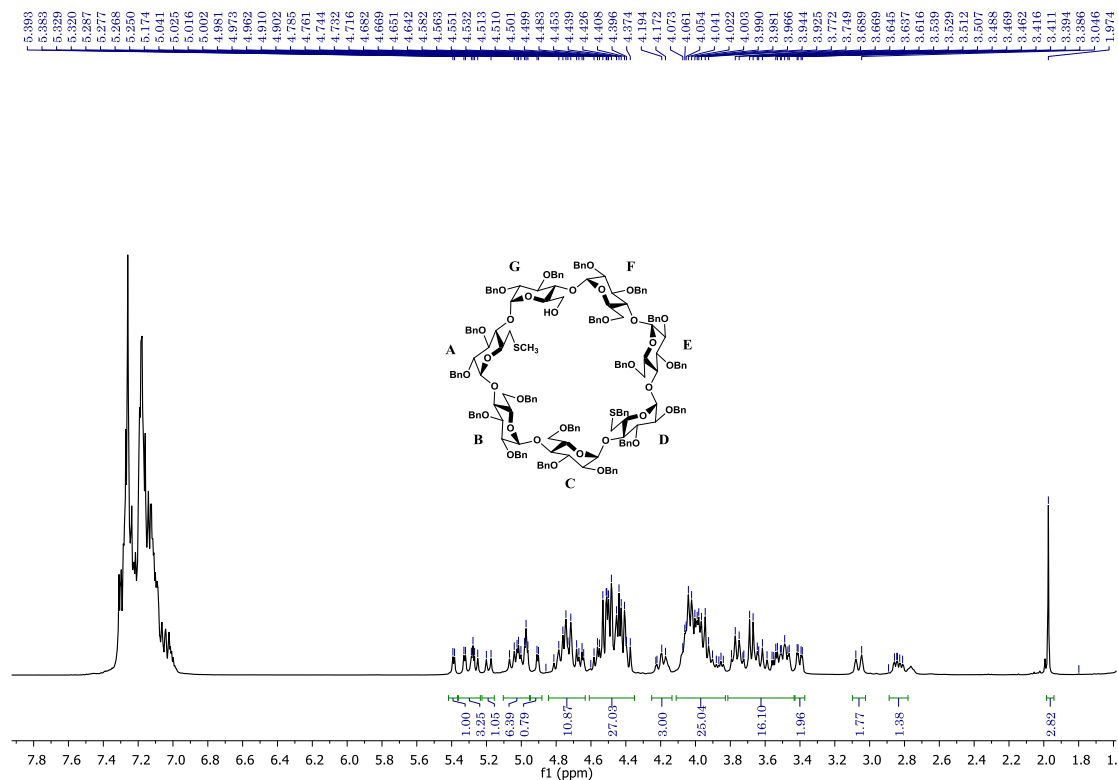
$R_f = 0.27$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.31-7.08 (m, 95H, 95×H-Ar.), 5.39 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 5.33 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1), 5.28 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1), 5.26 (d, 1H, <sup>2</sup>J = 10.7 Hz, CHPh), 5.19 (d, 1H, <sup>2</sup>J = 11.0 Hz, CHPh), 5.06 (d, 1H, <sup>2</sup>J = 11.0 Hz, CHPh), 5.02 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, H-1), 4.99 (d, 1H, <sup>2</sup>J = 11.5 Hz, CHPh), 4.97 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, H-1), 4.96 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.9 Hz, H-1), 4.91 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1), 4.81-4.71 (m, 9H, 9×CHPh), 4.66 (d, 1H, <sup>2</sup>J = 12.5 Hz, CHPh), 4.65 (d, 1H, <sup>2</sup>J = 12.5 Hz, CHPh), 4.58-4.37 (m, 21H, 21×CHPh), 4.23-4.17 (m, 3H, H-5, 2×H-6), 4.07-3.90 (m, 20H, 7×H-3, 4×H-4, 6×H-5, 3×H-6), 3.85 (dd, 1H, <sup>3</sup>J<sub>5,6</sub> = 5.7 Hz, <sup>2</sup>J<sub>6,6'</sub> = 10.8 Hz, H-6), 3.79-3.59 (m, 9H, 3×H-4, 2×SCH<sub>3</sub>Ph, 4×H-6), 3.56-3.46 (m, 5H, ×H-2), 3.40 (dd, 2H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.4 Hz, 2×H-2), 3.06 (d, 2H, <sup>2</sup>J<sub>6,6'</sub> = 12.9 Hz, 2×H-6), 2.86-2.81 (m, 2H, 2×H-6), 1.97 (s, 3H, SCH<sub>3</sub>)

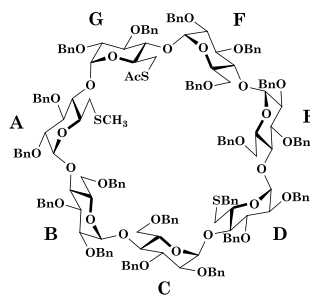
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.47, 139.42(2C), 139.29, 139.28, 139.21, 139.04, 138.68, 138.65, 138.63, 138.47, 138.45, 138.40, 138.39, 138.34, 138.30, 138.22(2C), 137.89 (19×C-Ar<sup>quat.</sup>), 128.98-126.95 (95×C-Ar<sup>tert.</sup>), 99.33, 98.98, 98.57, 98.45, 98.27, 98.20, 98.05 (7×C-1), 82.84 (C-4), 81.15, 81.01(2C), 80.94, 80.72, 80.63, (6×C-3), 80.46(2C) (C-3, C-4), 80.39(2C), 80.18 (3×C-4), 79.63, 79.35, 79.16, 79.07, 78.75, 78.41 (6×C-2), 77.75 (C-4), 77.17 (C-2), 76.19(2C) (2×CH<sub>2</sub>Ph), 76.05 (C-4), 75.84, 75.10, 75.03, 74.85, 74.76, 73.55(2C), 73.45, 73.40, 73.13, 73.03, 72.81(2C), 72.67, 72.63, 72.57 (18×CH<sub>2</sub>Ph), 72.14, 72.02, 71.87, 71.80, 71.73, 71.63, 71.60 (7×C-5), 69.72, 69.49, 69.27(2C), 61.53 (5×C-6), 37.92 (SCH<sub>2</sub>Ph), 36.77, 34.39 (2×C-6), 17.19 (SCH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>176</sub>H<sub>186</sub>O<sub>33</sub>S<sub>2</sub>Na [M+Na]<sup>1+</sup>: 2914.2146; Found: 2914.2210 (+2.2 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>D</sup>,6<sup>G</sup>-Trideoxy-6<sup>A</sup>-S-Methyl-6<sup>D</sup>-S-Benzyl-6<sup>G</sup>-S-Acetyl-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>B</sup>,6<sup>C</sup>,6<sup>E</sup>,6<sup>F</sup>-  
Octadeca-O-Benzyl- $\beta$ -Cyclodextrin (303a)**



Triethylamine (0.082 mL, 0.591 mmol, 2 eq.) followed by methanesulfonyl chloride (0.046 mL, 0.591 mmol, 2 eq.) was added to a solution of cyclodextrin **302a** (855 g, 0.296 mmol, 1 eq.) in DCM (10 mL) under nitrogen at r. t. The reaction mixture was stirred at r. t. for 1 h 30 min. Water (20 mL) was added, and the aqueous layer was extracted with DCM (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, concentrated *in vacuum* and dried to give the mesylated-cyclodextrin (855 mg) as a yellowish foam.

The formed mesylated-cyclodextrin (0.855 g, 0.288 mmol, 1 eq.) was dissolved in anhydrous DMF (10 mL) under nitrogen. Potassium thioacetate (132 mg, 1.151 mmol, 4 eq.) was added at r. t.. The reaction mixture was stirred overnight at 50°C. EtOAc (20 mL) was added and the organic layer was washed with brine (3×20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 5/1) gave thioacetate- $\beta$ -cyclodextrin **303a** (0.670 g, 76%) as a yellowish foam.

$\alpha_D = +40.7$  (c 1.0, CHCl<sub>3</sub>)

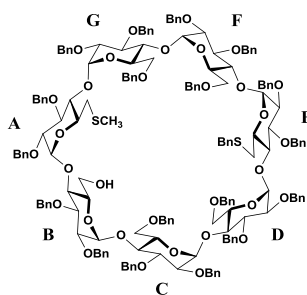
$R_f = 0.40$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.34-7.06 (m, 95H, 95×H-Ar.), 5.45 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 5.29 (d, 1H, <sup>2</sup>J = 11.6 Hz, CHPh), 5.27 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1), 5.26 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1), 5.24 (d, 2H, <sup>2</sup>J = 10.8 Hz, 2×CHPh), 5.21 (d, 1H, <sup>2</sup>J = 10.2 Hz, CHPh), 5.17 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1), 5.14 (d, 1H, <sup>2</sup>J = 11.3 Hz, CHPh), 5.12 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1), 5.11 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1), 5.05 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.2 Hz, H-1), 4.90-4.71 (m, 9H, 9×CHPh), 4.64-4.41 (m, 22H, 22×CHPh), 4.24-3.94 (m, 23H, 7×H-3, 5×H-4, 7×H-5, 4×H-6), 3.72-3.68 (m, 8H, H-4, 5×H-6, 2×SCH<sub>2</sub>Ph), 4.60-3.45 (m, 8H, 7×H-2, H-4), 3.15-2.87 (m, 5H, 5×H-6), 2.23 (s, 3H, S(O)CH<sub>3</sub>), 2.07 (s, 3H, SCH<sub>3</sub>)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  194.31 (S(O)CH<sub>3</sub>), 139.50, 139.44, 139.39, 139.36, 139.32, 139.29, 139.20, 138.31, 138.68, 138.59(2C), 138.53, 138.49, 138.46, 138.43, 138.41, 138.34, 138.31, 138.19 (19×C-Ar<sup>quat.</sup>), 129.05-126.90 (95×C-Ar<sup>tert.</sup>), 99.31, 99.02, 98.51, 98.34, 98.32, 98.23, 98.18 (7×C-1), 81.91, 81.68 (2×C-4), 81.07, 81.01(2C), 80.83, 80.79(2C), 80.27 (7×C-3), 80.18(2C), 80.13 (3×C-4), 79.73 (C-2), 79.42 (C-4), 79.25, 79.14, 78.92, 78.61 (4×C-2), 78.46 (C-4), 78.45(2C) (2×C-2), 76.09, 76.03, 75.85, 75.38, 75.28, 74.89, 74.70, 73.53, 73.44(3C), 73.32, 72.93(2C), 72.82, 72.65, 72.57, 72.50 (18×CH<sub>2</sub>Ph), 71.98, 71.81, 71.77, 71.70, 71.65, 71.41, 70.34 (7×C-5), 69.43(2C), 69.34, 69.32 (4×C-6), 37.93 (SCH<sub>2</sub>Ph), 37.14, 34.49, 32.03 (3×C-6), 30.66 (S(O)CH<sub>3</sub>), 17.23 (SCH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>178</sub>H<sub>188</sub>O<sub>33</sub>S<sub>3</sub>Na [M+Na]<sup>1+</sup>: 2972.2064; Found: 2972.2087 (+0.8 ppm)

**6<sup>A</sup>,6<sup>E</sup>-Dideoxy-6<sup>A</sup>-S-Methyl-6<sup>E</sup>-S-Benzyl-2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>C</sup>,6<sup>D</sup>,  
6<sup>F</sup>,6<sup>G</sup>-Octadeca-O-Benzyl-β-Cyclodextrin (302b)**



Potassium carbonate (49 mg, 0.355 mmol, 5 eq.) was added to a solution of thiol-monol-cyclodextrin **301b** (200 mg, 0.071 mmol, 1 eq.) in anhydrous DMF (5 mL) under nitrogen at 0°C. Benzyl bromide (0.042 mL, 0.355 mmol, 5 eq.) was added, and the reaction mixture was stirred for 2 h at r.t.. Until the TLC showed the reaction finished, Water (10 mL) was added and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash

chromatography of the residue (CyH/EtOAc: 5/1, then 4/1) gave β-cyclodextrin **302b** (187 mg, 91%) as a white foam.

$\alpha_D = +41.4$  (c 1.0, CHCl<sub>3</sub>)

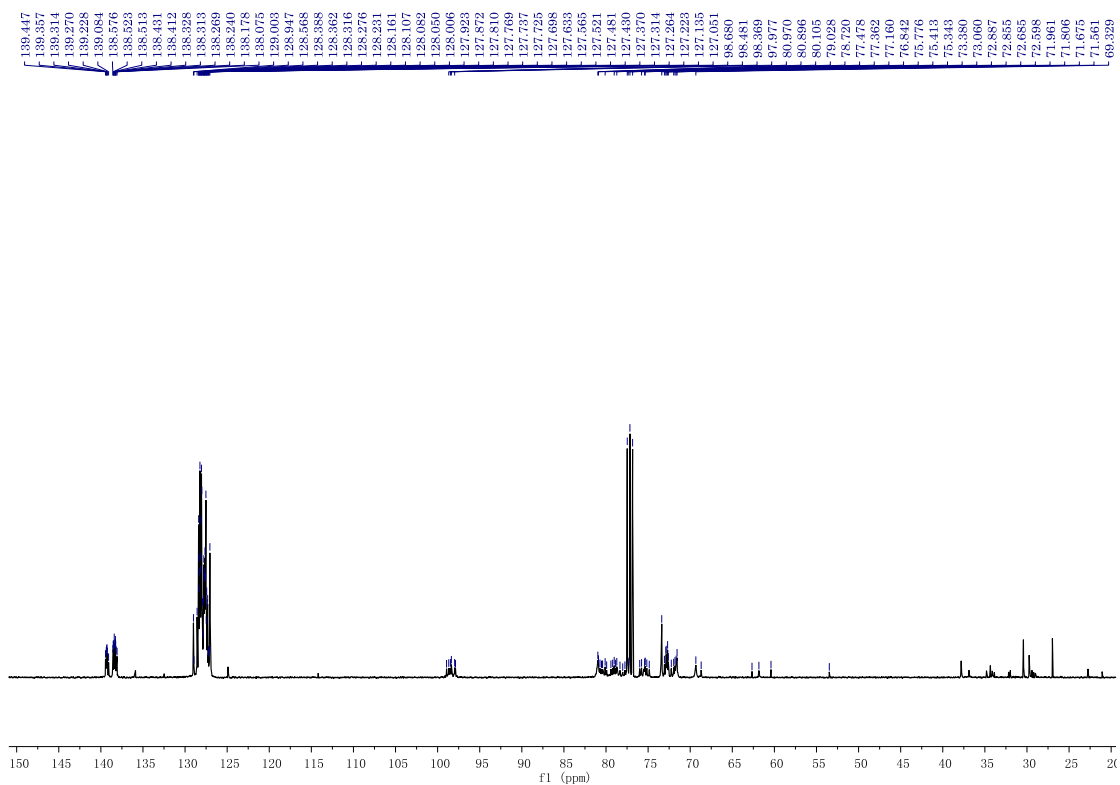
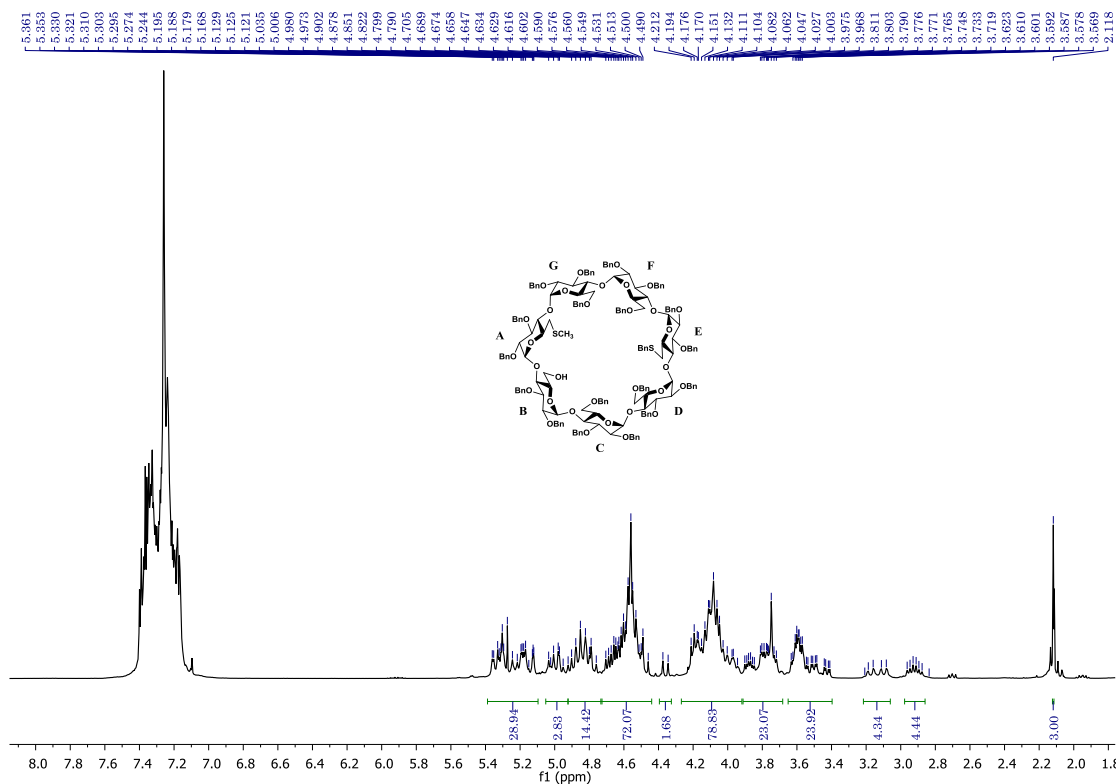
$R_f = 0.40$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.39-7.16 (m, 95H, 95×H-Ar.), 5.36 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, H-1), 5.33 (d, 1H, <sup>2</sup>J = 11.2 Hz, CHPh), 5.32 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1), 5.31 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1), 5.30 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1), 5.23 (d, 1H, <sup>2</sup>J = 11.0 Hz, CHPh), 5.20 (d, 1H, <sup>2</sup>J = 11.0 Hz, CHPh), 5.18 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 5.17 (d, 1H, <sup>2</sup>J = 10.5 Hz, CHPh), 5.13 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, H-1), 5.02 (d, 1H, <sup>2</sup>J = 11.5 Hz, CHPh), 4.98 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1), 4.92-4.75 (m, 10H, 10×CHPh), 4.70-4.46 (m, 21H, 21×CHPh), 4.36 (d, 1H, <sup>2</sup>J = 12.2 Hz, CHPh), 4.21-3.94 (m, 22H, 7×H-3, 4×H-4, 7×H-5, 4×H-6), 3.90-3.72 (m, 9H, 3×H-4, 2×SCH<sub>3</sub>Ph, 4×H-6), 3.63-3.54 (m, 6H, 5×H-2, H-6), 3.50 (dd, H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.5 Hz, H-2), 3.43 (dd, H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, H-2), 3.19-3.08 (m, 2H, 2×H-6), 2.96-2.88 (m, 2H, 2×H-6), 2.11 (s, 3H, SCH<sub>3</sub>)

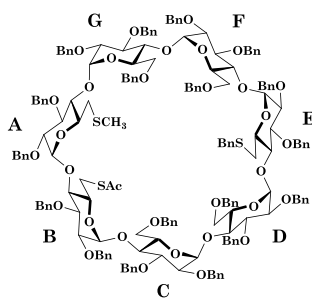
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  139.45, 139.36, 139.31, 139.27, 139.26, 139.23, 139.08, 138.58, 138.52, 138.51, 138.43, 138.41, 138.40, 138.33, 138.31, 138.27, 138.24, 138.18, 138.08 (19×C-Ar<sup>quat</sup>), 129.00-127.05 (95×C-Ar<sup>tert</sup>), 98.94, 98.68, 98.48, 98.37(2C), 97.98, 97.88 (7×C-1), 81.08 (C-4), 81.04, 80.97, 80.90, 80.72 (4×C-3), 80.54 (C-4), 80.41, 80.32 (2×C-3), 80.11(2C) (2×C-4), 79.42, 79.21 (2×C-2), 79.06 (C-4), 79.03, 78.86, 78.72, 78.63, 78.34 (5×C-2), 78.02, 77.75 (2×C-4), 76.00, 75.78, 75.51, 75.41, 75.34, 75.15, 74.86, 73.47, 73.38(3C), 73.06, 72.89, 72.86, 72.84, 72.69(2C), 72.60 (18×CH<sub>2</sub>Ph), 72.25, 71.96, 71.81, 71.68, 71.60, 71.56(2C) (7×C-5), 69.41, 69.33(2C), 68.70, 61.84 (5×C-6), 37.80 (SCH<sub>2</sub>Ph), 36.88, 34.12 (2×C-6), 17.21 (SCH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>176</sub>H<sub>186</sub>O<sub>33</sub>S<sub>2</sub>Na [M+Na]<sup>1+</sup>: 2914.2157; Found: 2914.2210 (+1.8 ppm)

EXPERIMENTAL PART



**6<sup>A</sup>,6<sup>B</sup>,6<sup>E</sup>-Trideoxy-6<sup>A</sup>-S-Methyl-6<sup>B</sup>-S-Acetyl-6<sup>E</sup>-S-Benzyl -2<sup>A-G</sup>,3<sup>A-G</sup>,6<sup>C</sup>,6<sup>D</sup>,  
6<sup>F</sup>,6<sup>G</sup>-Octadeca-O-Benzyl-β-Cyclodextrin (303b)**



Triethylamine (0.030 mL, 0.218 mmol, 2 eq.) followed by methanesulfonyl chloride (0.017 mL, 0.218 mmol, 2 eq.) was added to a solution of cyclodextrin **302b** (315 g, 0.109 mmol, 1 eq.) in dichloromethane (5 mL) under nitrogen at r. t. The reaction mixture was stirred at r.t. for 1 h 30 min. Water (10 mL) was added, and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, concentrated *in vacuo* and dried in

oil pump to give the mesylated-cyclodextrin (324 mg) as a yellowish foam.

The formed mesylated-cyclodextrin (0.324 g, 0.109 mmol, 1 eq.) was dissolved in anhydrous DMF (5 mL) under nitrogen. Potassium thioacetate (37 mg, 0.327 mmol, 3 eq.) was added at room temperature. The reaction mixture was stirred overnight at 50°C. EtOAc (10 mL) was added and the organic layer was washed with brine (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. Silica gel flash chromatography of the residue (CyH/EtOAc: 5/1) gave thioacetate-β-cyclodextrin **303b** (0.670 g, 62%) as a yellowish foam.

$\alpha_D = +41.5$  (c 1.0, CHCl<sub>3</sub>)

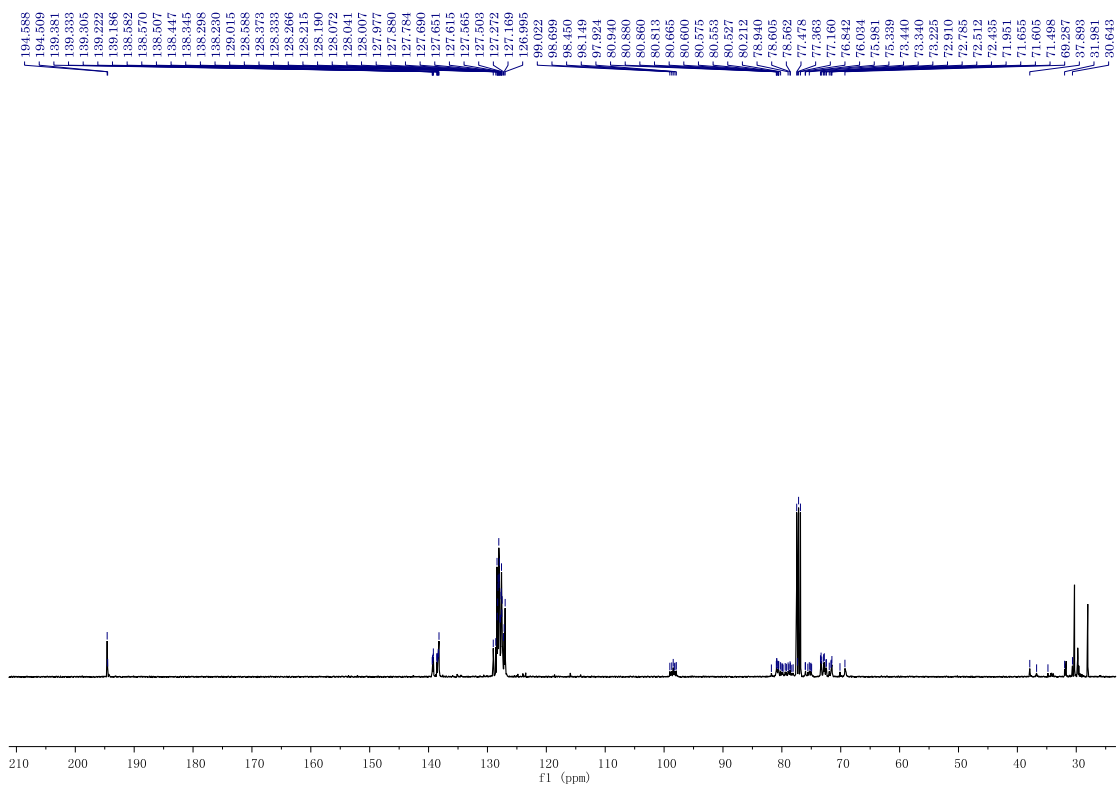
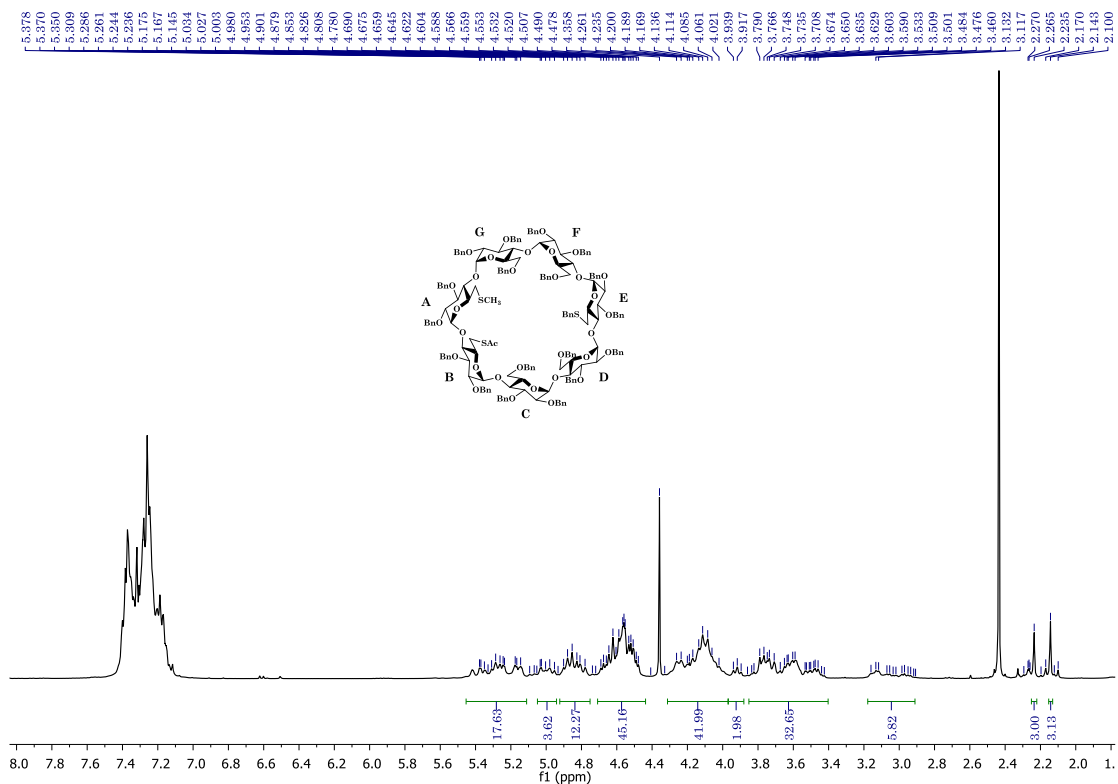
$R_f = 0.53$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.38-7.15 (m, 95H, 95×H-Ar.), 5.42 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1), 5.37 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1), 5.35 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1), 5.27 (d, 2H, <sup>2</sup>J = 10.4 Hz, 2×CHPh), 5.24 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.3 Hz, H-1), 5.17 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1), 5.16 (d, 1H, <sup>2</sup>J = 12.0 Hz, CHPh), 5.14 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, H-1), 5.03 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.0 Hz, H-1), 5.03-4.78 (m, 11H, 11×CHPh), 4.69-4.47 (m, 22H, 22×CHPh), 4.26-3.99 (m, 23H, 7×H-3, 5×H-4, 7×H-5, 4×H-6), 3.93-3.68 (m, 8H, H-4, 5×H-6, 2×SCH<sub>2</sub>Ph), 4.64-3.42 (m, 9H, 7×H-2, H-4, H-6), 3.16-2.94 (m, 4H, 4×H-6), 2.24 (s, 3H, S(O)CH<sub>3</sub>), 2.14 (s, 3H, SCH<sub>3</sub>)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  194.58 (S(O)CH<sub>3</sub>), 139.38, 139.33, 139.31, 139.22, 139.19(2C), 139.17, 138.58, 138.57, 138.51, 138.45, 138.35(2C), 138.30(2C), 138.23(4C) (19×C-Ar<sup>quat.</sup>), 129.02-127.00 (95×C-Ar<sup>tert.</sup>), 99.02, 98.70, 98.45(2C), 98.27, 98.15, 97.92 (7×C-1), 81.78 (C-4), 80.94, 80.88, 80.86, 80.81, 80.67, 80.58, 80.53 (7×C-3), 80.21, 80.00, 79.87, 79.80 (4×C-4), 79.43, 79.23, 78.94, 78.81, 78.61, 78.56, 78.31 (7×C-2), 78.08 (C-4), 76.03, 75.98, 75.59, 75.34, 75.18, 75.05, 74.94, 73.44, 73.34, 73.30, 73.23, 72.97, 72.91(2C), 72.79(2C), 72.51, 72.44 (18×CH<sub>2</sub>Ph), 71.95, 71.66, 71.61, 71.52(2C), 71.50(2C) (7×C-5), 69.29(2C), 69.24, 69.08 (4×C-6), 37.89 (SCH<sub>2</sub>Ph), 36.74, 34.81, 31.98 (3×C-6), 30.64 (S(O)CH<sub>3</sub>), 17.32 (SCH<sub>3</sub>)

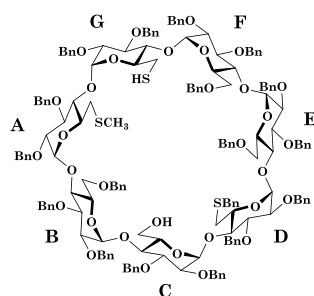
**HRMS (ESI):** Calcd. For C<sub>178</sub>H<sub>188</sub>O<sub>33</sub>S<sub>3</sub>Na [M+Na]<sup>1+</sup>: 2972.2093; Found: 2972.2087 (-0.2 ppm)

EXPERIMENTAL PART





**6A,6D,6G-Trideoxy-6A-S-Methyl-6D-S-Benzyl-6G-Thiol-2A-G,3A-G,6B,6E,  
6F-Heptadeca-O-Benzyl-β-Cyclodextrin (304a)**



DIBAL-H (1.5 M in toluene, 0.9 mL, 1.36 mmol, 20 eq.) was added to a solution of cyclodextrin **303a** (200 mg, 0.068 mmol, 1 eq.) in toluene (0.4 mL) under nitrogen at r. t. The reaction mixture was stirred at 55°C with a nitrogen balloon reflux for 10 min, until Mass spectrum indicated formation of thiol-monol as a major product, and then cooled to r.t. and poured into ice/water. Aqueous HCl (10 mL, 1 M) and EtOAc (10 mL) were added, and the solution was stirred for 1 h. The aqueous layer was extracted

with EtOAc (3×15 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuum*. Silica gel chromatography of the residue (CyH/EtOAc: 5/1, then 4/1) gave cyclodextrin **304a** (60 mg, 31%) as a yellowish foam.

$[\alpha]_D^{20} = +45.7$  (c 1.0, CHCl<sub>3</sub>)

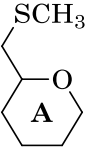
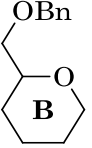
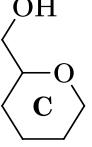
$R_f = 0.29$  (CyH/EtOAc: 3/1)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz): δ 7.39-7.10 (m, 90H, 90×H-Ar), 5.53 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1B), 5.35 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.6 Hz, H-1F), 5.30 (d, 1H, <sup>2</sup>J = 10.8 Hz, CHPh), 5.21-5.16 (m, 7H, H-1E, H-1G, 5×CHPh), 5.09 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1D), 5.08 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, H-1C), 4.96 (d, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.5 Hz, H-1A), 4.89-4.76 (m, 8H, 8×CHPh), 4.75-4.46 (m, 20H, 20×CHPh), 4.23-3.95 (m, 20H, H-3A, H-3B, H-3C, H-3D, H-3E, H-3F, H-3G, H-4B, H-4C, H-4E, H-4F, H-5A, H-5B, H-5D, H-5E, H-5G, H-6B, H-6C, H-6E, H-6F), 3.88-3.72 (m, 8H, H-4A, H-4D, H-4G, H-6B, H-6C, H-6F, 2×SCHPh), 3.70 (d, 1H, <sup>2</sup>J<sub>6,6'</sub> = 11.0 Hz, H-6E), 3.63 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.7 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.3 Hz, H-2B), 3.61 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.7 Hz, H-2F), 3.57-3.52 (m, 3H, H-2E, H-2C, H-2G), 3.50 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.4 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.3 Hz, H-2A), 3.48 (dd, 1H, <sup>3</sup>J<sub>1,2</sub> = 3.1 Hz, <sup>3</sup>J<sub>2,3</sub> = 9.5 Hz, H-2D), 3.18-3.14 (m, 3H, H-6D, H-6G, H-6A), 3.01-2.94 (m, 3H, H-6A, H-6D, H-6G), 2.13 (s, 3H, SCH<sub>3</sub>), 1.63 (t, 1H, <sup>3</sup>J<sub>SH,6</sub> = 7.8 Hz, SH)

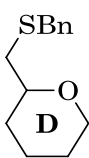
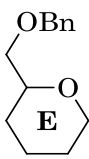
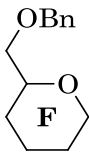
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz): δ 139.39(2C), 139.37, 139.29, 139.20, 139.16, 139.07, 138.70, 138.65, 138.43, 138.42, 138.39(2C), 138.32, 138.31, 138.25(2C), 138.01 (18×C-Ar<sup>quat.</sup>), 129.03-127.02 (90×C-Ar<sup>tert.</sup>), 99.05, 98.74, 98.62, 98.58, 98.18, 98.05, 97.93 (C-1E, C-1C, C-1G, C-1F, C-1D, C-1D, C-1A, C-1B), 82.71, 82.28 (C-4A, C-4D), 81.14, 80.98, 80.81, 80.79(2C), 80.68 (6×C-3), 80.23 (C-4E), 80.17(2C) (C-4B, C-3), 79.73 (C-4G), 79.47, 79.29, 79.20, 79.14 (C-2D, C-2A, C-2G, C-2C), 79.02 (C-4C), 78.83, 78.07, 77.41 (C-2E, C-2F, C-2B), 76.12, 75.85, 75.77, 75.52 (4×CH<sub>2</sub>Ph), 75.43 (C-4F), 75.10, 75.08, 74.73, 73.56(2C), 73.47, 73.43(2C), 72.98, 72.95, 72.89, 72.84, 72.69 (13×CH<sub>2</sub>Ph), 71.86, 71.83, 71.79, 71.77, 71.70, 71.68, 71.63 (7×C-5), 69.50(2C) (C-6B, C-6F), 69.28, 61.66 (C-6E, C-6C), 37.75 (SCH<sub>2</sub>Ph), 36.82, 34.10, 26.98 (C-6A, C-6D, C-6G), 17.19 (SCH<sub>3</sub>)

**HRMS (ESI):** Calcd. For C<sub>169</sub>H<sub>180</sub>O<sub>32</sub>S<sub>3</sub> Na [M+Na]<sup>1+</sup>: 2840.1569; Found: 2840.1512 (-2.0 ppm);

**EXPERIMENTAL PART**

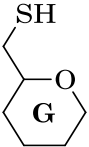
	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
 <p style="text-align: center;"><b>A</b></p>	H-1A	4.961	NOE: 3.965 ppm	H-4B
	C-1A	98.048		
	H-2A	3.499		
	C-2A	79.294		
	H-3A	4.044		
	C-3A			
	H-4A	3.790	NOE: 5.123 ppm	H-1G
	C-4A	82.712		
	H-5A	4.177		
	C-5A			
	H-6A	3.152		
		2.997		
	C-6A	36.818		
 <p style="text-align: center;"><b>B</b></p>	H-1B	5.528	NOE: 4.042 ppm	H-4C
	C-1B	97.926		
	H-2B	3.629		
	C-2B	77.409		
	H-3B	4.109		
	C-3B			
	H-4B	3.965	NOE: 4.961 ppm	H-1A
	C-4B	80.172		
	H-5B	4.142		
	C-5B			
	H-6B	3.869		
		4.157		
	C-6B	69.503		
 <p style="text-align: center;"><b>C</b></p>	H-1C	5.076	NOE: 3.830 ppm	H-4D
	C-1C	98.735		
	H-2C	3.536		
	C-2C	79.137		
	H-3C	4.110		
	C-3C			
	H-4C	4.042	NOE: 5.528 ppm	H-1B
	C-4C	79.024		
	H-5C			
	C-5C			
	H-6C	3.859		
		4.112		
	C-6C	61.662		

**EXPERIMENTAL PART**

	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1D	5.093	NOE: 4.045 ppm	H-4E
	C-1D	98.180		
	H-2D	3.484		
	C-2D	79.472		
	H-3D	4.058		
	C-3D			
	H-4D	3.830	NOE: 5.076 ppm	H-1C
	C-4D	82.276		
	H-5D	4.165		
	C-5D			
	H-6D	3.174		
		2.964		
	C-6D	34.101		
	H-1E	5.210	NOE: 4.038 ppm	H-4F
	C-1E	99.049		
	H-2E	3.533		
	C-2E	78.829		
	H-3E	4.103		
	C-3E			
	H-4E	4.045	NOE: 5.093 ppm	H-1D
	C-4E	80.232		
	H-5E	3.988		
	C-5E			
	H-6E	3.679		
		4.217		
	C-6E	69.281		
	H-1F	5.354	NOE: 3.857 ppm	H-4G
	C-1F	98.580		
	H-2F	3.612		
	C-2F	78.072		
	H-3F	4.116		
	C-3F			
	H-4F	4.038	NOE: 5.210 ppm	H-1E
	C-4F	75.425		
	H-5F			
	C-5F			
	H-6F	3.751		
		4.094		
	C-6F	69.503		

**EXPERIMENTAL PART**

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	Attribution	Signal (ppm)	Correlation(ppm)	Attribution
	H-1G	5.123	NOE: 3.790 ppm	H-4A
	C-1G	98.622		
	H-2G	3.529		
	C-2G	79.202		
	H-3G	4.072		
	C-3G			
	H-4G	3.857	NOE: 5.354 ppm	H-1F
	C-4G	79.731		
	H-5G	4.130		
	C-5G			
	H-6G	2.165		
		2.994		
	C-6G	26.983		

EXPERIMENTAL PART

